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Positron Emission Tomography of Neuroimmune Responses in Humans: Insights and Intricacies

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The brain's immune system plays a critical role in responding to immune challenges and maintaining homeostasis. However, dysregulated neuroimmune function contributes to neurodegenerative disease and neuropsychiatric conditions. *In vivo* positron emission tomography (PET) imaging of the neuroimmune system has facilitated a greater understanding of its physiology and the pathology of some neuropsychiatric conditions. This review presents an in-depth look at PET findings from human neuroimmune function studies, highlighting their importance in current neuropsychiatric research. Although the majority of human PET studies feature radiotracers targeting the translocator protein 18 kDa (TSPO), this review also considers studies with other neuroimmune targets, including monoamine oxidase B, cyclooxygenase-1 and cyclooxygenase-2, nitric oxide synthase, and the purinergic P2X7 receptor. Promising new targets, such as colony-stimulating factor 1, Sphingosine-1-phosphate receptor 1, and the purinergic P2Y12 receptor, are also discussed. The significance of validating neuroimmune targets and understanding their function and expression is emphasized in this review to better identify and interpret PET results.
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Introduction

Background

The brain's immune system is an important area of current neuropsychiatric research. Neurodegenerative diseases and psychiatric conditions are closely linked with neuroimmune responses in the brain. A neuroimmune response is the adaptive changes in the central nervous system (CNS) to various insults or stimuli, such as infections, toxins, or misfolded proteins.[1] Brain pathologies that are driven by the immune system and show classic inflammatory signs can be defined as neuroinflammation or neuroinflammatory disease, for example, multiple sclerosis. However, activated neuroimmune responses have been lumped together under the umbrella term "neuroinflammation," which is a poorly defined term.[2,3] For precision in language, we refer to tissue swelling or damage to the brain and spinal cord as "neuroinflammation." In contrast, we refer to a change in the neuroimmune system of the brain—which may be in the form of glial cells or other messenger molecules—as a neuroimmune response.

Abbreviations: ALS, amyotrophic lateral sclerosis; AUD, alcohol use disorder; BBB, blood-brain barrier; COX, cyclooxygenases; CSF1R, colony stimulating factor 1 receptor; GABA, γ-aminobutyric acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; MCI, mild cognitive impairment; MDD, major depressive disorder; MAO-B, monoamine oxidase B; NOS, nitric oxide synthase; S1PR1, sphingosine-1-phosphate receptor 1; SUD, substance use disorders; TSPO, 18-kDa translocator protein

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Neuroimmune responses primarily involve the activation or reduction of glial cells in the CNS via the release of secondary messengers and inflammatory mediators such as cytokines, chemokines, reactive oxygen species, and reactive nitrogen species. Activation at a cellular level is referred to as gliosis and involves the proliferation and hypertrophy of microglia, astrocytes, and oligodendrocytes.[4,5] Neuroimmune responses are healthy processes necessary for cell repair and re-establishing homeostasis.[6]

The first-line response to injury or other stimuli is the migration of local microglia to the site, known as microgliosis.[7] Microglia are the resident macrophages of the CNS and have been the focus of the field studying neuroimmune responses. Under typical conditions, microglia persist in a ramified surveillance state and use their motile branches to monitor the local surroundings (Fig. 1, left panel).[8] Microglia are in a state of rest until they detect a stimulus from the neighboring neurons or astrocytes, at which point they become active, transition into an ameboid shape, and begin to clear up and reduce the insult (Fig. 1, right panel).[9] Outside the local milieu, microglia chemotax and secrete cytokines to destroy neural debris and mend neurons. Microglia are extremely sensitive to stimuli, and their activation is typically rapid, with a response time of a few minutes.[10]

Theoretically, microglial phenotypes can be described using the M0/M1/M2 continuum. In this notion, a neuroimmune stimulus may activate homeostatic M0 microglia into an amoeboid-like morphology that can be polarized into M1 and M2 microglia.[11–13] M1 microglia are considered more proinflammatory and produce chemicals like reactive oxygen species (ROS), TNF-α, and prostaglandins to remove stimuli or insults. The M2 microglia attenuate the inflammatory response and protect neurons by releasing growth factors and other neuroprotective substances.[13] Nevertheless, the M0/M1/M2 conception is likely oversimplified and may better be considered as a diverse spectrum.[14] Oversimplification has resulted in microglial functional states being classed as a dichotomy, which should be considered a diverse spectrum. Transcriptomic analysis of microglia in distinct illness and response modes has found many more phenotypes.[15] Further research into the various phenotypes will provide a better understanding of the role of microglia in neurological and psychiatric disorders.

Astrogliosis, the proliferation of surrounding astrocytes, the main constituents of the glial scar, is the final component of gliosis.[16] This is usually a longer process that may take several days to a week.[17] Through astrogliosis and fibrosis, activated astrocytes produce a glial scar, which plays an important role in the recovery of injured tissue, blood-brain barrier (BBB) repair, limiting infection or inflammatory cell spread and neuroprotection against CNS diseases. Like microglia, astrocytes have also been categorized as A1 astrocytes and A2 astrocytes. However, like microglia, this continuum may also be oversimplified.

As seen in the M1/M2 and A1/A2 models, depending on the activation state of glial cells, the neuroimmune response can have both neurotoxic and neuroprotective effects.[18] In general, neuroimmune responses may be beneficial to the CNS by activating the innate immune system to minimize and repair insult-induced damage. However, microglia and astrocytes may be persistently activated with a sustained generation of proinflammatory factors in chronic neuroimmune conditions like neurodegenerative disorders. This leads to vicious cycles of inflammation, cellular dysregulation, injury, and degeneration.

Positron emission tomography (PET) is a befitting noninvasive imaging technique to visualize and quantify in vivo biochemical processes in real-time. A radioactive molecule

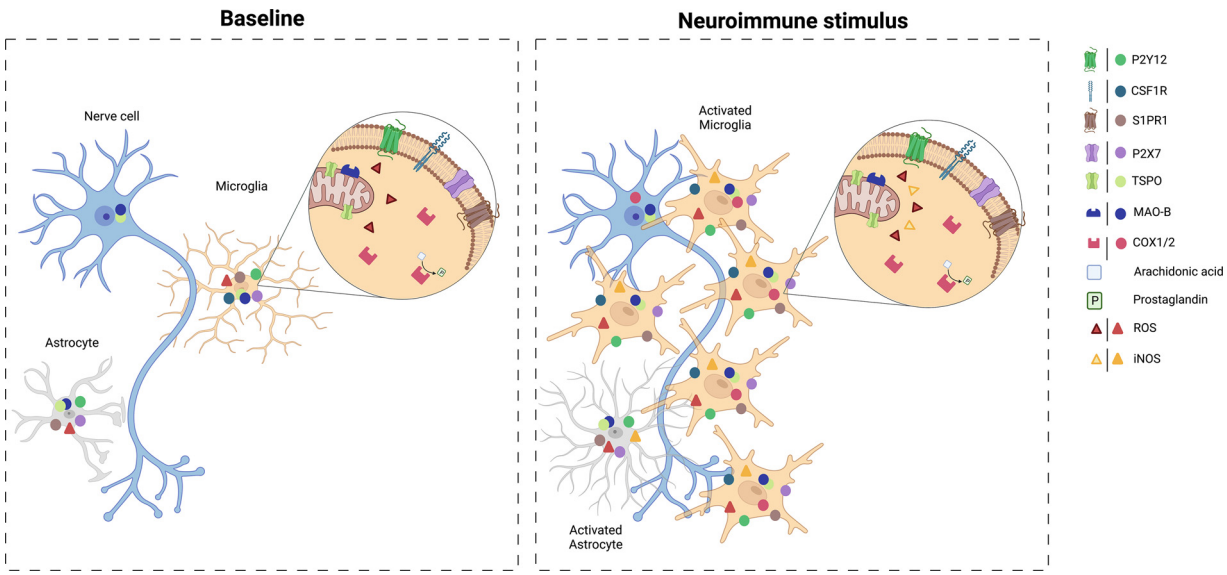

Figure 1 Neuroimmune response to a stimulus in the brain The first-line response of the central nervous system to such a stimulus is in the form of microgliosis, that is, the activation and proliferation of resting microglia. A similar activation is also seen on astrocytes, but the proliferation of astrocytes is a much slower process, which may require a few days, compared to microglia, which requires a few minutes. Created with BioRender.com.

with high affinity and selectivity for a target protein is injected into the bloodstream of a subject during a PET scan to measure brain proteins and receptors. Initial understanding of neuroimmune responses in neurologic and psychiatric disorders has been greatly aided by the use of PET.[19] In vivo studies of protein and receptor targets linked to both proinflammatory and anti-inflammatory processes are fascinating because they help us understand the disease and offer potential drug targets. However, developing novel radioligands for PET imaging of neuroimmune-related targets is difficult. Before a radiotracer can be used in human studies, it must undergo extensive preclinical and clinical testing. This review will focus on the translation, validation, and human application of PET imaging radiotracers for diverse neuroimmune targets.

Ideal Requirements for a Neuroimmune Target and PET Radiotracer

Successful PET imaging studies require both the target and radiotracer—as a pair—to meet key imaging properties such as facile radiolabelling; BBB penetration; suitably fast kinetics; high target affinity and specificity; metabolism; signal-to-noise ratio; variability; and safety. These have been extensively reviewed in the literature.[20–24] Beyond these basic requirements, we discuss additional considerations that may be important in selecting a target and developing specific radiotracers for neuroimmune imaging.

Sensitivity to Neuroimmune Stimuli

Radiotracers that have increased expression after a neuroimmune stimulus are of high interest as radiotracer targets. However, characterization of this property, often with repeated imaging sessions before and after the stimulus, requires careful consideration. Selecting an appropriate immune challenge is nontrivial, as different stimuli can elicit different neuroimmune responses.[25] Moreover, neuroimmune stimuli exhibit dramatic differences across species, often requiring orders of magnitude greater doses in rodents to elicit effects comparable to humans.[26] This places a high value on nonhuman primate evaluation of neuroimmune radiotracers prior to translation to human imaging. Additionally, for some immune targets such as cyclooxygenase-2 and ROS, baseline expression (i.e., B_{max}) can be quite small. This scenario does not exclude such targets for radiotracer development. However, in such instances, characterization of radiotracer kinetics and displacement should occur under conditions of increased expression. The timing of imaging relevant to the stimulus is a further consideration, as different targets exhibit different temporal responses to challenges. For example, microglia-related targets typically exhibit fast, transient responses, while astroglia-related targets tend to exhibit slower, more prolonged effects, although exceptions certainly occur.[27] Thus, characterization of PET radiotracers that assess brain immune dynamics poses additional challenges to the already difficult process of radiotracer development.

Biological Specificity

Ideal target proteins convey relevant biological information. Some targets, such as cyclooxygenases (COX) and purinergic receptors, have identified biological functions that are of high interest. While the cellular expression of these targets is relevant to the extent of functional differences across cell types, the biological interpretation of these targets may not be as heavily reliant on their cellular expression. In contrast, targets such as the 18-kDa translocator protein (TSPO) and monoamine oxidase B (MAO-B) are of interest because immune stimuli increase their expression by microglia and astrocytes, respectively. In these cases, the cellular specificity of target expression is critical, and indeed, a major limitation of TSPO and MAO-B is their expression across diverse cell types.[28,29] Moreover, understanding the mechanism of increased target expression is critical. For example, strong evidence indicates that LPS challenge in rodents increases the number of TSPO-expressing microglia, supporting the interpretation of TSPO radiotracers as markers of the number of TSPO-expressing cells.[25] Thus, cellular specificity is an important consideration for neuroimmune PET radiotracers. Finally, the phenotype or "flavor" of immune cells (i.e., proinflammatory or "M1-like" vs anti-inflammatory or "M2-like") is critical to the mechanistic understanding of neuroimmune dynamics. Consequently, determining the extent to which a radiotracer target may convey such information is an important consideration. The development of novel radiotracers targeting proteins that are highly relevant to one neuroimmune flavor over the other is of exceptionally high priority for future research.

TSPO Imaging

Physiology

TSPO, previously named the peripheral benzodiazepine receptor (PBR), is an evolutionary well-conserved mitochondrial protein involved in a variety of fundamental cellular processes, including steroidogenesis, heme biosynthesis, mitochondrial respiration, cell proliferation and differentiation, cell life/death balance, and oxidative stress.[30] TSPO has 169 amino acids and five transmembrane α-helix domains joined by two extramitochondrial and intramitochondrial loops, an extramitochondrial C-terminal and an intramitochondrial N-terminal[31] Li and colleagues[32] identified the cholesterol recognition amino acid consensus sequence that, together with a groove in TSPO, can bind a cholesterol molecule and is thus involved in cholesterol transport[33]. An A147T mutation in humans, rs6971 polymorphism (Ala^{147} to Thr^{147}), causes a lower-affinity conformational change and leads to decreased TSPO binding.[34]

Apart from its broad expression in peripheral tissues, TSPO is highly expressed in neuroimmune cells and is a proposed biomarker of microglial activation.[35] Indeed, other monocyte-derived cells and elevated levels of TSPO have been interpreted as neuroimmune activity.[36] Altered TSPO expression has been found in some pathological conditions.

Specifically, high TSPO expression levels have been found in cancer, brain injury, and neurodegenerative and neuropsychiatric conditions.

Current Studies With TSPO Radiotracers

More than 50 PET tracers have been developed to measure TSPO levels in neurodegenerative and neuropsychiatric conditions, including Alzheimer's and Parkinson's disease,[37] major depressive disorder (MDD),[38] and substance use disorders (SUD).[39,40] The PET radiotracer [^{11}C]PK11195 was the initial first-generation radiotracer developed in the 1980s.[41] However, subsequent work revealed that [^{11}C]PK11195 exhibited modest specific to nonspecific uptake,[42] spurring the development of second-generation radiotracers with higher specific binding, which include [^{11}C]PBR28, [^{11}C]DPA713, [^{18}F]DPA714, and [^{18}F]FEPPA.[43] However, these improvements in specific binding revealed that the affinity of TSPO radiotracers depends on individual expression of the *rs6971* genotype, with second-generation ligands having substantially higher affinity for the dominant allele compared to the recessive allele. Practically, this means that homozygotes for the minor allele must be prospectively excluded from scans with these radiotracers since they will not exhibit specific binding, and one degree of freedom is lost in statistical analyses to model this effect properly. More recent radiotracer development focused on TSPO-specific radiotracers with high affinity for both *rs6971* alleles has yielded a third-generation radiotracer, [^{11}C]ER176, which exhibits even higher specific binding than second-generation radiotracers, and high affinity for both alleles.[44]

Some methodological items with TSPO radiotracers bear further mention. First, because TSPO is ubiquitously expressed throughout the brain, there is no brain region devoid of TSPO to serve as a gold-standard reference, and use of pseudo-reference regions for outcome measures requires careful validation.[45,46] Second, TSPO is highly expressed in the periphery, and parent radiotracer in plasma can be dramatically affected by immune challenges or blockers.[47] Thus, accounting for these effects is critical in the quantification of TSPO radiotracers.[48,49] Diverse kinetic models have been proposed and implemented for the analysis of TSPO radiotracers,[50] but measurement of the metabolite-corrected input function for full kinetic modeling is generally accepted as the gold standard. These quantification considerations add complexity to evaluating the TSPO literature and likely contribute to some of the mixed findings reported across the field.

Neurodegenerative Disorders

Alzheimer's Disease and Mild Cognitive Impairment

Most PET studies using TSPO radiotracers (primarily [^{11}C]PK11195 and [^{11}C]PBR28) have been performed in Alzheimer's disease, where neuroimmune responses have been proposed to be initially neuroprotective and neurotoxic later in the progression of the disease.[51] The first PET study in Alzheimer's disease utilized [^{11}C]PK11195 and failed to demonstrate group differences in TSPO PET binding between those with a diagnosis of probable Alzheimer's disease compared to individuals who were healthy or with small cerebral glioma.[52] However, most other PET studies reported higher TSPO levels in patients at the clinical Alzheimer's disease stage, primarily in the entorhinal cortex, temporoparietal association cortex, and cingulate cortex.[53–55] TSPO PET radiotracers uptake in these brain areas correlated negatively with glucose metabolism using PET with [^{18}F]FDG.[53–55] TSPO PET uptake correlated with poorer cognitive (episodic memory) performance in Alzheimer's disease,[56,57] with MRI measures of resting state functional connectivity[58] and brain white matter hyperintensities.[59] The evidence for increased TSPO PET binding in mild cognitive impairment (MCI) has been less robust than for Alzheimer's disease, with some studies reporting greater TSPO binding[60] and other studies reporting no group differences when compared to controls.[56] In longitudinal TSPO PET studies in MCI patients, patients with high beta-amyloid fibril load ([^{11}C]PiB PET) demonstrated elevated initial TSPO binding, which significantly declined after 2 years, despite rising beta-amyloid levels.[61] This supported the hypothesis that neuroimmune activation initially may be protective in MCI and Alzheimer's disease.[51] Interestingly, in normal aging, higher TSPO PET binding has been found in cortical regions[62,63] and the thalamus,[64] which demonstrates the importance of controlling for age in these and other studies.

Frontotemporal Dementia

Frontotemporal dementia is a heterogeneous group of diseases, and neuroimmune function plays a central role.[65] PET studies have found elevated TSPO levels in brain areas affected by tau and beta-amyloid protein aggregation.[66,67] These effects are greatest in the temporal lobe in semantic dementia,[68] the premotor cortex in nonfluent primary progressive aphasia, and the frontal and temporal poles in behavioral variant frontotemporal dementia.[37,69]

Multiple Sclerosis

Multiple sclerosis is a chronic autoimmune disease of the CNS that leads to demyelination and neurodegeneration. As such, numerous TSPO PET studies have been conducted in patients with multiple sclerosis. In general, [^{11}C]PK11195 and [^{11}C]PBR28 studies have demonstrated diffuse areas of higher TSPO uptake involving normal-appearing white matter and possible gray matter, suggesting that TSPO PET unmasks active lesions not revealed by MRI.[70–72] Several studies have also identified more pronounced diffuse TSPO levels in normal-appearing white matter and normal-appearing gray matter in patients with progressive multiple sclerosis than in those with relapsing-remitting multiple sclerosis.[73]

Amyotrophic Lateral Sclerosis

Increased [^{11}C]PBR28 and [^{18}F]DPA714 uptake has been found in patients with amyotrophic lateral sclerosis (ALS) in the precentral and paracentral gyri/primary motor cortices,[74,75] which are affected in ALS. Moreover, a small study in 3 ALS patients and 6 healthy volunteers

demonstrated elevated binding with [^{18}F]DPA714 in the motor cortices but no signal with the purine receptor radiotracers [^{11}C]JNJ54173717.[76]

Parkinson's Disease

TSPO PET studies in Parkinson's disease have not been conclusive. Some studies show elevated TSPO PET binding in Parkinson's disease compared to controls in temporal, parietal, and occipital regions[77] and in the midbrain and frontal cortex.[78] However, other studies failed to demonstrate group differences in TSPO PET in this patient population[79,80] despite reduced dopamine transporter binding in the same study.[80]

Other Neurodegenerative Disorders

TSPO PET studies have been performed in other neurodegenerative disorders, including dementia with Lewy-Bodies, which have shown higher TSPO levels with [^{11}C]PK11195,[81,82] and Huntington's disease, for which symptomatic patients show elevated TSPO PET binding compared to controls.[83,84] A recent study was also able to differentially diagnose multiple system atrophy patients from Parkinson's disease patients, showing increased TSPO PET binding in the lentiform nucleus and cerebellar white matter.[79] Further, a recent pilot study indicated elevated [^{11}C]PBR28 binding in chronic stroke patients compared to controls in several brain regions outside the infarct zone, including regions with direct neuroanatomical connections to the infarct.[85]

Human Immunodeficiency Virus Infection

HIV-associated cognitive impairment in HIV-infected individuals has been studied using TSPO PET using [11C]PK11195, [11C]DPA-713, and [11C]PBR28 (Reviewed in[86]). In general, the results of comparing TSPO radiotracer uptake in people with HIV vs those in the control group have been inconsistent, possibly due to methodological differences. Most studies have observed no significant differences in TSPO PET uptake in people living with HIV compared to control participants.[87–91] Compared to control participants, one study showed a higher TSPO PET signal in the frontal cortex of cognitively impaired people with HIV,[90] while another showed higher levels in the globus pallidus, parietal cortex, and occipital cortex in cognitively unimpaired people with HIV.[92]

Neuropsychiatric Disorders

TSPO PET imaging studies were first performed in neurological disorders and later evaluated in psychiatric disorders. Although the pathological mechanisms or correlates of neuroimmune function in neurological disorders have often been identified, the pathophysiology in psychiatric disorders tends to be more heterogeneous and often has overlapping variance with healthy controls. Nevertheless, PET imaging of TSPO in neuropsychiatry has made significant advances in understanding the role of inflammation in several disorders, such as MDD, schizophrenia, psychosis, and SUD.[38]

Major Depressive Disorder

A total of nine PET studies have investigated TSPO levels in patients with MDD during a major depressive episode, of which the majority reported higher TSPO binding, primarily in the anterior cingulate cortex and prefrontal cortex[93–98] (Reviewed in[38,99,100]). The first published study in MDD, however, did not find group differences in [^{11}C]PBR28 binding between those with MDD compared to controls, and in fact, 7 out of 10 individuals with MDD showed lower [^{11}C]PBR28 binding in all brain regions of interest compared to genotype-matched controls.[101] One study performed a longitudinal study in MDD patients only and found that high baseline TSPO PET binding was associated with a significant reduction in depression severity after 8 weeks of celecoxib, an anti-inflammatory drug. Other findings related to clinical characteristics involved greater TSPO PET binding in those with a longer duration of untreated illness,[97] and TSPO PET binding was lower in patients receiving antidepressant treatment than in unmedicated patients.[96] Overall, these PET findings support the hypothesis of elevated TSPO in MDD, including associations with clinical characteristics in MDD patients.

Schizophrenia

Schizophrenia and psychosis have been studied frequently with TSPO PET. Although one [^{11}C]PBR28 study found lower TSPO binding in drug-naive patients with first-episode psychosis than in controls,[102] other PET studies utilizing second-generation TSPO ligands found elevated [^{11}C]PBR28 binding in individuals with schizophrenia and individuals at high risk for psychosis than in healthy controls,[103] or no group differences between patients with schizophrenia compared to controls.[104–107] A 2019 meta-analysis on summary statistics of 12 studies comprising 190 patients with schizophrenia and 200 healthy controls scanned with TSPO PET (both first and second generation tracers) concluded that TSPO radiotracers binding in schizophrenia patients was significantly higher than in controls when *BP* was used as an outcome measure (Hedge's $g = 0.31$), but there were no significant group differences when volume of distribution (V_T) was used (Hedge's $g = -0.22$).[108] Notably, a more recent meta-analysis that used individual participant data of 208 individuals (99 patients and 109 healthy control subjects) who were scanned with second-generation TSPO tracers only provided strong support for lower TSPO V_T in patients than in controls.[109] The discrepancy in the meta-analysis may be due to (1) the comparison of group statistics[108] vs individual data,[109] for which the latter may lead to a more accurate estimate of effect sizes, and (2) [^{11}C]PK11195 studies have low signal-to-noise ratio, which may have affected meta-analysis results by.[108] Plavén-Sigray et al[109] further indicated no effects of antipsychotic medication on TSPO PET and no associations between TSPO PET and disease duration or symptom levels.

Obsessive-Compulsive Disorder

One study has been performed in individuals with obsessive-compulsive disorder, which found elevated TSPO PET

binding ([^{11}C]PK11195) in patients with obsessive-compulsive disorder compared to controls, primarily in the cortico-striatal-thalamic circuit involving the orbitofrontal cortex.[110]

Substance Use Disorders

SUD are patterns of symptoms that arise from the use of substances that an individual continues to use despite experiencing negative consequences. SUDs are characterized by mental, physical, and behavioral symptoms related to substance use, including loss of control, craving, tolerance, and withdrawal. Over time and with repeated use, substance use induces changes in the CNS that contribute to continued use and relapse. A growing literature indicates that substance use can, directly and indirectly, modulate neuroimmune activity and alter neuroimmune responses.[39,111,112] The impact of substance use on the immune system and inflammatory responses may play a role in the development of compulsive-like behaviors underlying SUD[113,114] and has been the focus of several TSPO imaging studies.

Alcohol Use Disorder

The most studied SUD using TSPO PET imaging is alcohol. Three clinical PET studies in alcohol use disorder (AUD) consistently found lower [^{11}C]PBR28 binding in patients with AUD during early abstinence compared to non-dependent controls.[115–117] Hillmer et al and Kalk et al suggested that long-term alcohol abuse may lead to diminished proinflammatory function.[115,116] Indeed, Hillmer et al[115] observed a lower peripheral proinflammatory cytokine response to lipopolysaccharide stimulation in patients with AUD compared to healthy volunteers, suggesting that AUD is associated with diminished immune function in both the CNS and the periphery. Kim et al[117] only observed lower [^{11}C]PBR28 binding in mixed affinity binders, and explored whether this reflected competition of plasma cholesterol rather than downregulation of neuroimmune activity. In healthy cells, cholesterol binds to TSPO for transport during steroid synthesis, modifying the protein's structure.[118] Plasma cholesterol levels in both AUD and healthy control groups were inversely correlated with [^{11}C]PBR28 binding in the brain,[117] supporting a role of cholesterol competition in the downregulation of [^{11}C]PBR28 binding observed in people with AUD. Moreover, the rs6971 polymorphism was associated with alcohol withdrawal severity and with plasma cholesterol levels in people with AUD.[119] The timing of PET scanning after recent alcohol use seems particularly important since *in vivo* and *in vitro* preclinical studies have indicated increased TSPO radioligand binding ([^{11}C]DAA1106, [^{3}H]PK11195, and [^{18}F[DPA714) after acute or repeated binge drinking alcohol administration.[120–123] However, the extent to which these responses may adapt over timescales relevant to chronic alcohol use in people remains to be established. More work is needed to identify conclusively the mechanistic implications of lower TSPO in AUD.

Opioid Use Disorder

Opioids act on opioid receptors in the CNS, gastrointestinal tract, and immune cells. Opioids contribute to immune cells' function and innate and acquired immune responses. Previous research indicates that opioids have immunosuppressive and immunostimulatory effects.[124–126] To date, only two preclinical TSPO PET studies have examined neuroinflammatory changes following opioid exposure: one in baboons and one in rats. In baboons, acute morphine exposure increases [^{18}F]DPA-714 brain distribution.[127] In rats, morphine tolerance and withdrawal did not induce changes in [^{18}F]DPA-714 distribution or kinetics.[128] Together, these findings suggest that acute opioid exposure is proinflammatory and chronic exposure is immunosuppressive.

Cocaine Use Disorder

Clinical and preclinical studies indicate that cocaine increases proinflammatory and decreases anti-inflammatory cytokines.[129,130] TSPO PET studies in individuals who use cocaine suggest that cocaine does not alter TSPO expression. Only one PET study has examined TSPO binding in individuals with cocaine use disorder using [^{11}C]PBR28 and found individuals with cocaine use disorder who were abstinent for at least 14 days did not show changes in TSPO binding.[131]

Cannabis Use Disorder

Cannabinoids activate cannabinoid CB_1 and CB_2 receptors. CB_1 receptors are primarily expressed on neurons on axons and synaptic terminals, whereas CB_2 receptors are expressed on microglial and dendritic cells and are thought to play a role in microglial cell function in regulating immune-related functions.[132] To date, only one in vivo PET study, using [^{18}F]FEPPA, examined TSPO levels in people who use cannabis and healthy controls. The findings indicated that cannabis users showed higher TSPO levels than non-using controls, and TSPO levels correlated with C-reactive protein levels and subjective measures of stress and anxiety.[133]

Tobacco/Nicotine Use

Nicotine has proinflammatory and anti-inflammatory effects,[134,135] and compounds in cigarette smoke other than nicotine may affect inflammatory processes. Two PET studies using [^{11}C]DAA1106 indicate that people who do not smoke show lower TSPO levels than people who smoke, both during satiety and after overnight abstinence.[136,137] However, findings from a recent TSPO PET study using gold-standard quantification with [^{11}C]PBR28 (which has greater specific binding than [^{11}C]DAA1206) demonstrated comparable TSPO levels in the brains of people who do not smoke and those who do after at least two hours of abstinence.[138] Thus, smoking tobacco cigarettes is likely not associated with altered TSPO levels, although the extent to which this may be true for concurrent substance use remains to be examined.

Monoamine Oxidase-B Imaging

Physiology

Monoamine oxidase is a flavoenzyme that resides in the outer mitochondrial membrane.[139] It catalyzes the oxidative deamination of structurally diverse neurotransmitter (and other) amines.[140,141] There are two different isoforms: MAO-A and MAO-B. Both isoforms break down catecholamines, including tryptamine, tyramine, dopamine, epinephrine, and norepinephrine.[142] MAO-A is responsible for the breakdown of serotonin, whereas MAO-B is responsible for the breakdown of benzylamines and phenylethylamine.[142] Therapeutically, MAO-B inhibitors are used for the treatment of parkinsonism since they are hypothesized to inhibit the breakdown of dopamine and increase striatal dopamine.[139,143] However, some new evidence contradicts the dopamine involvement of MAO-B inhibitors while suggesting glial γ-Aminobutyric acid (GABA) synthesis.[144]

MAO-B is relevant to studying neuroimmune status because expression is increased in reactive astrocytes. Indeed, elevated MAO-B is associated with increased expression of the astrogliosis marker glial fibrillary acidic protein (commonly known as GFAP) in neuroinflammatory conditions like Alzheimer's disease, Parkinson's disease, pulmonary supranuclear palsy, multiple system atrophy, and ALS.[145–147] In the brain, MAO-B is found primarily in astrocytes and serotonergic neurons in the midbrain, although there is some expression in dopamine-containing cells in the substantia nigra.[29,148] The high level of MAO-B expression in the CNS and its role in monoamine metabolism and astrogliosis make it a target of interest for studying neuroimmune status.

MAO-B radiotracers have been thoroughly reviewed.[29] [^{11}C]deprenyl was the first PET MAO-B imaging agent to be used in the living human brain.[149] [^{11}C]L-deprenyl-D2 was also used for occupancy studies with potential therapeutic agents, which lies outside the scope of this review (see[29]). However, deprenyl and its derivatives suffer from a lack of reversibility, and there is evidence of radiometabolites that enter the BBB.[141] To improve on this, [^{11}C]SL25.1188, an oxazolidinone derivative, was developed as a reversible MAO-B radioligand with improved selectivity.[150] More recently, [^{18}F]SMBT-1 was developed from the neurofibrillary tangle radiotracer [^{18}F]THK-5351 as a lead molecule due to its high off-target affinity for MAO-B, with reasonable selectivity for MAO-B over MAO-A and tau proteins,[151,152] although off-target binding for the dopamine transporter may pose future challenges.

Human imaging generally supports higher MAO-B availability in Alzheimer's disease, based on studies using [^{11}C]L-deprenyl-D2 in prodromal Alzheimer's disease,[153] and [^{18}F]SMBT-1 in a larger cohort of subjects across various stages of Azhiemer's disease.[152] Higher MAO-B expression has also been reported with [^{11}C]L-deprenyl-D2 in patients with ALS,[154] and temporal lobe epilepsy.[155,156] Studies with [^{11}C]SL25.1188 indicated higher MAO-B expression in patients with MDD in the prefrontal cortex, where longer disease duration corresponded to higher [^{11}C]SL25.1188 V_T.[157] Studies with higher MAO-B binding have been attributed to astrocytosis and have been hypothesized to increase the synthesis of neurotoxic substances as well as increase the metabolism of non-serotonergic monoamines.[29,141] On the other hand, lower MAO-B binding using [^{11}C]L-deprenyl-D2 has been shown in cigarette smokers,[158,159] which is hypothesized to result from the occupancy of substances in cigarette smoke on MAO-B sites. Nevertheless, overnight self-reported abstinence from cigarettes shows that the lower MAO-B binding persisted.[160] Lower MAO-B expression was also reported with [^{11}C]SL25.1188 in subjects with post-traumatic stress disorder with comorbid MDD compared to healthy control and post-traumatic stress disorder only groups in a relatively small cohort.[161] More research is needed regarding the role of astrocytes in PTSD.[162]

Challenges

Although important findings have been reported with the MAO-B radiotracers, the target comes with some caveats. MAO-B expression is also not selective to astrocytes; it is also present in serotonergic and dopaminergic neurons.[148,163] The expression of MAO-B in microglia is poorly understood and requires more work. Additionally, MAO-B radiotracers can detect increases and decreases in MAO-B concentrations in the brain, but they cannot distinguish between changes in the state and/or transition of reactive astrocytes, and not all reactive astrocytes overexpress MAO-B.[29] While MAO-B radiotracers are only surrogate markers for reactive astrogliosis, they nonetheless provide the best currently available (albeit limited) tool for *in vivo* assessment of reactive astrocytes.

MAO-B is also ubiquitously expressed throughout the brain at relatively high levels, ranging between 1 and 5 ng/g protein.[148] As a result, no true reference region exists for the use of reference tissue methods with MAO-B PET imaging agents. Nevertheless, reference regions to calculate the ratio have been used for the MAO-B radiotracer: previously with [^{11}C]L-deprenyl-D2[156] and more recently with [^{18}F]SMBT-1.[152,164] While the cerebellum is commonly used as a reference region for studies in Alzheimer's disease populations because it is relatively spared, the use of reference regions with MAO-B radiotracers requires careful validation for use in larger studies. Thus, careful study design and interpretation of the results are critical for MAO-B PET studies to provide valuable insight into astrocyte function in human neuropathology.

Cyclooxygenases-1 and Cyclooxygenases-2 Imaging

Physiology

COX-1 and COX-2 are rate-limiting enzymes that convert arachidonic acid to prostaglandin H_2, which is cardinal to the activation of immune signaling processes.[165] These prostaglandins are then converted to bioactive prostanoids that

can ultimately produce chemokines, cytokines, and ROS.[166,167] COX-mediated prostaglandin release contributes to neuroinflammation and neurodegenerative diseases.[168] COX inhibitors like aspirin and ibuprofen have been widely used to relieve inflammation and pain symptoms.[169]

COX-1 is considered constitutively expressed in nearly all tissues, where it maintains physiological processes. In the brain, COX-1 is primarily found in microglia with some expression in neurons and no reported protein expression in astrocytes.[170] However, mRNA expression of COX-1 is shown to be 15-fold higher in astrocytes than in neurons.[171] Moreover, COX-1 is also involved in microglial activation, where pharmacological inhibition or genetic deletion decreases oxidative stress and neuronal damage.[165]

In contrast to COX-1, COX-2 is minimally expressed in most tissues under normal conditions but is rapidly induced by diverse proinflammatory stimuli, hormones, and growth factors.[172] The dynamic increase over a few hours, followed by a similarly rapid decrease, suggests that COX-2 may provide temporal specificity for inflammatory processes.[169] COX-2 is considered a proinflammatory enzyme and a chief target for the treatment of inflammatory diseases. However, COX-2 may further aid resolution in the later inflammatory phase by generating an alternative set of anti-inflammatory prostaglandins.[173] Expression of COX-2 is found mainly in neurons but also in microglia and astrocytes. COX-2 plays a central role in synaptic activity and long-term synaptic plasticity.[174] Multiple studies have demonstrated that overexpression of COX-2 causes neurological disorders.[165,169]

Current Studies

Two COX-1 radiotracers have been used and evaluated in humans: [^{11}C]KTP-Me and [^{11}C]PS13. [^{11}C]KTP-Me (ketoprofen methyl ester) displayed poor affinity and a lack of specificity, which made quantification challenging and likely limited the ability to detect a difference in a pilot cohort of patients with Alzheimer's disease compared to healthy subjects.[175] More recently, the novel high-affinity COX-1 radioligand [^{11}C]PS13 was evaluated in healthy volunteers.[176] [^{11}C]PS13 exhibits promising radiotracer properties and is of high interest for future work examining COX-1 in clinical populations.

COX-2 PET imaging has been even more challenging (Reviewed in[177]). Most potential radiotracers have only been studied in models of inflammation in rodents and nonhuman primates without being able to be applied in humans (Reviewed in[169]). [^{11}C]MC1, a high-affinity COX-2 radioligand with promising nonhuman primate results, is the only known radioligand that has been evaluated in healthy humans.[169,178]

Finally, radiolabeled arachidonic acid (1-[^{11}C]AA), the substrate for both COX isoforms, has been evaluated in healthy volunteers.[179] However, metabolism of this radiotracer results in [^{11}C]CO_2, which readily enters the brain, requiring additional plasma measurements and modeling for corrections. Nonetheless, a study in Alzheimer's disease patients found higher arachidonic acid metabolism throughout the brain, which the authors interpreted as evidence of neuroinflammation.[180] Another study used 1-[^{11}C]AA to measure dopaminergic neurotransmission in healthy humans by administering D1/D2 agonist apomorphine, which increased and decreased arachidonic acid metabolism in several brain regions.[181]

Challenges

Radiotracers for COX-1 and COX-2 theoretically show great potential as radiotracer targets for imaging neuroimmune function. Radioligand development for these targets has been extremely challenging; however, recent reports of [^{11}C]PS13 and [^{11}C]MC1 show much promise. One existing challenge is understanding the cellular localization of these respective targets, as the current literature is mixed in this regard. Nonetheless, their importance as drug targets (i.e., nonsteroidal anti-inflammatory drugs) makes such studies of high importance. Additionally, COX-2 is one example of brain immune targets with negligible specific binding under baseline conditions, which can add complexity to tracer characterization and potentially quantification but may provide high sensitivity for elevated COX-2 levels in the brain.

Purinergic P2X7 Imaging

Physiology

Adenosine triphosphate (ATP) is a neurotransmitter and energy-transmitting coenzyme in eukaryotic cells.[182] ATP is a crucial mediator of neuron−glia and glia−glia communication and targets purinergic receptors expressed on glial cells and postsynaptic neurons.[183–185] Of these purinergic receptors, the P2X7 receptor (previously known as P2Z) is an ATP-activated trimeric ligand-gated cation channel found in a variety of peripheral cell types, including hematopoietic cells (macrophages/monocytes and lymphocytes), dendritic cells, and many others.[186] In the CNS, P2X7 expression is found on microglia, oligodendrocytes, and Schwann cells.[187] P2X7 may also be expressed on astrocytes and neurons, though the definitive demonstration is complicated due to the large number of P2X7 splice variants and polymorphisms.[188,189]

P2X7R is considered inactive in normal physiology because high (mM) concentrations of ATP are required for activation and functional upregulation (Bhattacharya and Biber, 2016),[190]. P2X7R is strongly linked to neuroinflammation because its activation is associated with multiple signaling pathways, including the release of proinflammatory cytokines and ROS.[190,191] Thus, antagonistic actions on P2X7R are of high interest as neuro-immunomodulatory treatments activating brain-derived neurotrophic factor while promoting anti-inflammatory and neuroprotective conditions.[192,193] PET imaging probes that target P2X7 receptors could therefore aid in the development of P2X7 drugs.[194]

Current Studies With P2X7 Radiotracers

Although multiple radiotracers for the P2X7 target are available, they have not been widely utilized in clinical studies.[195,196] The first P2X7 radiotracer to be evaluated in humans was [^{11}C]GSK1482160, which exhibited poor brain uptake and was only suitable for imaging other potential organs.[197] [^{11}C]JNJ-54173717 demonstrated excellent preclinical efficacy and readily crossed the BBB in humans.[198] The radiotracers was found to quantify P2X7 levels effectively in the human brain. However, no significant differences in [^{11}C]JNJ-54173717 brain uptake were reported comparing Parkinson's disease patients[198] and patients with ALS[76] compared with control. [^{18}F]JNJ64413739 also demonstrated good pharmacokinetics in healthy subjects but high variance, hypothesized due to a genotype effect.[199] [^{11}C]SMW139 exhibited good pharmacokinetics and quantifiable uptake, with significantly higher V_T estimates in multiple sclerosis patients compared to healthy controls in all brain regions studied.[200] Nevertheless, radiotracers specific for P2X7 either exhibit limited brain uptake or have shown modest success in detecting group differences in neuroimmune-related conditions.

Challenges

P2X7 radiotracers were initially developed to aid P2X7 drug development. However, the dynamic range of this target in conditions with altered neuroimmune state is not well known and is likely limited due to the high concentrations of drug or endogenous agonist required for activation. Thus, these radiotracers may provide better tools to examine target engagement and drug response rather than biological state. In addition, the possible effect of genetic polymorphisms on receptor expression levels or radiotracer binding characteristics is currently unclear. However, a number of human genetic investigations have hypothesized the highly polymorphic P2X7 gene for mood disorders, and several mutations have been related to the modification of P2X7 channel activity in vitro.[186,199,201] Therefore, it is necessary to study whether P2X7R polymorphisms may also contribute to the variability of baseline P2X7 expression. Another disadvantage, similar to other neuroimmune targets, is a lack of a suitable brain reference region, which would allow the noninvasive assessment of P2X7 abundance in different brain regions.

iNOS and ROS Imaging

Physiology

The high metabolic demands of the brain result in strict regulation of oxygen.[202] Inflammatory processes bound to changes in oxygen regulation that occur in response to brain injury also represent excellent targets for neuroinflammation molecular probes. The electron transport chain supporting ATP synthesis constantly produces ROS and reactive nitrogen species (ROS/RNS).[203] Under normal conditions, ROS/RNS do not accumulate; however, a buildup of oxygen free radicals has been implicated in many types of brain injuries, including strokes, trauma, and neurodegenerative disease.[204,205] This mechanism of pathogenesis has also been hypothesized in addiction.[206] Specifically, ROS localizes to mitochondria (represented as red triangles in Fig. 1). Several probes targeting ROS have been developed,[207–210] and these probes have shown promise in robust preclinical models of cardiotoxicity via anthracycline chemotherapy injury.[208,209,211] However, few have shown promise in the brain, and no translational studies in human subjects have yet been published.[210,212]

There is strong evidence linking ROS regulation with the inducible isoform of nitric oxide synthase (iNOS).[213,214] Nitric oxide synthase (NOS) has three principal isoforms: eNOS (endothelial), nNOS (neuronal), and iNOS (inducible).[205,215,216] iNOS is expressed in the cytosol of activated neurons, astrocytes, and microglia (noted as yellow triangles in Fig. 1).[215] CNS expression of iNOS is tightly regulated and not normally present. iNOS expression is considered specific to inflammation, albeit occurring in both acute and chronic settings.

Current Studies With iNOS Radiotracers

To this point, two translational studies have used the iNOS targeting PET radiotracer [^{18}F]NOS. In patients who had undergone heart transplant, [^{18}F]NOS PET cardiac imaging revealed that radiotracers binding correlated with iNOS immunohistochemistry of tissue obtained via endomyocardial biopsy and predicted organ rejection.[217] In healthy volunteers, Huang et al unilaterally induced a limited region of endotoxic pulmonary injury and showed that [^{18}F]NOS PET lung imaging correlated with NOS immunohistochemistry of tissue acquired via bronchoscopy.[218]

Challenges

In order to extend the use of [^{18}F]NOS PET to imaging neuroinflammation and neuroimmune responses, several important challenges need to be recognized. First, [^{18}F]NOS has relatively rapid kinetics (i.e., it quickly binds and then unbinds from the target).[217,218] Consequently, PET studies using [^{18}F]NOS require precise coordination and execution, including careful analysis of radiotracers metabolism to best inform kinetic modeling. While it selectively binds to iNOS relative to nNOS and eNOS, the role of these other NOS isoforms needs to be considered in states of elevated neuroinflammation. However, with such attention to detail, the application of [^{18}F]NOS to neuroinflammation remains promising.

Other Upcoming Targets

Colony Stimulating Factor 1 Imaging

Colony stimulating factor 1 receptor (CSF1R) is a cell surface tyrosine kinase receptor that regulates the activation and

survival of macrophages and macrophage-like cells.[219] CSF1R is activated by the cytokines CSF1 and interleukin-34[220] to control the production, differentiation, and function of macrophages.[221] In the healthy brain, CSF1R is expressed solely in microglia, making it an attractive target as a microglia-specific PET biomarker.[222]

CSF1 radiotracer development has been ongoing since it was discovered to be expressed exclusively on microglia in the brain. Notable radiotracers with promising preclinical data include [^{11}C]CPPC,[223] [^{11}C]GW2580,[224] [^{11}C]NCGG401.[225] Very recently, [^{11}C]CPPC was evaluated in a small cohort of healthy humans.[226] [^{11}C]CPPC's kinetics and brain uptake were suitable, however[^{11}C]CPPC has limited sensitivity to low-density CSF1R regions in the healthy animal brain[227] and can only detect them after a challenge with lipopolysaccharide.[223] Nonetheless, CSF1 is a highly promising microglia-specific target for neuroimmune imaging.

Sphingosine-1-Phosphate Receptor 1 Imaging

Sphingosine-1-phosphate receptor 1 (S1PR1) is a G-protein coupled receptor activated by S1P, a sphingolipid that

Table 1 A Summary of the Human Radiotracers Evaluated for PET Imaging of Neuroimmune Responses That Target Proteins and Their Physiological Function

Target Protein	Radiotracer(s) Evaluated in Humans	Expression in Cells	Physiological Function	Reviews
Translocator protein 18 kDa (TSPO)	[^{11}C]PK-11195 [^{11}C]PBR-28 [^{18}F]FEPPA [^{11}C]DPA-713 [^{18}F]DPA-714 [^{11}C]ER1766	Microglia > Astrocytes > Neurons >> Endothelial cells	Receptor participates in mitochondrial physiological processes like metabolism and cellular bioenergetics, mitochondrial respiration, cholesterol transport and steroidogenesis, immunomodulation, porphyrin transport, and heme biosynthesis.	14,99,245–247
Nitric oxide synthase: inducible (iNOS)	[^{18}F]NOS	Microglia > Astrocytes > Neurons >>	Located in the cytosol. Expression specific inflammation	*
Monoamine Oxidase-B (MAO-B)	[^{11}C]L-deprenyl [^{11}C]L-deprenyl-D2 [^{11}C]SL25.1188 [^{18}F]SMBT-1	Astrocyte >> Serotonin neurons and Dopamine neurons	Oxidative deamination of structurally diverse neurotransmitter amines	29,141,248
Cyclooxygenase-1 (COX-1)	[^{11}C]KTP-Me [^{11}C]PS13	Microglia > Neurons > Astrocytes	Rate-limiting enzyme that controls the arachidonic acid metabolism pathway during "housekeeping"/ normal conditions	165
Cyclooxygenase-2 (COX-2)	[^{11}C]MC1	All neurons	Rate-limiting enzyme that controls the arachidonic acid metabolism pathway during proinflammatory function	165
Purinergic P2 × 7 receptors (P2X7)	[^{18}F]JNJ-64413739 [^{18}F]JNJ-54173717 [^{11}C]SMW-139	Microglia >> Astrocytes	Receptor activity mediates cell proliferation and death, as well as the formation of reactive oxygen and nitrogen species	196,195
Colony-stimulating factor 1 receptor (CSF1)	[^{11}C]CPPC	Microglia	Receptor for colony stimulating factor 1, which controls macrophage production, differentiation, and function	233,*
Sphingosine-1-phosphate receptor 1 (S1PR1)	[^{11}C]CS1P1	Astrocytes>> Microglia> Neurons> Endothelial cells	Receptor regulates microglial activation in brain injury	233,*
Purinergic P2Y12 receptors (P2Y12)	None	Microglia	Receptors mediate patrolling microglia and coordinate neuronal activity with microglia operation	242

*Reviews specific to the topic are currently unavailable.

promotes cellular survival and potently regulates immune responses in the brain.[228] Activation of S1PR1 induces an anti-inflammatory phenotype in the brain's immune system[229] while inhibiting S1PR1 attenuates proinflammatory chemokine release.[230] Interestingly, proinflammatory conditions functionally upregulate S1PR1,[230,231] likely as a compensatory mechanism. As a result, S1PR1 provides a valuable biomarker for assessing proinflammatory and anti-inflammatory neuroimmune responses.

S1PR1 is ubiquitously found throughout the brain, with high expression in gray matter and little to no expression in white matter.[232] The high B_{max} value indicates that S1PR1 is an ideal target for PET radioligands with sufficiently high estimates of specific binding.[232] Although initially challenging,[233] PET radioligands, [^{11}C]CS1P1 and [^{18}F]FS1P1, targeting S1PR1 with high selectivity and specificity, have been evaluated in nonhuman primates and preliminarily in humans.[232,234,235] These promising radiotracers exhibit high target affinity and brain penetration, but quantification may be limited by slower kinetic properties, particularly for the C-11 labeled compound. However, alternative F-18 labeled compounds with faster kinetic properties have been evaluated in rodents and nonhuman primates.[236,237]

Purinergic P2Y12 Imaging

Purinergic P2Y12 receptor (P2Y12R) is a G-protein coupled receptor predominantly expressed on brain microglia.[238–240] Interestingly, there is selective downregulation of P2Y12R expression on proinflammatory microglia and its upregulation on anti-inflammatory microglia.[241] Over the past 20 years, many high-affinity P2Y12 ligands have been developed, but none have yet demonstrated that they are suitable for studying or controlling its function in the brain.[242] Unfortunately, these radiotracers either do not cross the BBB or have negligible uptake,[242] and efforts to develop a radiotracer that addresses these limitations are ongoing.[243,244] Since P2Y12R is expressed exclusively on microglia and is linked to the elusive anti-inflammatory M2 phenotype, there is currently a high interest in developing a radiotracer specific for P2Y12R.

Outlook and Conclusion

PET neuroimaging holds the unique potential for invaluable measurements of brain immune targets in neurodegenerative and neuropsychiatric conditions. While novel radiotracer development for such targets poses significant challenges, there is much promise for many diverse, complementary targets. Future advancements in this vein will advance scientific understanding of brain immune mechanisms that contribute to the development and progression of such conditions, which can ultimately help improve public health outcomes. Table 1.

Declaration of Competing Interest

Authors declare they have no conflicts of interest.

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