

Chapter 13

Possible Therapeutic Targets in Microglia

Mami Noda

Abstract In recent years, microglial cells are becoming to stand in the limelight. They may play a major role not only under physiological condition but also under many pathophysiological conditions. Manipulating their function may lead to cure or attenuation of neurological diseases, traumatic injury, psychiatric disorders, or even sleepiness or aging. In this chapter, the properties of microglial cells including receptors for neurotransmitters and neurohormones/neuromodulators, transporters, and other signals which are related to therapeutic possibilities are summarized.

Keywords Microglia · Inflammation · Pain · Neurodegenerative disorders · Psychiatric disorders · Microglia · Neurotransmitter receptor · Neuropeptide receptor · Endocrine system · Neurohormone · Cytokine · Chemokine · Neuropathic pain · Neurodegenerative diseases · ALS · Traumatic brain injury · LPS · Sleep loss · Aging · Obesity · Psychiatric disorder · Autism

13.1 Introduction

Microglial cells are immune cells in the central nervous system (CNS). Their contributions towards physiological and pathophysiological processes have been well documented (Kettenmann et al. 2011; Eyo and Dailey 2013; Verkhratsky and Butt 2013). In pathophysiological condition, microglial cells rapidly respond to any kind of damage signals accompanying poly-etiological insults to the CNS. Microglial responses in the CNS may occur as a result of trauma, ischemia, infection or neurodegenerative stimuli. Microglial cells have been implicated, to some extent, in the pathogenesis of all of the common neurodegenerative disorders involving protein aggregation such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). However, the precise role they play in the development of these pathologies remains unclear and it seems that they contribute to the pathological process in different ways in a disease-specific manner. A better understanding of their

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varied roles is essential if they are to be the target for novel therapeutic strategies (Gentleman 2013).

Activated microglia proliferate rapidly, migrate to the site of injury or infection and elicit defense response by phagocytosis of cell debris, production of cytokines, chemokines and reactive oxygen species, and presentation of antigens to other immune cells. In addition, microglia participate in tissue repair by producing neurotrophic factors. However, chronically activated microglia become neurotoxic to the surrounding CNS parenchyma.

Chronic activation of microglia has been shown to augment neurodegeneration in PD, AD, brain injury and number of other CNS pathologies. Identification of factors that control microglial activation, therefore, has become the major focus of recent research (Rangarajan et al. 2013). Microglial dysfunction may also contribute to genetic neurobehavioral disorders (Benarroch 2013). At the sites of injury or any pathological area, classical “activated” microglia, with an amoeboid morphology, show different molecular and genetic characteristics compared to those in resting microglia. Recently, this subdivision into two main types (resting and activated microglia) is regarded as oversimplification and more sophisticated microglial activity states throughout an activation process were proposed (Hanisch and Kettenmann 2007; Eyo and Dailey 2013).

Microglial activation is also regarded as a biomarker for traumatic brain injury (Hernandez-Ontiveros et al. 2013). During a cascade of secondary cell death and multiple inflammatory responses accompanying traumatic brain injury, inflammatory cytokines and chemokines spreads to normal brain areas juxtaposed to the core impacted tissue. Among immune cells involved, microglia is a key player in propagating inflammation to tissues neighboring the core site of injury.

Multiple sclerosis (MS) exhibits many of the hallmarks of an inflammatory autoimmune disorder including breakdown of the blood-brain barrier (BBB), the recruitment of lymphocytes, microglia, and macrophages to lesion sites. Inflammatory cascade is amplified by pro-inflammatory cytokines, compromising the BBB, recruiting immune cells from the periphery, and activating resident microglia (see review; Ortiz et al. 2013). Genome-wide microarray analysis comparing micro-dissected active cortical MS lesions with those of tuberculous meningitis (inflammatory control) showed that more than 80% of the identified MS-specific genes were related to T cell-mediated inflammation, microglia activation, oxidative injury, DNA damage and repair, remyelination and regenerative processes (Fischer et al. 2013).

Correlation between neurodegenerative diseases and oxidative stress is also suggested since mitochondrial dysfunction, i.e. cell energy impairment, apoptosis and overproduction of reactive oxygen species (ROS), is a final common pathogenic mechanism in aging and in neurodegenerative disease such as AD, PD and ALS (Emerit et al. 2004).

In this chapter, receptors, and other molecules, which are expressed or up-regulated in activated microglia and possibly contributing to pathological conditions, are discussed as potential targets for medical intervention in microglia (Fig. 13.1).

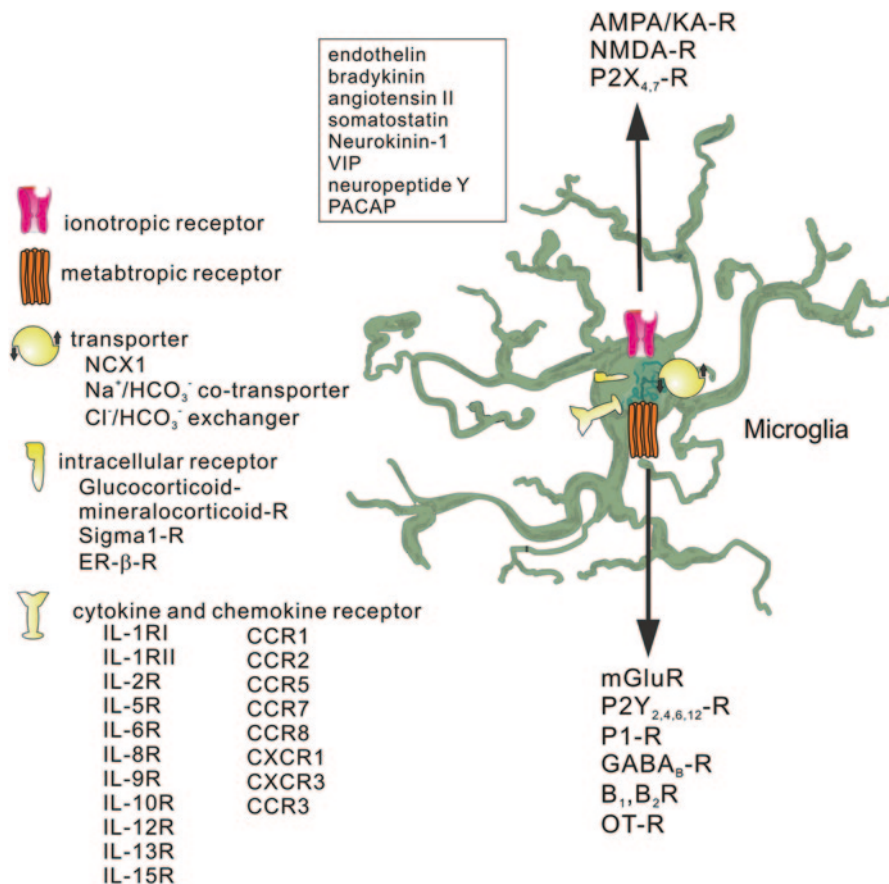


Fig. 13.1 Possible therapeutic targets in microglia. Neurotransmitter receptors, neuropeptide receptors, neuromodulatory receptors, cytokine and chemokine receptors, transporters, and various factors affecting microglial function

13.2 Neurotransmitter Receptors

Microglia express various types of neurotransmitter receptors (Kettenmann et al. 2011; Verkhratsky and Butt 2013; Kettenmann and Ransom 2013; Lee 2013), each of which can have a specific pathological role(s) which are discussed below.

13.2.1 Glutamate Receptors

13.2.1.1 AMPA Receptors

Microglia express functionally heterogeneous AMPA (α -amino-hydroxy-5-methylisoxazole-4-propionate)-type of receptors (Noda et al. 2000; Hagino et al. 2004) and

contribute to glutamate (Glu)-mediated neuron-glia interaction (Bezzi et al. 2001). Microglia express highly Ca^{2+} impermeable AMPA receptors due to the expression of GluA2 subunit. In addition, expression of plasmalemmal GluA2 subunits significantly increases upon activation of microglia, for example after treatment by lipopolysaccharide (LPS) (Beppu et al. 2013). Since a decreased expression of GluA2 was reported in some of the neurodegenerative diseases such as AD and Creutzfeldt-Jakob disease (Ferrer and Puig 2003; Carter et al. 2004), functional change in GluA2-deficient microglia was investigated, showing higher Ca^{2+} -permeability, consequently inducing significant increase in the release of pro-inflammatory cytokine, such as tumor necrosis factor- α (TNF- α). GluA2-deficient mouse brain also showed more neurotoxicity in response to kainic acid (Beppu et al. 2013). Therefore, involvement of microglia in glutamatergic synaptic transmission may be also important to understand the mechanism of some neurodegeneration in which low GluA2 is suggested (Noda and Beppu 2013).

In the hypothalamus and neurohypophysis of rats with streptozotocin (STZ)-induced diabetes, the expression of GluA2/3 was progressively down-regulated, being hardly detected at 4 months of STZ-diabetes, together with up-regulation of N-methyl D-aspartate receptor (NMDAR) subunit GluN1 and neuronal nitric oxide synthase (nNOS). In addition, both astrocytes and microglia appeared activated. Therefore, it was speculated that the glutamate receptors and NO are linked to over-activation of paraventricular and supraoptic nuclei leading ultimately to cell death (Luo et al. 2002). The lack of GluA2/3 in microglia may also contribute to the cell death.

13.2.1.2 Kainate Receptors

Microglia express kainate (KA) receptor subunits (Yamada et al. 2006; Noda et al. 2000) and KA-induced current was affected by application of concanavalin A which is a positive modulator selective for KA-preferring receptors (subunits GluR5–GluR7 and KA-1 or KA-2) (Huettner 1990; Partin et al. 1993; Wong and Mayer 1993), suggesting that only some of the KA-responsive cells express KA-preferring receptors and not only AMPA-preferring receptors (Noda et al. 2000). It was indicative of heterogeneous distribution of AMPA- and KA-preferring receptors among microglial cells; some cells express predominantly AMPA-preferring receptors, some cells express predominantly KA-preferring receptors, and some cells express both. The functional difference has not been identified yet.

13.2.1.3 NMDA Receptors

Although NMDA-induced membrane currents were not observed in primary cultured microglial cells (Noda et al. 2000), it was reported that cortical microglia express NMDAR subunits *in vitro* and *in vivo* and activation of the microglial NMDARs plays a pivotal role in neuronal cell death in the perinatal and adult brain

(Kaindl et al. 2012). Microglia have unique NMDAR subunit expression with a high level of the GluN2D subunit that is distinct from that found in neurons, indicating distinct NMDAR subunit assembly. The pathophysiologic relevance of microglial NMDARs is particularly high, as they confer sensitivity to excitotoxic cortical injury that is likely to be significant for a large variety of neurological diseases. For example, after stroke, glutamate released by damaged neurons in the infarct core can diffuse to nearby cells, and this can lead to an activation of microglia via their NMDARs and render them neurotoxic. Conversely, loss of function of the microglial NMDARs protects from gray matter damage.

13.2.1.4 Metabotropic Glutamate Receptors

Microglial cells also bear metabotropic glutamate receptors (mGluRs) (Biber et al. 1999; Farso et al. 2009; Taylor et al. 2002); mGluR1,5 (Group I) is linked to intracellular Ca^{2+} signaling, while mGluR2,3 (Group II) (Taylor et al. 2002) and mGluR4,6,8 (Group III) (Taylor et al. 2003) are coupled to adenosine 3':5' cyclic monophosphate (cAMP) and involved in regulation of TNF- α release and microglial cytotoxicity (Taylor et al. 2005). Since mGluRs is proposed as targets for multipotential treatment of neurological disorders (Byrnes et al. 2009), microglial mGluRs may be critical regulators in neuron to glia transmissions especially under pathological state.

13.2.2 Purinergic Receptors

The most widespread and possibly most functionally important receptors for microglia are purinoceptors (Verkhatsky et al. 2009b).

13.2.2.1 Ionotropic Purinoceptors (P2X Receptors)

The main type of ionotropic purinoceptors expressed in mature microglial cells are P2X₄ and P2X₇ receptors. The P2X₄ receptors are also constitutively expressed in microglia and contribute to microglial activation in particular in the context of neuropathic pain. Increased levels of P2X₄ receptors was found in activated microglia (Tsuda et al. 2003), whereas intrathecal injection of cultured microglia bearing P2X₄ receptors induced allodynia in the absence of peripheral nerve damage (Inoue and Tsuda 2009). Involvement of P2X₄ in KA-induced status epilepticus was also reported (Ulmann et al. 2013).

The P2X₇ receptors are involved in various neuropathologies (Franke et al. 2012) and contribute to various aspects of microglial reactions. P2X₇ receptors are abundantly present in immune cells and mediate many immune reactions, including the processing and the release of various cytokines. Microglial cells

constitutively express P2X₇ receptors and various brain lesions and neuropathologies (such as, for example, MS, ALS and AD) induce substantial up-regulation of P2X₇ receptors expression (Sperlagh et al. 2006; Verkhratsky et al. 2009a). Activation of P2X₇ receptors regulates multiple microglial processes from microglial activation to apoptotic death. Stimulation of P2X₇ receptors was reported to be necessary for microglial activation by amyloid- β (A β) protein (Sanz et al. 2009), and P2X₇ receptors control microglial secretion of pro-inflammatory factors (see (Kettenmann et al. 2011) and references therein). Incidentally, over-expression of P2X₇ receptors in microglia triggers their activation in the *in vitro* system in complete absence of any other exogenous factors (Monif et al. 2009). Recently P2X₇ receptor was reported to regulate microglial survival in living brain tissues (Eyo et al. 2013). Removal of extracellular Ca²⁺ or application of a potent P2X₇ receptor antagonist, protected microglial cell death. These pharmacological results were complemented by studies in tissue slices from P2X₇ receptor null mice, in which oxygen-glucose deprivation (OGD)-induced microglial cell death was reduced by nearly half. These results indicate that stroke-like conditions induce Ca²⁺-dependent microglial cell death that is mediated in part by P2X₇ receptor. Increased neocortical expression of the P2X₇ receptor after status epilepticus and anticonvulsant effect of P2X₇ receptor antagonist were also reported (Jimenez-Pacheco et al. 2013). From a therapeutic standpoint, these findings could help direct novel approaches to enhance microglial survival and function following stroke and other neuropathological conditions.

13.2.2.2 Metabotropic Purinoceptors (P2Y Receptors)

Microglia express several metabotropic purinoceptors with predominant appearance of P2Y₂, P2Y₆, P2Y₁₂, and P2Y₁₃ receptors. Stimulation of these receptors as a rule triggers Ca²⁺ signals that often involve endoplasmic reticulum Ca²⁺ release and store-operated Ca²⁺ influx; overstimulation of P2Y pathways can produce a long-lasting activation of the latter that can contribute to various aspects of microglial activation (Toescu et al. 1998). The P2Y₆ receptors, distinctively sensitive to UDP, regulate microglial phagocytosis (Koizumi et al. 2007), whereas ADP-preferring P2Y₁₂ receptors are fundamental for acute microglial responses to pathological insults, for morphological activation, membrane ruffling and chemotaxis (Verkhratsky et al. 2009a). In addition P2Y₁₂ receptors are linked to integrin- β 1 signaling, which regulates extension of microglial processes (Ohsawa et al. 2010; Eyo and Wu 2013). In the spinal cord P2Y₁₂ receptors are involved in the genesis of neuropathic pain (Inoue and Tsuda 2009).

As mentioned above, neuron-to-microglia purinergic signaling regulates microglial extension and retraction (see review (Eyo and Wu 2013)). In the event of neuronal injury, neurons release purines including ATP which can be degraded by endogenous enzymes into ADP and adenosine. Released purines diffuse in the extracellular space and activate P1 adenosine (A₃) and P2Y (P2Y₁₂) receptors on microglia that act in concert.

Recently, it was shown that soluble A β peptide 1–42 induced self-uptake in microglia through pinocytosis, a process involving activation of P2Y₄ receptors by autocrine ATP signaling. It demonstrates a previously unknown function of ATP as a “drink me” signal for microglia and P2Y₄ receptors as a potential therapeutic target for the treatment of AD (Li et al. 2013).

13.2.2.3 Adenosine (P1) Receptors

Adenosine receptors of P1 type are represented by classical seven-transmembrane spanning G protein-coupled receptors and are subclassified into adenosine A₁, A_{2A}, A_{2B}, and A₃ receptors with distinct pharmacological and functional properties. All four types of adenosine receptors were identified at the mRNA level in cultured rat microglia (Fiebich et al. 1996b). As mentioned above, purinergic activation leads to extension of microglial processes towards the injury site. Following microglial activation, adenosine can also activate A_{2A} receptors that mediate microglial branch retraction. First, a role for the adenosine A_{2A} receptor in microglial cytoskeletal rearrangements was suggested (Orr et al. 2009). Adenosine A_{2B} receptors mediate an increase in interleukin (IL)-6 in human astrogloma cells (Fiebich et al. 1996a). Recently, there was a report that microglia also express A₁ receptor which is up-regulated upon ATP treatment. Moreover, selective stimulation of A₁ receptors inhibits morphological activation of microglia, possibly by suppressing the Ca²⁺ influx induced by ATP. Microglial cells, pretreated with the A₁ receptor agonist, exhibit lower capability to facilitate the nociceptive neurons, as compared with the cells treated with ATP alone (Luongo et al. 2014).

13.2.3 GABA (γ -Aminobutyric Acid) Receptors

Functional GABA_B receptors were identified in a subpopulation of microglial cells in culture (Kuhn et al. 2004). The physiological role of microglial GABA_B receptors are described in Kettenmann et al. (2011), but their pathophysiological role needs to be identified.

13.2.4 Cholinergic Receptors

The expression of neuronal α 7 nicotinic receptors (nACh) was initially found in cultured mouse microglia (De Simone et al. 2005; Shytle et al. 2004). The activation of nACh receptors generally inhibits the immune response of microglial cells, thus representing endogenous “cholinergic anti-inflammatory pathway” (Shytle et al. 2004). On example is that nicotine was shown to inhibit P2X₇-mediated radical oxygen species (ROS) production in A β peptide 1–42 stimulated cultured microglial cells (Moon et al. 2008). Also, long-term (15 days) incubation of

corticostriatal organotypic slices with nicotine reduced the thrombin-dependent activation of microglia (Ohnishi et al. 2009). More recently, the $\alpha 7$ nACh receptor ligands reduced LPS-induced TNF- α release from microglia (Thomsen and Mikkelsen 2012).

13.2.5 Adrenergic Receptors

Accumulation of intracellular cAMP following stimulation of $\beta 2$ receptors provided the first evidence for the expression of adrenergic receptors in microglia (Prinz et al. 2001). While $\beta 2$ receptor stimulation suppressed LPS-induced release of IL-12p40 in cultured microglia (Prinz et al. 2001), stimulation of $\beta 1$ receptors increased expression of IL-1 β mRNA (Tanaka et al. 2002). Increasing intracellular cAMP suppressed proliferation of microglia (Fujita et al. 1998), inhibited ATP-induced release of TNF- α (Morioka et al. 2009) and modulate microglial migration and phagocytosis. Microglial adrenergic receptors could be relevant in pathogenesis of AD as early degeneration of locus coeruleus in AD and depletion of adrenergic input to the brain affects the ability of microglia to provide for effective clearance of A β (Heneka et al. 2010). Recently, it became obvious that norepinephrine modulates the motility of resting and activated microglia via different adrenergic receptors; $\beta 2$ receptors mediate microglial process dynamics in resting cells whereas α_{2A} receptors do in activated cells. In addition, the presence of cross-talk between adrenergic and purinergic signaling in microglia was suggested (Gyoneva and Traynelis 2013). These data show that norepinephrine can modulate microglial motility, which could affect microglial functions in pathogenic situations of either elevated or reduced norepinephrine levels.

13.2.6 Dopamine Receptors

The D_{1,2,3,4} (but not D₅) receptors were identified on translational level in microglia in culture and visualized by immunostaining in substantia nigra from Parkinsonian brains, suggesting that activation of microglia in PD triggers expression of dopamine receptors, which may explain an increase in microglia-related toxicity towards dopamine-producing neurons (Mastroeni et al. 2009). In PD, microglial cells in substantia nigra are activated and concentrated around dystrophic dopaminergic neurons (Rogers et al. 2007); the role of dopamine receptors in this specific activation and migration of microglia needs to be clarified further. The inhibition of D₄ receptors by specific agonist suppressed microglial activation in the spinal cord of superoxide dismutase 1 transgenic animal model of ALS; this reduced microglial activation coincided with slowing down the disease progression (Tanaka et al. 2008).

13.2.7 Serotonin Receptor

Microglia express 5-HT₂ serotonin receptors (Kettenmann et al. 2011; Kato et al. 2013b). There is a possibility that modulating microglia serotonin receptors may be a key target in the treatment of various psychiatric disorders, which likely will be a hot topic in the near future.

13.3 Neuropeptide Receptors

In addition to neurotransmitter receptors, microglia has receptors for a wide variety of neuropeptides, such as endothelin, bradykinin, angiotensin II, somatostatin, neurokinin-1, vasoactive intestinal peptide (VIP), neuropeptide Y (see (Kettenmann et al. 2011) (Kettenmann and Ransom 2013) for details). Bradykinin receptors, for example, have distinct effects on microglia from those on neurons. Inducible B₁ receptor stimulate microglial migration (Ifuku et al. 2007) and have rather neuroprotective effects against LPS-induced activation and inflammatory responses (Noda et al. 2006, 2007). Pituitary adenylate cyclase activating polypeptide (PACAP) activates a quinine-sensitive K⁺ outward current and modulates activities in microglia (Ichinose et al. 1998), VIP and PACAP inhibit the MEKK1/MEK4/JNK signaling pathway (Delgado 2002b) and CREB binding protein (CBP)-nuclear factor (NF)-κB interaction (Delgado 2002a) in endotoxin-activated microglia. Neuropeptide receptors in microglia could become a strong therapeutic target, especially for AD.

13.4 Hormones and Hormone Receptors

It was indicated that glial cells may play a significant role in the link between the endocrine and nervous systems (Garcia-Segura et al. 1996; Chowen et al. 1996). Glial cells express nuclear receptors for both thyroid and steroid hormones and participate in the metabolism of these hormones, resulting in the production of neuroactive metabolites. Furthermore, glial cells synthesize endogenous neuroactive steroids, including pregnenolone and progesterone, from cholesterol. It is known that thyroid hormones, glucocorticoids, gonadal steroids, and neurosteroids affect glial functions. Under physiological conditions, hormonal effects on glia may have important consequences for neuronal development, metabolism, and activity and for the formation and plasticity of synaptic connections. In addition, glucocorticoids, gonadal steroids, and neurosteroids may affect regenerative processes in neurons by modulating glial responses after injury. These effects include the activation of microglia, which is regulated by glucocorticoids. Therefore, endocrine impairments affect microglial function as well as other cell types in the CNS.

13.4.1 Sex Hormones

Estrogen has been shown to be neuroprotective in stroke and other neural injury models. The presence of estrogen receptor- β (ER- β) in rat microglial cells was reported a decade ago (Mor et al. 1999). Estrogen-mediated neuroprotection is critically dependent on insulin-like growth factor (IGF)-1 signaling. Microglia appears as the source of IGF-1 and the locus of estrogen-IGF-1 interactions in stroke neuroprotection (Sohrabji and Williams 2013).

Microglial cell line BV-2, responded to hypoxia by enhanced pro-inflammatory cytokine secretion and reduced phagocytic activity, which is prevented by sex steroids resulting in a switch of microglial cells from a pro-inflammatory to a more anti-inflammatory phenotype. Anti-inflammatory effects of gonadal steroids might directly be mediated through hormone-microglia interactions in addition to known effects via astroglial regulation (Habib et al. 2013a, b). Estrogen is also neuroprotective in the MS model (Wisdom et al. 2013) and encephalomyelitis (Spence et al. 2013; Wu et al. 2013). Also, testosterone, being metabolized to estradiol and dihydrotestosterone, decreases reactive astroglia and reactive microglia after brain injury in male rats: role of its metabolites, estradiol and dihydrotestosterone (Barreto et al. 2007).

Neuronal plasticity is regulated by the ovarian steroids estradiol and progesterone in many normal brain functions, as well as in acute response to injury and chronic neurodegenerative disease. In a female rat model of axotomy, the estradiol-dependent compensatory neuronal sprouting is antagonized by progesterone (Bali et al. 2013).

In developing rat brain, microglia are essential to masculinization of brain and behavior (Lenz et al. 2013). Estradiol up-regulates the synthesis of prostaglandin E2 (PGE2), originally in neurons, and then activate microglia and stimulates their own release of PGE2. This feed-forward loop of PGE2 production is required for the masculinization of the preoptic area and therefore of sexual behavior (Welberg 2013). Microglial dysfunction may be also involved in abnormalities of brain development and sexual behavior.

13.4.2 Cortisol Receptor

Glucocorticoid- and mineralocorticoid receptors in microglia were reported (Tanaka et al. 1997). Corticosterone suppresses the proliferation of BV2 microglia cells via glucocorticoid, but not mineralocorticoid receptor (Nakatani et al. 2012). Limitation of microglial activation was also reported in dopaminergic neurodegeneration and in acute stress model (Sugama et al. 2009; 2012). They suggest that glucocorticoids may serve as an important endogenous suppressive signal limiting neuroinflammation. Dexamethasone inhibits the Nox-dependent ROS production via suppression of MKP-1-dependent MAPK pathways in activated microglia, suggesting down-regulation of Nox-2 and overexpression of MKP-1 that regulate ROS and NO may form the potential therapeutic strategy for the treatment of neuroinflammation in neurodegenerative diseases (Huo et al. 2011).

13.4.3 Oxytocin Receptors

Oxytocin mediates social neuroprotection after cerebral ischemia. There is evidence for a direct suppressive action of oxytocin on cultured microglia, which is a key instigator in the development of neuroinflammation after cerebral ischemia (Karelina et al. 2011). Since oxytocin is important for social behavior (Eckstein and Hurlmann 2013), possible involvement of microglia via oxytocin needs to be investigated.

13.5 Cytokine and Chemokine Receptors

Microglial cells are in possession of several types of cytokine and chemokines receptors which regulate multitude of immune responses (see (Kettenmann et al. 2011; Kettenmann and Ransom 2013) for details). Microglia express multiple interleukin receptors (IL-1RI, IL-1RII, IL-5R, IL-6R, IL-8R, IL-9R, IL-10R, IL-12R, IL-13R, and IL-15R) (Lee et al. 2002) and the activation or cultured mouse microglia with LPS induced expression of IL-2 receptors (Sawada et al. 1995). Spinal cord microglia showed sensitivity to IL-6, connected with a signal transducer and activator of transcription (STAT) pathway, contributing to development of mechanical allodynia and neuropathic pain (Dominguez et al. 2008).

Among chemokine receptors (CCR) which are expressed in the cells of the CNS, microglial cells in particular express CCR1, CCR2, CCR7 and CCR5 (rodents) and CXCR1, CXCR3 and CCR3 (humans) (Boddeke et al. 1999a, b; Flynn et al. 2003). A major regulator of microglial activation and neurotoxicity in the CNS is the CX3CL1 (fractalkine, i.e. ligand)/CX3CR1 (fractalkine receptor) signaling axis (Zujovic et al. 2000; Cardona et al. 2006). On the other hand, it was suggested that CCR2/CCR5 antagonist has the potential for broad clinical use in neuropathic pain treatment (Padi et al. 2012) and decreased pain responses of CCR5 knockout mice to chemical or inflammatory stimuli was reported (Lee et al. 2013). In addition, another important chemokine, chemokine (C-C motif) ligand 1 (CCL-1), originally a well-characterized chemokine secreted by activated T cells, also plays an important role in neuropathic pain induced after partial sciatic nerve injury (Akimoto et al. 2013a). CCL-1 plays an important role in neuropathic pain induced by nerve injury and is also produced in various cell types in the CNS, especially in dorsal root ganglia. The specific receptor for CCL-1, CCR8, was found mainly in neurons but also in astrocytes and microglia. CCL-1 has multiple effects on microglia, i.e. increasing chemotaxis, motility, proliferation and phagocytosis. CCL-1 also activated microglia morphologically, promoted mRNA levels for brain-derived neurotrophic factor (BDNF) and IL-6, and increased the release of nitrite from microglia (Akimoto et al. 2013b). These indicate that CCL-1 may contribute to the development of neurological diseases, especially in neuropathic pain.

13.6 Other Receptors and Molecules

13.6.1 Toll Like-Receptors

Toll-like receptors (TLR1–9) are particularly diversified in microglia being involved in regulation of activation in response to multiple exogenous pathological factors. Activation of TLRs triggers several complex signaling cascades that often involve adaptor protein MyD88, transcription factors AP-1 and NF- κ B (Hansson and Edfeldt 2005; Leulier and Lemaitre 2008). Different TLRs detect different infectious agents. Stimulation of TLRs initiates activation of microglia, and the type or receptor involved may define specific activation programs. It was recently reported that microglia works as key mediators of post-traumatic brain edema and was suggested that high-mobility group box protein 1 (HMGB1)-TLR4 signaling promotes neurovascular dysfunction after traumatic brain injury (Laird et al. 2014).

13.6.2 Sigma Receptor

Sigma-1 receptor (S1R), an endoplasmic reticulum-resident receptor with chaperone-like activity, has recently attracted great interest. S1R is involved in several processes leading to acute and chronic neurodegeneration, including ALS pathology. Pharmacological manipulation of S1R seems to be a promising strategy to cure ALS. It pointed to increased availability of growth factors and modulation of astrocytosis and of macrophage/microglia as part of the mechanisms (Peviani et al. 2013).

13.6.3 Ion Transporters

Microglial plasmalemmal transporters such as Na⁺/Ca²⁺ exchanger (Ifuku et al. 2007), Na⁺/HCO₃⁻ co-transporter and/or Na⁺-dependent Cl⁻/HCO₃⁻ exchanger (Schwab 2001) and Na⁺/H⁺ exchanger isoform 1 (Shi et al. 2013) are important in microglial migration.

13.6.4 Macrophage Colony Stimulating Factor

Increased levels of macrophage colony stimulating factor, increased microglia and microglial activation are found in many different CNS pathologies including tumors, neurodegenerative diseases and injury (reviewed in Charles et al. (2012); El Khoury and Luster (2008); Imai and Kohsaka (2002); Loane and Byrnes (2010)).

13.7 Pathological Conditions Relating to Microglial Activation

13.7.1 *Sleep Deprivation*

Deficit of sleep triggers changes in inflammatory signaling pathways in the brain and periphery. The TLR4 receptors activate inflammatory signaling cascades in response to endogenous and pathogen-associated ligands known to be elevated in association with sleep loss. TLR4 is therefore a possible mediator of some of the inflammation-related effects of sleep loss (Wisor et al. 2011a). In agreement to this observation, microglial changes in the cerebral response were observed after sleep loss, which was modulated by minocycline, a compound that attenuates microglial activation occurring in association with neuroinflammatory events (Wisor et al. 2011c). Actually changes in the sleep/wake cycle that occur subsequent to administration of D-methamphetamine are modulated by cerebral microglia; the effects of D-methamphetamine on sleep/wake cycles are mediated in part by actions on microglia, including possibly nNOS activity and cytokine synthesis (Wisor et al. 2011b). Recently more information about interaction between microglial activation and sleep or circadian rhythm have been reported (Hayashi et al. 2013; Yang et al. 2013; Yu et al. 2013).

13.7.2 *Obesity*

In addition to neurodegenerative disorders, obesity is also considered to be associated with a state of chronic neuroinflammation. High-fat-diet exposure induces significant microglial activation not only in the hypothalamus (Yi et al. 2012) but also in the cerebellar white matter (Tapia-Gonzalez et al. 2011). Free fatty acid palmitate on its own induces activation of BV2 microglia cell line. Further, pre-exposure to palmitate changed the response of microglia to LPS, affecting the mRNA levels of the pro-inflammatory cytokines IL-1 β and IL-6 (Tracy et al. 2013).

13.7.3 *Aging*

With aging, microglia change their morphology and may display diminished capacity for normal functions related to migration, clearance, and the ability to shift from a pro-inflammatory to an anti-inflammatory state to regulate injury and repair. This shift in microglia potentially contributes to increased susceptibility and neurodegeneration as a function of age (Harry 2013), though aging itself is not a disease. However, age-related macular degeneration, as well as neurodegenerative diseases such as AD, PD, share two characteristics in common: (1) a disease prevalence that increases markedly with advancing age, and (2) microglia-related neuroinflammation. These characteristics have led to the hypothesis that pathogenic mechanisms

underlying age-related neurodegenerative disease involve aging changes in microglia (Wong 2013).

As mentioned above, microglia have been implicated in disease progression for several age-related brain disorders (Lai et al. 2013). Also, hypothalamic inflammation and control of systemic ageing was reported. The hypothalamus is important for the development of whole-body ageing in mice, and that the underlying basis involves hypothalamic immunity mediated by I κ B kinase- β , NF- κ B and related microglia–neuron immune crosstalk (Gabuzda and Yankner 2013; Zhang et al. 2013).

Considering these evidence mentioned above, understanding and controlling microglial aging and age-associated microglial priming, being increased inflammatory status, may represent an opportunity for elucidating disease mechanisms and for formulating novel therapies (Wong 2013; Norden and Godbout 2013).

13.7.4 Psychiatric Disorders Including Autism Spectrum Disorder

Microglial cells, are more and more considered to contribute to multiple neuropathologies, including neuropsychiatric and developmental disorders. Growing evidence indicates a role for deregulation or malfunction of glial cells and their neuroinflammatory response in the brains of autistic patients (Theoharides et al. 2013).

Recently neurobiological basis of oligodendroglial abnormalities in schizophrenia and microglial activity in the context of the disease, in neonatal brain injury and in various experimental models of white matter damage were described (Chew et al. 2013). Microglia, have recently been also suggested to play important roles in neuropsychiatric disorders (Kato et al. 2013a) and possibility that modulating microglia may be a key target in the treatment of various psychiatric disorders has been proposed (Kato et al. 2013b). Future investigations to clarify the correlation between neuroendocrine factors and microglia may contribute to a novel understanding of the pathophysiology of neuropsychiatric disorders.

Conclusion

Microglial cells are fundamental elements of neuropathology. Microglial cells are constantly scanning the brain tissue for any signs of damage and when these latter occur microglial launch a defensive response generally known as microglial activation. Microglia express variety of receptors and respond to many signals. Identification of those signaling and manipulating microglial functions may lead to promising therapeutic strategy for neuropathological processes.

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