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The peripheral benzodiazepine receptor (Translocator protein 18 kDa) in microglia: From pathology to imaging

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Abstract

Microglia constitute the primary resident immune surveillance cell in the brain and are thought to play a significant role in the pathogenesis of several neurodegenerative disorders, such as Alzheimer's disease, multiple sclerosis, Parkinson's disease and HIV-associated dementia. Measuring microglial activation in vivo in patients suffering from these diseases may help chart progression of neuroinflammation as well as assess efficacy of therapies designed to modulate neuroinflammation. Recent studies suggest that activated microglia in the CNS may be detected in vivo using positron emission tomography (PET) utilizing pharmacological ligands of the mitochondrial peripheral benzodiazepine receptor (PBR (recently renamed as Translocator protein (18 kDa)). Beginning with the molecular characterization of PBR and regulation in activated microglia, we examine the rationale behind using PBR ligands to image microglia with PET. Current evidence suggests these findings might be applied to the development of clinical assessments of microglial activation in neurological disorders.

Keywords: Positron emission tomography; Microglia; PK11195; Peripheral benzodiazepine receptor; Neuroinflammation

Contents

Abbreviations: [^{11}C], Carbon-11 isotope; [^{3}H], tritium isotope; AD, Alzheimer's disease; AIDS, acquired immunodeficiency syndrome; ANT, adenine nucleotide transporter; Aβ, amyloid beta; B_{max}, maximal bound receptors; BP, binding potential; CD 4+ T cell, cluster of differentiation type 4 T lymphocyte; CD68, lysosomal marker for activated macrophages; CNS, central nervous system; COX2, cyclooxygenase; CSF, cerebrospinal fluid; DAA1106, (*N*-(2,5-dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide); DV, distribution volume; DVR, distribution volume ration; Fc, constant fragment of antibody; GFAP, glial fibrillary acidic protein (marker for astrocytes); HIV, human immunodeficiency virus; HIVE, human immunodeficiency virus encephalitis; HPLC, high performance liquid chromatography; IL, interleukin; INF-γ, interferon-gamma; iNOS, inducible nitric oxide synthase; K_D, dissociation constant; LPS, lipopolysaccaride; MCP-1, monocyte chemoattractant protein-1; MDM, monocyte derived macrophages; min, minute; MIP-1a, macrophage inflammatory protein-1alpha; MIP-1b, macrophage inflammatory protein-1beta; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; NSAID, non-steroidal anti-inflammatory drugs; PBR, peripheral benzodiazepine receptor; PET, positron emission tomography; PK11195, [1-(2-chlorophenyl)-*N*-methyl-*N*-(1methylpropyl)-3-isoquinolinecarboxamide]; SIV, Simian immunodeficiency virus; SIVE, Simian immunodeficiency virus encephalitis; SRTM, simplified reference tissue model; T cell, T (thymic)-lymphocyte cell; Tg, transgenic mice; TNF-α, tumor necrosis factor alpha; VDAC, voltage-dependent anion channel

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1. Microglia in health and disease

1.1. Microglia: origin and function

Microglia constitute up to 10% of the total cell population of the brain. As resident macrophages (histiocytes), microglia phagocytose cellular debris, present foreign antigens and presumably serve many other vital functions in the brain (Minghetti and Levi, 1998). Del Rio Hortega first recognized the pathological importance of microglia in the central nervous system (CNS), and he also coined their name (Del Rio Hortega, 1932). Microglia are derived from cells of the monocyte lineage. During development embryonic mesodermal cells migrate from the bone marrow into the CNS during the mid-gestational period (Perry and Gordon, 1991). Based on tissue culture experiments, however, some assign a neuroectodermal origin to microglia (Fedoroff et al., 1997).

Microglia change from a resting to an activated state in response to CNS insults that stimulate them to function as phagocytes (reviewed in Gehrmann et al., 1995). This morphological change has been best documented in the facial-nerve transection model, where microglial activation can be assessed in an environment without blood–brain barrier disruption nor migration of new bone marrow-derived macrophages. This model demonstrates the capacity of resident microglia to undergo morphological changes and activation with expression of new surface markers and to proliferate around motor neurons of the facial nucleus (reviewed in Kreutzberg, 1996).

In addition to activation of resident brain microglia, monocytes migrate from the vascular compartment into the CNS during CNS-inflammation and there differentiate to form macrophages (reviewed in Guillemin and Brew, 2004). Such cells are termed perivascular macrophages. Since no reliable histologic markers exist that differentiate these cells, for simplicity we use the word microglia to include both these cell types.

Microglia were previously thought to be quiescent and non-motile in a resting state. However, recent in vivo imaging of fluorescently tagged microglia in transgenic mice using two-photon microscopy showed that these cells were far from static (Davalos et al., 2005; Nimmerjahn et al., 2005). They possess highly ramified processes that exhibit cycles of formation, extension and withdrawal. These cell processes in turn show foot-like appendages that form and withdraw repetitively. These authors hypothesize that microglia serve housekeeping functions whereby they sample and maintain homeostasis of local environments. Following laser-induced injury, time-lapse imaging shows rapid movement of ramified processes into the site of injury. Microglial processes fuse to form an area of containment separating healthy and injured tissues within about 30 s, suggesting that microglia may represent a first line of defense in CNS injury (Davalos et al., 2005; Fetler and Amigorena, 2005; Nimmerjahn et al., 2005).

The phagocytic function of microglia is mediated in a receptor-dependent fashion. Microglia express several receptors including Fc (constant fragment of antibodies) and complement, which enable them to engulf antibody-coated cells and opsonized antigen (Chan et al., 2003; Ulvestad et al., 1994; Webster et al., 2001). Microglia also express MHC II, which enables them to present antigen to CD4-T cells (Gehrmann et al., 1995). In addition, microglia express costimulatory substances, such as B7-1, B7-2 and CD40 that allow them to stimulate T cells and initiate immune reactions (Gonzalez-Scarano and Baltuch, 1999). The actions of phagocytosis and antigen presentation enable microglia to serve an immune surveillance function in the CNS.

1.2. Microglia in neurodegeneration

Microglia undergo changes from a resting phenotype to an activated phenotype in response to a wide variety of CNS insults. Various degrees of microglia activation are seen in neurodegenerative disorders. Neuritic plaques, which constitute the central pathology in Alzheimer's disease (AD), are surrounded by microglia (McGeer et al., 1988a). In multiple sclerosis, areas of demyelination are rich in activated microglia (Bauer et al., 1994). HIV-dementia is characterized by viral infection of microglia (Wiley et al., 1986). Activation of microglia in other neurodegenerative diseases, such as Parkinson's disease (McGeer et al., 1988b), Creutzfeldt-Jakob disease (Muhleisen et al., 1995) and amyotrophic lateral sclerosis (Sargsyan et al., 2005) is known but less well characterized.

A wealth of literature suggests that activated microglia, in addition to their phagocytic role, synthesize and secrete potential neurotoxins that may cause neuronal damage or aggravate underlying pathology. These neurotoxins include free radicals (Chao et al., 1995a), nitric oxide (Chao et al., 1992), proteinases (Colton et al., 1993), eicosanoids (Heyes et al., 1996) and excitotoxins (Giulian et al., 1990; Piani et al., 1992). In addition, activated microglia also secrete substances that influence neuronal function and viability, such as the cytokines interleukin-1 (Giulian et al., 1986), interleukin-6 (Righi et al., 1989), tumor necrosis factor α (Chao et al., 1995b) and chemokines, such as MIP-1α (Murphy et al., 1995), MIP-1β (McManus et al., 1998) and MCP-1 (D'Aversa et al., 2002). Although some of these studies are based on tissue culture systems and remain to be confirmed in vivo, it is generally