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REVIEW ARTICLE

Pharmacological Tools to Activate Microglia and their Possible use to Study Neural Network Patho-physiology

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Abstract: ***Background*:** Microglia are the resident immunocompetent cells of the CNS and also constitute a unique cell type that contributes to neural network homeostasis and function. Understanding microglia cell-signaling not only will reveal their diverse functions but also will help to identify pharmacological and non-pharmacological tools to modulate the activity of these cells.

***Methods*:** We undertook a search of bibliographic databases for peer-reviewed research literature to identify microglial activators and their cell-specificity. We also looked for their effects on neural network function and dysfunction.

***Results*:** We identified several pharmacological targets to modulate microglial function, which are more or less specific (with the proper control experiments). We also identified pharmacological targets that would require the development of new potent and specific modulators. We identified a wealth of evidence about the participation of microglia in neural network function and their alterations in pathological conditions.

***Conclusion*:** The identification of specific microglia-activating signals provides experimental tools to modulate the activity of this heterogeneous cell type in order to evaluate its impact on other components of the nervous system, and it also helps to identify therapeutic approaches to ease some pathological conditions related to microglial dysfunction.

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INTRODUCTION

Comprising between 5 and 12% of the total cell population in the central nervous system (CNS) [1], with an estimated 3.5 x 10^6 cells in the adult mouse brain [1], microglia are not just the resident immunocompetent cells of the CNS but a heterogeneous group of cells that also contributes to neural network homeostasis and function [1-4]. Classically, microglia were studied under immune and inflammatory contexts [1, 2, 5] due to their well-known ability to phagocytose foreign agents and debris [1, 2, 5] and release diverse injurious mediators including proinflammatory cytokines, reactive oxygen species (ROS), and nitric oxide (NO) [6]. However, it is clear now that microglia also act under non-inflammatory conditions, sensing neural function [2, 7, 8] and modulating network excitability and communication [4, 9]. Thus, in order to understand the role of this cell type in CNS physiological and pathological activities, it is important to comprehend its biology, not just by providing an overview of its diverse functions but also by revealing pharmacological and non-pharmacological tools to modulate its function. This endeavor has helped to understand the impact of microglia on brain function and has offered possible targets to prevent their pathological effects [10].

The biology of microglia is very complex, mainly because this cell type includes a heterogeneous population of cells. For instance, under physiological conditions, microglia show marked differences in cellular density and morphology between and within brain regions [1, 5, 11, 12] as well as phenotypic changes with age [12-17]. This diversity is reflected in their highly variable transcriptional identities, which also depend on age and region [12, 15-17]. Microglial subtypes can produce and release different combinations of autocrine and paracrine mediators [17, 18] and respond heterogeneously to specific stimuli [12, 15-17]. In the mature CNS, microglia are the most dynamic and morphologically plastic cell type [19, 20], since they are able to extend and retract their processes at a rate of 1.5 mm/min [20]. Furthermore, in response to a diverse combination of

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external and internal stimuli, microglia can acquire a variety of "activated" phenotypes which vary from the highly pro-inflammatory "M1 phenotype" to the neuroprotective (alternatively-activated) "M2 phenotype" [5, 11, 21-24]. Harmful stimuli, such as pathogen-associated molecular patterns and/or damage-associated molecular patterns, lead to microglia activation in the M1 phenotype, which produces pro-inflammatory cytokines, nitric oxide and reactive oxygen species [5, 11, 21-24]. In contrast, interleukin-4 and/or 13 induce the M2 alternatively-activated microglia which produce anti-inflammatory cytokines and neurotrophic factors [5, 11, 21-24]. Moreover, the amount and diversity of receptors expressed by microglia in these different activation states are dramatically dissimilar and change depending on the tissue conditions [5, 11, 21-24]. To make this scenario even more complex, it has been shown that all these microglial phenotypes can co-exist within the same brain region under normal conditions [21, 22], which might produce a delicate balance between pro-inflammatory and anti-inflammatory conditions [5, 11, 21-24]. It has been proposed that the alteration of this balance is involved in several pathological conditions [5, 11, 21-24]. Thus, this microglial diversity and its constant change must be taken into consideration while assessing the role of microglia in brain function and dysfunction.

As mentioned, microglia are a highly motile cell type that is constantly surveying neural activity by contacting pre- and post-synaptic elements [2, 7, 19, 20]. In fact, microglia are constantly modulating synaptic function [9]. For instance, microglia-depleted brain slices exhibit increased excitatory synaptic activity, which is mainly produced by increased synaptic innervation [9]. Furthermore, this modulation can be reversed when slices are replenished with new microglia [9]. *In vitro*, addition of microglia decreases synaptic activity [9] and increases Na^+ current density [25]. Moreover, an enhancement in the expression of NMDA receptors is observed when conditioned medium obtained from activated microglia is applied to primary cultures of hippocampal neurons or directly injected into the brain [26]. These modulatory effects of microglia, or of microglial mediators, are reflected in changes of synaptic coupling in the hippocampus [26]. Altogether, these observations clearly indicate that microglia themselves and/or their mediators are constantly regulating neuronal network excitability [4].

As microglia can regulate neuronal excitability and communication, neurons can exert a reciprocal modulation of microglial activity, which is revealed by the dramatic changes in microglial function produced by changes in neuronal activity. For instance, there is a reversible reduction in the dynamics of microglia-synapse contacts upon a reduction in neural circuit input [2,7]. Accordingly, the increase in neural network input increases microglia-neuron contacts [8]. In contrast, reducing neural network activity decreases the incidence of microglia-neuron physical contact [27]. Neuron-dependent regulation of microglial function involves neuronal release of different mediators such as ATP [28-30] (Table **1**), glutamate or GABA [29], which can be sensed by neighboring microglia [3]. Thus, microglia can survey their environment and respond to changes in it, not just by constant physical contact with neurons but by expressing an overwhelming diversity of receptors that includes receptors for all known neurotransmitters [3]. Microglia also express receptors for microglia-regulating signals that can be roughly divided into two broad categories: the so-called 'Off' and 'On' signals [31, 32]. Although the 'Off' signals have been classically associated maintaining the microglial "resting" state [32] and the 'On' signals have been classically associated with their "activation" [32], the evidence reviewed earlier indicates that the specific effects induced by the activation of any of these signals will be influenced by the phenotypic diversity of microglial cells present in any given neuronal circuit and the activity of such circuit, which is indeed constantly modulating microglial function and responsiveness. Thus, the purpose of this review is to evaluate the available information on the cell-specificity of several of the 'On' signals (Table **1**) and their possible use to understand the role of microglia in neural network function and dysfunction. The identification of specific microglia 'On' signals will provide experimental tools to modulate the activity of this cell type (Table **1**), in order to evaluate its impact on other components of the neural circuits, and will also contribute to the identification of therapeutic approaches to ease pathological conditions related to microglial dysfunction [33]. This review does not aim to provide information about all microglial 'On' signals, which have been extensively reviewed before [for examples, see 3, 34, 35], but aims instead to identify some receptors and experimental approaches that would modulate mainly microglial activity, without a major modulation of other cell types present in the CNS. Since such microglial-specific receptors and experimental approaches are virtually unknown, we will discuss several candidates that are currently being used and provide information on their microglial specificity by contrasting their effects with those produced on other cell types, if any. Finally, we will provide some examples of the use of these experimental approaches to understand the role of microglia in neural network activity under physiological and pathological conditions.

LIPOPOLYSACCHARIDE

The most popular pharmacological strategy to activate microglia has been lipopolysaccharide (LPS, also known as lipoglycan or endotoxin; Table **1**), which is the major component of the outer membrane of Gram-negative bacteria. LPS binds different receptors located on microglia including CD14 [36, 37], scavenger receptor A (SR-A or CD204, [38, 39]), Toll-like receptor 4 (TLR4, [37]) and complement receptor 3 (CR3, [40-42]) (Table **1**). In all cases, the activation of these receptors by LPS leads to microglial activation [43-46], the release of several cytokines [43, 45-48] and/or reactive oxygen species (ROS, [43, 48]) (Table **1**), which subsequently modulate several aspects of neural function [44, 45, 48]. Despite the broad variety of microglial receptors activated by LPS, most of its effects on microglia have been associated with the activation of TLR4 [44, 49-51], and to a lesser extent with the activation of CR3 [42] (Table **1**). Regarding the impact of LPS application on neural network function, it has been shown that acute LPS application activates microglia and increases excitatory synaptic activity [44, 52], neuron excitability [52] as well as population neural network activity [45, 52]. Neural network

Table 1. Main microglial activators.

Microglial Activator	Molecular Targets	Microglial Mediators	Refs.
Lipopolysaccharide	CD-14, SR-A or CD204, TLR4, CR3	Cytokine release, ROS and NO production	[36-48, 299]
High mobility group box 1	TLR4, CR3	Cytokine release, ROS and NO production	[76, 77, 107]
Heat shock proteins 60 & 70	TLR4, TREM-2	Cytokine release, ROS and NO production, phagocytosis	[76, 79, 80, 363]
Monophosphoryl Lipid A	TLR4,	Cytokine release, ROS and NO production	[76, 83]
Complement 3	CR3	Phagocytosis, ROS production	[42, 95, 97, 98, 103]
Amyloid beta	CR3, SR	Phagocytosis, ROS production	[42, 91, 185]
Zymosan	CR3, Dectin-1	Phagocytosis, ROS production	[97, 412]
CX3CL1 or fractalkine	CX3CR1	Cytokine release, phagocytosis, migration	[121-140]
ATP	P2X4, P2X7, P2Y2, P2Y6, P2Y12	Cytokine release, ROS and NO production, phagocytosis, migration	[146-180]
Fragmented DNA	SR-A	Cytokine release, phagocytosis	[187]
Unmethylated CpG dinucleotides	TLR9	Cytokine release, ROS and NO production, phagocytosis	[204-214]
Polyinosinic-polycytidylic acid	TLR3	Cytokine release	[68, 216, 217, 342]
Phosphatidylserine	SR-BI, CD36, PS-R, BAI1, TIM-4, MFG-E8, Gas6, TREM-2	Phagocytosis, PGE2 and TGF-β1 production, reduction of cytokine release, and of ROS and NO production	[223-231, 345]
CD200	CD200R	Reduction of cytokine release, and of ROS and NO production	[369-372]
Lysophosphatidic acid	LPA1–LPA6	Cytokine release, ROS and NO production, migration	[378-380]
β-glucan	Dectin-1, CR3, SR	Phagocytosis, ROS production	[68, 407, 410, 411]
Particulate β-glucan	Dectin-1	Phagocytosis, ROS production	[401, 409]

activity is also increased by chronic application of LPS [48,53], which is associated with changes in GABAergic innervation [53] and modulation of the amplitude of both GABAergic [47] and glutamatergic potentials [48]. LPS can also reduce both short-term [54] and long-term synaptic plasticity [54-56]. The changes in network excitability induced by LPS can lead to an overexcitatory state. In fact, LPS can directly induce epileptiform activity [33] or can exacerbate an already established hyperexcited state [44, 52]. Moreover, LPS increases the susceptibility for epileptic activity [46, 57-59]. Altogether, the reviewed data indicates that microglial activation with LPS modulates several aspects of neural network function but also can lead to pathological network states. In this regard, we have previously shown that microglial activation with LPS modulates the respiratory network, affecting breathing generation and autoresuscitation after hypoxic conditions [4], which agrees with previous findings that peripheral application of LPS affects breathing [60-64]. We also demonstrated that the effects of LPS were occluded in the presence of a microglial inhibitor (minocycline, [60]), were absent in microglia-depleted tissue, and were still present when astrocyte metabolism was blocked [4]. Together, these findings suggest that LPS-induced respiratory network modulation involves microglial activation.

Despite the fact that LPS has been a very popular pharmacological tool to evaluate the role of microglia in brain function and dysfunction, several caveats have to be taken into consideration. First of all, without ignoring the fact that TLR4 is abundantly and preferentially expressed in microglia [50, 51, 65, 66, 70-73], there is some contradictory evidence indicating the presence of TLR4 both in astrocytes [67, 68] and in subsets of neurons [69]. In most cases, the presence of TLR4 in non-microglial cells has been found under pro-inflammatory conditions [68, 69] and, if found, such expression is less than in microglia [66]. Although the presence of TLR4 in non-microglial cells could prevent the conclusion that any given effect of LPS is mediated exclusively by microglia, some evidence strongly supports the use of LPS as a plausible and specific TLR4-dependent microglial activator. First, there is evidence that purified neurons and astrocytes, in the absence of microglia, do not express TLR4 [44, 50, 51], that the activation of astrocytes by LPS requires the presence of microglia [44, 68, 70-73] and that the sensitivity of neurons to pro-inflammatory mediators, including LPS, requires the presence of microglia [74]. Alternatively, to evaluate the potential contribution of astrocytes to the effects induced by LPS, we and others have made the control experiment of testing the effect of LPS in the presence of inhibitors of astrocyte metabolism [4, 44]. In

our case, the effects of LPS on the activity of the respiratory network were similar to those observed in the presence of the astrogliotoxin fluorocitrate, as occurs in other preparations [75], leading us to conclude that the effects of LPS on the activity of the respiratory network were induced mainly by microglial activation and do not require active astrocytes [4]. Note that this has not always been the case, since some effects of LPS have been blocked by astrogliotoxins in other experimental paradigms [44]. In such cases, the results were interpreted as a secondary recruitment of astrocytes after primary microglial activation with LPS [44]. An alternative strategy that we and other groups have used to support the idea that the effects of LPS are mediated by microglia modulation, is to evaluate alternative microglial "activators" under identical conditions which, in our case, produced effects similar to those of LPS [4]. Finally, to confirm the participation of microglia in the effects of LPS, we and others have corroborated the reduction of such effects in the presence of microglia inhibitors (*e.g*., minocycline, [4]) or after depleting the tissue of microglia (*e.g*., liposomal clodronate, [4]). Thus, with the proper controls, the use of LPS is still a powerful tool to understand the role of microglia in brain function [4, 44]. Aside from LPS, TLR4 is a validated target to regulate microglia; this receptor can also be activated by alternative agonists including high mobility group box 1 (HMGB1, [76,77]) (Table **1**), Complete Freund's adjuvant (CFA, [78]), and heat shock protein 70 (Hsp70, [76, 79, 80]) (Table **1**). In contrast, TRL4 can be antagonized by LPS from *Rhodobacter sphaeroides* (LP-RS, [81]), hyaluronan [82], or even by TRL4 antibodies [77]. All these pharmacological tools can be used to study the role of microglia in neural function and dysfunction and can complement, or control, the results obtained with LPS. In fact, all these TLR4 regulators have been shown to alter synaptic transmission and its plasticity [82, 77-80]. Other TLR4 agonists such as Monophosphoryl Lipid A [76, 83] (Table **1**), Hsp60 [76] (Table **1**), surfactant protein A (SPA, [76]) and methemoglobin [81], or TLR4 antagonists such as TAK-242 [81], CLI-095 [84] and polymyxin B sulfate [85] have not yet been tested for their effects on neural network function.

As mentioned, LPS can activate different receptors besides TLR4, such as SR-A [38, 39] and CR3 [40-42] (Table **1**). Despite the fact that both receptors are abundantly expressed in microglia [42, 86-92], it must be considered that SR-A can also be expressed in astrocytes [42, 90, 93], and that there are reports of CR3 expression in some astrocytes [94] and neurons [94], as will be reviewed in the next section.

COMPLEMENT RECEPTOR 3

The complement system is a very well-conserved part of the immune response involved in lytic attack and removal of pathogens and debris by means of phagocytosis [95, 96]. Complement proteins, ligands and receptors are widely expressed in neurons and glia and seem to be involved in active synaptic remodeling as well [95, 97, 98]. Thus, mice lacking some complement proteins exhibit sustained defects in synaptic connectivity [97, 98]. The complement system is complex, and will not be reviewed here (for a review, see [95, 96]); it converges on complement 3 (C3), which binds to the C3 receptor (CR3, MAC-1 or CD11b/CD18) in phagocytic cells, including microglia [95,97,98] (Table **1**). Whereas astrocytes and neurons express high levels of C3 and other complement proteins in physiological [97-99] and especially in pathological conditions [99-103], microglia almost exclusively express CR3 [103]. In fact, the 0X42 antibody that recognizes CR3 has been widely used as a specific microglia marker [86, 87, 89]. Despite the over-whelming evidence that CR3 is expressed only in microglia, there are reports that CR3 can be found in astrocytic cell lines and primary astrocytes [94,104] as well as in subsets of neurons [8-18, 94, 103], mainly during early development [105, 106]. While CR3 is almost exclusively expressed by microglia, not all microglial cells express the same CR3 levels; some cells even lack CR3 expression in control conditions [21]. Thus, when evaluating the effects of microglial activation by CR3 on neural network function, it must be considered that such activation might involve different microglial populations and produce different levels of activation [21]. Despite this caveat, several pharmacological tools are available to modulate microglia through CR3. CR3 can be activated by its classical ligand C3 [97, 103], but also by fibrinogen [97, 98], amyloid beta [91] (Table **1**), HMGB1 [107] (Table **1**), ICAM-1 (CD54, [97, 98]), LPS [40, 41, 97, 98], gp63 [108], zymosan [97, 98] (Table **1**) and neutrophil inhibitory factor (NIF, [97]).

Stimulation of microglial CR3 results in phagocytosis and production of ROS [42, 97, 103] (Table **1**). As mentioned, CR3 participates in microglia-mediated synaptic remodeling [97, 109, 110] and the genetic ablation of CR3 and C3, as well as the pharmacological perturbations of these proteins, results in deficits in synaptic remodeling [97, 111, 112]. In contrast, lack of C3 avoids synapse and neuron loss induced by aging, which is reflected in improved synaptic plasticity and cognition [96]. Moreover, CR3 activation leads to an acute modulation of synaptic transmission that does not involve phagocytosis and structural remodeling. For instance, acute C3 application reduces synaptic density and dendritic complexity in hippocampal cultures, which is blocked by the CR3 antagonist SB290157 [106]. Interestingly, blocking endogenous activation of CR3 reduces synaptic density and dendritic complexity, indicating that basal activity of this receptor is required for proper synaptic function [106]. Furthermore, activation of CR3 in hypoxic conditions triggers long-term synaptic depression (LTD), which requires NADPH oxidase activation and the release of ROS [42]. CR3 activation leads to aberrant dendritic morphology and neuronal excitability [106]. Interestingly, a continuous lack of C3 changes short-term synaptic plasticity [103] and enhances cognitive performance in otherwise normal animals [103]. In contrast, blocking CR3 with SB290157 in APP transgenic mice (a model of Alzheimer's disease) ameliorates amyloid plaque load and microgliosis [103], which restores learning and memory in this model [106]. We found that activating CR3 with leukadherin 1 [113] alters respiratory rhythm generation [4]. Interestingly, leukadherin 1-induced effects were not identical to those produced by LPS, which indicates that different microglial phenotypes induced by these two

activators can differentially modulate neural network function [4].

Other receptors involved in the complement cascade, mainly CR5 and C1qR, have also been used to activate microglia [114] and have been shown to modulate neural function [115, 116]. However, correlating their effects with microglia-induced modulation would be harder than those induced by CR3, since it is well known that CR5 is abundantly expressed by astrocytes [117] and neurons [118]. Similarly, C1qR is also expressed by these two, non-microglial cell types [119, 120].

FRACTALKINE

Chemokine (C-X3-C motif) ligand 1 (CX3CL1 or fractalkine) and its receptor CX3CR1 represent a neuron-microglia bidirectional communicating system that modulates the activity of both cell types [121, 122] (Table **1**). CX3CL1, whose expression is higher in the brain than in the periphery [123], was the first chemokine found to be produced by neurons [121, 124-129], although it is also produced by astrocytes [125-127, 130, 131] or even by microglia [122, 130]. In contrast, CX3CR1 is almost exclusively expressed in microglia [121, 123, 124]. However, its expression has also been reported in subsets of neurons, mainly in culture [122, 124, 128, 132, 133]. CX3CR1 was reported in cultured astrocytes as well [130], which has not been confirmed by other groups *in vivo* [134]. Furthermore, the development of transgenic mice expressing different reporter proteins under the control of the promoter for the CX3CR1 gene have shown reporter expression exclusively in microglia [19, 20, 134, 135]. A recent report has indicated that when CX3CR1 are expressed by neurons, their ligand sensitivity is smaller than those expressed by microglia [129] and that a higher concentration of fractalkine would be required to activate CX3CR1 in this non-microglial cell-type [124, 129, 133].

Fractalkine has been extensively used to activate CX3CR1 on microglia, which induces migration, cytokine release and phagocytic activity [121, 135] (Table **1**). Regarding neural network modulation, fractalkine has been reported to reduce excitatory synaptic transmission [136] involving both presynaptic [124, 137, 138] and postsynaptic effects [132, 138, 139]. The latter are mainly mediated by adenosine release from microglia [138, 139]. In contrast to its effect on excitatory synapses, fractalkine enhances inhibitory synaptic transmission [128, 129, 140], and it also modulates long-term synaptic plasticity [129, 136, 141, 142]. These effects of fractalkine might have brain-wide consequences since a reduction in prefrontal-hippocampal theta coupling has been observed in mice lacking Cx3CR1 [143]. The effects of fractalkine can be reduced by antibodies against fractalkine itself [128] or against CX3CR1 [130, 134], as well as by Cx3CR1 antagonists such as F1 [133] and AZ12201182 [144]. The effects of these Cx3CR1 antagonists on neural network function are yet to be determined. We found that activating CX3CR1 with fractalkine modified respiratory rhythm generation [4], which agrees with a recent finding that knocking out CX3CR1 avoids respiratory alterations observed in a transgenic mouse model of Rett Syndrome [145].

P2Y6/12 RECEPTORS

When cells are injured, they release or leak ATP and other purines, as well as several of its metabolites, which activates microglia through a variety of purinergic receptors including P2X4, P2X7, P2Y2, P2Y6, and P2Y12 [146-150] (Table **1**). Purines are powerful microglia activators that induce chemotaxis, phagocytosis and cytokine release [146, 149-151] (Table **1**). However, most purinergic receptors expressed by microglia are also expressed by astrocytes and neurons [147, 148]. This seems not to be the case for P2Y6 and P2Y12, as will be reviewed next.

P2Y6 is expressed in microglia, but not in astrocytes [152, 153], although there is a pharmacological report suggesting the presence of P2Y6 in cultured astrocytes [154, 155], and some reports locate P2Y6 in subsets of neurons, mainly in the periphery [156, 157]. Interestingly, the expression P2Y6 in microglia is sensitive to neuronal excitability [158]. As mentioned, P2Y6-mediated microglial activation induces phagocytosis of debris at the site of damage [147, 148], which can also be induced by the endogenous P2Y6 agonist UDP [158]. The P2Y6R is activated preferentially by UDP and to a lesser extent by UTP [158]. Little is known about the role of P2Y6 in neuronal excitability and synaptic transmission. However, the UDP-sensitive P2Y6 receptor produces inhibitory effects on spinal pain transmission in a neuropathic pain model [159]. In addition, Barragán-Iglesias *et al*. [160, 161] showed that the selective P2Y6 antagonist MRS2578 [151] reduces tactile allodynia in spinal nerve ligated rats, a reduction that was reproduced by the microglial inhibitor minocycline. In contrast, allodynia can be pharmacologically induced by the selective P2Y6 agonist PSB0474. Moreover, they found that nerve injury increases P2Y6 levels in the same fashion as microglial activation. Finally, they demonstrated that minocycline reduced both microglial activation and P2Y6 overexpression during neuropathic pain [160, 161].

Another purinergic receptor that seems to be expressed almost exclusively in microglia is P2Y12 [30, 147, 148, 157, 162-165]. However, P2Y12 receptors have also been found in oligodendrocytes/myelinated fibers [166,167], in cultured astrocytes [168], as well as in some neurons [156, 167], mainly in the periphery [169]. This receptor, which is sensitive to ADP [170], is involved in microglial chemotaxis, and the loss of its expression in microglia results in decreased process extension and migration following focal injury [171, 172]. Consistent with this, P2Y12 knockdown using morpholinos in zebrafish results in a complete block of microglial response to injury [172]. Similarly to P2Y6, there is scarce evidence that P2Y12 modulates neural excitability. However, it has been shown that P2Y12 activation reduces synaptic transmission [173, 174] involving the activation of NADPH oxidase [174]. Moreover, it has been reported that P2Y12 regulates trigeminal excitability [169] and seems to be involved in spinal [164] and trigeminal [175] pain transmission. In fact, the P2Y12 antagonists MRS2395, AR-C69931MX or clopidogrel can reduce pain [163, 164]. Clopidogrel or lack of P2Y12 affect cortical plasticity induced by input deprivation [165]. Although the P2Y12 agonist 2MeSATP increases respiratory rhythm generation, this effect was associated primarily with P2Y1 [176]. Thus,

the development of more specific pharmacological tools to modulate purinergic receptors is required to test the role of these receptors in microglial activation and their influence on neural network function and dysfunction.

Another purinergic receptor that leads to the pro-inflammatory activation of microglia is P2X7 [177-180]. P2X7 is an ionotropic receptor expressed by microglia [177-179] and also by some neurons [177]. The expression of P2X7 in astrocytes is still uncertain [177, 178, 180]. The activation of P2X7 leads to the release of cytokines, nitric oxide and reactive oxygen species [178-180]. The P2X7 agonist benzoylbenzoyl-ATP can activate microglia and secondarily induce neuronal death [179], which can be prevented by the P2X7 antagonist Brilliant Blue G [179]. Another P2X7 antagonist is A740003, which can reduce ATP-mediated microglial activation [180]. Interestingly, the expression of P2X7 increases during the activation of neuronal networks [177] and, coincidentally, the P2X7 antagonist JNJ-47965567 can reduce neural network hyperexcitability [177].

SCAVENGER RECEPTORS

The scavenger receptor (SR) family represents a subset of pattern recognition receptors [90, 181] that bind polyanionic ligands [181], including advanced glycosylation end products (AGEs) [182], LPS [183] (Table **1**), and lipoteichoic acid [182, 184]; as well as amyloid beta [185] (Table **1**), viruses [186], and fragmented DNA [187] (Table **1**), among other molecules related to cell damage or foreign agents.

Until now, 6 families of SRs have been described, named from SR-A to SR-F, but there are still 3 SRs that remain unclassified: RAGE, CD136, and SR-PSOX [90]. All these receptors are expressed both in microglia and astrocytes [90, 188]. However, in contrast to other SRs, SR-A (CD204) is more prominently expressed by microglia [42,93,185, 189, 190], with some reports indicating its presence in astrocytes in culture [42, 93, 190]. SR-A activation leads to the induction of phagocytosis [88] and the production of IL-1beta, NO [93], and H_2O_2 [101]. Regarding the SR-A pharmacological interactions, as mentioned, SR-A binds to amyloid beta [42, 91] (Table **1**), the heptapeptide XD4 [42], fucoidan [92, 191], and fragmented DNA [187] (Table **1**). The SR-A inhibitor fucoidan is a sulfated, fucosylated polymer from brown algae that has been used as a microglial inhibitor [42, 91, 92, 192]. In fact, fucoidan has shown therapeutic potential for Alzheimer's disease [193], ischemia–reperfusion injury [194], and depression disorder [195]. Furthermore, fucoidan reduces allodynia and hyperalgesia by reducing inflammation [196]. Also, we have shown that fucoidan affects respiratory rhythm generation in a similar fashion as minocycline does [4].

As mentioned above, fragmented DNA can activate SR-A [187] (Table **1**). Interestingly, normal neuronal activity [197], as well as apoptosis or necrosis, induces DNA fragmentation [198], which then activates microglia [187, 199]. In fact, brief incubation with fragmented DNA activates microglia and induces interleukin-1β overexpression by a fucoidan-sensitive mechanism [187] (Table **1**). This effect is blocked by an SR-A antibody [187]. Interestingly, there are several pathological conditions, including neuro-inflammation, that induce DNA fragmentation and are correlated with alterations in synaptic markers [200, 201] and in synaptic plasticity [202, 203]. We have shown that fragmented DNA affects respiratory rhythm generation in a similar fashion as LPS does [4], suggesting that SR-A-mediated microglial activation regulates the respiratory network [4].

NUCLEIC ACIDS IN ABNORMAL CONFORMATIONS

As shown in the previous section, abnormal configurations of nucleic acids can activate microglia [187, 199]. Aside from fragmented DNA, there are other forms of nucleic acids that can activate microglia. For instance, bacterial and viral DNA containing motifs of unmethylated CpG dinucleotides (umCpG-DNA) induce microglial activation through TLR9 [204-210] (Table **1**), which is a TLR mainly expressed in microglia [211]. TLR9 activation in microglia induces the production and release of cytokines and NO as well as phagocytosis [43, 205, 207, 208, 212-214] (Table **1**). However, it is important to note that TLR9 receptors are also expressed by astrocytes [67, 204, 210] or even by subsets of neurons during development [213], and thus, astrocytes can also be activated by umCpG-DNA [209, 210, 214]. Nevertheless, regarding neural network modulation, it has been shown that TLR9 KO mice exhibit synaptic abnormalities [215]. It will be interesting to determine whether these alterations involve changes in microglia function.

Microglia can also be activated by double-stranded RNA (dsRNA) present in some viruses [216, 217]. Polyinosinic-polycytidylic acid (poly(I:C)) is a synthetic analog of dsRNA that activates TLR3 [68, 216, 217], which induces the production and release of various cytokines [68, 216, 217] (Table **1**). Despite the fact that astrocytes are also responsive to double-stranded RNA, as well as to other abnormal conformations of nucleic acids [218], poly(I:C)-induced astrocyte activation requires the presence of microglia [68]. Regarding neural network modulation, poly(I:C) induces epileptiform activity *via* production of interferon-β [219]. In contrast, TLR3 deficiency impairs synaptic transmission and its plasticity [220].

PHOSPHATIDYLSERINE

Phosphatidylserine (PS) is normally expressed on the inner surface of the membrane bilayer in healthy cells and becomes exoplasmic during cell apoptosis [221, 222]. PS can then be recognized by a variety of receptors including class B scavenger receptors type I (SR-BI) [223], CD36 [222] as well as the PS direct and specific receptor (PS-R) [224-227] (Table **1**). Activation of any of these receptors by PS leads to the induction of phagocytic activity [225, 228], but also reduces the production and release of cytokines and NO [225, 227-229]. Moreover, microglial modulation with PS leads to the production of anti-inflammatory mediators such as prostaglandin E2 (PGE2) and transforming growth factor-β1 (TGF-β1) [230, 231].

Different receptors can act as the PS-R, including brain angiogenesis inhibitor I (BAI1), stabilin-1 and 2 as well as T

cell immunoglobulin and mucin 4 (TIM-4) [162, 224, 232-234] (Table **1**). Regarding PS-induced phagocytosis, it was shown recently that BAI1 controls the formation of phagosomes and TIM-4 stabilizes them [234]. Additionally, indirect PS recognition by other receptors involves bridging proteins such as milk fat globule-EGF factor 8 [MFG-E8] and growth arrest specific gene 6 (Gas6) [235-241] (Table **1**). These proteins usually have two binding sites; one site binds PS and the other binds receptors on microglia such as the vitronectin receptor (VNR) or Mer receptor tyrosine kinase (MERTK) [235, 236, 239, 240, 242, 243]. Together, all of these receptors and bridging proteins mediate PS-dependent phagocytosis of apoptotic cells by microglia [235, 236, 239, 240, 342, 243]. However, it has to be considered that most of the PS receptors are expressed by astrocytes and even neurons [90, 244, 245].

As for the pharmacological tools to study this complex system, it has been shown that the interaction between PS and its direct receptors can be blocked with annexin V [151, 246-248], with an antibody against PS [247] or with O-phospho-L-serine, a molecule that mimics the PS head group but blocks microglial PS receptors [249], thereby interfering with the uptake of apoptotic neurons by microglia [249]. As mentioned, there are different receptors that recognize MFG-E8 bound to PS [235, 236, 239, 240, 242, 243] (Table **1**); this interaction can be blocked either by function-blocking MFG-E8 antibodies [250] or by the recombinant D89E mutant of MFG-E8 (rD89E) [236].

The VNRs, which are composed by the αvβ3 or the αvβ5 integrin, are found abundantly in microglia [240, 242, 243, 251], but also in astrocytes [252, 253]. VNR activation in microglia induces phagocytosis [254] and cytokine production [253]. Interestingly, VNR-induced TNF-α production by microglia is more pronounced than that induced by identical conditions in astrocytes [253]. Furthermore, VNR-induced TNF-α production by astrocytes requires the presence of microglia [253]. Thus, it is likely that VNR-mediated effects are mainly due to microglial activation, at least in the initial stages. The most common pharmacological tool used to modulate VNR is the VNR inhibitor peptide cyclo(RGDfV) [151,254]. VNR can also be antagonized by the peptide RGD or VNR antibodies [252, 255] as well as by the antagonist TETRAC [256]. As mentioned, another receptor for PS, when bound to either MFG-E8 or Gas6, is MERTK [239], which is abundantly expressed in microglia [239, 240] but can also be found in astrocytes [257]. MERTK activation with PS can be blocked either by function-blocking anti-MFG-E8 antibodies [250], the recombinant D89E mutant of MFG-E8 (rD89E) [236], a soluble form of MERTK [258], or by the synthetic antagonists UNC1062 and UNC2025 [259]. MERTK can be activated by MFG-E8, Gas6 or PROS1 [260, 261].

Regardless of their possible lack of specificity for microglia (due to the modulation of non-microglial cell-types), several of the components involved in the PS-induced cascade have been shown to modulate neural network function. For instance, PS increases both glutamatergic [262, 263] and GABAergic transmission [264], and it reverts the reduction of LTP induced by LPS [265, 266]. Accordingly, RGD peptides affect neuron excitability [265, 267, 268] and modulate network interactions by increasing presynaptic vesicle density [269] and postsynaptic receptor density and activity [270-275]. Thus, RGD peptides modulate synaptic transmission [274, 276] and its plasticity [277-280]. BAI1 not only regulates synaptogenesis [281], it also modulates synaptic plasticity in the adult. In fact, mice lacking BAI1 have enhanced LTP and impaired LTD, the latter of which is associated with cognitive impairment [245]. Finally, whereas vitronectin regulates neuronal excitability [255], MERTK is constantly remodeling synaptic connectivity, even in adults [257, 282].

LIPOSOMES AND ALTERNATIVE CARGO CARRIERS

We have previously mentioned that microglia can be activated by apoptotic bodies exhibiting PS, which then get phagocytized [235, 236, 239, 240, 342, 243]. Furthermore, microglia can establish a bidirectional communication with other cell types in the CNS through extracellular vesicles, namely microvesicles (or ectosomes) and exosomes [283-287]. All cell types can release extracellular vesicles [283-287]. These extracellular vesicles can transmit nucleic acids and/or protein cargo [283-287], including cytokines [283-287]. In some cases, however, extracellular vesicles can transport pathogenic proteins such as prions, amyloid beta peptide and/or tau [283-287]. In fact, it has been proposed that extracellular vesicles can contribute to disease by the spreading of these pathogenic proteins [283-287]. Moreover, extracellular vesicles can also contribute to neuroinflammation [283-287]. In contrast, under physiological conditions, extracellular vesicles can modulate neural network function and plastic changes, and they can protect neurons from insults [283-287] through the modulation of microglial activity (*e.g.*, synaptic pruning) and/or by the release of extracellular vesicles from microglia [283-287].

A synthetic alternative to extracellular vesicle-mediated communication is liposomes, which are artificially prepared spheres of a desired diameter, consisting of concentric phospholipid bilayers separated by aqueous compartments [288, 289]. These structures are formed when phospholipids (*e.g.*, PS or phosphatidylcholine) are dispersed in water. Thus, the phospholipid molecules will find a conformation in which their hydrophobic fatty acid chains are prevented from making contact with water. Part of the aqueous solution together with dissolved hydrophilic molecules can be encapsulated during the formation of liposomes [288, 289], making them a promising vehicle for drugs that would modulate the activity of cells that internalize them by phagocytosis [289], including microglia [289-292] and, to a lesser extent, astrocytes [293], Müller cells [290] or even neurons [294]. Liposomes are not toxic [288], but they can induce microglial cell death if they contain toxic compounds [292, 295, 296].

Liposomes have been used for several purposes while studying microglia. For example, PS-containing liposomes (PSLs) can mimic the effects of apoptotic cells [297, 298] and modulate microglia activity through the pathways described in the previous section [224, 227]. Regarding neural network function, it has been shown that PS-containing

liposomes can counteract LPS-induced impairment of LTP [265].

In addition to the use of liposomes as PS carriers, this preparation can be used to deliver a variety of agents including LPS [299], minocycline [299], antiinflammatory drugs [290, 300-303], RGD [301], enzymes [304-306], fluorescent dyes [290, 291], hormones [307, 308], antivirals [309], protease inhibitors [310], ion-channel modulators [311], antibiotics [312, 313], antioxidants [293, 306, 314], plasmids [315], signaling-pathway modulators [296] and toxic compounds [292, 295, 296]. Just to give an example of their use, liposomes containing superoxide dismutase can be incorporated into microglia, which increases their reductive power and favors retinal activity [306]. Furthermore, the same liposomal preparation is neuroprotective in different pathological conditions [304, 305]. Regarding neural functioning, a liposome containing hemoglobin can restore LTP in ischemic animals [316].

An alternative strategy to modify microglia function is to modulate its phenotype by transgene expression in genetically modified animals (for a recent review see [317]). Alternatively, microglia can be modified by transfecting them with genes using various techniques [318-320], including viral infection [321]. It is important to consider that microglia are refractory to most chemical and electrical transfection methods, yielding little or no gene delivery and causing toxicity and/or inflammatory activation [320, 322]. Previous studies with lentiviral vectors have shown effective gene transfer into microglia; however, lentiviral infection was associated with modest toxicity and mild inflammatory activation [320]. So far, it has been shown that microglia transfection with recombinant adeno-associated virus (rAAV), serotype 2 (rAAV2, [320]), yields high transduction and causes minimal toxicity or inflammatory response [320]. In contrast, rAAV of serotypes 5, 6, 8 and 9 can transduce microglia but might induce an undesired inflammatory reaction [320]. Another report has shown that hippocampal microglia have a preference for rAAV6 and rAAV8, while microglia in striatum and cortex exhibit different preferences [323], which is another manifestation of the well-documented microglial heterogeneity.

Aside from the wealth of evidence collected from transgenic animals supporting the role of microglia in proper network wiring (for a recent review see [317]), there are few studies regarding the role of microglia genetically modified by transfection in neural network function [324, 325]. For instance, it has been shown that the synaptic depression induced by oxygen and glucose deprivation is reduced when microglia express a dominant-negative form of RAGE [325]. In addition, when microglia lack proper KARAP/DAP12 function, LTP is enhanced and becomes NMDAR independent [324]. Moreover, down-regulation of microglial P2X7R blocks LTP [319].

Nanoparticles are an alternative to deliver cargo into microglia [217]. They can be coupled to drugs or other desired cargos [217, 326], which will be preferentially incorporated into microglia to modify their activity [327-330] or to become reporters of neuroinflammation [330]. However, nanoparticles can also be incorporated, though less efficiently, into other glial cells [328, 331] or even into neurons [331]. Nevertheless, nanoparticles have already been used to bring minocycline or other inhibitors into microglia [327, 328, 329]. Notably, some nanoparticles can damage [334-336] or have direct inhibitory [332] and excitatory [333-335] effects on microglia. Regarding their effects on neural network function, gold or silver nanoparticles were found to increase neuronal excitability and network activity [337, 338], whereas phenytoin-loaded nanoparticles reduce hyperexcitation [339]. Regarding synaptic transmission and its plasticity, nanoparticles containing zinc oxide restore LTP inhibited by LPS [340], and cholesterol-loaded nanoparticles prevent the synaptic dysfunction observed in Huntington-related transgenic animals [331]. In contrast, basal synaptic transmission [337] and LTP are affected by silver nanoparticles [337].

T CELL IMMUNOGLOBULIN AND MUCIN DOMAIN 3 (TIM-3)

T cell immunoglobulin and mucin domain 3 (Tim-3) is a galectin-9 receptor constitutively expressed on cells of the innate immune system in both mice and humans, where it can synergize Toll-like receptor function [195, 341-343]. In the CNS, Tim-3 is expressed almost exclusively in microglia [195, 341, 344-346], with negligible expression in astrocytes [195, 346]. In contrast, galectin-9 is produced by astrocytes and neurons [342, 345, 347, 348] and, when released onto microglia, it induces TNF production [342, 345]. Moreover, galectin-9 enhances poly(I:C)-induced microglial production of TNF and IL-6 [342]. As a pharmacological tool to manipulate Tim-3 in microglia, galectin-9 has the caveat of being recognized by diverse receptors besides Tim-3 [349-351]. Fortunately, there are both activating and inhibiting Tim-3 antibodies that can be more specific than galectin-9 [341, 345, 346]. As far as we are aware, there are no studies regarding the role of Tim-3 in neural network function.

TRIGGERING RECEPTORS EXPRESSED ON MYELOID CELLS 2 (TREM-2)

TREM-2 is a member of the immunoglobulin superfamily of receptors that mediates microglial activation acting with its co-receptor, the DNAX-activating protein of 12 kDa (DAP12, [352]). Interestingly, genome-wide association studies have identified changes in TREM-2 as risk factors for Alzheimer's Disease [353, 354]. TREM-2 is constitutively expressed on microglia [355-361] but not on astrocytes [360, 361]. Although the sporadic expression of TREM-2 in subpopulations of neurons and oligodendrocytes has been described [355, 360, 362], such expression has not been confirmed by other groups [360, 361]. Despite the fact that TREM-2 is expressed almost exclusively by microglia, not all microglial cells express the same levels of TREM-2, and some cells even lack TREM-2 expression under controlled conditions [360]. Among the pharmacological tools to modulate TREM-2, Hsp60 is the main endogenous agonist of the microglial TREM-2 receptor [363]. TREM-2 binds PS, as already mentioned [345], as well as anionic carbohydrates, anionic bacterial products, and other phospholipids [364, 365]. In a more specific manner, TREM-2 can be activated [366] or inhibited [367] by several

antibodies. TREM-2 activation leads to the induction of a phagocytic microglial state [345] and the promotion of microglial survival [345]. As for its influence on neural network function, the absence of DAP12 leads to reduced GluR1 and GluR2 levels in the post-synaptic density, whereas it increases the inward rectification of synaptic AMPARs [324] and increases the AMPA/NMDA ratio [368]. Furthermore, lack of DAP12 enhances LTP, which becomes NMDAR independent [324].

CD200 RECEPTOR

The Cluster of Differentiation 200 (CD200) receptor (CD200R, also named the OX2 receptor) and its ligand CD200 (OX2) are both cell surface glycoproteins that contain two immunoglobulin domains [369-372]. CD200 is expressed on astrocytes [370, 372, 373], neurons [369, 373, 374] and oligodendrocytes [370, 373] but not on microglia [371]. In contrast, expression of the CD200R is restricted almost entirely to microglia [369-372], although there is evidence that it can be expressed at very low levels in astrocytes and oligodendrocytes under inflammatory conditions [336, 373]. Regarding the pharmacological tools to study the influence of this receptor on microglia, it is possible to disrupt CD200-CD200R binding with CD200-blocking antibodies [375, 376]. Moreover, lack of CD200 [376] increases microglial activation, whereas agonistic antibodies [336] or CD200 itself [373, 377] reduce microglial activation. With respect to neural network functioning, LTP is impaired in CD200-deficient mice, which become more sensitive to pro-inflammatory conditions [77]. In contrast, CD200 application protects LTP against the impairment induced by aging and by LPS [377].

LYSOPHOSPHATIDIC ACID RECEPTOR 5

Lysophosphatidic acid (LPA) is a bioactive lipid mediator involved in many physiological functions including cellular proliferation, prevention of apoptosis, cell migration, cytokine and chemokine secretion, platelet aggregation, smooth muscle contraction, and neurite retraction [378]. LPA signals through six known G-protein-coupled receptors in a variety of cell types, including astrocytes and microglia [LPA1–LPA6, 378, 379]. Interestingly, LPA5 (GPR92) is expressed almost exclusively in microglia [379, 380] and is barely detectable in astrocytes [381, 382]. LPA5 is also expressed by peripheral neurons and their nerves [65, 383] as well as by neurons in the spinal cord [65]. However, we are aware of no publications regarding LPA5 expression in neurons located in other regions of the CNS. LPA5 leads to the activation of microglia and promotes their migration [380]. Pharmacological tools to modulate LPA5 activity include agonists such as farrnesyl pyrophosphate or monophosphate [384], sn-2 alkyl OMPT analogs [385] or antagonists such as diphenyl pyrazole carboxylic acid [386]. Regarding neural network function, despite the wealth of evidence showing that LPA modulates synaptic transmission and its plasticity [*e.g.*, 386], the role of LPA5 and microglia in these processes is still unknown. However, this receptor must be involved in the regulation of synaptic transmission or neural excitability since mice lacking LPA5 are protected against neuropathic pain [65].

SINGLE-IG-INTERLEUKIN-1 RELATED RECEPTOR (SIGIRR)

SIGIRR also known as TIR8/IL-1R8 is a receptor whose ligand-binding capacity and signal transduction are not yet known [387]. However, it exerts significant anti-inflammatory effects throughout the immune system [388, 389]. For instance, SIGIRR deficiency enhances susceptibility to multiple autoimmune and inflammatory-associated conditions [388, 389] as well as to the activation of IL-1R and TLR4 [390]. It has been proposed that sensitization of the immune response in the absence of SIGIRR is due to the increased expression of IL-1R and TLR4 [391]. Microglia, rather than astrocytes, are the primary glial cells expressing SIGIRR in the CNS [392]. Although SIGIRR has been found in astrocytes and neurons in culture [393], its functionality in these cell types has not yet been determined [391, 392]. Interestingly, SIGIRR seems to be involved in neural network function, since mice lacking SIGIRR show deficits in hippocampal-dependent memory and LTP, which correlates with an increase in TLR4-associated signaling and the overexpression of HMGB1 [392]. As far as we are aware, there are no SIGIRR-specific agonists or antagonists available to evaluate the role of SIGIRR and microglia in neural network function and dysfunction. However, the probiotic *Lactobacillus jensenii* and the TLR2 agonist Pam3Cys4 were reported to increase SIGIRR in a TLR2-dependent manner [394].

SIALIC ACID BINDING IG-LIKE LECTINS-3 (SIGLEC-3, CD33)

Siglecs bind to the sialic acid cap of the intact glycocalyx [34, 395]. Siglecs are single-pass (type 1) transmembrane proteins with variable numbers (1-16) of Ig-like constant region type 2 (C2-set Ig-like) domains and an amino-terminal Ig-like variable (V-set Ig-like) domain that bears the sialic-acid-binding site [396-398]. They associate with the ITAM-containing adaptor protein DAP12 *via* a positively charged lysine residue in their transmembrane domains [399]. A member of the Siglec family, Siglec-3, has been reported on macrophages and microglia [398, 400] and seems to be absent in astrocytes, oligodendrocytes and neurons [400]. As occurs for other microglial receptors, CD33 expression is increased in microglia by LPS [400]. Interestingly, genome-wide association studies have identified changes in CD33 as risk factors for Alzheimer's Disease [401]. CD33 SNP rs3865444, which protects against Alzheimer's Disease, leads to reductions in the microglial expression of CD33 and a decrease in the levels of insoluble amyloid beta in the Alzheimer's Disease brain [402]. Furthermore, murine microglia lacking CD33 show increased amyloid beta uptake [402]. As for the pharmacological tools to modulate CD33, it has been shown that antibodies against CD33 lead to the production of proinflammatory cytokines [403], an effect that is reproduced by sialic acid removal with neuraminidase and blocked with sialyllactosamine [403]. To the best of our knowledge, there are no reports of CD33-mediated modulation of neural network function. Of note, the CD33-related Siglec-E has also been detected on microglia, but not on neurons, and it seems to be involved in neuroprotection

[404]. The use of this receptor as a microglial-specific target needs still to be supported.

DENDRITIC-CELL ASSOCIATED C-TYPE LECTIN-1 (DECTIN-1)

Dectin-1 is a C-type lectin receptor of the C-type lectin NK receptor-like family that recognizes β-glucans [405, 406] and triggers a protective response, especially against fungi. Dectin-1 is expressed on macrophages, dendritic cells and microglia [407-413] but not on astrocytes or neurons [409]. Stimulation of dectin-1 leads to signaling that leads to phagocytosis and ROS generation but not to cytokine production in microglia [68, 407, 410, 411]. In fact, dectin-1-stimulated microglia display a diminished capacity to produce cytokines in response to both the TLR2 and TLR4 ligands [407]. However, there is a report suggesting that a dectin-1 interaction with tetraspanin CD37 regulates IL-6 expression [408]. As mentioned, dectin-1 can be stimulated by β-glucans [405], which are common constituents of various fungal walls. Despite the fact that β-glucans can also activate CR3 and SR [407], particulate β-glucan (also called curlan) seems to be more specific for dectin-1 [401, 409]. Other specific tools to activate dectin-1 are "depleted" zymosan and heat-killed *Saccharomyces cerevisiae* [68, 412, 414]. In contrast, laminarin and anti-Dectin-1 antibodies can function as dectin-1 antagonists [411]. There is little evidence that dectin-1 modulates neural network function. It has been shown that systemic administration of lentinan, a branched β-glucan, enhances LTP [414], but it has not yet been determined if such effect is mediated by dectin-1 and microglia.

MICROGLIA OR MICROGLIA-CONDITIONED MEDIUM

To conclude this review, we would like to mention that aside from the pharmacological tools available to activate microglia and test their role in neural network pathophysiology, an alternative experimental approach that has been used for quite a while is the application of microglia themselves or conditioned medium from microglial cultures to the neural tissue, in order to understand the impact of microglia on neural network pathophysiology. This approach has the advantage of using naïve microglia or, perhaps more interesting, of using modified microglia which have been previously manipulated, in isolation, with the pharmacological tools reviewed herein. It avoids most of the possible disadvantages of using a pharmacological tool that might also modulate non-microglial cell types, as has been reviewed in this article. This approximation, which has the caveat of introducing a group of cells to an already established tissue, has rendered very interesting findings. For instance, when labeled naïve microglia are applied on organotypic cultures, they protect the cultures against ischemic conditions [415]. Interestingly, if microglia are previously modulated by pharmacological means (*e.g*., with anisomycine or minocycline), their protective effect vanishes [415]. This protection is exerted by microglia but not by granulocytes [415]. A similar protective effect is observed when naïve microglia or microglia activated by interleukin-4 are applied to organotypic cultures [416], but when microglia are activated with LPS, the damage induced by ischemia in the same preparation is exacerbated [416]. This promising experimental approach has also been used *in vivo*, where intracerebral injection of microglia can protect against the neurodegeneration induced by occlusion of the middle cerebral artery [417, 418]. In fact, there are reports that microglia can be applied in the periphery; from there, they can migrate into the CNS and produce their protective effects [419]. Interestingly, pre-stimulation of isolated microglia with interferon enhances their neuroprotective effect [419]. In addition to the protective role of exogenous microglia against neurodegeneration, it has been shown that peripheral application of microglia can protect LTP against ischemia-induced deterioration [420]. Furthermore, the application of naïve microglia has also been used to correct pathological conditions involving abnormal microglia. For instance, transplantation of wild-type microglia into irradiated Mecp2-KO hosts (a mouse model of Rett-Syndrome) resulted in the engraftment of microglia onto brain parenchyma and the arrest of disease development [248; however, see 421]. This protective effect is reverted by application of annexin V to block PS-induced activation [248]. As for neural network function, it has been shown that microglia transferred into brain slice cultures produce an increase in NMDA expression [422], an effect that is reproduced by the application of microglia-conditioned medium [422]. Similarly, microglia-conditioned medium increases the frequency of excitatory spontaneous postsynaptic currents [420].

The effects of microglia-conditioned medium on neural network function can also be modulated if microglia are previously modified by the pharmacological tools reviewed herein. For instance, medium conditioned by naïve microglia increases the number of synapses between cortical neurons *in vitro* [423]; in contrast, the opposite effect is observed when the medium is conditioned by LPS-treated microglia [423]. In fact, conditioned medium collected from LPS-treated microglia can be neurotoxic [424]. In contrast, microglia-conditioned medium promotes astrocyte proliferation and neural-neurite growth [425]. Finally, when conditioned medium from kainate-treated microglia is injected into the brain it induces an enhancement of synaptic transmission [426]. Further research is required to determine which microglial modulators are responsible for the described modulations of neural function.

CONCLUSION

In this article, we have reviewed several pharmacological strategies that are currently in use to understand microglial influence on neural network pathophysiology. None of these pharmacological approaches is completely specific for modulating this cell type, mainly because most reviewed drugs are not completely specific for a receptor and/or because the receptors are not expressed exclusively by microglia (Table **1**) [427]. Despite these two major problems, we have reviewed all the alternative approaches that can be used to validate the findings obtained with these drugs in order to give certainty that the reported effects are produced mainly, or at least initially, by microglial modulation. A critical view clearly indicates that further research into microglia cell biology is required to reveal potential targets that can specifically modulate the activity of this heterogeneous cell type.

Furthermore, the development of more potent and specific agonists or antagonists of those new putative targets will be very useful not only to understand microglial physiology and its impact on neural network function, but also to offer opportunities for the treatment of diseases that involve microglial dysfunction.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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