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Possible Contribution of Microglial Glutamate Receptors to Inflammatory Response upon Neurodegenerative Diseases

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Abstract

Microglial cells actively contribute to tripartite synapses by direct contact or releasing diffusible factors. In neuron-microglia interaction, there are number of candidates as microglial signalling to neurons, for example neurotrophic factors, pro-inflammatory cytokines and chemokines. However, little is known about neuronal signalling to microglia. Microglial cells express various kinds of neurotransmitter receptors including glutamate receptors; both ionotropic and metabotropic glutamate receptors. Among them, microglial AMPA receptors are impermeable to Ca^{2+} due to the expression of GluA2. GluA2 is an important subunit in determining the functional properties of AMPA receptors, such as Ca^{2+} -permeability, conductance, assembly and trafficking. Activation of microglia induces membrane translocation of GluA2, while internalization of other subunits occurs, and nearly homomeric GluA2 subunits are suggested as the main reason for low conductance of AMPA receptors in activated microglia. Since low expression of GluA2 was reported in some neurodegenerative diseases, lack of GluA2 in microglia as well as in neurons contribute to excitotoxicity by excess release of proinflammatory cytokines such as TNF-α. 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.

Keywords: Tripartite synapse; Microglia; AMPA receptor; GluA2; Kainate; TNF-α; Neurodegeneration

Abbreviations: AMPA: α-amino-hydroxy-5-methyl-isoxazole-4-propionate; ATP: Adenosine Triphosphate; BDNF: Brain-Derived Neurotrophic Factor; CNS: Central Nervous System; EAAT: Excitatory Amino-Acid Transporter; FGF: Fibroblast Growth Factor; GDNF: Glial-Derived Neurotrophic Factor; GLAST: Glutamate Aspartate Transporter; GLT-1: Glutamate Transporter-1; NO: Nitric Oxide; IL-3: Interleukin-3; IL-6: interleukin-6; Glu: Glutamate; KA: Kainic Acid (kainite); mGluRs: Metabotropic Glutamate Receptors; NGF: Nerve Growth Factor; NMDA: N-methyl-D-aspartate; TGF-β1: Transforming Growth Factor-β1; TNF- α: Tumour Necrosis Factor- α

Introduction

The involvement of microglia in neurotransmission has been already proposed since many years ago. For example, NMDA-mediated synaptic response was potentiated by microglia [1] and it was through the activation of the glycine site by secreting soluble factors released from primary cultured microglia [2]. It is now well known that microglia release substances that can affect neurons. These factors include several types of cytokines and chemokines, trophic factors like BDNF, the gaseous transmitter NO or neurotransmitters (ATP and Glu) [3]. In the lesion to the facial nerve that carries axons of motoneurons located in the facial nucleus, various factors released from activated microglia were detected; neurotrophic factors such as NGF, neurotrophin-4/5, TGF-β1, GDNF, FGF, and IL-3, which affect neuronal survival [4], as well as proinflammatory mediators such as TNF-α, IL-6, or NO, which confer neurotoxicity. In addition to these secretory activity, microglia proliferate, migrate to and interact with motor neurons ultimately removing synaptic input to those neuronal cells [5], depending on the pathologic context [6]. This removal of synaptic input, i.e. removal of synapses from neuronal cell bodies by microglia, was first recognized in the facial nerve injury model and termed synaptic stripping [7] and was well documented due to the recent advancement of electron microphotograph and *in vivo* imaging and transgenic animals [8,9].

All these information describes signals from activated microglia to neurons, regardless "find-me" or "eat-me" signals [10]. In contrast, what about signals from neurons to microglia?

As mentioned above in microglial factors, neurotransmitters (ATP, Glu, and probably others, too) might be the most plausible factors from neurons and synapses.

Microglia express almost all kinds of neurotransmitter receptors [3,11]. Among them, glutamate (Glu) receptors including AMPA/KA receptors [12,13], NMDA receptors [14] and metabotropic glutamate receptors (mGluRs) [15-17] are expressed in microglia. In addition, activated microglia express Glu transporters, EAAT-1/GLAST and EAAT-2/GLT-1 [18]. They may play an important role with respect to Glu-mediated neuron-glia interaction [19]. Although the physiological role of glial Glu receptors and GluT remains largely unknown, their potential roles include regulation of proliferation and differentiation, and modulation of synaptic efficacy.

Recent anatomical and functional evidence indicates that Glu receptors on immature glia are activated through direct synaptic inputs. Therefore, Glu and its receptors appear to be involved in a continuous crosstalk between neurons and glia during development and also in the mature brain [20].

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Glu Receptors and Glu Transporters in Microglia

Microglia express various type of neurotransmitter receptors [3]. Among them, it is surprising that microglia, the brain's immune cell population, has Glu receptors, especially ionotropic types. The expression of microglial AMPA/KA receptors in resting state is heterogenous and low, about 20% of culture microglial cells show expression of AMPA/KA receptors [12,21]. Furthermore the electrophysiologically recorded membrane currents due to activation of AMPA/KA receptors were much smaller than neuronal ones (a couple of pA) unless the currents were augmented by cyclothiazide, an inhibitor of AMPAR desensitization. On the other hand, increase in KA receptor expression (GluA6 mRNA) in proliferating state in microglial cell line was reported [21], suggesting cell cycle-dependent regulation of KA receptors. The question was the functional role of these glutamate receptors in microglia. After the first report of AMPA/KA receptors in microglia, there is increasing evidence for primary cultured microglial AMPA receptor-induced events such as IGF-1 release [22], microglial chemotaxis [23], ATP release [23], TNF-α release [12,13] and upregulated *c-fos* expression [24]. However, the physiological and pathophysiological role of AMPA/KA receptors in microglia still remains unclear. Another type of ionotropic glutamate receptor, NMDA receptor, in microglia was first reported in rat microglia. Activation of microglial NMDA receptor triggers inflammation and neuronal cell death, which is probably only under pathologic condition; it was shown that damaged neurons further activate microglial NMDA receptor and trigger a release of neurotoxic factors from microglia *in vitro*, indicating that microglia can signal back to neurons and possibly induce, aggravate, and/or maintain neurologic disease [14].

Microglia also express mGluRs. Group I mGluR was the first glutamate receptor reported in microglia [15], followed by reports on group II and III mGluRs in microglia [16,17]. There is some evidence that stimulation of group I mGluRs may regulate LPS-induced microglial activation in primary cultures [15]. The stimulation of group II mGluRs, either by glutamate or agonist of group II mGluRs, triggered the activation of microglial cells and induced neurotoxicity mediated through microglial release of TNF-α [25]. It was also suggested to participate in the activation of primary cultured microglia induced by chromogranin A, a secretory peptide present in neuritic plaques in Alzheimer's disease [16]. In contrast, activation of group III receptors reduced microglial neurotoxicity following treatment with LPS or chromogranin A. On a molecular level, group III receptors inhibited activity of adenylate cyclase [17].

As for Glu transporter, it was reported that activated microglia express Glu transporters, EAAT-1/GLAST and EAAT-2/GLT-1, though baseline expression of GLT-1 and GLAST in naive animals is primarily localized in astrocytes [26] and it was reported that macrophages and microglia do not express GluTs as well as glutamine synthase in physiological conditions [27]. Insults to the CNS may upregulate microglial glutamate transporters. Reversed mode of the transporter can cause accumulation of Glu in the regions of injury. It was suggested that activated microglia prepared from primary culture trigger the elevation of extracellular Glu through their own release of Glu [28]. Treatment of primary cultured microglia with soluble amyloid β peptide also showed functional up-regulation of reverse-mode of GluT, suggesting the release of Glu from microglia [29]. On the other hand, it was also shown that microglial Glu transporter has the ability of Glu uptake via GLT-1 without any stimulation [30]. These functional measurements, especially electrophysiological recording, may need to be done at 33-34°C [29].

Importance of GluA2 in Synaptic Transmission

Among AMPAR subunits, GluA2 (previously named as GluR-B, GluR2 or GluR-K2 [31]) plays a key role in determining the functional properties of AMPARs, such as Ca^{2+}-permeability, conductance, assembly and trafficking [32]. In contrast, there are several reports suggesting a decreased expression of GluA2 in patients with neurodegenerative diseases such as Alzheimer's and Creutzfeldt-Jakob disease [33,34]. In neurons lacking the edited GluA2 subunit, AMPA receptors exhibit high Ca^{2+} permeability [35]. With GluA2 subunit but not on the membrane surface, repetitive synaptic activation of Ca^{2+} -permeable AMPARs causes a rapid reduction in Ca^{2+} permeability and a change in the amplitude of excitatory postsynaptic currents, owing to the incorporation of GluA2-containing AMPA receptors [36]. Whereas when primary microglial cells were activated with LPS, more GluA2 was incorporated to the membrane surface and the conductance of AMPA receptors channels became smaller [37]. Thus, the switch in receptor subtype of AMPA receptor seems to be regulated by multiple signalling pathway in neuron and microglia. Most of the primary cultured rodent microglial cells express GluA2 subunit, exhibiting low Ca^{2+} permeability [13]. However, under the pathological condition where less GluA2 subunits are expressed, high Ca^{2+} permeability and subsequent physiological responses are expected (Figure 1, left). On the other hand, under physiological condition with GluA2 subunit, expression of membrane surface GluA2 was upregulated depending on the activation of primary cultured microglia, limiting the conductance of AMPA receptor channel conductance [37] (Figure 1, right).

Dynamic Interaction of Microglial Processes with the Tripartite Synapse

It was already shown that processes from oligodendrocyte progenitor cells make close contact with neurons at pre- and postsynaptic structures [38]. Astrocytes have closer contact with synapses: in the grey matter, astrocytes are closely associated with

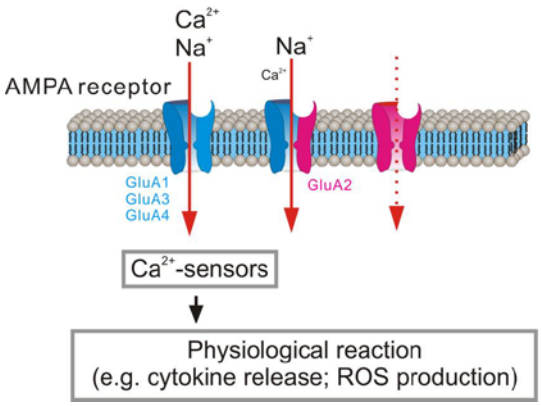

Figure 1: Different combination of AMPA receptor subunits in microglia. Microglia express AMPA-type of glutamate (Glu) receptors, which are highly Ca^{2+} impermeable due to the expression of GluA2 (center). However, when microglial cells are activated, for example by lipopolysaccharide, decreased expression of surface GluA1, GluA3, and GluA4 were indicated, while more surface GluA2 subunits were shown (right). Upregulation of GluA2 on the cell surface, probably by formation of GluA2 homomeric channels which causes very small current amplitudes. Under low expression of GluA2, which was reported in some neurodegenerative disorders such as Alzheimer's disease and Creutzfeldt-Jakob disease AMPA receptors with GluA1, GluA3 an GluA4 showed higher Ca^{2+}-permeability (left), consequently inducing significant increase in the release of proinflammatory cytokines or reactive oxygen species (ROS).

neuronal membranes. In many cases, astroglial membrane completely or partially enwrap pre-synaptic terminals as well as post-synaptic structures [39]. Microglial processes, too, enwrap synapses extensively [8]. Being visualized by *in vivo* two-photon imaging in double-transgenic mice in which microglial cells and neuronal structures can be simultaneously visualized, the microglial processes appear in a close proximity to presynaptic boutons, where they remain for about 5 min and then retract [40]. A rather specific apposition of microglial processes to pre- as well as post-synaptic compartments was found in the visual cortex of juvenile mice. Microglial process extrusions were typically associated with small and transiently growing dendritic spines [8].

Like mentioned above, the highly dynamic surveillant motility of microglia in the resting state is specifically targeted to synaptic structures [40-42]. Molecular cues that attract microglial processes to the synapses remain largely unknown, however, glutamate as well as ATP are good potential candidates, at least in the microenvironment in glutamatergic synapses.

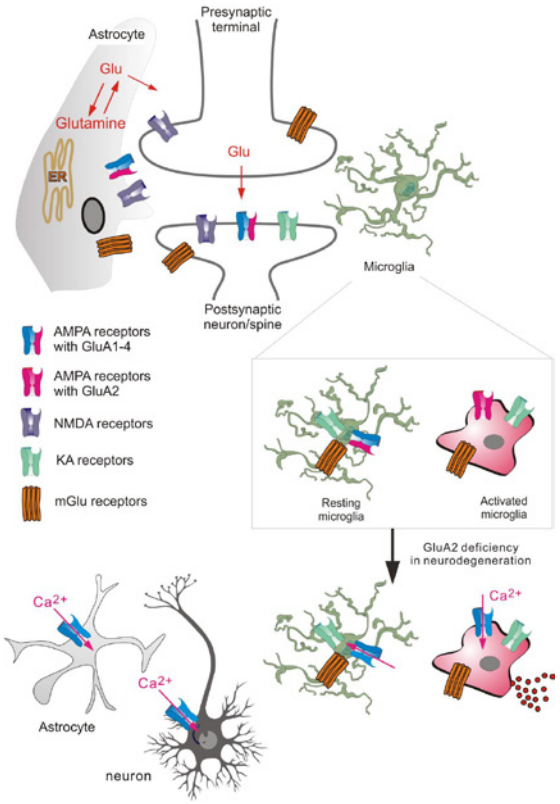

Figure 2: Effects of GluA2 deficiency on glutamate (Glu) transmission and tripartite synapse.
It has recently become evident that microglia constantly scan the brain environment and contact synapses. Under physiological condition, the highly dynamic surveillant motility of microglia is specifically targeted to synaptic structures: microglial processes dynamically contact the cellular compartments of the tripartite synapse, as well as the perisynaptic astroglial processes. Three cell types composing tripartite synapse, neuron, astrocytes and microglia, express various types of glutamate receptors (AMPA, NMDA, kainite (KA), and metabotropic glutamate (mGlu) receptors), though they are quite heterogenous and some of which in glial cells have not been confirmed electrophysiologically. Microglia are highly motile not only in morphologically but also functionally. Under any kind of pathological condition, microglia are activated and the subunit composition of AMPA receptors changes; more GluA2 on the surface membrane and limited conductance of the channel. However, in some neurodegenerative disorders, less GluA2 subunits are reported, leading more Ca^{2+} permeability in all cells composing tripartite synapse. Especially activated microglia, transforming from non-responsive cells to highly Ca^{2+} permeable cells in response to glutamate, may cause excess release of proinflammatory cytokines, contributing more glutamate toxicity to neurons.

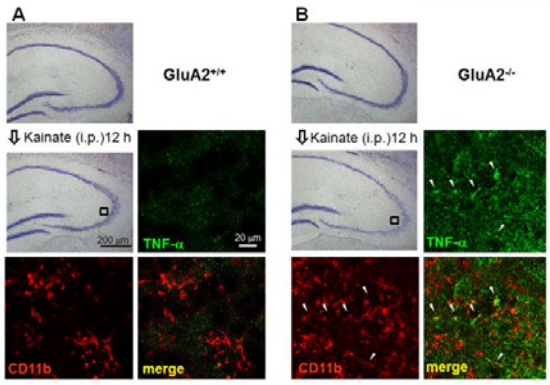

Figure 3: Lack of GluA2 in microglia induced more neurotoxicity in response to kainite (KA).
Nissl staining of hippocampal CA3 from either $GluA2^{+/+}$ or $GluA2^{-/-}$ mice with intraperitoneal (i.p) injection of KA (30 mg/kg). More neuronal loss was observed in $GluA2^{-/-}$ mice than in $GluA2^{+/+}$ mice. In the same CA3 region where black squares indicate, more TNF-α production and CD11b staining (marker of activated microglia) were observed in $GluA2^{-/-}$ mice than in $GluA2^{+/+}$ mice after injection of KA (i.p.).

The wide potential of microglia to sense various activities of their adjacent cellular neighbours suggest that processes of microglia as well as astrocytes are in close proximity to synapses. While astroglial contacts are considered to be a permanent component of the "tripartite synapse," microglial processes are much more dynamic than astroglial ones and display only transient interactions [41] (Figure 2).

What Happens if Expression of GluA2 is Low?

As mentioned above, GluA2 plays an important role in activated microglia due to increased expression on the surface membrane, attenuating Glu-induced response in activated microglia, as has been proposed in neurons [43]. Several reports provided *in vivo* immunohistochemical analysis of GluA2 expression in microglia upon neurodegenerative diseases such as brain hypoxia or multiple sclerosis [22,44], suggesting the possibility of importance of microglial GluA2. In Alzheimer's or Creutzfeldt-Jakob disease, total expression of GluA2 is decreased although cell type was not determined [33,34]. To verify importance of microglial GluA2 in these diseases, we should investigate cell type expression pattern of GluA2 and its causal relationship with microglial inflammatory response. We propose that if microglial GluA2 is also decreased together with neuronal one, microglial inflammatory response would be augmented, due to increased Ca^{2+} permeability (Figure 2).

It was reported that the Glu-mediated neuronal damage is strongly influenced by the AMPA receptors subtypes expressed in the CNS [34]. Within regions of high sensitivity in hippocampus, the AMPA receptor subunits GluA2 and GluA2/3 were decreased in accordance with the Braak stages of Alzheimer's disease [34]. To investigate the effects of lack of GluA2 in microglia, $GluA2^{-/-}$ microglia was used [37]. The result from primary cultured microglia showed that Ca^{2+}-permeability through AMPARs was much higher in $GluA2^{-/-}$ than $GluA2^{+/+}$ microglia and Glu-induced TNF-α release was increased in $GluA2^{-/-}$ compared to $GluA2^{+/+}$ microglia. Furthermore, it was demonstrated that the increased inflammatory response in

GluA2$^{-/-}$microglia led to more neuronal damages than in GluA2 microglia. Thus, the low expression of GluA2 in microglia, as well as in neurons, leads to severe Glu-toxicity in pathological conditions. In fact, intraperitoneal injection of KA caused apparent neuronal loss in hippocampal CA3 *in vivo* (Figure 3A). In the same area from GluA2$^{-/-}$ mice, neuronal loss was exaggerated (Figure 3B). The amount of TNF-α was significantly greater and more activation of microglia was observed as well in GluA2$^{-/-}$ than GluA2$^{+/+}$ mouse brain. In order to test out the contributions made by glia and neurons to KA-induced brain damage, cell type specific GluA2$^{-/-}$ mice will be useful.

Conclusions and Discussion

Dynamic translocation and increased surface expression of GluA2 occur in activated microglia as well as repetitively stimulated glutamatergic neurons, suggesting the loss of Glu-sensitivity under pathological condition. In microglia, GluA2 regulates not only Ca^{2+} permeability but also inflammatory response such as TNF-α release in response to Glu. Therefore, lack or decrease of GluA2 in microglia would induce more inflammatory response, and subsequently more neuronal loss. In our previous research, treatment with LPS increased GluA2 expression in microglia *in vitro* and *in vivo* condition. Actually, LPS is frequently used as a mouse model for sickness behaviour induced by peripheral inflammation, such as fever, anorexia, and lethargy [45], and also hyperalgesia [46]. In addition, TLR4, a receptor for LPS has been shown to be the main regulator for neuroinflammation in Alzheimer's disease [47]. Thus, regulation of inflammatory response by GluA2 in microglia seems to have effects on these diseases. In the future, more precise investigation on the mechanism of GluA2 trafficking in microglia as well as that of internalization of other subunits should be solved. Understanding of these dynamic translocations of specific receptor subunits may lead to modification of synaptic transmission and rescuing neuronal excitotoxicity.

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