

Radioisotopic Imaging of Neuroinflammation

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Inflammatory responses are closely associated with many neurologic disorders and influence their outcome. In vivo imaging can document events accompanying neuroinflammation, such as changes in blood flow, vascular permeability, tightness of the blood-to-brain barrier, local metabolic activity, and expression of specific molecular targets. Here, we briefly review current methods for imaging neuroinflammation, with special emphasis on nuclear imaging techniques.

Key Words: neuroinflammation; microglia; blood-brain barrier; cell tracking; positron emission tomography; peripheral benzodiazepine receptor

J Nucl Med 2010; 51:1–4

DOI: 10.2967/jnumed.109.065680

Depicted as “fire in the organs,” the cardinal signs of inflammation—*rubor, tumor, calor, and dolor* (respectively, redness, edema, temperature, and pain)—were described by Celsus 2,000 y ago. Recognizing these signs is straightforward in acute cutaneous inflammation but much trickier in chronic inflammation of deep organs, for example, viral infections or neurodegenerative disorders, for which inflammation can remain unnoticed for years.

Inflammatory reactions of multicellular organisms to aggression toward their tissues delimits and confines the site of injury, prevents the aggressor from further injuring the tissue, and prepares and organizes tissular regeneration. When successful, inflammation leads to suppression of its cause and to functional recovery, with minimal consequences. In contrast, inflammatory reactions that fail to eliminate the cause of aggression may lead to chronic inflammation, starting a vicious circle of further damage to tissues. Hence, noninvasive imaging is increasingly applied for inflammation in the CNS to improve diagnosis and develop and monitor therapies. Many strategies, targets, and probes to image neuroinflammation have been proposed using optics, MRI, CT, SPECT, and PET (1–4). Depending on the modality and the event (activity) addressed, imaging may monitor processes indirectly related to neuroinflammation—for example, MRI enhanced with gadolinium–diethylenetriaminepentaacetic acid (DTPA) or ^{99m}Tc–pertechnetate (^{99m}TcO₄) SPECT—as indices of blood–brain barrier (BBB) disruption. The first line of the inflammatory reaction is a local increase in blood flow and vascular permeability, mediated by the local release of diffusible chemical factors. The second line is the recruitment and activation of circulating white blood

cells or resident immune-competent cells involved in the inflammatory reaction. With increasingly precise demarcation of the target, imaging may address the vascular events associated with the initial inflammation reaction; tag and follow blood cells that migrate to, or proliferate in, inflammatory zones; underscore metabolic events associated with cellular activity; and reveal gene expression specifically induced in the tissues by inflammation (Fig. 1). Here, we give an overview of the contribution of radioisotopic probes and methods to factual and molecular imaging of neuroinflammation.

IMAGING OF VASCULAR CHANGES OF NEUROINFLAMMATION

The CNS is a site of relative immune privilege because the BBB tightly excludes most circulating cells, macromolecules, and hydrophilic solutes and efficiently separates the CNS from the internal milieu. Inflammation disrupts the BBB and increases vascular permeability. Nuclear imaging of BBB disruption can be performed using SPECT agents, such as ^{99m}TcO₄, ^{99m}Tc–DTPA, and ²⁰¹Tl- and ⁶⁷Ga-citrate, or PET agents, such as ⁶⁸Ga-ethylenediaminetetraacetic acid (2). Yet, the imaging of the BBB disruption monitors a downstream event and not the inflammatory process per se. As these classic nuclear imaging techniques are now challenged by MRI using gadolinium–DTPA (1), in the future, radioisotopic imaging may not be the method of choice for routine imaging of the integrity of the BBB. Nevertheless, nuclear medicine has established reference quantitative parameters for measuring blood perfusion of tissues that should be confronted with the results obtained by MRI. The field would also greatly benefit from the development of combined PET/MRI instruments (5).

TAGGING AND FOLLOW-UP OF CIRCULATING CELLS ATTRACTED TO INFLAMMATORY ZONE

When chemo-attracted to inflamed tissues, circulating leukocytes adhere to endothelial cells through cell-adhesion molecules such as vascular cell-adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) and adopt a rolling behavior on the vessel walls, extravasating through endothelial cell junctions into the inflamed tissue (6). Intravital optical imaging has nicely documented these events in animal models and identified key molecular players of the leukocyte infiltration (7). The chemical signal attracting white blood cells to inflammation sites was uncovered recently by elegant optical imaging experiments using a genetically encoded fluorescent sensor. Wounding of zebrafish larvae triggered the production of a hydrogen peroxide gradient responsible for attracting white blood cells as soon as 3 min after wounding (8). Nuclear imaging of radioisotopically labeled leukocytes has been performed clinically for decades. Circulating white blood cells are isolated from a patient, labeled in vitro with ¹¹¹In or ^{99m}Tc, and reinjected into the patient to monitor leukocyte trafficking to sites of inflammation (9). Several studies using SPECT demonstrated a correlation between signal intensity and severity of tissue damage, but

Received Aug. 4, 2009; revision accepted Oct. 7, 2009.

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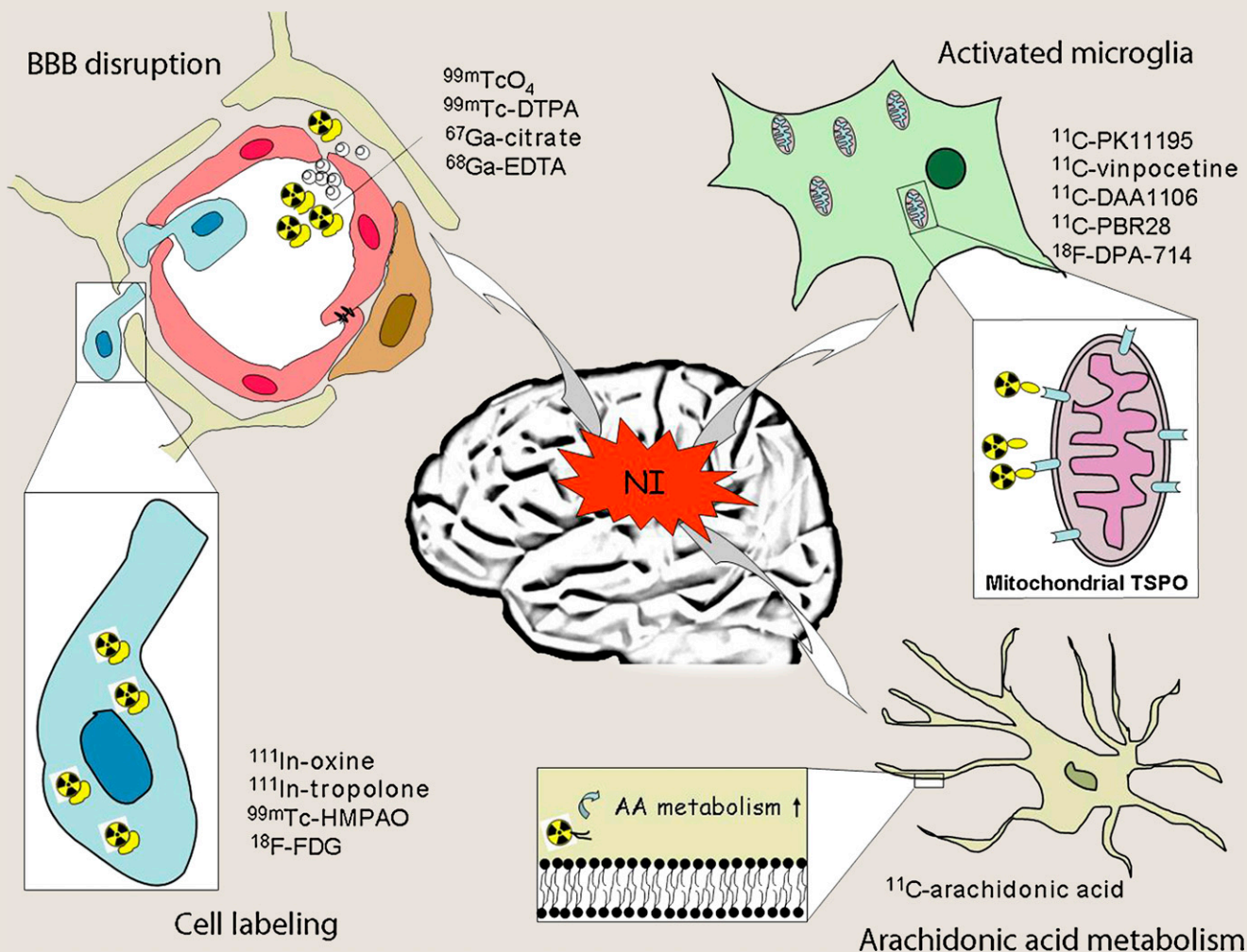


FIGURE 1. Schematic display of radioisotopic imaging targets for neuroinflammation. Counterclockwise starting from upper left and with increasing nearness and relevance to neuroinflammation process: BBB disruption, labeled inflammatory cells, AA metabolism, and mitochondrial PBR/TSPO of activated microglia. EDTA = ethylenediaminetetraacetic acid; HMPAO = hexamethylpropyleneamine oxime; NI = neuroinflammation.

radioisotopic methods are of limited use because of the tedious and operator-dependant extemporaneous labeling, low amount of radioactivity that can be injected when working with ^{111}In , and instability of ^{99m}Tc labeling that complicates the interpretation of imaging results.

Imaging of magnetically labeled cells with MRI techniques recently benefited from the development of polymeric-coated particles containing high loads of iron. When injected intravenously, ultrasmall superparamagnetic iron oxide (USPIO) particles are taken up by white blood cells with phagocytic activity (which are mostly circulating macrophages). Iron-loaded macrophages attracted to inflammatory sites induce changes in T1- and T2-weighted MRI signals that may be detected *in vivo* during several days (1). MRI of USPIOs has the advantage of being nonisotopic, which may facilitate a translational approach. USPIO-MRI performs well in the periphery and could become a method of choice to detect macrophages in atherosclerotic plaques. In the CNS, uptake of USPIO into inflammatory brain lesions has been imaged in animal models of multiple sclerosis (MS) (10), MS patients (11), and ischemic stroke patients (12). MRI with USPIOs is a promising technique for clinical neuroinflammation imaging, although it is not perfectly clear from which cellular (subpopulations of macrophages, other white blood cells, or cerebral tissue cells) or extracellular compartment (USPIOs entering directly

the cerebral parenchyma) the MRI signals originate and whether they require prior disruption of the BBB (1). Vellinga et al. showed that USPIO images differed in their pattern from those obtained with gadolinium-DTPA, suggesting that macrophages can infiltrate the inflamed parenchyma independently of BBB leakage (13). Attempts to image VCAM-1, an endothelial receptor for leukocytes, have been made recently using iron-loaded microparticles conjugated to a VCAM-1 antibody in a mouse model of acute inflammation (14).

IMAGING OF METABOLIC CHANGES ASSOCIATED WITH NEUROINFLAMMATION

A high rate of glucose metabolism is found in active white blood cells, and ^{18}F -FDG PET has been performed in several studies of infection and inflammation (15). Radu et al. applied ^{18}F -FDG PET combined with CT to monitor neuroinflammation in a mouse model of MS (16). Alterations in ^{18}F -FDG uptake colocalized with inflammatory infiltrates in the spinal cord and were sensitive to immunosuppressive therapy with dexamethasone. However, one should keep in mind that ^{18}F -FDG consumption gives an estimate of tissue metabolic disturbance but may not allow the precise quantification of glucose demand in

diseased tissue because of changes in the lumped constant (17). Some investigators have also proposed that metabolic correlates of neuroinflammation be imaged by visualization of the brain arachidonic acid (AA) metabolism or turnover in an animal model of neuroinflammation (18). Preliminary results with ^{11}C -AA in patients diagnosed with Alzheimer's disease (AD), compared with age-matched controls, showed increased regional brain coefficients of incorporation (k^*), suggesting an elevated AA metabolism. Further studies exploring the clinical value of ^{18}F -FDG, ^{11}C -AA, and other metabolic pathways in neuroinflammation are needed.

IMAGING OF IMMUNE-COMPETENT RESIDENT CELL ACTIVATION

Tissue-resident cells with an immune competence (dendritic cells, mastocytes, tissue macrophages, and other cells of the monocytic lineage) are in charge of the surveillance of biologic tissues, an essential sentinel role that ensures a rapid local inflammatory reaction and the precise coordination of its subsequent evolution. Microglia are the CNS-resident macrophages initially identified by Virchow in the 19th century and further characterized by Rio del Horta (19). The phenotypic traits of microglia vary according to their tissular environment. In the healthy adult CNS, microglia appear as small branched monocytic cells, with little apparent activity, and have long been considered quiescent. However, biphotonic imaging of fluorescent microglia in the rodent brain recently showed that microglial branches are continuously sensing their environment, each cell acting like a “cop on the beat” controlling a defined volume of brain parenchyma (3). During inflammation, microglia undergo drastic changes in their morphology, migrate toward the lesion site, proliferate, and produce neurotoxic factors such as proinflammatory cytokines (e.g., tumor necrosis factor- α and interleukin- β) and reactive oxygen species. Recently, evidence arose that microglia may also have antiinflammatory and, thus, neuroprotective activity (20).

These dramatic changes in microglial phenotype are observed in all acute (e.g., trauma, stroke, encephalitis) and chronic (e.g., MS, AD, Parkinson's disease) pathologies. Cerebral ischemia induces strong inflammatory reactions in the brain, leading to activation of microglia and astrocytes and recruitment of leukocytes to the ischemic area. In MS, microglia and blood-borne macrophages are rapidly activated and recruited to sites of demyelination. Reports have convincingly demonstrated a precise spatial overlap between the presence of activated microglia and the characteristic hallmarks of neurodegenerative diseases, such as neuritic plaques in AD or neuronal loss in Parkinson's disease and Huntington's disease (4,21). The close inflammation–neurodegeneration relationship and the rising incidence of these diseases yield considerable interest in the detection and follow-up of neuroinflammation and in the monitoring of antiinflammatory treatments (22). In addition, the generation of neuroinflammatory patterns of individual patients may help in stratifying patients for immunomodulatory therapies (2,23).

MICROGLIA AS MOLECULAR TARGETS TO IMAGE NEUROINFLAMMATION

A major hallmark of microglial activation is the expression of the peripheral benzodiazepine receptor (PBR), also known as the translocator protein TSPO (18 kDa) (21). Gene-expression studies in brains of rodents, primates, and humans have shown that PBR/TSPO expression is nearly absent in microglia patrolling the intact CNS parenchyma but rapidly increases on inflammation. This makes PBR/TSPO a biomarker and an attractive target for the imaging of cerebral inflammation (24). The isoquinoline carboxamide derivative PK11195, a nonbenzodiazepine ligand specifically binding to PBR/TSPO, has been widely used for its

functional characterization and for the identification of its cellular origin in brain tissue. Labeling of PK11195 with ^{11}C allowed PET of neuroinflammation in animal models and patients with various CNS diseases (21,24). PET of PBR/TSPO expression with ^{11}C -PK11195 has been reported in animal models of focal and global cerebral ischemia (23–25) and ischemic stroke patients (26,27). Activated microglia or macrophages expressing PBR/TSPO are located mainly in the core and margin of focal cerebral ischemia in rats (23,25), whereas expression in astrocytes was observed in a rim surrounding the epicenter of the lesion (25). Increased ^{11}C -PK11195 PET binding was observed between 72 h and 150 d after stroke in the core infarction and the periinfarct area in stroke patients (26,27). ^{11}C -PK11195-PET has also been proposed to study PBR/TSPO expression after Wallerian degeneration in areas remote from the primary lesion (26). With few exceptions (28), PBR/TSPO is measured by modeling the binding potential (BP), a parameter that mixes receptor density with ligand affinity. Therefore, changes in BP may reflect both the overexpression of PBR/TSPO and a change in affinity.

MRI techniques are currently the predominant method for diagnosing and monitoring MS (29), and nuclear imaging of PBR/TSPO in MS concerns mainly research on animal models. However, PBR/TSPO expression within the CNS–microglia/macrophages of MS patients has been illustrated by immunohistochemistry in scattered fibrillary astrocytes and phagocytic macrophages throughout demyelinated plaques (30). Accordingly, PET using ^{11}C -PK11195 demonstrated increased uptake in areas of active focal inflammatory lesions over normal white matter, and uptake of ^{11}C -PK11195 in normal-appearing white matter correlated with brain atrophy (31). Another radiotracer for PBR/TSPO, ^{11}C -vinpocetine, was compared with ^{11}C -PK11195 in a small number of MS patients. Interestingly, the regions of maximal uptake of these 2 tracers around the plaques did not overlap, suggesting different binding sites (32).

Histologic hallmarks of AD are the presence of extracellular β -amyloid plaques and the formation of intracellular neurofibrillary tangles. Activated microglia colocalize with β -amyloid deposits and seem to be implicated in the clearance of these deposits. Conversely, it was hypothesized that β -amyloid formation activates microglial cells, leading to plaque-associated inflammatory reactions and secondary tissue damage via the release of neurotoxic factors. Until now, ^{11}C -PK11195 PET studies in patients with AD or mild cognitive impairment have yielded conflicting results. In AD patients, Cagnin et al. (33) showed a significant increase of ^{11}C -PK11195 binding in regions known to display the highest level of neurodegenerative changes. However, recent studies in AD and mild cognitive impairment examining the distribution of ^{11}C -PK11195 and ^{11}C -Pittsburgh compound B, a radiotracer with high affinity for fibrillar amyloid deposits, found no relationship between microglial activation and amyloid- β deposition (34,35). The discrepancies may originate from the lack of a standard modeling method analyzing ^{11}C -PK11195 data and from the numerous limitations of this radiotracer, including a high level of nonspecific binding and poor signal-to-noise ratio (36). In addition, labeling with ^{11}C limits the extensive clinical use of ^{11}C -PK11195.

FUTURE OF PBR/TSPO IMAGING

Accordingly, the last decade witnessed a spectacular increase in new radioligands of PBR/TSPO that challenged the efficacy of ^{11}C -PK11195 (36), and promising results in preclinical studies are now being translated into clinical studies. ^{11}C -DAA1106, a phenoxyarylacетamide, demonstrated a significant increase of its binding in the brains of AD patients, compared with that in controls (28), even though some of the regions with increased binding are not typically associated with AD.

Results are pending from an ongoing National Institutes of Health study exploring another phenoxyarylacetylamide, ¹¹C-PBR28, in frontotemporal dementia (37). The ¹⁸F-labeled pyrazolo[1,5-a]pyrimidin-3-yl acetamide ¹⁸F-DPA-714 recently demonstrated high affinity for PBR/TSPO (38). In vivo comparison in rodent models of acute neuroinflammation showed a decreased nonspecific uptake and an improved bioavailability of ¹⁸F-DPA-714 over ¹¹C-PK11195, leading to a higher binding potential in brain tissue (39). ¹⁸F-DPA-714 is now entering preliminary clinical PET studies for the detection of microglial activation in amyotrophic lateral sclerosis (40) and MS (Bruno Stankoff and Michel Bottlaender, oral communication, February 2009). Comparative performance of these new radioligands relative to ¹¹C-PK11195 in neurologic disorders is under way.

CONCLUSION

Plenty of room exists for the development of new radioisotopic probes and methods to image neuroinflammation more accurately at the biochemical and cellular levels. A growing body of evidence indicates that molecular imaging of neuroinflammation will shortly enter the clinical field.

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