Chapter 5
Regulation by Nicotinic Acetylcholine Receptors of Microglial Glutamate Transporters: Role of Microglia in Neuroprotection

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Abstract  Accumulated evidence shows that activation of microglia is associated with a change in morphology, from ramified to globular, which also represents a transition to M1 microglia. M1 microglia contribute to the induction and development of various neuroinflammatory disorders, including stroke, spinal cord injury, multiple sclerosis, Parkinson’s disease, Alzheimer’s disease psychiatric disorders, neuropathic pain and epilepsy. Thus, inhibition of microglial activation would be crucial in treating neurological disorders. Recent studies suggest a number of attractive molecular targets for blocking microglial activation. Among them, the nicotinic ACh receptor (nAChR), which especially contains the α7 subunit, contributes to the regulation of microglial activity through the inhibition of the synthesis of proinflammatory molecules. In addition, the glutamate transporter GLAST expressed in microglia is upregulated by α7 nAChR stimulation, which is mediated through both inositol triphosphate-Ca^{2+}/calmodulin-dependent protein kinase II and fibroblast growth factor-2 pathways. It is possible, then, that activation of microglial α7 nAChR could be neuroprotective through inhibition of the production of proinflammatory molecules and enhancement of glutamate clearance from the synapse. This chapter will give an overview of the role of the α7 nAChR in microglial functioning and its potential as a therapeutic target for neurological disorders.

Keywords  Microglia · α7 nicotinic ACh receptor · Glutamate transporter · GLAST · Ca^{2+} · Calmodulin-dependent protein kinase II · Fibroblast growth factor-2

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5.1 Microglia

Neuroinflammation is involved in the induction of various neurodegenerative and neuropsychiatric disorders including stroke, spinal cord injury, multiple sclerosis, Parkinson’s disease, Alzheimer’s disease, depressive disorders, schizophrenia, neuropathic pain and epilepsy (Blank and Prinz 2013; Frank-Cannon et al. 2009; Yrjänheikki et al. 1998). Neuroinflammation is mainly mediated by CNS glial cells such as microglia and astrocytes. Microglia, originally derived from the reticuloendothelial system, have a pivotal role as the main effector cells of the immune system (Kettenmann and Verkhratsky 2008). Although present in all region of the CNS, microglia are not uniformly distributed, representing between 0.5 and 16.6% of all cells in human and mouse brain (Lawson et al. 1990; Mittelbronn et al. 2001). Microglia act as a type of macrophage in peripheral tissues. Microglia are highly ramified, with long processes and small cell bodies, under the normal physiological state (Kettenmann et al. 2011). The recent emergence of live cell imaging technology reveals that microglia have highly motile processes that continuously survey the surrounding environment (Nimmerjahn et al. 2005; Davalos et al. 2005). This state represents the “resting” phenotype, which is involved in maintaining homeostasis (Kettenmann et al. 2011). Therefore, changes in microglial activity and functionality are indicative of pathological conditions.

5.2 Neuroinflammatory and Neuroprotective Roles of Microglia

It is widely known that activation of microglia, in response to illness, infection and injury, lead to morphological changes, from the highly ramified configuration to a globular, amoeboid shape (Kitamura et al. 1978; Stence et al. 2001; Thomas 1992). Activated microglia demonstrate increased proliferation, migration to the site of injury, scavenging of exogenous substances, cellular debris and pathogens, and production of proinflammatory molecules, including cytokines, chemokines, prostaglandins, nitric oxide and reactive oxygen species (Suzuki et al. 2004; Hide et al. 2000; Koizumi et al. 2007; Stence et al. 2001; Nolte et al. 1996; Morioka et al. 2013; Garrido-Gil et al. 2013; Fernandes et al. 2014). Cells that exhibit this phenotype are identified as “M1 microglia” (Kigerl et al. 2009). In fact, it has been demonstrated that hyper- or chronic activation of microglia could lead to the initiation of neurodegenerative disorders (Moehle and West 2015; Henkel et al. 2009). In addition, treatment with the microglial inhibitor minocycline, a tetracycline antibiotic, reduces inflammation in animal models of neurodegeneration (Wu et al. 2002; Hou et al. 2016).

At the same time, microglia also contribute to tissue recovery. Microglia produce anti-inflammatory and neuroprotective molecules, such as brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), transforming
growth factor-β (TGF-β), tumor necrosis factor (TNF), interleukin-4 (IL-4) and interleukin-10 (IL-10) (Suzuki et al. 2004; Lai and Todd 2008; Polazzi and Monti 2010; Amantea et al. 2015). Microglia showing anti-inflammatory and neuroprotective properties are called “M2 microglia”. Stimulation of microglia with IL-4 and interleukin-13 (IL-13), which are secreted by Th2 lymphocytes (Freilich et al. 2013), induces the M2 phenotype. M2 microglia express markers such as heparin-binding lectin, cysteine-rich protein FIZZ-1 and arginase-1 (Freilich et al. 2013). Transient middle cerebral artery occlusion induces brain tissue infraction and cell apoptosis. The number of apoptotic cells in infarcted tissue in transgenic mice in which microglia were selectively ablated was significantly more than that of wild-type mice (Lalancette-Hébert et al. 2007). Microglial phenotype is altered depending on environmental conditions—thus, microglial functioning show apparently opposing properties, either pro-inflammatory or anti-inflammatory (Ponomarev et al. 2007). Previous findings also indicate that blockade of microglial activity alone may not be sufficient as a treatment for neuroinflammatory disorders, so further elucidating changes in microglial phenotypes and properties under specific pathological conditions is crucial. Although there are a number of studies on the role of M1 microglia in proinflammatory responses and their involvement in neurological disorders, their roles in neuroprotection and their function in neuroinflammatory and neurodegenerative diseases have yet to be fully elaborated. In this vein, more research is necessary on identifying the neuroprotective molecules released by microglia under pathological conditions.

5.3 Nicotinic Acetylcholine Receptors and Microglia

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels, consisting of hetero- or homo-pentameric subunits. These receptors have important roles in neurobiological processes such as memory, learning, locomotion, attention and anxiety (Dajas-Bailador and Wonnacott 2004; Dani and Bertrand 2007; Zoli et al. 2015). In the mammalian brain, 12 genes each encode a subunit, and nine different nAChR subunits have been identified (α2-α10 and β2-β4) (Dani and Bertrand 2007). The homomeric α7 nAChR is one of the most abundantly expressed and widely distributed subtype in the brain (Gotti and Clementi 2004; Sargent 1993). The α7 nAChR is expressed not only in neurons, but also in non-neuronal cells such as astrocytes, microglia, oligodendrocyte precursor cells and brain endothelial cells (Liu et al. 2015; Kihara et al. 2001; Suzuki et al. 2006; Hawkins et al. 2005; Rogers et al. 2001). Human microglia express the α3, α5, α7 and β4 subunits (Rock et al. 2008), whereas the α7 nAChR is the only functional nAChR subtype in rat cortical microglia (Morioka et al. 2014). The rat cortical microglia, then, makes an ideal system to study the neurobiological role of the α7 nAChR.

The α7 nAChR appears to have a critical role in neuroprotection. Peripheral macrophages express α7 nAChR, which regulate the systemic response to inflammation
Microglial α7 nAChR could be responsible for modulating the response to inflammation in the mouse brain. Prevention of lipopolysaccharide (LPS)-induced TNF release from murine microglia is mediated through activation of the α7 nAChR (Shytle et al. 2004). Activation of microglial α7 nAChR suppresses the production of a number of proinflammatory molecules (Suzuki et al. 2006; Giunta et al. 2004; De Simone et al. 2005; Rock et al. 2008; Zhang et al. 2017). Furthermore, stimulation of the α7 nAChR suppresses the production of reactive oxygen species (ROS) in microglia stimulated with fibrillar β-amyloid peptide (Moon et al. 2008), in addition, treatment of cultured microglia with galantamine, a nAChR allosteric ligand, induces phagocytosis of β-amyloid in an α7 nAChR-dependent manner (Takata et al. 2010), suggesting a potential role of the α7 nAChR in the pathophysiology of Alzheimer’s disease. Stimulation of the α7 nAChR also increases expression of anti-inflammatory and neuroprotective molecules such as TGF-β1, IL-4, IL-10 and heme oxygenase-1 (De Simone et al. 2005; Parada et al. 2013; Rock et al. 2008; Zhang et al. 2017). Treatment of a microglial cell line BV2 with an α7 nAChR agonist increases autophagy, an anti-inflammatory response (Shao et al. 2017). Furthermore, treatment with nicotine inhibits LPS-induced H+ currents through α7 nAChR (Noda and Kobayashi 2017). It is known that H+ channel-mediated currents are required for NAPDH oxidase-dependent ROS generation in brain microglia, a key step in the neuroinflammatory pathway (Wu et al. 2012). While it is currently unknown whether the stimulation of α7 nAChR induces the switching of microglial phenotype from M1 to M2, studies clearly indicate the importance of microglia-expressed α7 nAChR in reducing neuroinflammation, and suggest that microglial α7 nAChR could be utilized as a therapeutic target for the treatment of neuropathological disorders (Table 5.1).

5.4 Glutamate Transporters and Microglia

Glutamate is not only one of the major excitatory neurotransmitters mediating memory, learning and acute pain perception, but is excitotoxic at high concentrations in the synapse. Therefore, the regulation of synaptic glutamate concentration, to prevent the overstimulation of post-synaptic neurons, is important in preventing excitotoxicity, and is mainly conducted through Na+/K+-dependent glutamate transporters located in glial cells and neurons (Robinson and Dowd 1997). Thus far, five glutamate transporters have been cloned and pharmacologically characterized: excitatory amino acid transporter (EAAT) 1 (glutamate/aspartate transporter; GLAST) and EAAT2 (glutamate transporter 1; GLT-1), which are mainly expressed in glial cells, and EAAT3 (excitatory amino acid carrier 1; EAAC1), EAAT4 and EAAT5, which are mainly expressed in neurons (Arriza et al. 1997; Fairman et al. 1995; Kanai and Hediger 1992; Pines et al. 1992). In general, astrocytic GLAST and GLT-1 are important for maintaining low concentration of glutamate (Shibata et al. 1997), and astrocytic glutamate uptake at synapses account for about 90% of total clearance under physiological conditions (Tanaka et al. 1997).
Microglial glutamate transporters contribute to synaptic glutamate homeostasis. Activated microglia express GLAST and GLT-1 in both in vivo and in vitro (Noda et al. 1999). Under excitotoxic conditions, microglial glutamate uptake is enhanced. Table 5.1 summarizes the effects of α7 nAChR stimulation on microglial function:

| Authors              | Species | Cell types       | Agonists                  | Actions                                                                 |
|----------------------|---------|------------------|---------------------------|-------------------------------------------------------------------------|
| Shytle et al. (2004) | Mouse   | Primary culture  | ACh, nicotine             | Inhibition of LPS-induced TNF expression                                |
| Giunta et al. (2004) | Mouse   | Primary culture  | Nicotine+galantamine      | Inhibition of gp120+IFN-γ-induced TNF expression, NO production, and ERK phosphorylation |
| Noda and Kobayashi (2017) | Mouse | Primary culture  | Nicotine                  | Inhibition of LPS-induced proton current                                |
| De Simone et al. (2005) | Rat  | Primary culture  | Nicotine                  | Inhibition of LPS-induced TNF, NO, and IL-10 expression increase of LPS-induced PGE2; no effect on IL-1β expression |
| Suzuki et al. (2006) | Rat     | Primary culture  | Nicotine                  | Inhibition of LPS-induced TNF production, increased ATP-induced TNF production |
| Moon et al. (2008)  | Rat     | Primary culture  | Nicotine                  | Inhibition of Aβ-induced ROS production                                |
| Takada et al. (2010) | Rat    | Primary culture  | Nicotine, galantamine     | Enhancement of Aβ clearance                                             |
| Parada et al. (2013) | Rat    | Organotypic hippocampal cultures | PNU282987 | Induction of heme oxygenase-1 expression                                |
| Rock et al. (2008)  | Human   | Primary culture  | Nicotine                  | Increased TGF-β1, IL-4, CX3CL1, CCR2, CXCR6 expression, inhibition of IL-8, IL-10, TNF, CCL2, CXCR4 expression |
| Zhang et al. (2017) | Mouse   | BV2              | ACh                       | Inhibition of LPS-induced IL-1β and IL-6 expression, p38 phosphorylation increased IL-4, and IL-10 expression rescue of LPS-suppressed JAK/STAT3 phosphorylation, and PI3K/Akt phosphorylation |
| Shao et al. (2017)  | Mouse   | BV2              | PNU282987                 | Increased autophagy                                                     |

Microgliarexpress functional glutamate transporters, which are involved in regulating glutamate homeostasis in synapses (Morioka et al. 2008). It has been shown that activated microglia express GLAST and GLT-1 both in vivo and in vitro (Noda et al. 1999). Microglial glutamate uptake at synapses is about 10% of that of astrocytes under physiological conditions (Persson et al. 2005; Shaked et al. 2005). Under excitotoxic conditions induced by high concentrations of glutamate, however, activity and expression of microglial glutamate transporters are enhanced by exclud-
ing excess glutamate. For example, GLT-1 expression is increased in activated microglia following nerve injury (López-Redondo et al. 2000). Furthermore, stimulation of cultured microglia with LPS increases GLT-1 expression and glutamate transport capacity (Persson et al. 2005). A clinical study demonstrated that microglial glutamate transporters are involved in the control of neuronal damage in traumatic brain injury. Upregulation of GLAST expression in microglia is observed in brain white matter 1 week after ischemia (Beschorner et al. 2007). In addition, the expression of glutamate transporters (GLAST, GLT-1 and EAAC1) is observed in microglia/macrophages within the infract region at 7 and 28 days after ischemia (Arranz et al. 2010). Thus, these observations indicate that microglial glutamate transporters could be crucial in reducing glutamate-mediated excitotoxicity. Although astrocytes generally have a crucial role in clearing glutamate from the synapses, the activity of glutamate transport in astrocytes is in fact downregulated under pathological conditions (Fine et al. 1996; Xin et al. 2009). Therefore, microglial glutamate transporters, which are upregulated under pathological conditions, serve as a back-up to astrocytic glutamate uptake (López-Redondo et al. 2000; Xin et al. 2009). However, microglial glutamate transporter function and the functional relationship between α7 nAChR and glutamate transporters in microglia, have yet to be elaborated.

5.5 Nicotinic Acetylcholine Receptor and Glutamate Transporters

A number of studies have described significant interactions between nAChR and monoamine transporters, which comprise of noradrenaline, dopamine and serotonin transporters. For example, treatment with nicotine induced increased expression and functioning of these transporters in frontal cortical neurons and other cell types (Danielson et al. 2011; Itoh et al. 2010; Awtry and Werling 2003; Middleton et al. 2004). By contrast, few studies have demonstrated a positive functional interaction between the nAChR and glutamate transporters. Basal glutamate uptake in cultured glial cells derived from rat pups prenatally exposed to nicotine is higher than normal (Lim and Kim 2001). Furthermore, increased activity of astrocytic glutamate transporters (GLAST and GLT-1) is observed following neuronal nAChR stimulation, which increases synaptic levels of glutamate (Poitry-Yamate et al. 2002). Chronic treatment of Xenopus oocytes overexpressing EAAC1 with nicotine reduces EAAC1 activity (Yoon et al. 2014). Stimulation of cultured cerebellar astrocytes with nicotine modulates glutamate uptake, which is probably mediated through either a cAMP-independent or cAMP-dependent mechanism (Lim and Kim 2003).
5.6 Alpha7 Nicotinic Acetylcholine Receptors and Microglial Glutamate Transporters

Although nicotine modulates activity and expression of glutamate transporters in the CNS, the actual nAChR subtype involved and the intracellular signal cascade mediating the transporter’s response to nAChR stimulation are not clear. Furthermore, a potential role of α7 nAChR modulating microglial glutamate transporters has yet to be elaborated. A recent study showed that activation of the microglial α7 nAChR system is crucial in the regulation of glutamate transporters (Morioka et al. 2014, 2015). Cultured rat cortical microglia mainly express GLAST and not GLT-1, as shown by RT-PCR and pharmacological analysis using selective inhibitors for GLAST and GLT-1. Treatment with nicotine increases GLAST mRNA expression and glutamate transport activity and the effect of nicotine is blocked by pretreatment with a selective α7 nAChR antagonist, indicating that α7 nAChR mediates nicotine-induced GLAST expression. Understanding the role of the α7 subtype, this is the only nAChR subtype expressed in the cortical microglia.

The concentration of nicotine needed to induce GLAST expression is relatively high (300–1000 μM) compared to concentrations utilized in other in vitro assays. It is possible that, compared to α7 nAChR expressed in other cell types, cortical microglial α7 nAChR has unique properties. Microglial α7 nAChR demonstrates a different pattern of electrical current compared with that demonstrated by neurons, in which stimulation of cortical microglia with nicotine does not evoke current, although ATP treatment evokes current (Suzuki et al. 2006). Furthermore, the α7 nAChR has two isoforms with different pharmacological properties: a low and a high affinity nicotinic binding site (Severance et al. 2004). In fact, high concentrations of nicotine (>1000 μM) is used to stimulate microglia/macrophage α7 nAChR (Takata et al. 2010; Sun et al. 2013). Thus, in the case of microglial α7 nAChR, high concentrations of nicotine may be needed to activate microglia. Further investigation is necessary to elucidate precise pharmacological and functional properties of α7 nAChR.

Various intracellular signal molecules are involved following stimulation of α7 nAChR in vitro (Kihara et al. 2001; Arredondo et al. 2006; Maouche et al. 2013). In rat cortical microglia, stimulation of the α7 nAChR induced a rapid and transient increase in the concentration of cytosolic Ca\(^{2+}\) through the activation of phospholipase C (PLC) and the release of Ca\(^{2+}\) from inositol triphosphate (IP\(_3\))-sensitive intracellular stores, but not through the influx of extracellular Ca\(^{2+}\) (Suzuki et al. 2006). Increased cytosolic Ca\(^{2+}\) concentration through an IP\(_3\) receptor-dependent mechanism is one of the key events underlying nicotine-α7 nAChR-mediated GLAST expression, block of the IP\(_3\) receptor, but not removal of extracellular Ca\(^{2+}\), inhibits nicotine’s effect. Likewise, Mashimo et al. previously demonstrated that an IP\(_3\) receptor signaling cascade is crucial in the regulation of GLAST expression in Bergmann glial cells, which are a type of astrocyte found in the cerebellum (Mashimo et al. 2010).
A number of studies have indicated that several signaling molecules are activated following increased cytosolic Ca\(^{2+}\) concentration in microglia (Takata et al. 2010; Suzuki et al. 2006; Hide et al. 2000). The calmodulin-Ca\(^{2+}\)/calmodulin-dependent protein kinase II (CaMKII) pathway is activated following an α7 nAChR-mediated Ca\(^{2+}\) influx, eventually leading to microglia phagocytosis of amyloid β (Takata et al. 2010). CaMKII activation is crucial since inhibiting CaMKII blocks nicotine-induced GLAST expression and glutamate transport in cortical microglia. Others have confirmed that CaMKII activity has an important role in glutamate uptake in cortical astrocytes induced through other pharmacological stimuli (Smith and Navratilova 1999). By contrast, other signal molecules, including protein kinase A, protein kinase C, phosphatidylinositol 3-kinase, janus-activated kinase, Src tyrosine kinase and extracellular signal-regulated protein kinase, do not appear to have a major role in nicotine-mediated GLAST expression in microglia.

Increased cytosolic Ca\(^{2+}\) concentration is observed within 1–2 min following nicotine treatment (Suzuki et al. 2006). Thus, it is speculated that CaMKII is rapidly activated in parallel with increased intracellular Ca\(^{2+}\). However, upregulation of GLAST mRNA expression is observed only after 18 h of nicotine treatment. Therefore, this delay between increased cytosolic Ca\(^{2+}\) concentration and GLAST expression suggests the induction of intermediary molecules which could have a role in GLAST expression. In fact, the protein synthesis inhibitor cycloheximide blocks nicotine-induced GLAST mRNA expression, indicating the presence of a protein intermediary between increased Ca\(^{2+}\) concentration and GLAST expression.

Stimulation of nAChRs contributes to the production of several molecules such as cytokines, chemokines, and neurotrophic factors (Hawkins et al. 2015; Maggio et al. 1998; Son and Winzer-Serhan 2009; Takarada et al. 2012). These substances in turn could enhance clearance of glutamate from the synapse by increasing GLAST expression. A number of studies have demonstrated that growth factors, including epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1) and TGF-β1, modulate GLAST expression in astrocytes (Figiel et al. 2003; Lee et al. 2009; Suzuki et al. 2001). In addition, treatment of cultured microglia with nicotine increases FGF-2 mRNA, but not EGF, IGF-1 and TGF-β1 mRNAs, via the stimulation of the α7 nAChR. FGF-2 protein is also increased after treatment with nicotine. Thus, these findings indicate that FGF-2 could be the crucial intermediary between α7 nAChR and GLAST upregulation.

In fact, treatment of cultured microglia with recombinant FGF-2 increases expression of GLAST and increases glutamate transport. In addition, pretreatment with a selective inhibitor of FGF receptor (FGFR) tyrosine kinase blocks the stimulatory effect of nicotine on GLAST expression and glutamate transport. The FGFR has four subtypes (FGFR1–FGFR4). Cultured cortical microglia express FGFR1 mRNA, but not FGFR2 mRNA, FGFR3 mRNA, and FGFR4 mRNA. In neurons, FGF2 exerts neuroprotection by activating FGFR1, thereby decreasing glutamate-induced damage of hippocampal neurons through the production of GDNF (Lenhard et al. 2002). Thus, the microglial α7 nAChR-FGF-2-FGFR1 pathway elicited by nicotine could be neuroprotective through the enhancement of glutamate clearance.
FGF-2 has a neuroprotective role in preclinical animal models of neuroinflammation and neurodegenerative disorders. FGF-2 secreted from injured neurons could lead to microglia transformation and neuroprotective activities such as migration and phagocytosis (Noda et al. 2014). Enhancing brain FGF-2 expression restores hippocampal functioning in a preclinical model of Alzheimer’s disease (Kiyota et al. 2011).

Although further investigation is needed to elaborate the relationship between transformed M2 microglia and neuroprotection, the findings so far indicate that the nicotine-α7 nAChR system modulates microglial GLAST function and regulates the clearance of synaptic glutamate (Fig. 5.1).

### 5.7 Drug Development Targeting α7 nAChR for Neurological Disorders

Targeting the α7 nAChR is a potential strategy to treat neurological disorders which currently have no effective treatments. In fact, a selective α7 nAChR agonist reduces 6-hydroxydopamine-induced dopaminergic neuronal damage in a rat model of Parkinson’s disease (Suzuki et al. 2013; Bordia et al. 2015). Furthermore, the α7 nAChR is a potential target for the treatment of cognitive dysfunction associated with Alzheimer’s disease. Systemic treatment with selective α7 nAChR agonists, either PHA-543613 or galantamine, improves cognitive dysfunction in...
β-amyloid-treated mice (Sadigh-Eteghad et al. 2015). In addition, the α7 nAChR may be involved in regulating nociceptive transduction, as α7 nAChR agonists ameliorate experimental painful peripheral neuropathies (Di Cesare Mannelli et al. 2014; Freitas et al. 2013). Studies uncovering the relationship between α7 nAChR and microglial function in particular suggest the possibility that α7 nAChR expressed by microglia are a novel therapeutic target for the treatment of neurological disorders. For example, stimulation of the α7 nAChR enhances microglial β-amyloid clearance (Takata et al. 2010). Direct activation of microglial α7 nAChR is neuroprotective, through upregulation of heme oxygenase-1, against oxygen and glucose deprivation in organotypic hippocampal culture (Parada et al. 2013). Recent findings also demonstrate that stimulation of α7 nAChR enhances GLAST expression and glutamate transport in microglia, suggesting that enhancing glutamate reuptake at the synapse is crucial in maintaining normal functioning of the glutamatergic system. Furthermore, it is also possible that downregulation of the α7 nAChR itself is associated with the induction of neurological disorders. Thus, direct stimulation of α7 nAChR or gene therapy to enhance α7 nAChR expression, especially in microglia, could be useful for treatment of various neurological disorders.

5.8 Conclusions

Hyperactivation of microglia, especially transitioning to the M1 phenotype, contributes to the induction of neuropathology in the CNS, suggesting that targeting M1 microglia could be an appropriate treatment for neurological disorders. Although mechanisms regulating the switching of microglial phenotypes have yet to be fully elaborated, inducing the transitioning of microglia from the M1 phenotype to the M2 phenotype could be an alternate therapeutic approach. As described above, the α7 nAChR contributes to the regulation of a number of microglial functions, especially in the reduction of neuroinflammatory responses and the clearance of potentially excitotoxic levels of synaptic glutamate. Therefore, further understanding of the molecular and cellular mechanisms underlying α7 nAChR expressed in microglia could aid in the development of therapeutic strategies for neuroinflammatory and neurodegenerative diseases, which in general, are lacking in effective treatments.

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