Peer reviewed publications

   
   Impact factor: 7.12

   **Abstract:** Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS. Activated microglia/macrophages play a key role in the immunopathogenesis of MS and its corresponding animal models, experimental autoimmune encephalomyelitis (EAE). Microglia activation begins at early stages of the disease and is associated with elevated expression of the 18 kDa mitochondrial translocator protein (TSPO). Thus, positron emission tomography (PET) imaging of microglial activation using TSPO-specific radioligands could be valuable for monitoring disease-associated neuroinflammatory processes. EAE was induced in rats using a fragment of myelin basic protein, yielding acute clinical disease that reflects extensive spinal cord inflammation. Enhanced TSPO expression in spinal cords of EAE rats versus those of controls was confirmed by Western blot and immunohistochemistry. Biodistribution studies in control and EAE rats were performed using the TSPO radioligand [¹⁸F]DPA-714 \( (N,N\text{-diethyl-2-(2-(4-(2-fluoroethoxy)phenyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidin-3-yl)acetamide}) \). At 1 h after injection, almost fivefold higher levels of [¹⁸F]DPA-714 were measured in spinal cords of EAE rats versus controls. The specific binding of [¹⁸F]DPA-714 to TSPO in spinal cords was confirmed in competition studies, using unlabeled \((R,S)\text{-PK11195 ((R,S)-N-methyl-N-(1-methylpropyl)-1-(2-chlorophenyl)isoquinoline-3-carboxamide})\) or DPA-714 in excess. MicroPET studies affirm that this differential radioactivity uptake in spinal cords of EAE versus control rats could be detected and quantified. Using [¹⁸F]DPA-714, neuroinflammation in spinal cords of EAE-induced rats could be visualized by PET, offering a sensitive technique for monitoring neuroinflammatory lesions in the CNS and particularly in the spinal cord. In addition to current MRI protocols, this approach could provide molecular images of neuroinflammation for detection, monitoring, and research in MS.

   
   Impact factor: 6.75

   **Abstract:** Alpha-synuclein (αSYN) aggregation plays a pivotal role in the pathogenesis of Parkinson's disease and other synucleinopathies. In this multistep process, oligomerization of αSYN monomers is the first step in the formation of fibrils and intracytoplasmic inclusions. Although αSYN oligomers are generally considered to be the culprit of these diseases, the methodology currently available to follow-up oligomerization in cells and in brain is inadequate. We developed a split firefly luciferase complementation system to visualize oligomerization of viral vector-encoded αSYN fusion proteins. αSYN oligomerization resulted in successful luciferase complementation in cell culture and in
mouse brain. Oligomerization of αSYN was monitored noninvasively with bioluminescence imaging in the mouse striatum and substantia nigra up to 8 months after injection. Moreover, the visualized αSYN oligomers retained their toxic and aggregation properties in both model systems. Next, the effect of two small molecules, FK506 and (-)-epigallocatechin-3-gallate (EGCG), known to inhibit αSYN fibril formation, was investigated. FK506 inhibited the observed αSYN oligomerization both in cell culture and in mouse brain. In conclusion, the split firefly luciferase-αSYN complementation assay will increase our insight in the role of αSYN oligomers in synucleinopathies and opens new opportunities to evaluate potential αSYN-based neuroprotective therapies.

   doi: 10.1016/j.bpj.2012.05.006
   Impact factor: 3.653

Abstract: Partitioning of polypeptides between protein folding and amyloid formation is of outstanding pathophysiological importance. Using yeast phosphoglycerate kinase as model, here we identify the features of the energy landscape that decide the fate of the protein: folding or amyloidogenesis. Structure formation was initiated from the acid-unfolded state, and monitored by fluorescence from 10 ms to 20 days. Solvent conditions were gradually shifted between folding and amyloidogenesis, and the properties of the energy landscape governing structure formation were reconstructed. A gradual transition of the energy landscape between folding and amyloid formation was observed. In the early steps of both folding and misfolding, the protein searches through a hierarchically structured energy landscape to form a molten globule in a few seconds. Depending on the conditions, this intermediate either folds to the native state in a few minutes, or forms amyloid fibers in several days. As conditions are changed from folding to misfolding, the barrier separating the molten globule and native states increases, although the barrier to the amyloid does not change. In the meantime, the native state also becomes more unstable and the amyloid more stable. We conclude that the lower region of the energy landscape determines the final protein structure.

   Impact factor: 3.844

Abstract: PURPOSE: The type 2 cannabinoid receptor (CB2R) is part of the human endocannabinoid system and is involved in central and peripheral inflammatory processes. In vivo imaging of the CB2R would allow study of several (neuro)inflammatory disorders. In this study we have investigated the safety and tolerability of [11C]-NE40, a CB2R positron emission tomography (PET) ligand, in healthy human male subjects and determined its biodistribution and radiation dosimetry.
PROCEDURE: Six healthy male subjects (age 20-65 years) underwent a dynamic series of nine whole-body PET/CT scans for up to 140 min, after injection of an average bolus of 286 MBq of [11C]-NE40. Organ absorbed and total effective doses were calculated through OLINDA.

RESULTS: [11C]-NE40 showed high initial uptake in the spleen and a predominant hepatobiliary excretion. In the brain, rapid uptake and swift washout were seen. Organ absorbed doses were largest for the small intestine and liver, with 15.6 and 11.5 μGy/MBq, respectively. The mean effective dose was 3.64 ± 0.81 μSv/MBq. There were no changes with aging observed. No adverse events were encountered.

CONCLUSIONS: This first-in-man study of [11C]-NE40 showed an expected biodistribution compatible with lymphoid tissue uptake and appropriate fast brain kinetics in the healthy human brain, underscoring the potential of this tracer for further application in central and peripheral inflammation imaging. The effective dose is within the typical expected range for 11C ligands.

   Impact factor: 5.563

Abstract: There is a great need for the monitoring of microglial activation surrounding multiple sclerosis lesions because the activation of microglia is thought to drive widespread neuronal damage. Recently, second-generation PET radioligands that can reveal the extent of microglial activation by quantifying the increased expression of the 18-kDa translocator protein have been developed. Here, we investigate whether PET imaging can be used to demonstrate the reduction in microglial activation surrounding a chronic focal multiple sclerosis (MS)-like lesion after treatment with fingolimod, an established MS therapy.

METHODS: Chronic focal experimental autoimmune encephalitis (EAE)-like lesions were induced in Lewis rats (n = 24) via stereotactic intrastriatal injection of heat-killed bacillus Calmette-Guérin (BCG) and subsequent activation using an intradermal injection of BCG in complete Freund adjuvant. This process resulted in a delayed-type hypersensitivity (DTH)-like EAE lesion. The extent of neuroinflammation surrounding the lesion was measured using (18)F-GE180 as a PET radioligand. The imaging was performed before and after treatment with fingolimod (0.3 mg/kg/d by mouth, 28 d) or vehicle as a control. In addition to imaging, autoradiography and immunohistochemistry experiments were performed to verify the in vivo results.

RESULTS: The chronic DTH EAE lesion led to increased ligand binding in the ipsilateral, compared with contralateral, hemisphere when PET imaging was performed with the translocator protein-binding radioligand (18)F-GE180. Treatment with fingolimod led to a highly significant reduction in the binding potential, which could be demonstrated using both in vivo and ex vivo imaging (fingolimod vs. vehicle treatment, P < 0.0001). The area of increased (18)F-GE180 signal mapped closely to the area of activated microglial cells detected by immunohistochemistry.

CONCLUSION: PET imaging, unlike MR imaging, can be used to visualize the microglial activation surrounding a chronic DTH EAE lesion. Importantly, the treatment effect of
fingolimod can be monitored in vivo by measuring the degree of microglial activation surrounding the chronic DTH EAE lesion. This work gives promise for the introduction of new outcome measures applicable in treatment studies of progressive MS.


Abstract: On the one hand, the translocator protein (TSPO) radioligand N,N-diethyl-2-(2-(4-(2-(18)F-fluoroethoxy)phenyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidin-3-yl)acetamide ((18)F-DPA-714) has been suggested to serve as an alternative radiotracer to image human glioma, and on the other hand the alkylphosphocholine erufosine (ErPC3) has been reported to induce apoptosis in otherwise highly apoptosis-resistant glioma cell lines. The induction of apoptosis by ErPC3 requires TSPO, a mitochondrial membrane protein highly expressed in malignant gliomas. In this preclinical study, we monitored the effect of ErPC3 treatment in vivo using (18)F-DPA-714 PET.

METHODS: In vitro studies investigated the antitumor effect of ErPC3 in 9L rat gliosarcoma cells. In vivo, glioma-bearing rats were imaged with (18)F-DPA-714 for the time of treatment.

RESULTS: A significant decrease in 9L cell proliferation and viability and a significant increase in apoptosis and caspase-3 activation were demonstrated on ErPC3 treatment in cell culture. In the rat model, ErPC3 administration resulted in significant changes in (18)F-DPA-714 tumor uptake over the course of the treatment. Immunohistochemistry revealed reduced tumor volume and increased cell death in ErPC3-treated animals accompanied by infiltration of the tumor core by CD11b-positive microglia/macrophages and glial fibrillary acidic protein-positive astrocytes.

CONCLUSION: Our findings demonstrate a potent antitumour effect of ErPC3 in vitro, in vivo, and ex vivo. PET imaging of TSPO expression using (18)F-DPA-714 allows effective monitoring and quantification of disease progression and response to ErPC3 therapy in intracranial 9L gliomas.


Abstract: A novel method is presented to perform material map segmentation from preclinical MRI for corresponding PET attenuation correction. MRI does not provide attenuation ratio, hence segmenting a material map from it is challenging. Furthermore the MRI images often suffer from ghost artifacts. On the contrary MRI has no radiation dose. Our method operated with fast spin echo scout pairs that had perpendicular frequency directions. This way the direction of the ghost artifacts were perpendicular as well. Our body-air segmentation method built on this a priori information
and successfully erased the ghost artifacts from the final binary mask. Visual and quantitative validation was performed by two preclinical specialists. Results indicate that our method is effective against MRI scout ghost artifacts and that PET attenuation correction based on MRI makes sense even on preclinical images.

Impact factor: 3.432

**Abstract:** Sixteen new phenyl alkyl ether derivatives (12, 14-28) of the 5,7-dimethylpyrazolo[1,5-a]pyrimidin-3-ylacetamide (DPA) class were synthesized and evaluated in a competition binding assay against [(3)H]PK11195 using 18 kDa translocator protein (TSPO) derived from rat kidney mitochondrial fractions. All analogues showed superior binding affinities for TSPO compared to DPA-713 (5) and DPA-714 (6). Picomolar affinities were observed for this class of TSPO ligands in this assay for the first time, with phenethyl ether 28 showing the greatest affinity (Ki = 0.13 nM). Additionally, all analogues increased pregnenolone biosynthesis (134-331% above baseline) in a rat C6 glioma cell steroidogenesis assay.

Impact factor: 3.87

**Abstract:** Two novel adamantane derivatives, adamantant-1-yl(1-pentyl-1H-indol-3-yl)methanone (AB-001) and N-(adamtan-1-yl)-1-pentyl-1H-indole-3-carboxamide (SDB-001), were recently identified as cannabimimetic indoles of abuse. Conflicting anecdotal reports of the psychoactivity of AB-001 in humans, and a complete dearth of information about the bioactivity of SDB-001, prompted the preparation of AB-001, SDB-001, and several analogues intended to explore preliminary structure-activity relationships within this class. This study sought to elucidate which structural features of AB-001, SDB-001, and their analogues govern the cannabimimetic potency of these chemotypes in vitro and in vivo. All compounds showed similar full agonist profiles at CB1 (EC50 = 16-43 nM) and CB2 (EC50 = 29-216 nM) receptors in vitro using a FLIPR membrane potential assay, with the exception of SDB-002, which demonstrated partial agonist activity at CB2 receptors. The activity of AB-001, AB-002, and SDB-001 in rats was compared to that of Δ(9)-tetrahydrocannabinol (Δ(9)-THC) and cannabimimetic indole JWH-018 using biotelemetry. SDB-001 dose-dependently induced hypothermia and reduced heart rate (maximal dose 10 mg/kg) with potency comparable to that of Δ(9)-tetrahydrocannabinol (Δ(9)-THC, maximal dose 10 mg/kg), and lower than that of JWH-018 (maximal dose 3 mg/kg). Additionally, the changes in body temperature and heart rate affected by SDB-001 are of longer duration than those of Δ(9)-THC or JWH-018, suggesting a different pharmacokinetic profile. In contrast, AB-001, and its homologue, AB-002, did not produce
significant hypothermic and bradycardic effects, even at relatively higher doses (up to 30 mg/kg), indicating greatly reduced potency compared to Δ(9)-THC, JWH-018, and SDB-001.

   doi: 10.1074/jbc.M112.366419
   Impact factor: 4.773

Abstract: Recent evidence highlights the peroxisome proliferator-activated receptors (PPARs) as critical neuroprotective factors in several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). To gain new mechanistic insights into the role of these receptors in the context of ALS, here we investigated how PPAR transcriptional activity varies in hSOD1(G93A) ALS transgenic mice. We demonstrate that PPARγ-driven transcription selectively increases in the spinal cord of symptomatic hSOD1(G93A) mice. This phenomenon correlates with the up-regulation of target genes, such as lipoprotein lipase and glutathione S-transferase α-2, which are implicated in scavenging lipid peroxidation by-products. Such events are associated with enhanced PPARγ immunoreactivity within motor neuronal nuclei. This observation, and the fact that PPARγ displays increased responsiveness in cultured hSOD1(G93A) motor neurons, points to a role for this receptor in neutralizing deleterious lipoperoxidation derivatives within the motor cells. Consistently, in both motor neuron-like cultures and animal models, we report that PPARγ is activated by lipid peroxidation end products, such as 4-hydroxynonenal, whose levels are elevated in the cerebrospinal fluid and spinal cord from ALS patients. We propose that the accumulation of critical concentrations of lipid peroxidation adducts during ALS progression leads to the activation of PPARγ in motor neurons. This in turn triggers self-protective mechanisms that involve the up-regulation of lipid detoxification enzymes, such as lipoprotein lipase and glutathione S-transferase α-2. Our findings indicate that anticipating natural protective reactions by pharmacologically modulating PPARγ transcriptional activity may attenuate neurodegeneration by limiting the damage induced by lipid peroxidation derivatives.

   doi: 10.1007/s11307-014-0765-9
   Impact factor: 2.869

Abstract: PURPOSE: The purpose of the study was to validate [18F]DPA-714, a translocator protein (TSPO) 18 kDa radioligand, as a probe to non-invasively quantify the inflammatory state in inflammatory bowel disease (IBD) animal models.
PROCEDURES: Quantitative positron emission tomography (PET) imaging of intestinal inflammation was conducted with 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) a glucose metabolism surrogate marker and [18F]DPA-714 a ligand of the 18 kDa TSPO, on two IBD models. The first model was induced using dextran sodium sulfate (DSS), creating global inflammation in the colon. The second model was induced by rectally administering trinitrobensensulfonic acid (TNBS), creating local and acute inflammation.
RESULTS: The level of inflammation was analyzed using PET imaging on days 7 and 8. The analysis obtained with [18F]DPA-714, yielded a significant difference between the DSS treated (0.50 ± 0.17%ID/cc) and non-treated rats (0.35 ± 0.15%ID/cc). [18F]FDG on the other hand did not yield a significant difference. We did observe a mean glucose consumption in the colon increase from 0.40 ± 0.11 %ID/cc to 0.54 ± 0.17 %ID/cc. In the TNBS model, the uptake level of [18F]DPA-714 increased significantly from 0.46 ± 0.23%ID/cc for the non-treated group, to 1.30 ± 0.62%ID/cc for those treated. PET signal was correlated with increased TSPO expression at cellular level.

CONCLUSIONS: Results indicate that [18F]DPA-714 is suitable for studying inflammation in IBD models. [18F]DPA-714 could be a good molecular probe to non-invasively evaluate the level and localization of inflammation. Moreover, in vivo imaging using this TSPO ligand is potentially a powerful tool to stage and certainly to follow the evolution and therapeutic efficiency at molecular level within this disease family.


Abstract: PURPOSE: Neuroinflammation plays a critical role in various neuropathological conditions, and hence there is renewed interest in the translocator protein (TSPO) as a biomarker of microglial activation and macrophage infiltration in the brain. This is reflected in the large amount of research conducted seeking to replace the prototypical PET radiotracer 11C-R-PK11195 with a TSPO ligand with higher performance. Here we report the in vivo preclinical investigation of the novel TSPO tracer 18F-GE-180 in a rat model of stroke.

METHODS: Focal cerebral ischaemia was induced in Wistar rats by 60-min occlusion of the middle cerebral artery (MCAO). Brain damage was assessed 24 h after MCAO by T2 MRI. Rats were scanned with 11C-R-PK11195 and 18F-GE-180 5 or 6 days after MCAO. Specificity of binding was confirmed by injection of unlabelled R-PK11195 or GE-180 20 min after injection of 18F-GE-180. In vivo data were confirmed by ex vivo immunohistochemistry for microglial (CD11b) and astrocytic biomarkers (GFAP).

RESULTS: 18F-GE-180 uptake was 24 % higher in the core of the ischaemic lesion and 18 % lower in the contralateral healthy tissue than that of 11C-R-PK11195 uptake (1.5 ± 0.2-fold higher signal to noise ratio). We confirmed this finding using the simplified reference tissue model (BPND = 3.5 ± 0.4 and 2.4 ± 0.5 for 18F-GE-180 and 11C-R-PK11195, respectively, with R 1 = 1). Injection of unlabelled R-PK11195 or GE-180 20 min after injection of 18F-GE-180 significantly displaced 18F-GE-180 (69 ± 5 % and 63 ± 4 %, respectively). Specificity of the binding was also confirmed by in vitro autoradiography, and the location and presence of activated microglia and infiltrated macrophages were confirmed by immunohistochemistry.

CONCLUSION: The in vivo binding characteristics of 18F-GE-180 demonstrate a better signal to noise ratio than 11C-R-PK11195 due to both a better signal in the lesion and lower nonspecific binding in healthy tissue. These results provide evidence that 18F-GE-180 is a strong candidate to replace 11C-R-PK11195.

doi: 10.1371/journal.pone.0056441
Impact factor: 4.09

Abstract: PURPOSE: Neuroinflammation is involved in several brain disorders and can be monitored through expression of the translocator protein 18 kDa (TSPO) on activated microglia. In recent years, several new PET radioligands for TSPO have been evaluated in disease models. [(18)F]DPA-714 is a TSPO radiotracer with great promise; however results vary between different experimental models of neuroinflammation. To further examine the potential of [(18)F]DPA-714, it was compared directly to [(11)C]PK11195 in experimental cerebral ischemia in rats.

METHODS: Under anaesthesia, the middle cerebral artery of adult rats was occluded for 60 min using the filament model. Rats were allowed recovery for 5 to 7 days before one hour dynamic PET scans with [(11)C]PK11195 and/or [(18)F]DPA-714 under anaesthesia.

RESULTS: Uptake of [(11)C]PK11195 vs [(18)F]DPA-714 in the ischemic lesion was similar (core/contralateral ratio: 2.84±0.67 vs 2.28±0.34 respectively), but severity of the brain ischemia and hence ligand uptake in the lesion appeared to vary greatly between animals scanned with [(11)C]PK11195 or with [(18)F]DPA-714. To solve this issue of inter-individual variability, we performed a direct comparison of [(11)C]PK11195 and [(18)F]DPA-714 by scanning the same animals sequentially with both tracers within 24 h. In this direct comparison, the core/contralateral ratio (3.35±1.21 vs 4.66±2.50 for [(11)C]PK11195 vs [(18)F]DPA-714 respectively) showed a significantly better signal-to-noise ratio (1.6 (1.3-1.9, 95%CI) fold by linear regression) for [(18)F]DPA-714.

CONCLUSIONS: In a clinically relevant model of neuroinflammation, uptake for both radiotracers appeared to be similar at first, but a high variability was observed in our model. Therefore, to truly compare tracers in such models, we performed scans with both tracers in the same animals. By doing so, our result demonstrated that [(18)F]DPA-714 displayed a higher signal-to-noise ratio than [(11)C]PK11195. Our results suggest that, with the longer half-life of [(18)F] which facilitates distribution of the tracer across PET centre, [(18)F]DPA-714 is a good alternative for TSPO imaging.


doi: 10.1007/s12035-014-8657-1
Impact factor: 5.286

Abstract: This article gives a comprehensive overview of cytokine and other inflammation associated protein levels in plasma, serum and cerebrospinal fluid (CSF) of patients with Alzheimer’s disease (AD) and mild cognitive impairment (MCI). We reviewed 118 research articles published between 1989 and 2013 to compare the reported levels of 66 cytokines and other proteins related to regulation and signaling in inflammation in the blood or CSF obtained from MCI and AD patients. Several cytokines are evidently regulated in (neuro-) inflammatory processes associated with neurodegenerative disorders. Others do not display changes in the blood or CSF during disease progression. However, many reports on
cytokine levels in MCI or AD are controversial or inconclusive, particularly those which provide data on frequently investigated cytokines like tumor necrosis factor alpha (TNF-α) or interleukin-6 (IL-6). The levels of several cytokines are possible indicators of neuroinflammation in AD. Some of them might increase steadily during disease progression or temporarily at the time of MCI to AD conversion. Furthermore, elevated body fluid cytokine levels may correlate with an increased risk of conversion from MCI to AD. Yet, research results are conflicting. To overcome interindividual variances and to obtain a more definite description of cytokine regulation and function in neurodegeneration, a high degree of methodical standardization and patients collective characterization, together with longitudinal sampling over years is essential.


Impact factor: 4.09

Abstract: Automated voxel-based or pre-defined volume-of-interest (VOI) analysis of small-animal PET data in mice is necessary for optimal information usage as the number of available resolution elements is limited. We have mapped metabolic ($[^{18}\text{F}]$FDG) and dopamine transporter ($[^{18}\text{F}]$FECT) small-animal PET data onto a 3D Magnetic Resonance Microscopy (MRM) mouse brain template and aligned them in space to the Paxinos coordinate system. In this way, ligand-specific templates for sensitive analysis and accurate anatomical localization were created. Next, using a pre-defined VOI approach, test-retest and intersubject variability of various quantification methods were evaluated. Also, the feasibility of mouse brain statistical parametric mapping (SPM) was explored for $[^{18}\text{F}]$FDG and $[^{18}\text{F}]$FECT imaging of 6-hydroxydopamine-lesioned (6-OHDA) mice.

METHODS: Twenty-three adult C57BL6 mice were scanned with $[^{18}\text{F}]$FDG and $[^{18}\text{F}]$FECT. Registrations and affine spatial normalizations were performed using SPM8. $[^{18}\text{F}]$FDG data were quantified using (1) an image-derived-input function obtained from the liver (cMRglc), using (2) standardized uptake values (SUVglc) corrected for blood glucose levels and by (3) normalizing counts to the whole-brain uptake. Parametric $[^{18}\text{F}]$FECT binding images were constructed by reference to the cerebellum. Registration accuracy was determined using random simulated misalignments and vectorial mismatch determination.

RESULTS: Registration accuracy was between 0.21-1.11 mm. Regional intersubject variabilities of cMRglc ranged from 15.4% to 19.2%, while test-retest values were between 5.0% and 13.0%. For $[^{18}\text{F}]$FECT uptake in the caudate-putamen, these values were 13.0% and 10.3%, respectively. Regionally values of cMRglc positively correlated to SUVglc measured within the 45-60 min time frame (spearman r=0.71). Next, SPM analysis of 6-OHDA-lesioned mice showed hypometabolism in the bilateral caudate-putamen and cerebellum, and an unilateral striatal decrease in DAT availability.

CONCLUSION: MRM-based small-animal PET templates facilitate accurate assessment and spatial localization of mouse brain function using VOI or voxel-based analysis. Regional intersubject- and test-retest variations indicate that for these targets accuracy comparable to humans can be achieved.
doi: 10.3233/JAD-141275
Impact factor: 3.612

Abstract: Posterior cortical atrophy (PCA) is characterized by basic visual and high order visual-spatial dysfunctions. In this study, we investigated long-distance deafferentation processes within the frontal-parietal-occipital network in ten PCA patients using a MRI-PET combined approach. Objective voxel-based [18F]FDG-PET imaging measured metabolic changes in single patients. Comprehensive investigation of diffusion tensor imaging (DTI) metrics and grey-matter density with voxel-based morphometry were obtained in a subgroup of 6 patients. Fractional anisotropy in the superior longitudinal fasciculus correlated with the PET metabolic changes within the inferior parietal and frontal eye field regions. [18F]FDG-PET analysis showed in each PCA case the typical bilateral hypometabolic pattern, involving posterior temporal, parietal, and occipital cortex, with additional hypometabolic foci in the frontal eye fields. Voxel-based morphometry showed right-sided atrophy in the parieto-occipital cortex, as well as a limited temporal involvement. DTI revealed extensive degeneration of the major anterior-posterior connecting fiber bundles and of commissural frontal lobe tracts. Microstructural measures in the superior longitudinal fasciculus were correlated with the PET metabolic changes within the inferior parietal and frontal eye field regions. Our results confirmed the predominant occipital-temporal and occipital-parietal degeneration in PCA patients. [18F]FDG-PET and DTI-MRI combined approaches revealed neurodegeneration effects well beyond the classical posterior cortical involvement, most likely as a consequence of deafferentation processes within the occipital-parietal-frontal network that could be at the basis of visuo-perceptual, visuo-spatial integration and attention deficits in PCA.

doi: 10.2174/15701611113116660168
Impact factor: 2.821

Abstract: Neuroinflammation is a complex biological response to any injury occurring to the central nervous system. It is mainly characterized by the recruitment of immune system cells, namely the microglial cells, in the site of injury. Once activated, microglia expresses a cholesterol transporter protein (TPSO), previously also known as peripheral type benzodiazepine receptor. PK11195 is a ligand for TPSO and, labelled with a positron emitter, it is also the most used tracer for PET molecular imaging to in vivo map the microglia activation in various neurological disorders, including ischemic stroke. Recent [11C]PK11195 PET studies proved activated microglia both locally in the area of the infarct and at distance along the affected fibre tracts, suggesting the presence of two different microglia subtypes with peculiar functions in disease progression. The aim of this review is to discuss the most recent knowledge about imaging neuroinflammation in ischemic stroke and in the atherosclerotic and vascular inflammatory disorders, trying to elucidate the interplay between the clinical course and the activation of a microglial response.
doi: 10.1002/mrc.3919
Impact factor: 1.437

**Abstract:** DPA-713 is the lead compound of a recently reported pyrazolo[1,5-a]pyrimidineacetamide series, targeting the translocator protein (TSPO 18 kDa), and as such, this structure, as well as closely related derivatives, have been already successfully used as positron emission tomography radioligands. On the basis of the pharmacological core of this ligands series, a new magnetic resonance imaging probe, coded DPA-C(6)-(Gd)DOTAMA was designed and successfully synthesized in six steps and 13% overall yield from DPA-713. The Gd-DOTA monoamide cage (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) represents the magnetic resonance imaging reporter, which is spaced from the phenylpyrazolo[1,5-a]pyrimidineacetamide moiety (DPA-713 motif) by a six carbon-atom chain. DPA-C(6)-(Gd)DOTAMA relaxometric characterization showed the typical behavior of a small-sized molecule (relaxivity value: 6.02 mM(-1) s(-1) at 20 MHz). The good hydrophilicity of the metal chelate makes DPA-C(6)-(Gd)DOTAMA soluble in water, affecting thus its biodistribution with respect to the parent lipophilic DPA-713 molecule. For this reason, it was deemed of interest to load the probe to a large carrier in order to increase its residence lifetime in blood. Whereas DPA-C(6)-(Gd)DOTAMA binds to serum albumin with a low affinity constant, it can be entrapped into liposomes (both in the membrane and in the inner aqueous cavity). The stability of the supramolecular adduct formed by the Gd-complex and liposomes was assessed by a competition test with albumin.

doi: 10.1007/s00259-014-2859-7
Impact factor: 5.217

**Abstract:** PURPOSE: The Alzheimer's disease (AD) pathology is characterized by fibrillar amyloid deposits and neurofibrillary tangles, as well as the activation of astrocytosis, microglia activation, atrophy, dysfunctional synapse, and cognitive impairments. The aim of this study was to test the hypothesis that astrocytosis is correlated with reduced gray matter density in prodromal AD.

**METHODS:** Twenty patients with AD or mild cognitive impairment (MCI) underwent multitracer positron emission tomography (PET) studies with 11C-Pittsburgh compound B (11C-PIB), 18 F-Fluorodeoxyglucose (18 F-FDG), and 11C-deuterium-L-deprenyl (11C-DED) PET imaging, as well as magnetic resonance imaging (MRI) scanning, cerebrospinal fluid (CSF) biomarker analysis, and neuropsychological assessments. The parahippocampus was selected as a region of interest, and each value was calculated for four different imaging modalities. Correlation analysis was applied between DED slope values and gray matter (GM) densities by MRI. To further explore possible relationships, correlation analyses were performed between the different variables, including the CSF biomarker.
RESULTS: A significant negative correlation was obtained between DED slope values and GM density in the parahippocampus in PIB-positive (PIB + ve) MCI patients (p = 0.025) (prodromal AD). Furthermore, in exploratory analyses, a positive correlation was observed between PIB-PET retention and DED binding in AD patients (p = 0.014), and a negative correlation was observed between PIB retention and CSF Aβ42 levels in MCI patients (p = 0.021), while the GM density and CSF total tau levels were negatively correlated in both PIB + ve MCI (p = 0.002) and MCI patients (p = 0.001). No significant correlation was observed with FDG-PET and with any of the other PET, MRI, or CSF biomarkers.

CONCLUSIONS: High astrocytosis levels in the parahippocampus of PIB + ve MCI (prodromal AD) patients suggest an early preclinical influence on cellular tissue loss. The lack of correlation between astrocytosis and CSF tau levels, and a positive correlation between astrocytosis and fibrillar amyloid deposition in clinical demented AD together indicate that parahippocampal astrocytosis might have some causality within the amyloid pathology.

Impact factor: 4.4

Abstract: There is growing evidence of activated microglia and inflammatory processes in the cerebral cortex in amyotrophic lateral sclerosis (ALS). Activated microglia is characterized by increased expression of the 18 kDa translocator protein (TSPO) in the brain and may be a useful biomarker of inflammation. In this study, we evaluated neuroinflammation in ALS patients using a radioligand of TSPO, (18)F-DPA-714. Ten patients with probable or definite ALS (all right-handed, without dementia, and untreated by riluzole or other medication that might bias the binding on the TSPO), were enrolled prospectively and eight healthy controls matched for age underwent a PET study. Comparison of the distribution volume ratios between both groups were performed using a Mann-Whitney's test. Significant increase of distribution of volume ratios values corresponding to microglial activation was found in the ALS sample in primary motor, supplementary motor and temporal cortex (p = 0.009, p = 0.001 and p = 0.004, respectively). These results suggested that the cortical uptake of (18)F-DPA-714 was increased in ALS patients during the "time of diagnosis" phase of the disease. This finding might improve our understanding of the pathophysiology of ALS and might be a surrogate marker of efficacy of treatment on microglial activation.

doi: 10.1007/7854_2012_232
Impact factor:

Abstract: Although significant inconsistencies remain to be clarified, a role for neurogenesis in hippocampal functions, such as cognition, has been suggested by several reports. Yet, investigation in various species of mammals, including humans, revealed that
rates of hippocampal neurogenesis are steadily declining with age. The very low levels of hippocampal neurogenesis persisting in the aged brain have been suspected to underlie the cognitive deficits observed in elderly. However, current evidence fails to support the hypothesis that decrease of neurogenesis along normal ageing leads to hippocampal dysfunction. Nevertheless, current studies are suggestive for a distinct role of hippocampal neurogenesis in young versus adult and old brain.

   doi: 10.1016/j.drudis.2014.01.003
   Impact factor: 5.964

Abstract: Drug development represents a highly complex, inefficient and costly process. Over the past decade, the widespread use of nuclear imaging, owing to its functional and molecular nature, has proven to be a determinant in improving the efficiency in selecting the candidate drugs that should either be abandoned or moved forward into clinical trials. This helps not only with the development of safer and effective drugs but also with the shortening of time-to-market. The modern concept and future trends concerning molecular imaging will presumably be hybrid or multimodality imaging, including combinations between high sensitivity and functional (molecular) modalities with high spatial resolution and morphological techniques.

   doi: 10.1002/jlcr.3252
   Impact factor: 1.187

Abstract: DPA-714 (N,N-diethyl-2-(2-(4-(2-fluoroethoxy)phenyl)-5,7dimethylpyrazolo[1,5-a]pyrimidin-3-yl)acetamide) is a recently discovered fluorinated ligand of the translocator protein 18 kDa (TSPO). Labelled with the short-lived positron emitter fluorine-18, this structure is today the radioligand of reference for in vivo imaging of microglia activation and neuroinflammatory processes with positron emission tomography. In the present work, an isotopically tritium-labelled version was developed ([(3)H]DPA-714), in order to access high resolution in vitro and ex vivo microscopic autoradiography studies, repeated and long-lasting receptor binding studies and in vivo pharmacokinetic determination at late time points. Briefly, DPA-714 as reference, and its 3,5-dibrominated derivative as precursor for labelling, were both prepared from DPA-713 in nonoptimized 32% (two steps) and 10% (three steps) yields, respectively. Reductive debromination using deuterium gas and Pd/C as catalyst in methanol, performed at the micromolar scale, confirmed the regioselective introduction of two deuterium atoms at the meta positions of the phenyl ring. Tritiodebromination was analogously performed using no-carrier tritium gas. HPLC purification provided >96% radiochemically pure [(3)H]DPA-714 (7 GBq) with a 2.1 TBq/mmol specific radioactivity. Interestingly, additional hydrogen-for-tritium exchanges were also observed at the 5-methyl and 7-methyl positions of the pyrazolo[1,5-a]pyrimidine, opening novel perspectives in the labelling of compounds featuring this heterocyclic core.

doi: 10.1002/jlcr.2992

Impact factor: 1.24

Abstract: The TSPO (translocator protein), also known as the peripheral benzodiazepine receptor, is upregulated in the brain of subjects suffering from neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's disease. Moreover, this overexpression has been proved to be linked to microglia activation making thus the TSPO a marker of choice of neuroinflammatory processes and therefore a potential target for the development of radioligands for positron emission tomography imaging. The discovery of selective TSPO ligands and their labelling with the short-lived positron-emitter isotopes carbon-11 and fluorine-18 emerged in the mid-1980s with the preparation of the 3-isoquinolinecarboxamide [(11) C]PK11195. To date, an impressive number of promising compounds-[(11) C]PK11195-challengers have been developed; some radioligands-for example, [(11) C]PBR28, [(11) C]DPA-713, [(18) F]FEDAA1106 and [(18) F]DPA-714-are currently used in clinical trials. As illustrated in this review, the methodologies applied for the preparation of these compounds remain mainly [(11) C]methylations using [(11) C]MeI or [(11) C]MeOTf and SN 2-type nucleophilic aliphatic [(18) F]fluorinations-two processes illustrating the state-of-the-art arsenal of reactions that involves these two short-lived radioisotopes-but alternative processes, such as [(11) C]carbonylations using [(11) C]CO and [(11) C]COCl2 as well as SN Ar-type nucleophilic [(18) F]fluorinations, have also been reported and as such, reviewed herein.


doi: 10.1186/scrt312

Impact factor: 3.65

Abstract: Over the past decade a lot of research has been performed towards the therapeutic use of mesenchymal stem cells (MSCs) in neurodegenerative and neuroinflammatory diseases. MSCs have shown to be beneficial in different preclinical studies of central nervous system (CNS) disorders due to their immunomodulatory properties and their capacity to secrete various growth factors. Nevertheless, most of the transplanted cells die within the first hours after transplantation and induce a neuroinflammatory response. In order to increase the efficacy of MSC transplantation, it is thus imperative to completely characterise the mechanisms mediating neuroinflammation and cell death following MSC transplantation into the CNS. Consequently, different components of these cell death- and neuroinflammation-inducing pathways can be targeted in an attempt to improve the therapeutic potential of MSCs for CNS disorders.
Impact factor: 12.958.

Abstract: In female animals, energy metabolism and fertility are tightly connected, and reciprocally regulated. However, the relative contributions of metabolic and reproductive pathways have changed over the course of evolution. In oviparous animals, metabolic factors take precedence over fertility, enabling egg production to be inhibited in a nutritionally poor environment. By contrast, in placental mammals, the opposite occurs: the need to feed a developing embryo and neonate forces metabolic pathways to adapt to these reproductive needs. This physiological necessity explains why in female mammals alterations of gonadal activity, including age-dependent cessation of ovarian functions, are associated with a disruption of metabolic homeostasis and consequent inflammatory reactions that trigger the onset of metabolic, cardiovascular, skeletal and neural pathologies. This Review discusses how metabolic homeostasis and reproductive functions interact to optimize female fertility and explains the pathogenic mechanisms underlying the disordered energy metabolism associated with human ovarian dysfunction owing to menopause, polycystic ovary syndrome and Turner syndrome. Finally, this article highlights how hormone replacement therapy might aid the restoration of metabolic homeostasis in women with ovarian dysfunction.

Impact factor: 7.633

Abstract: Perfluorocarbon (PFC) particles are currently on the rise as cell labeling agents for ¹⁹F-MRI tracking of dendritic cell (DC)-based vaccines. In this work, we design theranostic PFC particles for single-step loading of DCs with both antigenic protein and with a liquid PFC for ¹⁹F-MRI detection of the antigen-loaded cells. Upon addition to DCs in vitro, the antigen-loaded PFC particles are efficiently internalized, resulting in intracellular presence of up to 40 pmol ¹⁹F atoms per cell. At the same time, the DCs become loaded with antigenic proteins, that can be efficiently processed, without important effects on cell viability or altering the DC's phenotype and the cell's capacity to respond to danger signals. In addition, antigen-loaded PFC particle containing DCs are capable of inducing extensive proliferation of antigen-specific CD8⁺ T cells in vitro. Importantly, the antigen-coated PFC particles allow in vitro ¹⁹F-MRI-based detection of the antigen-containing DCs with detection limits as low as 10³ cells μl⁻¹. The dual-modality characteristics of the designed particles could assure that only those DCs that have taken up the antigen, and hence are responsible for an immune response, are traceable via ¹⁹F-MRI. Taken together, these novel dual-modality particles represent an interesting strategy in the development of a traceable DC vaccine.

doi: 10.2967/jnumed.113.125625
Impact factor: 5.774

Abstract: It remains unclear how different translocator protein (TSPO) ligands reflect the spatial extent of astrocyte or microglial activation in various neuroinflammatory conditions. Here, we use a reproducible lipopolysaccharide (LPS)-induced model of acute central nervous system inflammation to compare the binding performance of a new TSPO ligand (18)F-GE-180 with (11)C-(R)-PK11195. Using immunohistochemistry, we also explore the ability of the TSPO ligands to detect activated microglial cells and astrocytes.

METHODS: Lewis rats (n = 30) were microinjected with LPS (1 or 10 μg) or saline (1 μL) into the left striatum. The animals were imaged in vivo at 16 h after the injection using PET radiotracers (18)F-GE-180 or (11)C-(R)-PK11195 (n = 3 in each group) and were killed afterward for autoradiography of the brain. Immunohistochecmical assessment of OX-42 and glial fibrillary acidic protein (GFAP) was performed to identify activated microglial cells and reactive astrocytes.

RESULTS: In vivo PET imaging revealed an increase in the ipsilateral TSPO binding, compared with binding in the contralateral hemisphere, after the microinjection of 10 μg of LPS. No increase was observed with vehicle. By autoradiography, the TSPO radiotracer binding potential in the injected hemisphere was increased after striatal injection of 1 or 10 μg of LPS. However, the significant increase was observed only when using (18)F-GE-180. The area of CD11b-expressing microglial cells extended beyond that of enhanced GFAP staining and mapped more closely to the extent of (18)F-GE-180 binding than to (11)C-(R)-PK11195 binding. The signal from either PET ligand was significantly increased in regions of increased GFAP immunoreactivity and OX-42 colocalization, meaning that the presence of both activated microglia and astrocytes in a given area leads to increased binding of the TSPO radiotracers.

CONCLUSION: (18)F-GE-180 is able to reveal sites of activated microglia in both gray and white matter. However, the signal is increased by the presence of activated astrocytes. Therefore, (18)F-GE-180 is a promising new fluorinated longer-half-life tracer that reveals the presence of activated microglia in a manner that is superior to (11)C-(R)-PK11195 due to the higher binding potential observed for this ligand.


doi: 10.2967/jnumed.114.143727
Impact factor: 5.563

Abstract: This study provides the first comprehensive quantification of translocator protein (TSPO) binding using SPECT and 6-chloro-2-(4'-123I-iodophenyl)-3-(N,N-diethyl)-
imidazo[1,2-a]pyridine-3-acetamide ((123)I-CLINDE) in neurologic patients. (123)I-CLINDE is structurally related to well-known PET ligands such as (18)F-PBR111 and (18)F-DPA-714.

METHODS: Six patients with cerebral stroke and 4 patients with glioblastoma multiforme (GBM) underwent 150-min dynamic SPECT scans with arterial blood sampling. Four of the patients were rescanned. All patients were genotyped for the rs6971 polymorphism. Volumes of interest were delineated on the individual SPECT scans and the coregistered MR images. Compartmental and graphical models using arterial input or the cerebellum as a reference region were used to quantify (123)I-CLINDE binding.

RESULTS: Among the 6 models investigated, the 2-tissue-compartment model with arterial input described the time-activity data best. Time-stability analyses suggested that acquisition time should be at least 90 min. Intersubject variation in the cerebellar distribution volume (VT) was clearly related to the TSPO genotype. In the stroke patients the VT in the perinfarction zone, compared with VT in the ipsilateral cerebellum, ranged from 1.4 to 3.4, and in the GBM patients the VT in the tumor, compared with the VT in the cerebellum, ranged from 1.8 to 3.4. In areas of gadolinium extravasation, (123)I-CLINDE binding parameters were not significantly changed. Thus, (123)I-CLINDE binding does not appear to be importantly affected by blood-brain barrier disruption.

CONCLUSION: As demonstrated within a group of stroke and GBM patients, (123)I-CLINDE SPECT can be used for quantitative assessment of TSPO expression in vivo. Because of the absence of a region devoid of TSPO, reference tissue models should be used with caution. The 2-tissue-compartment kinetic analysis of a 90-min dynamic scan with arterial blood sampling is recommended for the quantification of (123)I-CLINDE binding with SPECT.

doi: 10.1007/s11307-012-0603-x
Impact factor: 3.884

Abstract: PURPOSE: This study is aimed at demonstrating the in vivo potential of Gd(III)-loaded glucan particles (Gd-GPs) as magnetic resonance imaging (MRI)-positive agents for labeling and tracking phagocytic cells.

PROCEDURE: GPs were obtained from Saccharomyces cerevisae and loaded with the water-insoluble complex Gd-DOTAMA(C(18))(2). The uptake kinetics of Gd-GPs by murine macrophages was studied in vitro and the internalization mechanism was assessed by competition assays. The in vivo performance of Gd-GPs was tested at 7.05 T on a mouse model of acute liver inflammation.

RESULTS: The minimum number of Gd-GPs-labeled J774.A1 macrophages detected in vitro by MRI was ca. 300 cells/μl of agar, which is the lowest number ever reported for cells labeled with a positive T(1) agent. Intravenous injection of macrophages labeled with Gd-GPs in a mouse model of liver inflammation enabled the MRI visualization of the cellular infiltration in the diseased area.

CONCLUSIONS: Gd-GPs represent a promising platform for tracking macrophages by MRI as a T(1) alternative to the golden standard T(2)-based iron oxide particles.

Abstract: A new class of nanovesicles formed by the self-assembly of amphiphilic Janus dendrimers, dendrimersomes, loaded with hydrophilic or amphiphilic magnetic resonance imaging chelates shows promising properties as a novel, efficient and versatile nanoplatform for biomedical imaging.


Abstract: The signaling molecule histamine plays a key role in the mediation of immune reactions, in gastric secretion, and in the sensory system. In addition, it has an important function as a neurotransmitter in the central nervous system, acting in pituitary hormone secretion, wakefulness, motor and cognitive functions, as well as in itch and nociception. This has raised interest in the role of the histaminergic system for the treatment and diagnosis of various pathologies such as allergy, sleeping and eating disorders, neurodegeneration, neuroinflammation, mood disorders, and pruritus.

In the past 20 years, several ligands targeting the four different histamine receptor subtypes have been explored as potential radiotracers for positron emission tomography (PET). This contribution provides an overview of the developments of subtype-selective carbon-11-labeled and fluorine-18-labeled compounds for imaging in the brain. Using specific radioligands, the H1R expression in human brain could be examined in diseases such as schizophrenia, depression, and anorexia nervosa. In addition, the sedative effects of antihistamines could be investigated in terms of H1R occupancy. The H3R is of special interest because of its regulatory role in the release of various other neurotransmitters, and initial H3R PET imaging studies in humans have been reported. The H4R is the youngest member of the histamine receptor family and is involved in neuroinflammation and various sensory pathways. To date, two H4R-specific 11C-labeled ligands have been synthesized, and the imaging of the H4R in vivo is in the early stage.


Abstract: Microglial cell function receives increasing interest. To date, the majority of experiments are performed by using immortalized microglia-like cells or primary microglia prepared from pre- or postnatal rodent brain. As those may not adequately reflect the microglial biology in the adult brain, this protocol advocates a procedure which allows for the isolation, purification, and subsequent analysis of microglial cells. Once isolated, the principal state of activation, M1 or M2, can be determined in adult microglia using
fluorescence-activated cell sorting, quantitative PCR, and/or Western blotting. Likewise, adult microglia generated by this protocol can be used for functional analysis through cell cultivation for a limited time.

   Impact factor: 4.787
   
   Abstract: Glucan particles (GPs) are monodisperse microspheres derived from baker's yeast and represent an interesting class of microcarriers for theranostic applications as they show a high affinity toward immune system cells. The typical loading strategy was to harness the ability of the molecule to be loaded to interact with nano-/microassembled systems through electrostatic or hydrophobic forces. However, small water-soluble chemicals could not be steadily retained by the leaky shell of GPs. In this work, we propose an alternative loading approach for small water-soluble compounds that is based on their entrapment in the aqueous core of liposomes that are directly formed into the microparticles through the reverse phase evaporation method (REV). The construct obtained may act as biocompatible carrier to deliver and release, even in a triggerable way, bioactive compounds.

   Impact factor: 5.339
   
   Abstract: Fluorine-18 labelled N,N-diethyl-2-[4-(2-fluoroethoxy)phenyl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-yl)acetamide ([18F]DPA-714) binds to the 18-kDa translocator protein (TSPO) with high affinity. The aim of this initial methodological study was to develop a plasma input tracer kinetic model for quantification of [18F]DPA-714 binding in healthy subjects and Alzheimer's disease (AD) patients, and to provide a preliminary assessment whether there is a disease-related signal. Ten AD patients and six healthy subjects underwent a dynamic positron emission tomography (PET) study along with arterial sampling and a scan protocol of 150 minutes after administration of 250±10 MBq [18F]DPA-714. The model that provided the best fits to tissue time activity curves (TACs) was selected based on Akaike Information Criterion and F-test. The reversible two tissue compartment plasma input model with blood volume parameter was the preferred model for quantification of [18F]DPA-714 kinetics, irrespective of scan duration, volume of interest, and underlying volume of distribution (VT). Simplified reference tissue model (SRTM)-derived binding potential (BPND) using cerebellar gray matter as reference tissue correlated well with plasma input-based distribution volume ratio (DVR). These data suggest that [18F]DPA-714 cannot be used for separating individual AD patients from...
heathy subjects, but further studies including TSPO binding status are needed to substantiate these findings.

   doi: 10.1016/j.nucmedbio.2014.09.006
   Impact factor: 2.408

Abstract: INTRODUCTION: The present study was designed to assess whether [(18)F]PK-209 (3-(2-chloro-5-(methylthio)phenyl)-1-(3-((18)F)fluoromethoxy)phenyl)-1-methylguanidine) is a suitable ligand for imaging the ion-channel site of N-methyl-D-aspartate receptors (NMDArs) using positron emission tomography (PET).

METHODS: Dynamic PET scans were acquired from male rhesus monkeys over 120 min, at baseline and after the acute administration of dizocilpine (MK-801, 0.3 mg/kg; n=3/condition). Continuous and discrete arterial blood samples were manually obtained, to generate metabolite-corrected input functions. Parametric volume-of-distribution (VT) images were obtained using Logan analysis. The selectivity profile of PK-209 was assessed in vitro, on a broad screen of 79 targets.

RESULTS: PK-209 was at least 50-fold more selective for NMDArs over all other targets examined. At baseline, prolonged retention of radioactivity was observed in NMDAr-rich cortical regions relative to the cerebellum. Pretreatment with MK-801 reduced the VT of [(18)F]PK-209 compared with baseline in two of three subjects. The rate of radioligand metabolism was high, both at baseline and after MK-801 administration.

CONCLUSIONS: PK-209 targets the intrachannel site with high selectivity. Imaging of the NMDAr is feasible with [(18)F]PK-209, despite its fast metabolism. Further in vivo evaluation in humans is warranted.

   doi: 10.1016/j.neuroimage.2013.07.080
   Impact factor: 6.252

Abstract: Multiple sclerosis is a devastating demyelinating disease of the central nervous system (CNS) in which endogenous remyelination, and thus recovery, often fails. Although the cuprizone mouse model allowed elucidation of many molecular factors governing remyelination, currently very little is known about the spatial origin of the oligodendrocyte progenitor cells that initiate remyelination in this model. Therefore, we here investigated in this model whether subventricular zone (SVZ) neural stem/progenitor cells (NSPCs) contribute to remyelination of the splenium following cuprizone-induced demyelination. Experimentally, from the day of in situ NSPC labeling, C57BL/6J mice were fed a 0.2% cuprizone diet during a 4-week period and then left to recover on a normal diet for 8 weeks.
Two in situ labeling strategies were employed: (i) NSPCs were labeled by intraventricular injection of micron-sized iron oxide particles and then followed up longitudinally by means of magnetic resonance imaging (MRI), and (ii) SVZ NSPCs were transduced with a lentiviral vector encoding the eGFP and Luciferase reporter proteins for longitudinal monitoring by means of in vivo bioluminescence imaging (BLI). In contrast to preceding suggestions, no migration of SVZ NSPC towards the demyelinated splenium was observed using both MRI and BLI, and further validated by histological analysis, thereby demonstrating that SVZ NSPCs are unable to contribute directly to remyelination of the splenium in the cuprizone model. Interestingly, using longitudinal BLI analysis and confirmed by histological analysis, an increased migration of SVZ NSPC-derived neuroblasts towards the olfactory bulb was observed following cuprizone treatment, indicative for a potential link between CNS inflammation and increased neurogenesis.

   doi: 10.1016/j.ijdevneu.2014.07.005
   Impact factor: 2.918.

Abstract: Cerebrolysin (EVER Neuro Pharma GmbH, Austria) is a peptidergic drug indicated for clinical use in stroke, traumatic brain injury and dementia. The therapeutic effect of Cerebrolysin is thought to ensure from its neurotrophic activity, which shares some properties with naturally occurring neurotrophic factors. However, the exact mechanism of action of Cerebrolysin is yet to be fully deciphered. This study aimed to investigate the neuroprotective effect of Cerebrolysin in a widely used in vitro model of hypoxia-induced neuronal cytotoxicity, namely cobalt chloride (CoCl2)-treatment of PC12 cells. CoCl2-cytotoxicity was indicated by a reduced cell-diameter, cell shrinkage, increased pro-apoptotic Caspase-activities and a decreased metabolic activity. Cerebrolysin maintained the cell-diameter of CoCl2-treated naïve PC12 cells, decreased the activation of Caspase 3/7 in CoCl2-stressed naïve PC12 cells and restored the cells' metabolic activity in CoCl2-impaired naïve and differentiated PC12 cells. Cerebrolysin treatment also decreased the levels of superoxide observed after exposure to CoCl2. Investigating the mechanism of action, we could demonstrate that Cerebrolysin application to CoCl2-stressed PC12 cells increased the phosphorylation of GSK3β, resulting in the inhibition of GSK3β. This might become clinically relevant for Alzheimer's disease, since GSK3β activity has been linked to the production of amyloid beta. Taken together, Cerebrolysin was found to have neuroprotective effects in CoCl2-induced cytotoxicity in PC12 cells.

   doi: 10.1155/2014/574159
   Impact factor: 3.608.

Abstract: The time of pregnancy, birth, and lactation, is characterized by numerous specific alterations in several systems of the maternal body. Peripartum-associated changes in physiology and behavior, as well as their underlying molecular mechanisms,
have been the focus of research since decades, but are still far from being entirely understood. Also, there is growing evidence that pregnancy and lactation are associated with a variety of alterations in neural plasticity, including adult neurogenesis, functional and structural synaptic plasticity, and dendritic remodeling in different brain regions. All of the mentioned changes are not only believed to be a prerequisite for the proper fetal and neonatal development, but moreover to be crucial for the physiological and mental health of the mother. The underlying mechanisms apparently need to be under tight control, since in cases of dysregulation, a certain percentage of women develop disorders like preeclampsia or postpartum mood and anxiety disorders during the course of pregnancy and lactation. This review describes common peripartum adaptations in physiology and behavior. Moreover, it concentrates on different forms of peripartum-associated plasticity including changes in neurogenesis and their possible underlying molecular mechanisms. Finally, consequences of malfunction in those systems are discussed.

   doi: 10.1002/hipo.22258
   Impact factor: 5.492

Abstract: The peripartum period is a time of high susceptibility for mood and anxiety disorders, some of which have recently been associated with alterations in hippocampal neurogenesis. Several factors including stress, aging, and, perhaps unexpectedly, lactation have been shown to decrease hippocampal neurogenesis. Intriguingly, lactation is also a time of reduced stress responsivity suggesting that the effect of stress on neurogenic processes may differ during this period. Therefore, the aim of the present study was to assess the effect of repeated stress during lactation [2 h restraint stress from lactation day (LD) 2 to LD13] on brain weight, hippocampal volume, cell proliferation and survival, and on neuronal and astroglial differentiation. In addition to confirming the known lactation-associated decrease in cell proliferation and survival, we could reveal that stress reversed the lactation-induced decrease in cell proliferation, while it did not affect survival of newly born cells, nor the number of mature neurons, nor did it alter immature neuron production or the number of astroglial cells in lactation. Stress exposure increased relative brain weight and hippocampal volume mirroring the observed changes in neurogenesis. Interestingly, hippocampal volume and relative brain weight were lower in lactation as compared to nulliparous females under nonstressed conditions. This study assessed the effect of stress during lactation on hippocampal neurogenesis and indicates that stress interferes with important peripartum adaptations at the level of the hippocampus.

   doi: 10.1002/hipo.22107
   Impact factor: 5.176

Abstract: Sex differences in basal as well as in stress-induced hippocampal neurogenesis processes have been reported in the literature. However, studies directly comparing sex
differences on multiple neurogenesis processes under such conditions are lacking to date. Therefore, the aim of the present study was to directly compare cell proliferation and survival, neuronal and astroglial differentiation as well as stem cells quiescence in male and female Wistar rats under both basal and chronic stress conditions (12 days of 2 h restraint stress (RS)). In addition, corticosterone (CORT) levels and spatial working memory were assessed. Under baseline conditions, only the number of immature neurons within the hippocampal dentate gyrus was higher in males compared with females. In contrast, chronic stress resulted in a number of sex-specific alterations. Thus, stress exposure reduced cell proliferation in males with a concurrent increase in stem cell quiescence, while it did not alter either parameter in females but decreased cell survival. Analysis of astroglial and neuronal differentiation patterns revealed that chronic stress specifically diminished the number of mature neurons in females, with no effect in males. Despite the observed sex differences in adult hippocampal neurogenesis, spatial working memory was not altered by stress exposure in either sex. While basal CORT levels were higher, chronic stress exposure did not affect this parameter in either sex across the initial stress period. This study presents the first direct and detailed evaluation of sex-dependent and chronic stress-induced changes in adult hippocampal neurogenesis not only showing changes in cell proliferation and survival, but moreover immature neuron production, differentiation patterns, stem cell quiescence and therefore contributes to a better understanding of sex differences in neurogenesis processes.


doi: 10.1111/nan.12199
Impact factor: 4.97

Abstract: AIMS: Multiple Sclerosis (MS) is a progressive inflammatory neurological disease affecting myelin, neurons and glia. Demyelination and neurodegeneration of cortical grey matter contributes to a more severe disease and inflammation of the forebrain meninges associates with pathology of the underlying neocortical grey matter, particularly in deep sulci. We assessed the extent of meningeal inflammation of the cerebellum, another structure with a deeply folded anatomy, to better understand the association between subarachnoid inflammation and grey matter pathology in progressive MS.

METHODS: We examined demyelinating and neuronal pathology in the context of meningeal inflammation in cerebellar tissue blocks from a cohort of 27 progressive MS cases previously characterized on the basis of the absence/ presence of lymphoid-like aggregates in the forebrain meninges, in comparison to 11 non-neurological controls.

RESULTS: Demyelination and meningeal inflammation of the cerebellum was greatest in those cases previously characterised as harbouring lymphoid-like structures in the forebrain regions. Meningeal inflammation was mild to moderate in cerebellar tissue blocks and no lymphoid-like structures were seen. Quantification of meningeal macrophages, CD4+, CD8+ T lymphocytes, B cells and plasma cells revealed that the density of meningeal macrophages associated with microglial activation in the grey matter, and the extent of grey matter demyelination correlated with the density of macrophages and plasma cells in the overlying meninges, and activated microglia of the parenchyma.
CONCLUSIONS: These data suggest that chronic inflammation is widespread throughout the subarachnoid space and contributes to a more severe subpial demyelinating pathology in the cerebellum.

   Impact factor: 3.274

Abstract: BACKGROUND: Reactive microgliosis, hallmark of neuroinflammation, may contribute to neuronal degeneration, as shown in several neurodegenerative diseases. We in vivo evaluated microglia activation in early dementia with Lewy bodies, still not reported, and compared with early Parkinson's disease, to assess possible differential pathological patterns.

METHODS: We measured the [(11)C]-PK11195 binding potentials with Positron Emission Tomography, using a simplified reference tissue model, as marker of microglia activation, and cerebral spinal fluid protein carbonylation levels, as marker of oxidative stress. Six dementia with Lewy bodies and 6 Parkinson's disease patients within a year from the onset, and eleven healthy controls were included. Clinical diagnosis was confirmed at a 4-year follow-up.

RESULTS: In dementia with Lewy bodies as well as in Parkinson's disease, we found significant (p < 0.001) [(11)C]-PK11195 binding potential increases in the substantia nigra and putamen. Patients with Lewy bodies dementia had extensive additional microglia activation in several associative cortices. This was evident also at a single subject level. Significant increase of Cerebral Spinal Fluid protein carbonylation was shown in both patients' groups.

CONCLUSIONS: [(11)C]-PK11195 Positron Emission Tomography imaging revealed neuroinflammation in dementia with Lewy bodies and Parkinson's disease, mirroring, even at a single subject level, the common and the different topographical distribution of neuropathological changes, yet in the earliest stages of the disease process. Focusing on those events that characterize parkinsonisms and Parkinson's disease may be the key to further advancing the understanding of pathogenesis and to taking these mechanisms forward as a means of defining targets for neuroprotection.

   doi: 10.1016/j.stemcr.2014.01.006
   Impact factor: NA yet

Abstract: Neurons generated from pluripotent stem cells (PSCs) self-organize into functional neuronal assemblies in vitro, generating synchronous network activities. Intriguingly, PSC-derived neuronal assemblies develop spontaneous activities that are independent of external stimulation, suggesting the presence of thus far undetected intrinsically active neurons (IANs). Here, by using mouse embryonic stem cells, we provide
Evidence for the existence of IANs in PSC-neuronal networks based on extracellular multielectrode array and intracellular patch-clamp recordings. IANs remain active after pharmacological inhibition of fast synaptic communication and possess intrinsic mechanisms required for autonomous neuronal activity. PSC-derived IANs are functionally integrated in PSC-neuronal populations, contribute to synchronous network bursting, and exhibit pacemaker properties. The intrinsic activity and pacemaker properties of the neuronal subpopulation identified herein may be particularly relevant for interventions involving transplantation of neural tissues. IANs may be a key element in the regulation of the functional activity of grafted as well as preexisting host neuronal networks.

Impact factor: 5.008

Abstract: Inflammation is a highly dynamic and complex adaptive process to preserve and restore tissue homeostasis. Originally viewed as an immune-privileged organ, the central nervous system (CNS) is now recognized to have a constant interplay with the innate and the adaptive immune systems, where resident microglia and infiltrating immune cells from the periphery have important roles. Common diseases of the CNS, such as stroke, multiple sclerosis (MS), and neurodegeneration, elicit a neuroinflammatory response with the goal to limit the extent of the disease and to support repair and regeneration. However, various disease mechanisms lead to neuroinflammation (NI) contributing to the disease process itself. Molecular imaging is the method of choice to try to decipher key aspects of the dynamic interplay of various inducers, sensors, transducers, and effectors of the orchestrated inflammatory response in vivo in animal models and patients. Here, we review the basic principles of NI with emphasis on microglia and common neurologic disease mechanisms, the molecular targets which are being used and explored for imaging, and molecular imaging of NI in frequent neurologic diseases, such as stroke, MS, neurodegeneration, epilepsy, encephalitis, and gliomas.

Impact factor: 1.187

Abstract: Neuroinflammation, in particular activation of microglia, is thought to play an important role in the progression of neurodegenerative diseases. In activated microglia, the purinergic P2X7 receptor is upregulated. A-740003, a highly affine and selective P2X7 receptor antagonist, is a promising candidate for the development of a radiotracer for imaging of neuroinflammation by positron emission tomography. For this purpose, [(11) C]A-740003 was synthesised and evaluated in vivo with respect to both tracer metabolism and biodistribution. In plasma, a moderate metabolic rate was seen. In healthy rat brain, only marginal uptake of [(11) C]A-740003 was observed and, therefore, metabolites in brain could not be determined. Whether the minimal brain uptake is due to the low
expression levels of the P2X7 receptor in healthy brain or to limited transport across the blood-brain barrier has yet to be elucidated.

   doi: 10.1109/TIP.2014.2353854
   Impact factor: 3.199

**Abstract:** In this paper, we extend the gradient vector flow field for robust variational segmentation of vector-valued images. Rather than using scalar edge information, we define a vectorial edge map derived from a weighted local structure tensor of the image that enables the diffusion of the gradient vectors in accurate directions through the 4D gradient vector flow equation. To reduce the contribution of noise in the structure tensor, image channels are weighted according to a blind estimator of contrast. The method is applied to biological volume delineation in dynamic PET imaging, and validated on realistic Monte Carlo simulations of numerical phantoms as well as on real images.

   doi: 10.1212/WNL.0000000000001278
   Impact factor: 8.303

**Abstract:** No abstract available.

   doi: 10.1002/mrm.24990
   Impact factor: 3.267

**Abstract:** PURPOSE: The use of resting-state functional MRI (rsfMRI) in preclinical research is expanding progressively, with the majority of resting-state imaging performed in anesthetized animals. Since anesthesia may change the physiology and, in particular, the neuronal activity of an animal considerably, it may also affect rsfMRI findings. Therefore, this study compared rsfMRI data from awake mice with rsfMRI results obtained from mice anesthetized with α-chloralose (120 mg/kg), urethane (2.5 g/kg), or isoflurane (1%).

**METHODS:** Functional connectivity (FC) was estimated using both independent component analysis (40 components) and ROI-based analysis to zoom in on the effect of different anesthetics on inter-hemispheric FC.

**RESULTS:** The data revealed an important diminishment of cortical interhemispheric FC in both the α-chloralose and urethane groups in comparison with the isoflurane and awake groups.

**CONCLUSION:** When performing FC analysis in anesthetized mice, the impact of anesthetics must be taken into account. The required doses for stable anesthesia during MRI significantly decrease interhemispheric FC.

Abstract: Members of the transforming growth factor (TGF)-β family govern a wide range of mechanisms in brain development and in the adult, in particular neuronal/glial differentiation and survival, but also cell cycle regulation and neural stem cell maintenance. This clearly created some discrepancies in the field with some studies favouring neuronal differentiation/survival of progenitors and others favouring cell cycle exit and neural stem cell quiescence/maintenance. Here, we provide a unifying hypothesis claiming that through its regulation of neural progenitor cell (NPC) proliferation, TGF-β signalling might be responsible for (i) maintaining stem cells in a quiescent stage, and (ii) promoting survival of newly generated neurons and their functional differentiation. Therefore, we performed a detailed histological analysis of TGF-β1 signalling in the hippocampal neural stem cell niche of a transgenic mouse that was previously generated to express TGF-β1 under a tetracycline regulatable Ca-Calmodulin kinase promoter. We also analysed NPC proliferation, quiescence, neuronal survival and differentiation in relation to elevated levels of TGF-β1 in vitro and in vivo conditions. Finally, we performed a gene expression profiling to identify the targets of TGF-β1 signalling in adult NPCs. The results demonstrate that TGF-β1 promotes stem cell quiescence on one side, but also neuronal survival on the other side. Thus, considering the elevated levels of TGF-β1 in ageing and neurodegenerative diseases, TGF-β1 signalling presents a molecular target for future interventions in such conditions.


Abstract: Amyloid β25–35 (Aβ25–35) is a toxic fragment of Alzheimer’s beta peptide. We have previously shown that Aβ25–35 fibrils form a trigonally oriented network on mica by epitaxial growth mechanisms. Chemical reactivity can be furnished to the fibril by introducing a cysteine residue (Aβ25–35_N27C) while maintaining oriented assembly properties. Previously we have shown that fibril binding to mica is strongly influenced by KCl concentration. In the present work we explored the kinetics of epitaxial assembly of the mutant fibrils at different peptide and KCl concentrations by using in situ time-resolved AFM. We measured the length of Aβ25–35_N27C fibrils as a function of time. Increasing free peptide concentration enhanced fibril growth rate, and the critical peptide concentration of fibril assembly was 3.92 μM. Increasing KCl concentration decreased the number of fibrils bound to the mica surface, and above 20 mM KCl fibril formation was completely abolished even at high peptide concentrations. By modulating peptide and KCl
concentrations in the optimal ranges established here the complexity of the Aβ25-35_N27C network can be finely tuned.

   doi: 10.1007/s10495-014-0970-7
   Impact factor: 3.949

Abstract: Nuclear autoantibodies have been found in patients with autoimmune diseases. One possible source for nuclear antigens are apoptotic cells. However, the mechanism of how apoptotic cells make nuclear factors accessible to the immune system is still elusive. In the present study, we investigated the redistribution of nuclear components after UV irradiation in the microglial cell line BV-2 and in primary mouse microglia at the ultrastructural level. We used transmission electron microscopy-coupled electron energy loss spectroscopy (EELS) to measure phosphorus as an indicator for nucleic acids and immunogold labeling to detect histone H3 and lamin B1 in apoptotic cells. EELS revealed elevated concentrations of phosphorus in nuclear and cytoplasmic condensed chromatin compared to the remaining cytoplasm. Furthermore, immunolabeling of lamin B1 and histone H3 was detected in apoptotic microglia not only in the nucleus, but also in the cytoplasm, and even at the plasma membrane. Confocal images of apoptotic microglia, which were not previously permeabilized, showed patches of histone H3 and lamin B1 labeling at the cell surface. The pan-caspase inhibitor Z-VAD-FMK (carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone) prevented the occurrence of cytoplasmic condensed chromatin in apoptotic microglia. Our findings indicate that nuclear components leak from the nucleus into the cytoplasm in apoptotic microglia. At least histone H3 and lamin B1 reach the cell surface, this may promote autoreactive processes.

   doi: 10.1212/01.wnl.0000435568.38352.2e
   Impact factor: 8.25

Abstract: Since the first report of amyloid imaging with Pittsburgh compound B (PiB), special attention has been given to the individuals who, though cognitively normal by testing, have substantial amounts of fibrillar amyloid-β (Aβ) pathology in their brain.(1) This state, previously predicted by several postmortem studies,(2) is also the focus of research criteria for preclinical Alzheimer disease (AD).(3) With these criteria, the pathophysiologic spectrum of AD was stretched past the earliest clinically detectable stages such as mild cognitive impairment (MCI)(4) to include cognitively normal individuals who show evidence of brain amyloid deposition by CSF analysis or amyloid PET. This concept of preclinical AD currently forms the foundation of a trial aimed at preventing the emergence of AD in amyloid-positive individuals-the Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4) trial.(5) Clearly, it is important to understand this state of asymptomatic β-amyloidosis as fully as possible.
Impact factor: 13.765

Abstract: Chemokines are important modulators of neuroinflammation and neurodegeneration. In the brains of Alzheimer’s disease (AD) patients and in AD animal models, the chemokine CXCL10 is found in high concentrations, suggesting a pathogenic role for this chemokine and its receptor, CXCR3. Recent studies aimed at addressing the role of CXCR3 in neurological diseases indicate potent, but diverse, functions for CXCR3. Here, we examined the impact of CXCR3 in the amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mouse model of AD. We found that, compared with control APP/PS1 animals, plaque burden and Aβ levels were strongly reduced in CXCR3-deficient APP/PS1 mice. Analysis of microglial phagocytosis in vitro and in vivo demonstrated that CXCR3 deficiency increased the microglial uptake of Aβ. Application of a CXCR3 antagonist increased microglial Aβ phagocytosis, which was associated with reduced TNF-α secretion. Moreover, in CXCR3-deficient APP/PS1 mice, microglia exhibited morphological activation and reduced plaque association, and brain tissue from APP/PS1 animals lacking CXCR3 had reduced concentrations of proinflammatory cytokines compared with controls. Further, loss of CXCR3 attenuated the behavioral deficits observed in APP/PS1 mice. Together, our data indicate that CXCR3 signaling mediates development of AD-like pathology in APP/PS1 mice and suggest that CXCR3 has potential as a therapeutic target for AD.

Impact factor: 6.747

Abstract: To assess the consequences of locus ceruleus (LC) degeneration and subsequent noradrenaline (NA) deficiency in early Alzheimer’s disease (AD), mice overexpressing mutant amyloid precursor protein and presenilin-1 (APP/PS1) were crossed with Ear2(-/-) mice that have a severe loss of LC neurons projecting to the hippocampus and neocortex. Testing spatial memory and hippocampal long-term potentiation revealed an impairment in APP/PS1 Ear2(-/-) mice, whereas APP/PS1 or Ear2(-/-) mice showed only minor changes. These deficits were associated with distinct synaptic changes including reduced expression of the NMDA 2A subunit and increased levels of NMDA receptor 2B in APP/PS1 Ear2(-/-) mice. Acute pharmacological replacement of NA by L-threo-DOPS partially restored phosphorylation of β-CaMKII and spatial memory performance in APP/PS1 Ear2(-/-) mice. These changes were not accompanied by altered APP processing or amyloid β peptide (Aβ) deposition. Thus, early LC degeneration and subsequent NA reduction may contribute to cognitive deficits via CaMKII and NMDA receptor dysfunction independent of Aβ and suggests that NA supplementation could be beneficial in treating AD.
doi: 10.1186/alzrt258
Impact factor: 3.5

Abstract: Alzheimer’s disease pathology is closely connected to the processing of the amyloid precursor protein (APP) resulting in the formation of a variety of amyloid-beta (Aβ) peptides. They are found as insoluble aggregates in senile plaques, the histopathological hallmark of the disease. These peptides are also found in soluble, mostly monomeric and dimeric, forms in the interstitial and cerebrospinal fluid. Due to the combination of several enzymatic activities during APP processing, Aβ peptides exist in multiple isoforms possessing different N-termini and C-termini. These peptides include, to a certain extent, part of the juxtamembrane and transmembrane domain of APP. Besides differences in size, post-translational modifications of Aβ - including oxidation, phosphorylation, nitration, racemization, isomerization, pyroglutamylation, and glycosylation - generate a plethora of peptides with different physiological and pathological properties that may modulate disease progression.

doi: 10.1007/s12035-014-8743-4
Impact factor: 5.286

Abstract: Alzheimer’s disease (AD) is a neurodegenerative condition that leads to neuronal death and memory dysfunction. In the past, specific peroxisome proliferator-activated receptor (PPAR)γ-agonists, such as pioglitazone, have been tested with limited success to improve AD pathology. Here, we investigated the therapeutic efficacy of GFT1803, a novel potent PPAR agonist that activates all the three PPAR isoforms (α/δ/γ) in the APP/PS1 mouse model in comparison to the selective PPARγ-agonist pioglitazone. Both compounds showed similar brain/plasma partitioning ratios, although whole body and brain exposure to GFT1803 was significantly lower as compared to pioglitazone, at doses used in this study. Oral treatment of APP/PS1 mice with GFT1803 decreased microglial activation, amyloid β (Aβ) plaque area, Aβ levels in sodium dodecyl sulfate- and formic acid-soluble fractions in a concentration-dependent manner. With a single exception of Aβ38 and Aβ40 levels, measured by ELISA, these effects were not observed in mice treated with pioglitazone. Both ligands decreased glial fibrillary acidic protein (GFAP) expression to similar extent and did not affect ApoE expression. Finally, GFT1803 increased insulin-degrading enzyme expression. Analysis of spatial memory formation in the Morris water maze demonstrated that both compounds were able to partially revert the phenotype of APP/PS1 mice in comparison to wild-type mice with GFT1803 being most effective. As compared to pioglitazone, GFT1803 (pan-PPAR agonist) produced both quantitatively superior and qualitatively different therapeutic effects with respect to amyloid plaque burden, insoluble Aβ content, and neuroinflammation at significantly lower whole body and brain exposure rates.
Impact factor: 6.551

Abstract: Brain pericytes (BrPCs) are essential cellular components of the central nervous system neurovascular unit involved in the regulation of blood flow, blood-brain barrier function, as well as in the stabilization of the vessel architecture. More recently, it became evident that BrPCs, besides their regulatory activities in brain vessel function and homeostasis, have pleiotropic functions in the adult CNS ranging from stromal and regeneration promoting activities to stem cell properties. This special characteristic confers BrPC cell plasticity, being able to display features of other cells within the organism. BrPCs might also be causally involved in certain brain diseases. Due to these properties BrPCs might be potential drug targets for future therapies of neurological disorders. This review summarizes BrPC properties, disorders in which this cell type might be involved, and provides suggestions for future therapeutic developments targeting BrPCs.

doi: 10.1111/nan.12092
Impact factor: 4.837

Abstract: AIMS: Pathological heterogeneity within patients with Frontotemporal lobar degeneration (FTLD) in general precludes the accurate assignment of diagnostic subtype in life. The aim of this study was to assess the extent of microglial cell activation in FTLD in order to determine whether it might be possible to employ this as a diagnostic marker in vivo using PET ligand [11C](R)-PK11195 in order to differentiate cases of FTLD according to histological subtype.
METHODS: The distribution and extent of microglial cell activation was assessed semi-quantitatively in cortical grey and subcortical white matter of CD68 immunostained sections of frontal and temporal cortex from 78 pathologically confirmed cases of FTLD, 13 of Alzheimer’s disease (AD) and 13 controls.
RESULTS: Significantly higher levels of microglial cell activation than controls occurred in all 4 regions in FTLD, and in 3 of the 4 regions in AD. Microglial activation was greater in frontal subcortical white matter in FTLD than AD, whereas it was higher in temporal cortical grey matter in AD than FTLD. Microglial cell activation was significantly higher in temporal subcortical white matter in FTLD-MAPT than in other genetic (GRN, C9ORF72) or non-genetic forms of FTLD.
CONCLUSIONS: The present study suggests that high levels of microglial cell involvement in temporal lobe (subcortical white matter) might serve as a marker of inherited FTLD associated with intronic mutations in MAPT, with a relatively intense signal in this region in PET studies using [11C](R)-PK11195 as microglial cell marker could indicate the presence of MAPT mutation in vivo.

doi: 10.3233/JAD-142952
Impact factor: 3.612

Abstract: Background: Alzheimer’s disease (AD) pathology can be quantified in vivo using cerebrospinal fluid (CSF) levels of amyloid-β1-42 (Aβ1-42), total-tau (t-tau), and phosphorylated tau (p-tau181p), as well as with positron emission tomography (PET) using [11C]Pittsburgh compound-B ([11C]PIB). Studies assessing concordance between these measures, however, have provided conflicting results. Moreover, it has been proposed that [11C]PIB PET may be of great clinical utility in terms of identifying patients with mild cognitive impairment (MCI) who will progress to the dementia phase of AD. Objective: To determine concordance and classification accuracy of CSF biomarkers and [11C]PIB PET in a cohort of patients with MCI and AD. Methods: 68 patients (MCI, n = 33; AD, n = 35) underwent [11C]PIB PET and CSF sampling. Cutoffs of >1.41 ([11C]PIB), <450 pg/mL (Aβ1-42), <6.5 (Aβ1-42/p-tau181p), and 1.14 (Aβ1-42/t-tau), were used to determine concordance. Logistic regression was used to determine classification accuracy with respect to stable MCI (sMCI) versus MCI who progressed to AD (pMCI). Results: Concordance between [11C]PIB and Aβ1-42 was highest for sMCI (67%), followed by AD (60%) and pMCI (33%). Agreement was increased across groups using Aβ1-42 <550 pg/mL, or Aβ1-42 to tau ratios. Logistic regression showed that classification accuracy of [11C]PIB, between sMCI and pMCI, was superior to Aβ1-42 (73% versus 58%), Aβ1-42/p-tau181p (63%), and Aβ1-42/p-tau181p (65%). Conclusion: In the present study, [11C]PIB proved a better predictor of progression to AD in patients with MCI, relative to CSF measures of Aβ1-42 or Aβ1-42 tau. Discordance between PET and CSF markers for Aβ1-42 suggests they cannot be used interchangeably, as is currently the case.


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Impact factor: 4.09

Abstract: The objective of this study was to investigate the effects of modulating brain amyloid-β (Aβ) levels at different stages of amyloid pathology on synaptic function, inflammatory cell changes and hippocampal neurogenesis, i.e. processes perturbed in Alzheimer’s disease (AD). Young (4- to 6-month-old) and older (15- to 18-month-old) APPSWE transgenic (Tg2576) mice were treated with the AD candidate drug (+)-phenserine for 16 consecutive days. We found significant reductions in insoluble Aβ1-42 levels in the cortices of both young and older transgenic mice, while significant reductions in soluble Aβ1-42 levels and insoluble Aβ1-40 levels were only found in animals aged 15-18 months. Autoradiography binding with the amyloid ligand Pittsburgh Compound B ((3)H-PIB) revealed a trend for reduced fibrillar Aβ deposition in the brains of older phenserine-treated Tg2576 mice. Phenserine treatment increased cortical synaptophysin levels in younger mice, while decreased interleukin-1β and increased monocyte
Chemoattractant protein-1 and tumor necrosis factor-alpha levels were detected in the cortices of older mice. The reduction in Aβ1-42 levels was associated with an increased number of bromodeoxyuridine-positive proliferating cells in the hippocampi of both young and older Tg2576 mice. To determine whether the increased cell proliferation was accompanied by increased neuronal production, the endogenous early neuronal marker doublecortin (DCX) was examined in the dentate gyrus (DG) using immunohistochemical detection. Although no changes in the total number of DCX(+) expressing neurons were detected in the DG in Tg2576 mice at either age following (+)-phenserine treatment, dendritic arborization was increased in differentiating neurons in young Tg2576 mice. Collectively, these findings indicate that reducing Aβ1-42 levels in Tg2576 mice at an early pathological stage affects synaptic function by modulating the maturation and plasticity of newborn neurons in the brain. In contrast, lowering Aβ levels in Tg2576 mice when Aβ plaque pathology is prominent mainly alters the levels of proinflammatory cytokines and chemokines.


Abstract: In recent years several studies demonstrated the presence of estrogen receptors in mammalian tissues and significantly improved our understanding of their ability to control biological processes in reproductive as well as non-reproductive organs. Considering the manifold mechanisms and organs that are involved in estrogen action and the implication of estrogens in human female physiology, innovative approaches are required to shed light on the widespread activities of estrogen receptors in woman physiology. This is particularly relevant for the definition of novel, more efficacious hormonal replacement therapies or for the evaluation of the risk associated with the exposure to endocrine disruptors. The introduction of genetic engineering and the development and application of in vivo imaging techniques offer new tools for pre-clinical studies. The generation of the ERE-Luc mouse, a reporter animal developed for in vivo studies of the estrogen receptor activity, allows assessing the activity state of the ER signaling pathway in all target tissues and organs at once, under physiological stimuli or as a result of a pharmacological treatment. This review summarizes the main steps in the generation and appraisal of the estrogen receptor reporter mouse ERE-Luc, designed for in vivo molecular imaging studies, and describes examples demonstrating the suitability of the ERE-Luc model for drug development and for the investigation of the effects of endogenous, environmental, and dietary estrogens in vivo. This article is part of a Special Issue entitled 'Phytoestrogens'.

Abstract: We recently reported that young (3 to 4 months old) mice lacking Exon 1 of the Smad7 gene (S7ΔEx1 mice) show enhanced proliferation of neural stem and progenitor cells (NPCs) in the hippocampal dentate gyrus (DG) and in the subventricular zone (SVZ) of the lateral ventricles. It remained unclear, however, whether this phenotype would persist along aging, the latter typically being associated with a profound decrease in neurogenesis. Analysis of NPCs' proliferation based on the cell cycle marker PCNA in 12-month-old S7ΔEx1 mice revealed a reversal of the phenotype. Hence, in contrast to their younger counterparts, 12-month-old S7ΔEx1 mice had a reduced number of proliferating cells, compared to wildtype (WT) mice. At the same time, the survival of newly generated cells was enhanced in the aged transgenic animals. 12-month-old S7ΔEx1 mice further displayed a reduced level of neurogenesis based on the numbers of cells expressing doublecortin (DCX), a marker for newborn neurons. The reduced neurogenesis in aged S7ΔEx1 mice was not due to a stem cell depletion, which might have occurred as a consequence of hyperproliferation in the young mice, since the number of Nestin and Sox2 positive cells was similar in WT and S7ΔEx1 mice. Instead, Nestin positive cells in the DG as well as primary neurosphere cultures derived from 12-month-old S7ΔEx1 mice had a reduced capability to proliferate. However, after passaging, when released from their age- and niche-associated proliferative block, neurospheres from aged S7ΔEx1 mice regained the hyperproliferative property. Further, pSmad2 antibody staining intensity was elevated in the DG and SVZ of 12-month old transgenic compared to WT mice, indicating increased intracellular TGF-beta signaling in the aged S7ΔEx1 mice. In summary, this points toward differential effects of S7ΔEx1 on neurogenesis: (i) a hyperproliferation in young animals caused by a cell autonomous mechanism, and (ii) a TGF-beta dependent modulation of neurogenesis in aged S7ΔEx1 animals that abrogates the cell-intrinsic hyperproliferative properties and results in reduced proliferation, increased stem cell quiescence, and enhanced survival of newly generated cells.

Impact factor: 5.9

Abstract: Titin is a giant elastomeric muscle protein that has been suggested to function as a sensor of sarcomeric stress and strain, but the mechanisms by which it does so are unresolved. To gain insight into its mechanosensory function we manipulated single titin molecules with high-resolution optical tweezers. Discrete, step-wise transitions, with rates faster than canonical Ig domain unfolding occurred during stretch at forces as low as 5 pN. Multiple mechanisms and molecular regions (PEVK, proximal tandem-Ig, N2A) are likely to be involved. The pattern of transitions is sensitive to the history of contractile events. Monte-Carlo simulations of our experimental results predicted that structural transitions begin before the complete extension of the PEVK domain. High-resolution atomic force microscopy (AFM) supported this prediction. Addition of glutamate-rich PEVK domain fragments competitively inhibited the viscoelastic response in both single titin molecules and muscle fibers, indicating that PEVK domain interactions contribute significantly to sarcomere mechanics. Thus, under non-equilibrium conditions across the physiological force range, titin extends by a complex pattern of history-dependent discrete
conformational transitions, which, by dynamically exposing ligand-binding sites, could set the stage for the biochemical sensing of the mechanical status of the sarcomere.

   doi: 10.1371/journal.pone.0085847
   Impact factor: 3.730

Abstract: Titin is a giant elastomeric protein responsible for the generation of passive muscle force. Mechanical force unfolds titin's globular domains, but the exact structure of the overstretched titin molecule is not known. Here we analyzed, by using high-resolution atomic force microscopy, the structure of titin molecules overstretched with receding meniscus. The axial contour of the molecules was interrupted by topographical gaps with a mean width of 27.7 nm that corresponds well to the length of an unfolded globular (immunoglobulin and fibronectin) domain. The wide gap-width distribution suggests, however, that additional mechanisms such as partial domain unfolding and the unfolding of neighboring domain multimers may also be present. In the folded regions we resolved globules with an average spacing of 5.9 nm, which is consistent with a titin chain composed globular domains with extended interdomain linker regions. Topographical analysis allowed us to allocate the most distal unfolded titin region to the kinase domain, suggesting that this domain systematically unfolds when the molecule is exposed to overstretching forces. The observations support the prediction that upon the action of stretching forces the N-terminal β-sheet of the titin kinase unfolds, thus exposing the enzyme's ATP-binding site and hence contributing to the molecule's mechanosensory function.

   Impact factor: 4.35

Abstract: BACKGROUND: The pathological features in Alzheimer's disease (AD) brain include the accumulation and deposition of β-amyloid (Aβ), activation of astrocytes and microglia and disruption of cholinergic neurotransmission. Since the topographical characteristics of these different pathological processes in AD brain and how these relate to each other is not clear, this motivated further exploration using binding studies in postmortem brain with molecular imaging tracers. This information could aid the development of specific biomarkers to accurately chart disease progression.

RESULTS: In vitro binding assays demonstrated increased [³H]-PIB (fibrillar Aβ) and [³H]-PK11195 (activated microglia) binding in the frontal cortex (FC) and hippocampus (HIP), as well as increased binding of [³H]-L-deprenyl (activated astrocytes) in the HIP, but a decreased [³H]-nicotine (α4β2 nicotinic acetylcholine receptor (nAChR)) binding in the FC of AD cases compared to age-matched controls. Quantitative autoradiography binding studies were also performed to investigate the regional laminar distributions of [³H]-L-
deprenyl, [³H]-PIB as well as [²⁵I]-α-bungarotoxin (α7 nAChRs) and [³H]-nicotine in hemisphere brain of a typical AD case. A clear lamination pattern was observed with high [³H]-PIB binding in all layers and [³H]-deprenyl in superficial layers of the FC. In contrast, [³H]-PIB showed low binding to fibrillar Aβ, but [³H]-deprenyl high binding to activated astrocytes throughout the HIP. The [³H]-PIB binding was also low and the [³H]-deprenyl binding high in all layers of the medial temporal gyrus and insular cortex in comparison to the frontal cortex. Low [³H]-nicotine binding was observed in all layers of the frontal cortex in comparison to layers in the medial temporal gyrus, insular cortex and hippocampus. Immunohistochemical detection in the AD case revealed abundant glial fibrillary acidic protein positive (GFAP+) reactive astrocytes and α7 nAChR expressing GFAP+ astrocytes both in the vicinity and surrounding Aβ neuritic plaques in the FC and HIP. Although fewer Aβ plaques were observed in the HIP, some hippocampal GFAP+ astrocytes contained Aβ-positive (6 F/3D) granules within their somata.

CONCLUSIONS: Astrocytosis shows a distinct regional pattern in AD brain compared to fibrillar Aβ, suggesting that different types of astrocytes may be associated with the pathophysiological processes in AD.


doi: 10.1016/j.brainresbull.2013.01.001
Impact factor: 2.818

Abstract: We aimed to evaluate the novel high-affinity and relatively lipophilic CB(1) receptor (CB(1)R) antagonist radioligand [(125)I]SD7015 for SPECT imaging of CB(1)Rs in vivo using the multiplexed multipinhole dedicated small animal SPECT/CT system, NanoSPECT/CT(PLUS) (Mediso, Budapest, Hungary), in knock-out CB(1) receptor knock-out (CB(1)R-/-) and wildtype mice. In order to exclude possible differences in cerebral blood flow between the two types of animals, HMPAO SPECT scans were performed, whereas in order to confirm the brain uptake differences of the radioligand between knock-out mice and wildtype mice, in vivo scans were complemented with ex vivo autoradiographic measurements using the brains of the same animals. With SPECT/CT imaging, we measured the brain uptake of radioactivity, using %SUV (% standardised uptake values) in CB(1)R-/- mice (n=3) and C57BL6 wildtype mice (n=7) under urethane anaesthesia after injecting [(125)I]SD7015 intravenously or intraperitoneally. The Brookhaven Laboratory mouse MRI atlas was fused to the SPECT/CT images by using a combination of rigid and non-rigid algorithms in the Mediso Fusion™ (Mediso, Budapest, Hungary) and VivoQuant (inviCRO, Boston, MA, USA) softwares. Phosphor imager plate autoradiography (ARG) was performed on 4μm-thin cryostat sections of the excised brains. %SUV was 8.6±3.6 (average±SD) in CB(1)R-/- mice and 22.1±12.4 in wildtype mice between 2 and 4h after injection (p<0.05). ARG of identically taken sections from wildtype mouse brain showed moderate radioactivity uptake when compared with the in vivo images, with a clear difference between grey matter and white matter, whereas ARG in CB(1)R(-/-) mice showed practically no radioactivity uptake. [(125)I]SD7015 enters the mouse brain in sufficient amount to enable SPECT imaging. Brain radioactivity distribution largely coincides with that of the known CB(1)R expression pattern in rodent brain. We conclude that
[(125)I]SD7015 should be a useful SPECT radioligand for studying brain CB(1)R in mouse and rat disease models.

   doi: 10.1002/jlcr.3199
   Impact factor: 1.24

Abstract: DPA-C5yne, the lead compound of a novel series of DPA-714 derivatives in which the fluoroethoxy chain linked to the phenylpyrazolopyrimidine scaffold has been replaced by a fluoroalkynyl moiety, is a high affinity (Ki : 0.35 nM) and selective ligand targeting the translocator protein 18 kDa. In the present work, DPA-C5yne was labelled with no-carrier-added [(18) F]fluoride based on a one-step tosyloxy-for-fluorine nucleophilic substitution reaction, purified by cartridge and HPLC, and formulated as an i.v. injectable solution using a TRACERLab FX N Pro synthesizer. Typically, 4.3-5.2 GBq of [(18) F]DPA-C5yne, ready-to-use, chemically and radiochemically pure (> 95%), was obtained with specific radioactivities ranging from 55 to 110 GBq/µmol within 50-60 min, starting from a 30 GBq [(18) F]fluoride batch (14-17%). LogP and LogD of [(18) F]DPA-C5yne were measured using the shake-flask method and values of 2.39 and 2.51 were found, respectively. Autoradiography studies performed on slices of ((R,S)-α-amino-3-hydroxy-5-methyl-4-isoxazolopropionique (AMPA) -lesioned rat brains showed a high target-to-background ratio (1.9 ± 0.3). Selectivity and specificity of the binding for the translocator protein was demonstrated using DPA-C5yne (unlabelled), PK11195 and Flumazenil (central benzodiazepine receptor ligand) as competitors. Furthermore, DPA-C5yne proved to be stable in plasma at 37°C for at least 90 min.

   doi: 10.1016/j.bmcl.2014.01.080
   Impact factor: 2.338

Abstract: A series of four novel analogues of DPA-714, bearing a fluoroalkynyl side chain (with a length ranging from three to six carbon atoms) in replacement of the fluoroethoxy motif, have been synthetized in six steps from commercially available methyl 4-iodobenzoate. The synthetic strategy for the preparation of these N,N-diethyl-2-(2-(4-(ω-fluoroalk-1-ynyl)phenyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidin-3-yl)acetamides (7a-d) consisted in derivatizing a key iodinated building block featuring the pyrazolopyrimidine acetamide backbone of DPA-714, by Sonogashira couplings with various alkynyl reagents. The resulting alkynyls were subsequently fluorinataed, yielding the expected target derivatives. All four analogues exhibited slightly higher affinity and selectivity towards the TSPO 18kDa (Ki vs [(3)H]PK11195: 0.35-0.79nM; Ki vs [(3)H]flunitrazepam: >1000nM) when compared to DPA-714 (Ki vs [(3)H]PK11195: 0.91nM; Ki vs [(3)H]flunitrazepam: >1000nM).
Lipophilicities (HPLC, logD7.4) increased with the chain length (from 3.6 to 4.3) and were significantly higher than the one determined for DPA-714 (2.9). Preliminary in vitro metabolism evaluation using rat microsomal incubations and LC-MS analyses showed, for all four novel analogues, the absence of defluorinated metabolites. Among them, the fluoropentynyl compound, DPA-C5yne (7c), was selected, labelled in one single step with fluorine-18 from the corresponding tosylate and in vivo evaluated with PET on our in-house-developed rat model of acute local neuroinflammation.

doi: 10.1039/c4ob00810c
Impact factor: 3.568

Abstract: Bifunctional chelating agents (BFCAs) combine the complexing properties of a multidentate ligand with the presence of a free reactive functional group, mainly devoted to conjugation purposes. Indeed, products obtained by conjugation of a BFCA to a biomolecule and coordination of a suitable metal ion are widely applied in medicine nowadays as diagnostic and therapeutic agents. BFCAs are generally prepared through multi-step syntheses and with extensive application of protection-deprotection strategies, due to the large number of functional groups involved. Hydrolytic enzymes, with their unique chemoselectivity, provided the best results in the preparation of three different BFCAs based on very useful and well known ligand platforms.

doi: 10.1088/0031-9155/58/19/6931
Impact factor: 2.701

Abstract: Segmentation is often required for the analysis of dynamic positron emission tomography (PET) images. However, noise and low spatial resolution make it a difficult task and several supervised and unsupervised methods have been proposed in the literature to perform the segmentation based on semi-automatic clustering of the time activity curves of voxels. In this paper we propose a new method based on spectral clustering that does not require any prior information on the shape of clusters in the space in which they are identified. In our approach, the p-dimensional data, where p is the number of time frames, is first mapped into a high dimensional space and then clustering is performed in a low-dimensional space of the Laplacian matrix. An estimation of the bounds for the scale parameter involved in the spectral clustering is derived. The method is assessed using dynamic brain PET images simulated with GATE and results on real images are presented. We demonstrate the usefulness of the method and its superior performance over three other clustering methods from the literature. The proposed approach appears as a promising pre-processing tool before parametric map calculation or ROI-based quantification tasks.

doi: 10.1016/j.bmc.2012.10.050
Impact factor: 2.921

Abstract: The aim of this project was to synthesize and evaluate three novel fluorine-18 labeled derivatives of propargyl amine as potential PET radioligands to visualize monoamine oxidase B (MAO-B) activity. The three fluorinated derivatives of propargyl amine ((S)-1-fluoro-N,4-dimethyl-N-(prop-2-ynyl)-pent-4-en-2-amine (5), (S)-N-(1-fluoro-3-(furan-2-yl)propan-2-yl)-N-methylprop-2-yn-1-amine (10) and (S)-1-fluoro-N,4-dimethyl-N-(prop-2-ynyl)pentan-2-amine (15)) were synthesized in multi-step organic syntheses. IC(50) values for inhibition were determined for compounds 5, 10 and 15 in order to determine their specificity for binding to MAO-B. Compound 5 inhibited MAO-B with an IC(50) of 664 ± 48.08 nM. No further investigation was carried out with this compound. Compound 10 inhibited MAO-B with an IC(50) of 208.5 ± 13.44 nM and compound 15 featured an IC(50) of 131.5 ± 0.71 nM for its MAO-B inhibitory activity. None of the compounds inhibited MAO-A activity (IC(50) > 2 μM). The fluorine-18 labeled analogues of the two higher binding affinity compounds (10 and 15) (S)-N-(1-[(18)F]fluoro-3-(furan-2-yl)propan-2-yl)-N-methylprop-2-yn-1-amine (16) and (S)-1-[(18)F]fluoro-N,4-dimethyl-N-(prop-2-ynyl)pentan-2-amine (18) were both prepared from the corresponding precursors 9A, 9B and 14A, 14B by a one-step fluorine-18 nucleophilic substitution reaction. Autoradiography experiments on human postmortem brain tissue sections were performed with 16 and 18. Only compound 18 demonstrated a high selectivity for MAO-B over MAO-A and was, therefore, chosen for further examination by PET in a cynomolgus monkey. The initial uptake of 18 in the monkey brain was 250% SUV at 4 min post injection. The highest uptake of radioactivity was observed in the striatum and thalamus, regions with high MAO-B activity, whereas lower levels of radioactivity were detected in the cortex and cerebellum. The percentage of unchanged radioligand 18 was 30% in plasma at 90min post injection. In conclusion, compound 18 is a selective inhibitor of MAO-B in vitro and demonstrated a MAO-B specific binding pattern in vivo by PET in monkey. It can, therefore, be considered as a candidate for further investigation in human by PET.


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Impact factor: 2.903

Abstract: The objective of this study was to synthesize and evaluate a novel fluorine-18 labeled deuterium substituted analogue of rasagiline (9, [18F]fluororasagiline-D2) as a potential PET radioligand for studies of monoamine oxidase B (MAO-B). The precursor compound (6) and reference standard (7) were synthesized in multi-step syntheses. Radiolabeling of 9 was accomplished by a two-step synthesis, compromising a nucleophilic substitution followed by hydrolysis of the sulfamidate group. The incorporation radiochemical yield from fluorine-18 fluoride was higher than 30%, the
radiochemical purity was >99% and the specific radioactivity was >160GBq/μmol at the time of administration. In vitro compound 7 inhibited the MAO-B activity with an IC50 of 173.0±13.6nM. The MAO-A activity was inhibited with an IC50 of 9.9±1.1μM. The fluorine-18 version 9 was characterized in the cynomolgus monkey brain where a high brain uptake was found (275% SUV at 4min). There was a higher uptake in the striatum and thalamus compared to the cortex and cerebellum. A pronounced blocking effect (50% decrease) was observed in the specific brain regions after administration of l-deprenyl (0.5mg/kg) 30min prior to the administration of 9. Radiometabolite studies demonstrated 40% of unchanged radioligand at 90min post injection. An efficient radiolabeling of 9 was successfully established and in the monkey brain 9 binds to MAO-B rich regions and its binding is blocked by the selective MAO-B compound l-deprenyl. The radioligand 9 is a potential candidate for human PET studies.


Impact factor: 9.915

Abstract: Imaging fibrillar amyloid-β deposition in the human brain in vivo by positron emission tomography has improved our understanding of the time course of amyloid-β pathology in Alzheimer's disease. The most widely used amyloid-β imaging tracer so far is (11)C-Pittsburgh compound B, a thioflavin derivative but other (11)C- and (18)F-labelled amyloid-β tracers have been studied in patients with Alzheimer's disease and cognitively normal control subjects. However, it has not yet been established whether different amyloid tracers bind to identical sites on amyloid-β fibrils, offering the same ability to detect the regional amyloid-β burden in the brains. In this study, we characterized (3)H-Pittsburgh compound B binding in autopsied brain regions from 23 patients with Alzheimer's disease and 20 control subjects (aged 50 to 88 years). The binding properties of the amyloid tracers FDDNP, AV-45, AV-1 and BF-227 were also compared with those of (3)H-Pittsburgh compound B in the frontal cortices of patients with Alzheimer's disease. Saturation binding studies revealed the presence of high- and low-affinity (3)H-Pittsburgh compound B binding sites in the frontal cortex (K(d1): 3.5 ± 1.6 nM; K(d2): 133 ± 30 nM) and hippocampus (K(d1):5.6 ± 2.2 nM; K(d2): 181 ± 132 nM) of Alzheimer's disease brains. The relative proportion of high-affinity to low-affinity sites was 6:1 in the frontal cortex and 3:1 in the hippocampus. One control showed both high- and low-affinity (3)H-Pittsburgh compound B binding sites (K(d1): 1.6 nM; K(d2): 330 nM) in the cortex while the others only had a low-affinity site (K(d2): 191 ± 70 nM). (3)H-Pittsburgh compound B binding in Alzheimer's disease brains was higher in the frontal and parietal cortices than in the caudate nucleus and hippocampus, and negligible in the cerebellum. Competitive binding studies with (3)H-Pittsburgh compound B in the frontal cortices of Alzheimer's disease brains revealed high- and low-affinity binding sites for BTA-1 (Ki: 0.2 nM, 70 nM), florbetapir (1.8 nM, 53 nM) and florbetaben (1.0 nM, 65 nM). BF-227 displaced 83% of (3)H-Pittsburgh compound B binding, mainly at a low-affinity site (311 nM), whereas FDDNP only partly displaced (40%). We propose a multiple binding site model for the amyloid tracers (binding sites 1, 2 and 3), where AV-45 (florbetapir), AV-1 (florbetaben), and Pittsburgh compound B, all show nanomolar affinity for the high-affinity site (binding site 1), as visualized by positron emission tomography. BF-227 shows mainly binding to site 3.
and FDDNP shows only some binding to site 2. Different amyloid tracers may provide new insight into the pathophysiological mechanisms in the progression of Alzheimer’s disease.

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Impact factor: not yet available (new from 2013)

Abstract: Recent development in molecular imaging enables measurement of fibrillar amyloid plaque in Alzheimer (AD) brain using positron emission tomography (PET). Three tracers (florbetapir, flutemetamol, florbetaben) have been approved by FDA and EMA for use in clinical assessment of memory impairment to exclude AD. The use of amyloid PET imaging is considered to be appropriate in patients with persistent and progressive unexplained mild cognitive impairment (MCI), in patients with established dementia with atypical clinical course or aetiology and in young patients with atypical-onset dementia. The focus of amyloid PET has so far been to understand the time course of amyloid plaque levels in AD and to use amyloid PET to discriminate between AD and patient with mild cognitive impairment (MCI) who will most likely or less likely convert to AD, respectively, at clinical follow-up. Very few studies have so far directly tested the added value of amyloid imaging as biomarker in diagnostic procedure and patient management in a clinical context. The present study reviews studies describing the possible role of PET amyloid imaging in excluding AD as well as strengthen the diagnosis of AD and detecting prodromal AD. Some studies report as a change in diagnosis following amyloid PET imaging and in therapeutic management and planning for the future for the patient and their family. Future clinical studies are needed to evaluate the appropriate clinical use of amyloid PET imaging in relation to cerebral glucose PET imaging, and CSF biomarkers.

doi: 10.1159/000356333
Impact factor: 3.410

Abstract: The time course and order of the pathological-physiological processes in Alzheimer’s disease (AD) are still under investigation and it is expected that molecular imaging will provide important insight into early brain pathology. Multi-tracer positron emission tomography studies visualizing fibrillar amyloid, inflammatory changes including astrocytosis and activation of microglia as well as cerebral glucose metabolism indicate that AD pathological processes are initiated and ongoing decades before the onset of cognitive symptoms. Therefore, prevention might be a new promising target for AD therapy.

doi: 10.1016/j.jnutbio.2013.06.005
Abstract: Flavonoids target a variety of pathophysiological mechanisms and are therefore increasingly considered as compounds encompassed with therapeutic potentials in diseases such as cancer, diabetes, arteriosclerosis, and neurodegenerative diseases and mood disorders. Hops (Humulus lupulus L.) is rich in flavonoids such as the flavanone 8-prenylnaringenin, which is the most potent phytoestrogen identified so far, and the prenylchalcone xanthohumol, which has potent tumor-preventive, anti-inflammatory and antiviral activities. In the present study, we questioned whether hops-derived prenylflavonoids and synthetic derivatives thereof act on neuronal precursor cells and neuronal cell lines to induce neuronal differentiation, neurite outgrowth and neuroprotection. Therefore, mouse embryonic forebrain-derived neural precursors and Neuro2a neuroblastoma-derived cells were stimulated with the prenylflavonoids of interest, and their potential to activate the promoter of the neuronal fate-specific doublecortin gene and to stimulate neuronal differentiation and neurite outgrowth was analyzed. In this screening, we identified highly "neuroactive" compounds, which we termed "enhancement of neuronal differentiation factors" (ENDFs). The most potent molecule, ENDF1, was demonstrated to promote neuronal differentiation of neural stem cells and neurite outgrowth of cultured dorsal root ganglion neurons and protected neuronal PC12 cells from cobalt chloride-induced as well as cholinergic neurons of the nucleus basalis of Meynert from deafferentation-induced cell death. The results indicate that hops-derived prenylflavonoids such as ENDFs might be powerful molecules to promote neurogenesis, neuroregeneration and neuroprotection in cases of chronic neurodegenerative diseases, acute brain and spinal cord lesion and age-associated cognitive impairments.


doi: 10.1186/1750-1326-8-44
Impact factor: 4.01

Abstract: Background: Alpha-synuclein is a key protein implicated in the pathogenesis of Parkinson’s disease (PD). It is the main component of the Lewy bodies, a cardinal neuropathological feature in the disease. In addition, whole locus multiplications and point mutations in the gene coding for alpha-synuclein lead to autosomal dominant monogenic PD. Over the past decade, research on PD has impelled the development of new animal models based on alpha-synuclein. In this context, transgenic mouse lines have failed to reproduce several hallmarks of PD, especially the strong and progressive dopaminergic neurodegeneration over time that occurs in the patients. In contrast, viral vector-based models in rats and non-human primates display prominent, although highly variable, nigral dopaminergic neuron loss. However, the few studies available on viral vector-mediated overexpression of alpha-synuclein in mice report a weak neurodegenerative process and no clear Lewy body-like pathology. To address this issue, we performed a comprehensive comparative study of alpha-synuclein overexpression by
means of recombinant adeno-associated viral vectors serotype 2/7 (rAAV2/7) at different doses in adult mouse substantia nigra.

Results: We noted a significant and dose-dependent alpha-synucleinopathy over time upon nigral viral vector-mediated alpha-synuclein overexpression. We obtained a strong, progressive and dose-dependent loss of dopaminergic neurons in the substantia nigra, reaching a maximum of 82% after 8 weeks. This effect correlated with a reduction in tyrosine hydroxylase immunoreactivity in the striatum. Moreover, behavioural analysis revealed significant motor impairments from 12 weeks after injection on. In addition, we detected the presence of alpha-synuclein-positive aggregates in the remaining surviving neurons. When comparing wild-type to mutant A53T alpha-synuclein at the same vector dose, both induced a similar degree of cell death. These data were supported by a biochemical analysis that showed a net increase in soluble and insoluble alpha-synuclein expression over time to the same extent for both alpha-synuclein variants.

Conclusions: In conclusion, our in vivo data provide evidence that strong and significant alpha-synuclein-induced neuropathology and progressive dopaminergic neurodegeneration can be achieved in mouse brain by means of rAAV2/7.


Abstract: Several lines of evidence imply early alterations in endocannabinoid and phosphodiesterase 10A (PDE10A) signaling in Huntington disease (HD). Using [18F]MK-9470 and [18F]JNJ42259152 small-animal positron emission tomography (PET), we investigated for the first time cerebral changes in type 1 cannabinoid (CB1) receptor binding and PDE10A levels in vivo in presymptomatic, early symptomatic, and late symptomatic HD (R6/2) mice, in relation to glucose metabolism ([18F]FDG PET), brain morphology (magnetic resonance imaging) and motor function. Ten R6/2 and 16 wild-type (WT) mice were investigated at 3 different time points between the age of 4 and 13 weeks. Parametric CB1 receptor and PDE10A images were anatomically standardized to Paxinos space and analyzed voxelwise. Volumetric microMRI imaging was performed to assess HD pathology. In R6/2 mice, CB1 receptor binding was decreased in comparison with WT in a cluster comprising the bilateral caudate-putamen, globus pallidus, and thalamic nucleus at week 5 (-8.1% ± 2.6%, p = 1.7 × 10-5). Longitudinal follow-up showed further progressive decline compared with controls in a cluster comprising the bilateral hippocampus, caudate-putamen, globus pallidus, superior colliculus, thalamic nucleus, and cerebellum (late vs. presymptomatic age: -13.7% ± 3.1% for R6/2 and +1.5% ± 4.0% for WT, p = 1.9 × 10-5). In R6/2 mice, PDE10A binding potential also decreased over time to reach significance at early and late symptomatic HD (late vs. presymptomatic age: -79.1% ± 1.9% for R6/2 and +2.1% ± 2.7% for WT, p = 1.5 × 10-4). The observed changes in CB1 receptor and PDE10A binding were correlated to anomalies exhibited by R6/2 animals in motor function, whereas no correlation was found with magnetic resonance imaging-based striatal volume. Our findings point to early regional dysfunctions in endocannabinoid and PDE10A signaling, involving the caudate-putamen and lateral globus pallidus, which may play a role in the progression of the disease in R6/2 animals. PET quantification of in vivo...
CB1 and/or PDE10A binding may thus be useful early biomarkers for HD. Our results also provide evidence of subtle motor deficits at earlier stages than previously described.

Impact factor: 3.288

Abstract: Neuroinflammation is a well-orchestrated, dynamic, multicellular process playing a major role in neurodegenerative disorders. The microglia which make up the innate immune system of the central nervous system are key cellular mediators of neuroinflammatory processes. In normal condition they exert a protective function, providing tissue repair by releasing anti-inflammatory cytokines and neurotrophic factors. Upon neuronal injury or infection, they become overactivated, thereby releasing neurotoxic substances, amplifying neuroinflammation leading to neurodegeneration. Positron emission tomography (PET) provides a sensitive non-invasive imaging technique to study and quantify receptor and enzyme expression. A radiolabelled tracer for a protein (over)expressed in neuroinflammation and more specifically for the overactivated microglia would be useful as a diagnostic tool in the follow-up of neuroinflammation progression and to study the efficacy of anti-inflammatory therapy over time. In this manuscript, an overview of potential PET tracer targets upregulated during neuroinflammation is provided together with the current radiotracers used to image these targets. In addition, lead structures to develop radiotracers for new targets are suggested.

Impact factor: 4.90

Abstract: Background: Acquisition of the M1 or M2 phenotypes by microglia has been shown to occur during the development of pathological conditions, with M1 activation being widely involved in neurotoxicity in relation with the anatomical localization and the reactivity of subtypes of microglia cells. On the contrary, little is known on the ability of microglia to undergo M2 polarization by interleukin-4 (IL4), the typical M2a polarization signal for peripheral macrophages. Methods: Recombinant mouse IL4 was injected in the third cerebral ventricle of mice to induce brain alternative polarization. The mRNA levels of Fizz1, Arg1, and Ym1 genes, known to be up-regulated by IL4 in peripheral macrophages, together with additional polarization markers, were evaluated in the striatum and frontal cortex at different time intervals after central administration of IL4; in parallel, M2a protein expression was evaluated in tissue extracts and at the cellular level. Results: Our results show that the potency and temporal profile of IL4-mediated M2a gene induction vary depending on the gene analyzed and according to the specific brain area analyzed, with the striatum showing a reduced M2a response compared with the frontal cortex, as further substantiated by assays of polarization protein levels. Of notice, Fizz1 mRNA induction reached 100-fold level, underscoring the potency of this specific IL4 signaling pathway in the brain. In addition, immunochemistry assays demonstrated the localization of the M2
response specifically to microglia cells and, more interestingly, the existence of a subpopulation of microglia cells amenable to undergoing M2a polarization in the healthy mouse brain. Conclusions: These results show that the responsiveness of brain macrophages to centrally administered IL4 may vary depending on the gene and brain area analyzed, and that M2a polarization can be ascribed to a subpopulation of IL4-responsive microglia cells. The biochemical pathways that enable microglia to undergo M2a activation represent key aspects for understanding the physiopathology of neuroinflammation and for developing novel therapeutic and diagnostic agents.


Abstract: Diagnostic accuracy in FDG-PET imaging highly depends on the operating procedures. In this clinical study on dementia, we compared the diagnostic accuracy at a single-subject level of a) Clinical Scenarios, b) Standard FDG Images and c) Statistical Parametrical (SPM) Maps generated via a new optimized SPM procedure. We evaluated the added value of FDG-PET, either Standard FDG Images or SPM Maps, to Clinical Scenarios. In 88 patients with neurodegenerative diseases (Alzheimer’s Disease-AD, Frontotemporal Lobar Degeneration-FTLD, Dementia with Lewy bodies-DLB and Mild Cognitive Impairment-MCI), 9 neuroimaging experts made a forced diagnostic decision on the basis of the evaluation of the three types of information. There was also the possibility of a decision of normality on the FDG-PET images. The clinical diagnosis confirmed at a long-term follow-up was used as the gold standard. SPM Maps showed higher sensitivity and specificity (96% and 84%), and better diagnostic positive (6.8) and negative (0.05) likelihood ratios compared to Clinical Scenarios and Standard FDG Images. SPM Maps increased diagnostic accuracy for differential diagnosis (AD vs. FTD; beta 1.414, p = 0.019). The AUC of the ROC curve was 0.67 for SPM Maps, 0.57 for Clinical Scenarios and 0.50 for Standard FDG Images. In the MCI group, SPM Maps showed the highest predictive prognostic value (mean LOC = 2.46), by identifying either normal brain metabolism (exclusionary role) or hypometabolic patterns typical of different neurodegenerative conditions.


Abstract: PURPOSE OF REVIEW: The availability of PET neuroimaging tools for the in-vivo assessment of metabolic dysfunction and amyloid burden in Alzheimer’s disease has opened important methodological and practical issues in the diagnostic design and the conduct of new clinical trials. This review, addressing the different molecular information that the amyloid-PET and fluorodeoxyglucose-PET (FDG-PET) tools can provide, highlights
their diverging paths in Alzheimer’s disease and possible new perspectives in research and clinical applications.

RECENT FINDINGS: Senile plaques and neurofibrillary tangles are prominent neuropathological hallmarks in Alzheimer’s disease and are considered to be targets for therapeutic intervention and biomarkers for diagnostic in-vivo imaging agents. Alzheimer’s disease is a slowly progressing disorder, in which pathophysiological abnormalities, detectable in vivo by PET biomarkers, precede clinical symptoms by many years to decades. The unitary view of Alzheimer’s disease as a sequential pathological pathway, with beta-amyloid (Aβ) as the only initial and causal event (the ‘amyloid cascade hypothesis’), is likely to be progressively replaced by a more complex picture, also on the basis of recent PET imaging findings showing that neuronal injury biomarkers and tau pathology can be independent of β-amyloid deposition.

SUMMARY: The different molecular paths that PET in-vivo biomarkers can reveal in the timeframe of Alzheimer’s disease progression reflect the events leading to deposition of Aβ and phosphorylated tau, neuronal injury and neurodegeneration, which can run in parallel instead of in a sequential manner. The amyloid and neuronal injury paths may diverge along the Alzheimer’s disease cascade and bear separate relationships with Alzheimer’s disease symptoms and clinical phenotypes. All these evidences are crucial for the diagnosis and the development of new drugs aimed at slowing or preventing dementia.

Impact factor: 5.398

Abstract: Stroke induces inflammation that can aggravate brain damage. This work examines whether interleukin-10 (IL-10) deficiency exacerbates inflammation and worsens the outcome of permanent middle cerebral artery occlusion (pMCAO). Expression of IL-10 and IL-10 receptor (IL-10R) increased after ischemia. From day 4, reactive astrocytes showed strong IL-10R immunoreactivity. Interleukin-10 knockout (IL-10 KO) mice kept in conventional housing showed more mortality after pMCAO than the wild type (WT). This effect was associated with the presence of signs of colitis in the IL-10 KO mice, suggesting that ongoing systemic inflammation was a confounding factor. In a pathogen-free environment, IL-10 deficiency slightly increased infarct volume and neurologic deficits. Induction of proinflammatory molecules in the IL-10 KO brain was similar to that in the WT 6 hours after ischemia, but was higher at day 4, while differences decreased at day 7. Deficiency of IL-10 promoted the presence of more mature phagocytic cells in the ischemic tissue, and enhanced the expression of M2 markers and the T-cell inhibitory molecule CTLA-4. These findings agree with a role of IL-10 in attenuating local inflammatory reactions, but do not support an essential function of IL-10 in lesion resolution. Upregulation of alternative immunosuppressive molecules after brain ischemia can compensate, at least in part, the absence of IL-10.
doi: 10.1007/s00401-014-1381-0
Impact factor: 9.777

Abstract: Neutrophils are rapidly recruited in response to local tissue infection or inflammation. Stroke triggers a strong inflammatory reaction but the relevance of neutrophils in the ischemic brain is not fully understood, particularly in the absence of reperfusion. We investigated brain neutrophil recruitment in two murine models of permanent ischemia induced by either cauterization of the distal portion of the middle cerebral artery (c-MCAo) or intraluminal MCA occlusion (il-MCAo), and three fatal cases of human ischemic stroke. Flow cytometry analyses revealed progressive neutrophil recruitment after c-MCAo, lesser neutrophil recruitment following il-MCAo, and absence of neutrophils after sham operation. Confocal microscopy identified neutrophils in the leptomeninges from 6 h after the occlusion, in the cortical basal lamina and cortical Virchow-Robin spaces from 15 h, and also in the cortical brain parenchyma at 24 h. Neutrophils showed signs of activation including histone-3 citrullination, chromatin decondensation, and extracellular projection of DNA and histones suggestive of extracellular trap formation. Perivascular neutrophils were identified within the entire cortical infarction following c-MCAo. After il-MCAo, neutrophils prevailed in the margins but not the center of the cortical infarct, and were intraluminal and less abundant in the striatum. The lack of collaterals to the striatum and a collapsed pial anastomotic network due to brain edema in large hemispheric infarctions could impair neutrophil trafficking in this model. Neutrophil extravasation at the leptomeninges was also detected in the human tissue. We concluded that neutrophils extravasate from the leptomeningeal vessels and can eventually reach the brain in experimental animal models and humans with prolonged arterial occlusion.

doi: 10.1186/ar4508
Impact factor: 4.3

Abstract: INTRODUCTION: Rheumatoid arthritis (RA) is a chronic disease, affecting 0.5-1% of adults in industrialized countries, in which systemic inflammation and synovitis drive joint destruction. [18F]DPA-714 is a specific tracer of the 18 kDa Translocator Protein (TSPO), which is overexpressed on activated macrophages, and proposed as a biomarker of neuroinflammation. Today, diagnosis of patients with early inflammatory arthritis is limited by poor sensitivity and specificity. The present study aims to investigate the potential of [18F]DPA-714 to monitor in vivo inflammatory processes at a preclinical stage via positron emission tomography (PET).

METHODS: RA was induced in Dark Agouti rats by subcutaneous injection of inactivated mycobacterium tuberculosis. Development of arthritis clinical signs was investigated daily and the severity of the disease evaluated. Animals were imaged at the peak of inflammation using [18F]DPA-714 and a small-animal PET-CT tomograph.
RESULTS: The first clinical signs appeared at 10 days post-injection, with a peak of inflammation at 20 days. At this time, PET-analyses showed a clear uptake of [18F]DPA-714 in swollen ankles, with mean values of $0.52 \pm 0.18\%\text{ID/cc}$ for treated ($n = 11$) and $0.19 \pm 0.09$ for non-treated ($n = 6$) rats. A good correlation between [18F]DPA-714’s uptake and swelling was also found. Immunohistochemistry showed an enhanced TSPO expression in hind paws, mainly co-localized with the macrophages specific antigen CD68 expressing cells.

CONCLUSION: These preliminary results demonstrates that the TSPO 18 kDa specific radioligand [18F]DPA-714 is adapted for the study and follow up of inflammation linked to RA in our experimental model, suggesting also a strong potential for clinical imaging of peripheral inflammation.

Impact factor: 10.284

Abstract: The cuprizone mouse model allows the investigation of the complex molecular mechanisms behind nonautoimmune-mediated demyelination and spontaneous remyelination. While it is generally accepted that oligodendrocytes are specifically vulnerable to cuprizone intoxication due to their high metabolic demands, a comprehensive overview of the etiology of cuprizone-induced pathology is still missing to date. In this review we extensively describe the physico-chemical mode of action of cuprizone and discuss the molecular and enzymatic mechanisms by which cuprizone induces metabolic stress, oligodendrocyte apoptosis, myelin degeneration and eventually axonal and neuronal pathology. In addition, we describe the dual effector function of the immune system which tightly controls demyelination by effective induction of oligodendrocyte apoptosis, but in contrast also paves the way for fast and efficient remyelination by the secretion of neurotrophic factors and the clearance of cellular and myelinic debris. Finally, we discuss the many clinical symptoms that can be observed following cuprizone treatment, and how these strengthened the cuprizone model as a useful tool to study human multiple sclerosis, schizophrenia and epilepsy.

doi: 10.3727/096368914X682800
Impact factor: 3.57

Abstract: While multiple rodent pre-clinical studies, and to a lesser extent human clinical trials, claim the feasibility, safety and potential clinical benefit of cell grafting in the central nervous system (CNS), currently only little convincing knowledge exists regarding the actual fate of the grafted cells and their effect on the surrounding environment (or vice versa). Our preceding studies already indicated that only a minor fraction of the initially
grafted cell population survives the grafting process, while the surviving cell population becomes invaded by highly activated microglia/macrophages and surrounded by reactive astrogliosis. In the current study, we further elaborate on early cellular and inflammatory events following syngeneic grafting of eGFP+ mouse embryonic fibroblasts (mEFs) in the CNS of immune-competent mice. Based on obtained quantitative histological data, we here propose a detailed mathematically-derived working model that sequentially comprises hypoxia-induced apoptosis of grafted mEFs, neutrophil invasion, neo-angiogenesis, microglia/macrophage recruitment, astrogliosis and eventually survival of a limited number of grafted mEFs. Simultaneously, we observed that the cellular events following mEF grafting activates the sub-ventricular zone neural stem and progenitor cell compartment. This proposed model therefore further contributes to our understanding of cell graft-induced cellular responses, and will eventually allow for successful manipulation of this intervention.

   doi: 10.1161/STROKEAHA.111.000495
   Impact factor: 6.158
   Abstract: no abstract available

   doi: 10.1016/j.tibtech.2013.01.008
   Impact factor: 9.660
   Abstract: Stem cells offer great potential for regenerative medicine because they regenerate damaged tissue by cell replacement and/or by stimulating endogenous repair mechanisms. Although stem cells are defined by their functional properties, such as the potential to proliferate, to self-renew, and to differentiate into specific cell types, their identification based on the expression of specific markers remains vague. Here, profiles of stem cell metabolism might highlight stem cell function more than the expression of single genes/markers. Thus, systematic approaches including spectroscopy might yield insight into stem cell function, identity, and stemness. We review the findings gained by means of metabolic and spectroscopic profiling methodologies, for example, nuclear magnetic resonance spectroscopy (NMRS), mass spectrometry (MS), and Raman spectroscopy (RS), with a focus on neural stem cells and neurogenesis.

   Impact factor: 6.189
Abstract: In Alzheimer’s disease (AD), persistent microglial activation as sign of chronic neuroinflammation contributes to disease progression. Our study aimed to in vivo visualize and quantify microglial activation in 13- to 15-month-old AD mice using [(11)C]-(R)-PK11195 and positron emission tomography (PET). We attempted to modulate neuroinflammation by subjecting the animals to an anti-inflammatory treatment with pioglitazone (5-weeks’ treatment, 5-week wash-out period). [(11)C]-(R)-PK11195 distribution volume values in AD mice were significantly higher compared with control mice after the wash-out period at 15 months, which was supported by immunohistochemistry data. However, [(11)C]-(R)-PK11195 μPET could not demonstrate genotype- or treatment-dependent differences in the 13- to 14-month-old animals, suggesting that microglial activation in AD mice at this age and disease stage is too mild to be detected by this imaging method.


doi: 10.1186/scrt147
Impact factor: 3.21

Abstract: INTRODUCTION: Transplantation of neural stem cells (NSCs) is increasingly suggested to become part of future therapeutic approaches to improve functional outcome of various central nervous system disorders. However, recently it has become clear that only a small fraction of grafted NSCs display long-term survival in the (injured) adult mouse brain. Given the clinical invasiveness of NSC grafting into brain tissue, profound characterisation and understanding of early post-transplantation events is imperative to claim safety and efficacy of cell-based interventions.

METHODS: Here, we applied in vivo bioluminescence imaging (BLI) and post-mortem quantitative histological analysis to determine the localisation and survival of grafted NSCs at early time points post-transplantation.

RESULTS: An initial dramatic cell loss (up to 80% of grafted cells) due to apoptosis could be observed within the first 24 hours post-implantation, coinciding with a highly hypoxic NSC graft environment. Subsequently, strong spatiotemporal microglial and astroglial cell responses were initiated, which stabilised by day 5 post-implantation and remained present during the whole observation period. Moreover, the increase in astrocyte density was associated with a high degree of astroglial scarring within and surrounding the graft site. During the two-week follow up in this study, the NSC graft site underwent extensive remodelling with NSC graft survival further declining to around 1% of the initial number of grafted cells.

CONCLUSIONS: The present study quantitatively describes the early post-transplantation events following NSC grafting in the adult mouse brain and warrants that such intervention is directly associated with a high degree of cell loss, subsequently followed by strong glial cell responses.

Abstract: BACKGROUND: Cerebral stroke is a severe and frequent condition that requires rapid and reliable diagnosis. If administered shortly after the first symptoms manifest themselves, IV thrombolysis has been shown to increase the functional prognosis by restoring brain reperfusion. However, a better understanding of the pathophysiology of stroke should help to identify potential new therapeutic targets. Stroke is known to induce an inflammatory brain reaction that involves overexpression of the 18-kDa translocator protein (TSPO) in glial cells and infiltrated leukocytes, which can be visualised by positron emission tomography (PET). We aimed to evaluate post-stroke neuroinflammation using the PET TSPO radioligand (18)F-DPA-714.

METHODS: Nine patients underwent (18)F-DPA-714 PET and magnetic resonance imaging (MRI) between 8 and 18 days after the ictus. Co-registration of MRI and PET images was used to define three volumes of interest (VOIs): core infarction, contralateral region, and cerebellum ipsilateral to the stroke lesion. Time activity curves were obtained from each VOI, and ratios of mean and maximum activities between the VOIs were calculated.

RESULTS: We observed an increased uptake of (18)F-DPA-714 co-localised with the infarct tissue and extension beyond the region corresponding to the damage in the blood brain barrier. No correlation was identified between (18)F-DPA-714 uptake and infarct volume. (18)F-DPA-714 uptake in ischemic lesion (mainly associated with TSPO expression in the infarct area and in the surrounding neighbourhood) slowly decreased from 10 min pi to the end of the PET acquisition, remaining higher than that in both contralateral region and ipsilateral cerebellum.

CONCLUSION: Our results show that (18)F-DPA-714 uptake after acute ischemia is mainly associated with TSPO expression in the infarct area and in the surrounding neighbourhood. We also demonstrated that the kinetics of (18)F-DPA-714 differs in injured tissue compared to normal tissue. Therefore, (18)F-DPA-714 may be useful in assessing the extent of neuroinflammation associated with acute stroke and could also help to predict clinical outcomes and functional recovery, as well as to assess therapeutic strategies, such as the use of neuroprotective/anti-inflammatory drugs.


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Impact factor: 5.339

Abstract: [(11)C]TMSX ((7-N-methyl-(11)C)-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine) is a selective adenosine A2A receptor (A2AR) radioligand. In the central nervous system (CNS), A2AR are linked to dopamine D2 receptor function in striatum, but they are also important modulators of inflammation. The golden standard for kinetic modeling of brain [(11)C]TMSX positron emission tomography (PET) is to obtain arterial input function via arterial blood sampling. However, this method is laborious, prone to errors and unpleasant for study subjects. The aim of this work was to evaluate alternative input function acquisition methods for brain [(11)C]TMSX PET imaging. First, a noninvasive, automated method for the extraction of gray matter reference region using supervised clustering (SCgm) was developed. Second, a method for obtaining a population-based
arterial input function (PBIF) was implemented. These methods were created using data from 28 study subjects (7 healthy controls, 12 multiple sclerosis patients, and 9 patients with Parkinson's disease). The results with PBIF correlated well with original plasma input, and the SCgm yielded similar results compared with cerebellum as a reference region. The clustering method for extracting reference region and the population-based approach for acquiring input for dynamic [(11)C]TMSX brain PET image analyses appear to be feasible and robust methods, that can be applied in patients with CNS pathology.

Impact factor: 5.563

Abstract: Patients with secondary progressive multiple sclerosis (SPMS) are lacking efficient medication to slow down the progression of their disease. PET imaging holds promise as a method to study, at the molecular level and in vivo, the central nervous system pathology of SPMS. PET might thus help to elucidate potential therapeutic targets and be useful as an imaging biomarker in future treatment trials of progressive multiple sclerosis. The objective of this study was to evaluate whether translocator protein (TSPO) imaging could be used to visualize the diffuse inflammation located in the periplaque area and in the normal-appearing white matter (NAWM) in the brains of patients with SPMS.

METHODS: This was an imaging study using MR imaging and PET with 11C-PK11195 binding to TSPO, which is expressed in activated, but not in resting, microglia. Ten SPMS patients with a mean expanded disability status scale score of 6.3 (SD, 1.5) and eight age-matched healthy controls were studied. The imaging was performed using High-Resolution Research Tomograph PET and 1.5-T MR imaging scanners. Microglial activation was evaluated as the distribution volume ratio (DVR) of 11C-PK11195 from dynamic PET images. DVR estimations were performed with special interest in NAWM and gray matter using region-of-interest and parametric image-based approaches.

RESULTS: The DVR of 11C-PK11195 was significantly increased in the periventricular and total NAWM (P = 0.016 and P < 0.001, respectively) and in the thalamic ROIs (P = 0.027) of SPMS patients, compared with the control group. Similarly, parametric image analysis showed widespread increases of 11C-PK11195 in the white matter of SPMS patients, compared with healthy controls. Increased perilesional TSPO uptake was present in 57% of the chronic T1 lesions in MR imaging.

CONCLUSION: The finding of increased 11C-PK11195 binding in the NAWM of SPMS patients is in line with the neuropathologic demonstration that activated microglial cells are the source of diffuse NAWM inflammation. Evaluating microglial activation with TSPO-binding PET ligands provides a unique tool to assess diffuse brain inflammation and perilesional activity in progressive multiple sclerosis in vivo.

Impact factor: 1.029
Abstract: Multiple sclerosis (MS) is a demyelinating immune-mediated disease of the central nervous system (CNS). It is the most frequent neurological disease in young adults and affects over 2 million people worldwide. Current treatments reduce the relapse rate and the formation of inflammatory lesions in the CNS, but with only temporary and limited success. Despite the presence of endogenous oligodendroglial progenitors (OPCs) and of spontaneous remyelination, at least in early MS its levels and its qualities are apparently insufficient for a sustained endogenous functional repair. Therefore, novel MS therapies should consider not only immunemodulatory but also myelin repair activities. Mesenchymal stem cells (MSCs) represent an attractive alternative to develop a cell-based therapy for MS. MSCs display stromal features and exert bystander immunemodulatory and neuroprotective activities. Importantly, MSCs induce oligodendrocyte fate decision and differentiation/maturation of adult neural progenitors, suggesting the existence of MSC-derived remyelination activity. Moreover, transplanted MSCs promote functional recovery and myelin repair in different MS animal models. Here, we summarize the current knowledge on endogenous mechanisms for remyelination and proposed autologous MSC therapy as a promising strategy for MS treatment.


Abstract: Speculations on the involvement of hippocampal neurogenesis, a form of neuronal plasticity, in the aetiology of depression and the mode of action of antidepressive therapies, started to arise more than a decade ago. But still, conclusive evidence that adult neurogenesis contributes to antidepressive effects of pharmacological and physical therapies has not been generated yet. This review revisits recent findings on the close relation between the mode(s) of action of electroconvulsive therapy (ECT), a powerful intervention used as second-line treatment of major depression disorders, and the neurogenic response to ECT. Following application of electroconvulsive shocks, intricate interactions between neurogenesis, angiogenesis, and microglia activation, the hypothalamic-pituitary-adrenal axis and the secretion of neurotrophic factors have been documented. Furthermore, considering the fact that neurogenesis strongly diminishes along aging, we investigated the response to electroconvulsive shocks in young as well as in aged cohorts of mice.


Abstract: Neurogenesis in the adult central nervous system has been well documented in several mammals including humans. By now, a plethora of data has been generated with the aim of understanding the molecular and cellular events governing neurogenesis. This growing comprehension will provide the basis for modulation of neurogenesis for
therapeutic purposes, in particular in neurodegenerative diseases. Herein, we review the current knowledge on neurogenesis, in particular in the frame of epilepsy, since seizures have massive effects on neurogenesis. Conversely, some studies have suggested that aberrant neurogenesis might contribute to the development or manifestation of epilepsy and, moreover, chronic inhibition of neurogenesis in epilepsy might contribute to comorbidities of epilepsy such as cognitive deficits. Therefore, a better understanding of neurogenesis in the context of epilepsy is still required for future therapeutic purposes.

Impact factor: 4.558

Abstract: Spinocerebellar ataxia type 2 (SCA2) is an autosomal-dominant degenerative disorder that is neuropathologically characterized primarily by infratentorial damage, although less severe supratentorial involvement may contribute to the clinical manifestation. Diffusion-weighted imaging (DWI)-Magnetic Resonance Imaging (MRI) studies of SCA2 have enabled in vivo quantification of neurodegeneration in infratentorial regions, whereas supratentorial regions have been explored less thoroughly. We measured microstructural changes in both infratentorial and supratentorial regions in 13 SCA2 patients (9 men, 4 women; mean age, 50 ± 12 years) and 15 controls (10 men, 5 women; mean age, 49 ± 14 years) using DWI-MRI and correlated the DWI changes with disease severity and duration. Disease severity was evaluated using the International Cooperative Ataxia Rating Scale and the Inherited Ataxia Clinical Rating Scale. Cerebral diffusion trace ($D^+$) values were generated, and regions of interest (ROIs) and voxel-based analysis with Statistical Parametric Mapping (SPM) were used for data analysis. In SCA2 patients, ROI analysis and SPM confirmed significant increases in $D^+$ values in the pons, cerebellar white matter (CWM) and middle cerebellar peduncles. Moreover, SPM analysis revealed increased $D^+$ values in the right thalamus, bilateral temporal cortex/white matter, and motor cortex/pyramidal tract regions. Increased diffusivity in the frontal white matter (FWM) and the CWM was significantly correlated with ataxia severity. DWI-MRI revealed that both infratentorial and supratentorial microstructural changes may characterize SCA2 patients in the course of the disease and might contribute to the severity of the symptoms.

Impact factor: 4.077

Abstract: BACKGROUND: An effective NMDA antagonist imaging model may find key utility in advancing schizophrenia drug discovery research. We investigated effects of
subchronic treatment with the NMDA antagonist memantine by using behavioural observation and multimodal MRI.

METHODS: Pharmacological MRI (phMRI) was used to map the neuroanatomical binding sites of memantine after acute and subchronic treatment. Resting state fMRI (rs-fMRI) and diffusion MRI were used to study the changes in functional connectivity (FC) and ultra-structural tissue integrity before and after subchronic memantine treatment. Further corroborating behavioural evidences were documented.

RESULTS: Dose-dependent phMRI activation was observed in the prelimbic cortex following acute doses of memantine. Subchronic treatment revealed significant effects in the hippocampus, cingulate, prelimbic and retrosplenial cortices. Decreases in FC amongst the hippocampal and frontal cortical structures (prelimbic, cingulate) were apparent through rs-fMRI investigation, indicating a loss of connectivity. Diffusion kurtosis MRI showed decreases in fractional anisotropy and mean diffusivity changes, suggesting ultra-structural changes in the hippocampus and cingulate cortex. Limited behavioural assessment suggested that memantine induced behavioural effects comparable to other NMDA antagonists as measured by locomotor hyperactivity and that the effects could be reversed by antipsychotic drugs.

CONCLUSION: Our findings substantiate the hypothesis that repeated NMDA receptor blockade with nonspecific, noncompetitive NMDA antagonists may lead to functional and ultra-structural alterations, particularly in the hippocampus and cingulate cortex. These changes may underlie the behavioural effects. Furthermore, the present findings underscore the utility and the translational potential of multimodal MR imaging and acute/subchronic memantine model in the search for novel disease-modifying treatments for schizophrenia.

Impact factor: 2.517

Abstract: INTRODUCTION: We examined whether $^{18}$F-LBT-999 ((E)-N-(4-fluorobut-2-enyl)2β-carbomethoxy-3β-(4'-tolyl)nortropane) is an efficient positron emission tomography (PET) tracer for the quantification of the dopamine transporter (DAT) in the healthy rat brain.

METHODS: PET studies were performed using several experimental designs, i.e. test-retest, co-injection with different doses of unlabelled LBT, displacement with GBR12909 and pre-injection of amphetamine.

RESULTS: The uptake of $^{18}$F-LBT-999 confirmed its specific binding to the DAT. The non-displaceable uptake (BP(ND)) in the striatum, between 5.37 and 4.39, was highly reproducible and reliable, and was decreased by 90% by acute injection of GBR12909. In the substantia nigra/ventral tegmental area (SN/VTA), the variability was higher and the reliability was lower. Pre-injection of amphetamine induced decrease of $^{18}$F-LBT-999 BP(ND) of 50% in the striatum.

CONCLUSIONS: $^{18}$F-LBT-999 allows the quantification of the DAT in living rat brain with high reproducibility, sensitivity and specificity. It could be used to quantify the DAT in rodent models, thereby allowing to study neurodegenerative and neuropsychiatric diseases.
doi: 10.1371/journal.pone.0084241
Impact factor: 3.730

Abstract
Introduction: Functional connectivity (FC) studies have gained immense popularity in the evaluation of several neurological disorders, such as Alzheimer’s disease (AD). AD is a complex disorder, characterised by several pathological features. The problem with FC studies in patients is that it is not straightforward to focus on a specific aspect of pathology. In the current study, resting state functional magnetic resonance imaging (rsfMRI) is applied in a mouse model of amyloidosis to assess the effects of amyloid pathology on FC in the mouse brain.
Methods: Nine APP/PS1 transgenic and nine wild-type mice (average age 18.9 months) were imaged on a 7T MRI system. The mice were anesthetized with medetomidine and rsfMRI data were acquired using a gradient echo EPI sequence. The data were analysed using a whole brain seed correlation analysis and interhemispheric FC was evaluated using a pairwise seed analysis. Qualitative histological analyses were performed to assess amyloid pathology, inflammation and synaptic deficits.
Results: The whole brain seed analysis revealed an overall decrease in FC in the brains of transgenic mice compared to wild-type mice. The results showed that interhemispheric FC was relatively preserved in the motor cortex of the transgenic mice, but decreased in the somatosensory cortex and the hippocampus when compared to the wild-type mice. The pairwise seed analysis confirmed these results. Histological analyses confirmed the presence of amyloid pathology, inflammation and synaptic deficits in the transgenic mice.
Conclusions: In the current study, rsfMRI demonstrated decreased FC in APP/PS1 transgenic mice compared to wild-type mice in several brain regions. The APP/PS1 transgenic mice had advanced amyloid pathology across the brain, as well as inflammation and synaptic deficits surrounding the amyloid plaques. Future studies should longitudinally evaluate APP/PS1 transgenic mice and correlate the rsfMRI findings to specific stages of amyloid pathology.

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Impact factor: 3.730

Abstract: Background: The purpose of the study was to evaluate the applicability of 18F-labelled amyloid imaging positron emission tomography (PET) agent [18F]flutemetamol to detect changes in brain beta-amyloid (Aβ) deposition in vivo in APP23, Tg2576 and APPswε-PS1dE9 mouse models of Alzheimer’s disease. We expected that the high specific activity of [18F]flutemetamol would make it an attractive small animal Aβ imaging agent.

Methods: [18F]flutemetamol uptake in the mouse brain was evaluated in vivo at 9 to 22 months of age with an Inveon Multimodality PET/CT camera (Siemens Medical Solutions USA, Knoxville, TN, USA). Retention in the frontal cortex (FC) was evaluated by Logan distribution volume ratios (DVR) and FC/cerebellum (CB) ratios during the late washout phase (50 to 60 min). [18F]flutemetamol binding to Aβ was also evaluated in brain slices by in vitro and ex vivo autoradiography. The amount of Aβ in the brain slices was determined with Thioflavin S and anti-Aβ1−40 immunohistochemistry.

Results: In APP23 mice, [18F]flutemetamol retention in the FC increased from 9 to 18 months. In younger mice, DVR and FC/CB50-60 were 0.88 (0.81) and 0.88 (0.89) at 9 months (N = 2), and 0.98 (0.93) at 12 months (N = 1), respectively. In older mice, DVR and FC/CB50-60 were 1.16 (1.15) at 15 months (N = 1), 1.13 (1.16) and 1.35 (1.35) at 18 months (N = 2), and 1.05 (1.31) at 21 months (N = 1). In Tg2576 mice, DVR and FC/CB50-60 showed modest increasing trends but also high variability. In APPswε-PS1dE9 mice, DVR and FC/CB50-60 did not increase with age. Thioflavin S and anti-Aβ1−40 positive Aβ deposits were present in all transgenic mice at 19 to 22 months, and they co-localized with [18F]flutemetamol binding in the brain slices examined with in vitro and ex vivo autoradiography.

Conclusions: Increased [18F]flutemetamol retention in the brain was detected in old APP23 mice in vivo. However, the high specific activity of [18F]flutemetamol did not provide a notable advantage in Tg2576 and APPswε-PS1dE9 mice compared to the previously evaluated structural analogue [(11)C]PIB. For its practical benefits, [18F]flutemetamol imaging with a suitable mouse model like APP23 is an attractive alternative.


Impact factor: 5.114

Abstract: PURPOSE: Translocator protein (TSPO) is a biomarker of neuroinflammation that can be imaged by PET using [(11)C]- (R)PK11195. We sought to characterize the [(11)C]- (R)PK11195 kinetics in gliomas of different histotypes and grades, and to compare two reference tissue input functions (supervised cluster analysis versus cerebellar grey matter) for the estimation of [(11)C]- (R)PK11195 binding in gliomas and surrounding brain structures.

METHODS: Twenty-three glioma patients and ten age-matched controls underwent structural MRI and dynamic [(11)C]- (R)PK11195 PET scans. Tissue time-activity curves (TACs) were extracted from tumour regions as well as grey matter (GM) and white matter (WM) of the brains. Parametric maps of binding potential (BPND) were generated with the
simplified reference tissue model using the two input functions, and were compared with each other. TSPO expression was assessed in tumour tissue sections by immunohistochemistry.

RESULTS: Three types of regional kinetics were observed in individual tumour TACs: GM-like kinetics (n = 6, clearance of the tracer similar to that in cerebellar GM), WM-like kinetics (n = 8, clearance of the tracer similar to that in cerebral WM) and a form of mixed kinetics (n = 9, intermediate rate of clearance). Such kinetic patterns differed between low-grade astrocytomas (WM-like kinetics) and oligodendrogliomas (GM-like and mixed kinetics), but were independent of tumour grade. There was good agreement between parametric maps of BPND derived from the two input functions in all controls and 10 of 23 glioma patients. In 13 of the 23 patients, BPND values derived from the supervised cluster input were systematically smaller than those using the cerebellar input. Immunohistochemistry confirmed that TSPO expression increased with tumour grade.

CONCLUSION: The three types of [(11)C]- -(R)PK11195 kinetics in gliomas are determined in part by tracer delivery, and indicated that kinetic analysis is a valuable tool in the study of gliomas with the potential for in vivo discrimination between low-grade astrocytomas and oligodendrogliomas. Supervised cluster and cerebellar input functions produced consistent BPND estimates in approximately half of the gliomas investigated, but had a systematic difference in the remainder. The cerebellar input is preferred based on theoretical and practical considerations.

   doi: 10.2967/jnumed.114.151621
   Impact factor: 5.563

Abstract: The 18-kDa mitochondrial translocator protein (TSPO) is up-regulated in high grade astrocytomas and can be imaged by positron emission tomography (PET) using the selective radiotracer 11C-(R)PK11195. We investigated 11C-(R)PK11195 binding in human gliomas and its relationship with TSPO expression in tumor tissue and glioma associated microglia/macrophages within the tumors.

METHODS: Twenty-two glioma patients underwent dynamic 11C-(R)PK11195 PET scans and perfusion MRI acquisition. Parametric maps of 11C-(R)PK11195 binding potential (BPND) were generated. Co-registered MR/PET images were used to guide tumor biopsy. The tumor tissue was quantitatively assessed for TSPO expression and infiltration of glioma associated microglia/macrophages (GAMs) using immunohistochemistry and double immunofluorescence. The imaging and histopathologic parameters were compared among different histotypes and grades, and correlated with each other.

RESULTS: BPND of 11C-(R)PK11195 in high-grade gliomas were significantly higher than in low-grade astrocytomas and low-grade oligodendrogliomas. TSPO in gliomas was expressed predominantly by neoplastic cells, and its expression correlated positively with BPND in the tumors. Glioma associated microglia/macrophages only partially contributed to the overall TSPO expression within the tumors, and TSPO expression in GAMs did not correlate with tumor BPND.
CONCLUSION: PET with 11C-(R)PK11195 in human gliomas predominantly reflects TSPO expression in tumor cells. It therefore has the potential to effectively stratify patients that are suitable for TSPO targeted treatment.

   Impact factor: ??

Abstract: Background: Neurodegenerative diseases are characterized by key features such as loss of neurons, astrocytosis, and microglial activation/proliferation. These changes cause differences in the density of cell types between control and disease subjects, confounding results from gene expression studies. Chromosome X (ChrX) is known to be specifically important in the brain. We hypothesized the existence of a chromosomal signature of gene expression associated with the X-chromosome for neurological conditions not normally associated with that chromosome. The hypothesis was investigated using publicly available microarray datasets from studies on Parkinson’s disease, Alzheimer’s disease, and Huntington’s disease. Data were analyzed using Chromowave, an analytical tool for detecting spatially extended expression changes along chromosomes. To examine associations with neuronal density and astrocytosis, the expression of cell specific reporter genes was extracted. The association between these genes and the expression patterns extracted by Chromowave was then analyzed. Further analyses of the X:Autosome ratios for laser dissected neurons, microglia cultures and whole tissue were performed to detect cell specific differences. Results: We observed an extended pattern of low expression of ChrX consistent in all the neurodegenerative disease brain datasets. There was a strong correlation between mean ChrX expression and the pattern extracted from the autosomal genes representing neurons, but not with mean autosomal expression. No chromosomal patterns associated with the neuron specific genes were found on other chromosomes. The chromosomal expression pattern was not present in datasets from blood cells. The X:Autosome expression ratio was also higher in neuronal cells than in tissues with a mix of cell types.
Conclusions: The results suggest that neurological disorders show as a reduction in mean expression of many genes along ChrX. The most likely explanation for this finding relates to the documented general up-regulation of ChrX in brain tissue which, this work suggests, occurs primarily in neurons. If validated, this cell specific ChrX expression warrants further research as understanding the biological reasons and mechanisms for this expression, may help to elucidate a connection with the development of neurodegenerative disorders.

   doi: 10.1007/s00429-014-0970-y
   Impact factor: 4.567
Abstract: Adequate estimation of neuroinflammatory processes following ischemic stroke is essential for better understanding of disease mechanisms, and for the development of treatment strategies. With the TSPO (18 kDa translocator protein) positron emission tomography (PET) radioligand [11C]PBR28, we monitored longitudinally the inflammatory response post-transient cerebral ischemia in rats, using a recently developed rat stroke model that produces isolated focal cortical infarcts with clinical relevance in size and pathophysiology. Six Sprague-Dawley rats were subjected to 90 min transient endovascular occlusion of the M2 segment of the middle cerebral artery (M2CAO). Animals were imaged with a nanoScan® PET/MRI system at 1, 4, 7 and 14 days after M2CAO with a bolus injection of [11C]PBR28. In the infarct region, we found a significantly increased uptake of [11C]PBR28 on day 4, 7 and 14 compared to day 1 as well as compared to the contralateral cortex. No significant increase was detected in the contralateral cortex during the 14 days of imaging. The activation in the infarct region gradually decreased between day 4 and day 14. In an additional group of animals (n = 26), immunofluorescence studies were performed with antibodies for activated microglia/monocytes (Cd11b), phagocytes (Cd68), astrocytes (glial fibrillary acidic protein) and TSPO. The TSPO immunofluorescence signal indicated reactive microgliosis post injury, corresponding to PET findings. The present clinically relevant animal model and TSPO PET ligand appear to be well suited for studies on neuroinflammation after ischemic stroke.


Abstract: Alpha-synuclein (α-synuclein) is considered a key player in Parkinson's disease (PD), but the exact relationship between α-synuclein aggregation and dopaminergic neurodegeneration remains unresolved. There is increasing evidence that neuroinflammatory processes are closely linked to dopaminergic cell death, but whether the inflammatory process is causally involved in PD or rather reflects secondary consequences of nigrostriatal pathway injury is still under debate. We evaluated the therapeutic effect of the immunophilin ligand FK506 in a rAAV2/7 α-synuclein overexpression rat model. Treatment with FK506 significantly increased the survival of dopaminergic neurons in a dose-dependent manner. No reduction in α-synuclein aggregation was apparent in this time window, but FK506 significantly lowered the infiltration of both T helper and cytotoxic T cells and the number and subtype of microglia and macrophages. These data suggest that the anti-inflammatory properties of FK506 decrease neurodegeneration in this α-synuclein-based PD model, pointing to a causal role of neuroinflammation in the pathogenesis of PD.


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doi: 10.1016/j.neurobiolaging.2014.11.015
Impact factor: 4.853

Abstract: Testing of new therapeutic strategies for Parkinson's disease (PD) is currently hampered by the lack of relevant and reproducible animal models. Here, we developed a robust rat model for PD by injection of adeno-associated viral vectors (rAAV2/7) encoding alpha-synuclein into the substantia nigra, resulting in reproducible nigrostriatal pathology and behavioral deficits in a 4-week time period. Progressive dopaminergic dysfunction was corroborated by histopathologic and biochemical analysis, motor behavior testing and in vivo microdialysis. L-DOPA treatment was found to reverse the behavioral phenotype. Non-invasive positron emission tomography imaging and magnetic resonance spectroscopy allowed longitudinal monitoring of neurodegeneration. In addition, insoluble alpha-synuclein aggregates were formed in this model. This alpha-synuclein rat model shows improved face and predictive validity, and therefore offers the possibility to reliably test novel therapeutics. Furthermore, it will be of great value for further research into the molecular pathogenesis of PD and the importance of alpha-synuclein aggregation in the disease process.

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Impact factor: 5.186

Abstract: Endogenous neural stem cells (eNSCs) reside in defined regions of the adult brain and have the potential to generate new brain cells, including neurons. Stimulation of adult neurogenesis presents an enormous potential for regenerative therapies in the central nervous system. However, the methods used to monitor the proliferation, migration, differentiation, and functional integration of eNSCs and their progeny are often invasive and limited in studying dynamic processes. To overcome this limitation, novel techniques and contrast mechanisms for in vivo imaging of neurogenesis have recently been developed and successfully applied. In vivo labeling of endogenous neuronal progenitor cells in situ with contrast agents or tracers enables longitudinal visualization of their proliferation and/or migration. Labeling of these cells with magnetic nanoparticles has proven to be very useful for tracking neuroblast migration with MRI. Alternatively, genetic labeling using reporter gene technology has been demonstrated for optical and MR imaging, leading to the development of powerful tools for in vivo optical imaging of neurogenesis. More recently, the iron storage protein ferritin has been used as an endogenously produced MRI contrast agent to monitor neuroblast migration. The use of specific promoters for neuronal progenitor cell imaging increases the specificity for visualizing neurogenesis. Further improvements of detection sensitivity and neurogenesis-specific contrast are nevertheless required for each of these imaging techniques to further improve the already high utility of this toolbox for preclinical neurogenesis research.
List of publications – Period 1-3


Abstract: Brain injury following stroke affects neurogenesis in the adult mammalian brain. However, a complete understanding of the origin and fate of the endogenous neural stem cells (eNSCs) in vivo is missing. Tools and technology that allow non-invasive imaging and tracking of eNSCs in living animals will help to overcome this hurdle. In this study, we aimed to monitor eNSCs in a photothrombotic (PT) stroke model using in vivo bioluminescence imaging (BLI). In a first strategy, inducible transgenic mice expressing firefly luciferase (Fluc) in the eNSCs were generated. In animals that received stroke, an increased BLI signal originating from the infarct region was observed. However, due to histological limitations, the identity and exact origin of cells contributing to the increased BLI signal could not be revealed. To overcome this limitation, we developed an alternative strategy employing stereotactic injection of conditional lentiviral vectors (Cre-Flex LVs) encoding Fluc and eGFP in the subventricular zone (SVZ) of Nestin-Cre transgenic mice, thereby specifically labeling the eNSCs. Upon induction of stroke, increased eNSC proliferation resulted in a significant increase in BLI signal between 2 days and 2 weeks after stroke, decreasing after 3 months. Additionally, the BLI signal relocalized from the SVZ towards the infarct region during the 2 weeks following stroke. Histological analysis at 90 days post stroke showed that in the peri-infarct area, 36% of labeled eNSC progeny differentiated into astrocytes, while 21% differentiated into mature neurons. In conclusion, we developed and validated a novel imaging technique that unequivocally demonstrates that nestin(+) eNSCs originating from the SVZ respond to stroke injury by increased proliferation, migration towards the infarct region and differentiation into both astrocytes and neurons. In addition, this new approach allows non-invasive and specific monitoring of eNSCs over time, opening perspectives for preclinical evaluation of candidate stroke therapeutics.


Impact factor: 2.964

Abstract: Purpose: Amyloid deposition in the brain is considered an initial event in the progression of Alzheimer’s disease. We hypothesized that the presence of amyloid plaques in the brain of APP/presenilin 1 mice leads to higher diffusion kurtosis measures due to increased microstructural complexity. As such, our purpose was to provide an in vivo proof of principle for detection of amyloidosis by diffusion kurtosis imaging (DKI).

Methods: APPKM670/671NL/presenilin 1 L166P mice (n=5) and wild-type littermates (n=5) underwent DKI at the age of 16 months. Averaged diffusion and diffusion kurtosis parameters were obtained for multiple regions (hippocampus–cortex–thalamus–cerebellum). After DKI, mice were sacrificed for amyloid staining.
Results: Histograms of the frequency distribution of the DKI parameters tended to shift to higher values. After normalization of absolute values to the cerebellum, a nearly plaque-free region, mean, radial, and axial diffusion kurtosis were significantly higher in APP/presenilin 1 mice as compared to wildtype in the cortex and thalamus, regions demonstrating substantial amyloid staining.

Conclusion: The current study, although small-scale, suggests increased DKI metrics, in the absence of alterations in diffusion tensor imaging metrics in the cortex and thalamus of APP/presenilin 1 mice with established amyloidosis. These results warrant further investigations on the potential of DKI as a sensitive marker for Alzheimer’s disease.

Impact factor: 5.217

Abstract: PURPOSE: Imaging of the 18-kDa translocator protein (TSPO) is a potential tool for examining microglial activation and neuroinflammation in early Alzheimer’s disease (AD). [18F]FEMPA is a novel high-affinity second-generation TSPO radioligand that has displayed suitable pharmacokinetic properties in preclinical studies. The aims of this study were to quantify the binding of [18F]FEMPA to TSPO in AD patients and controls and to investigate whether higher [18F]FEMPA binding in AD patients than in controls could be detected in vivo.

METHODS: Ten AD patients (five men, five women; age 66.9 ± 7.3 years; MMSE score 25.5 ± 2.5) and seven controls (three men, four women; age 63.7 ± 7.2 years, MMSE score 29.3 ± 1.0) were studied using [18F]FEMPA at Turku (13 subjects) and at Karolinska Institutet (4 subjects). The in vitro binding affinity for TSPO was assessed using PBR28 in a competition assay with [3H]PK11195 in seven controls and eight AD patients. Cortical and subcortical regions of interest were examined. Quantification was performed using a two-tissue compartment model (2TCM) and Logan graphical analysis (GA). The outcome measure was the total distribution volume (V T). Repeated measures analysis of variance was used to assess the effect of group and TSPO binding status on V T.

RESULTS: Five AD patients and four controls were high-affinity binders (HABs). Three AD patients and three controls were mixed-affinity binders. V T estimated with Logan GA was significantly correlated with V T estimated with the 2TCM in both controls (r = 0.97) and AD patients (r = 0.98) and was selected for the final analysis. Significantly higher V T was found in the medial temporal cortex in AD patients than in controls (p = 0.044) if the TSPO binding status was entered as a covariate. If only HABs were included, significantly higher V T was found in the medial and lateral temporal cortex, posterior cingulate, caudate, putamen, thalamus and cerebellum in AD patients than in controls (p < 0.05).

CONCLUSION: [18F]FEMPA seems to be a suitable radioligand for detecting increased TSPO binding in AD patients if their binding status is taken into account.

Abstract: PURPOSE: The aim of this paper is to present a simple and quantitative data analysis method with a new potential in the application of liver single-photon emission computed tomography (SPECT) imaging. We have established quantitative SPECT/computed tomography (CT) in vivo imaging protocols for determination of liver tumor burden based on the known role of Kupffer cells in cancer of the liver.

PROCEDURES: As it is also known that functional Kupffer cells accumulate particulate material contained in the arterial blood of liver supply, we used radiolabeled macro-aggregated albumin particles ([99mTc]-MAA) injected intravenously to image liver disease. Quantification of cold spot liver lesion imaging was also a general objective.

METHODS: We examined a healthy control group (BALB/C mice, n = 6) and group of induced hepatocellular carcinoma (HCC, matrilin-2 transgenic KO mice, n = 9), where hepatocellular carcinoma was induced by diethylnitrosamine. We used [99mTc]-MAA as radiopharmaceutical for liver SPECT imaging in a small animal SPECT/CT system. A liver radioactivity overview map was generated. Segmentation of the liver was calculated by Otsu thresholding method. Based on the segmentation the radioactivity volume and the summarized liver activity were determined.

RESULTS: Tumor burden of the livers was quantitatively determined by creating parametric data from the resulting volumetric maps. Ex vivo liver mass data were applied for the validation of in vivo measurements. An uptake with cold spots as tumors was observed in all diseased animals in SPECT/CT scans. Isotope-labeled particle uptake (standardized uptake concentration) of control (median 0.33) and HCC (median 0.18) groups was significantly different (p = 0.0015, Mann Whitney U test).

CONCLUSION: A new potential application of [99mTc]-MAA was developed and presents a simple and very effective means to quantitatively characterize liver cold spot lesions resulting from Kupffer cell dysfunctions as a consequence of tumor burden.


Abstract: Neuroglia are represented by several population of cells heterogeneous in structure and function that provide for the homeostasis of the brain and the spinal cord. Neuronal cells are also central for neuroprotection and defence of the central nervous system against exogenous insults. At the early stages of neurodegenerative diseases including Alzheimer’s disease neuroglial cells become asthenic and lose some of their homeostatic, neuroprotective, and defensive capabilities. Astroglial reactivity, for example, correlates with preservation of cognitive function in patients with mild cognitive impairment and prodromal Alzheimer’s disease. Here, we overview the experimental data indicating glial paralysis in neurodegeneration and argue that loss of glial function is fundamental for defining the progression of neurodegenerative diseases.
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Impact factor: 2.408.

Abstract: INTRODUCTION: The translocator protein 18kDa (TSPO), a biochemical marker of neuroinflammation, is highly expressed in the brain activated microglia and it is also expressed by peripheral inflammatory cells and normal peripheral tissues. Thus, development of radioligands for the TSPO may contribute to further understanding the in vivo TSPO function in central and peripheral inflammatory processes and other pathologies. Here, we report the biodistribution, the specific binding and the radiometabolites of [(18)F]DPA-714, a promising fluorinated PET radiotracer, in normal mice using a microPET/CT scanner.

METHODS: The in vivo biodistribution and kinetics of [(18)F]DPA-714 were measured in mice brain and peripheral tissues. Specific binding to TSPO sites was assessed using pharmacological competitive studies by means of saturation experiments performed by i.v. injection of 1mg/kg of unlabeled DPA-714 or 3mg/kg of unlabeled PK11195. A region of interest analysis was performed to generate time-activity curves in the brain, heart, lung, kidney, spleen and liver. Metabolites assay was performed in the plasma and peripheral organs by radio-HPLC.

RESULTS: [(18)F]DPA-714 reached high concentration in lung, heart, kidney and spleen, tissues well known to be rich in TSPO sites. [(18)F]DPA-714 kinetics were faster in the lung and slower in the kidney. Pre-injection of unlabeled DPA-714 or PK11195 inhibited about 80% of [(18)F]DPA-714 uptake in the lung and heart (p<0.0005). The percentage of inhibition in the kidney was lower and achieved at later times only with DPA-714 (p<0.05) but not with PK11195. Sixty minutes after radiotracer injection only unmetabolized radioligand was found in the brain, lung, heart and spleen.

CONCLUSION: These results suggest that [(18)F]DPA-714 is a suitable PET ligand for imaging in mice brain and peripheral tissues since it binds with high specificity TSPO binding sites and it is almost unchanged at 60 minutes after radiotracer injection in the brain and TSPO-rich regions.

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Impact factor: 4.21.

Abstract: Relative to other polycyclic frameworks (1-3), a carborane cage (4 and Cs-5) exerts a significant biological effect as an inhibitor of the purinergic P2X7 receptor (P2X7R) which allows one to target depression in vivo and thus demonstrate, for the first time, that a carborane has the capacity to modify CNS activity.
Impact factor: 5.008

Abstract: Performance of two supervised cluster analysis (SVCA) algorithms for extracting reference tissue curves was evaluated to improve quantification of dynamic (R)-[11C]PK11195 brain positron emission tomography (PET) studies. Reference tissues were extracted from images using both a manually defined cerebellum and SVCA algorithms based on either four (SVCA4) or six (SVCA6) kinetic classes. Data from controls, mild cognitive impairment patients, and patients with Alzheimer’s disease were analyzed using various kinetic models including plasma input, the simplified reference tissue model (RPM) and RPM with vascular correction (RPMV(b)). In all subject groups, SVCA-based reference tissue curves showed lower blood volume fractions (V(b)) and volume of distributions than those based on cerebellum time-activity curve. Probably resulting from the presence of specific signal from the vessel walls that contains in normal condition a significant concentration of the 18 kDa translocation protein. Best contrast between subject groups was seen using SVCA4-based reference tissues as the result of a lower number of kinetic classes and the prior removal of extracerebral tissues. In addition, incorporation of V(b) in RPM improved both parametric images and binding potential contrast between groups. Incorporation of V(b) within RPM, together with SVCA4, appears to be the method of choice for analyzing cerebral (R)-[11C]PK11195 neurodegeneration studies.
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