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REVIEW ARTICLE

The Potential Role of Dysfunctions in Neuron-Microglia Communication in the Pathogenesis of Brain Disorders

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Abstract: The bidirectional communication between neurons and microglia is fundamental for the proper functioning of the central nervous system (CNS). Chemokines and clusters of differentiation (CD) along with their receptors represent ligand-receptor signalling that is uniquely important for neuron – microglia communication. Among these molecules, CX3CL1 (fractalkine) and CD200 (OX-2 membrane glycoprotein) come to the fore because of their cell-type-specific localization. They are principally expressed by neurons when their receptors, CX3CR1 and CD200R, respectively, are predominantly present on the microglia, resulting in the specific axis which maintains the CNS homeostasis. Disruptions to this balance are suggested as contributors or even the basis for many neurological diseases.

In this review, we discuss the roles of CX3CL1, CD200 and their receptors in both physiological and pathological processes within the CNS. We want to underline the critical involvement of these molecules in controlling neuron – microglia communication, noting that dysfunctions in their interactions constitute a key factor in severe neurological diseases, such as schizophrenia, depression and neurodegeneration-based conditions.

Keywords: Schizophrenia, depression, Alzheimer's disease, Parkinson's disease, CX3CL1-CX3CR1, CD200-CD200R.

1. INTRODUCTION

Bidirectional communication and interaction between neurons and the neighbouring microenvironment belong to the most essential aspects of healthy brain functioning. The exchange of signals linking microglia with neurons is required for the maintenance of housekeeping functions and homeostasis within the CNS. This communication is crucial in brain functions, including angiogenesis [1], axonal outgrowth [2], development [3], neurogenesis [4], neuronal circuit remodelling [5], plasticity [6, 7] and immune responses [8]. As a consequence, it translates into the proper functioning of the organism at cognitive, emotional and behavioural levels.

A double-sided character is a key feature of the cooperation between neurons and microglia. This means that both neuronal cells can control the activity of microglia, but also conversely – microglia regulate the functioning of neurons. Neurons secrete a number of factors that influence the state of microglial activation [9]. A hallmark of microglia during homeostasis is remaining significantly quiescent while fulfilling complex surveillance roles in a healthy brain [10]. To some extent, neuronal signals are not only in control of keeping the microglia in the "resting" phenotype [11, 12] but also regulate basal motility [13], proliferation and phagocytosis of microglia [9].

The influence of microglia on neurons is more extensively covered by literature. First, as shown using two-photon imaging to study the mouse cortex, microglial cells make physical contact with neuronal dendritic spines [14]. In line with this observation, the results of Tremblay *et al.* [15] showed that microglia created contact with neurons, including synaptic spines, in the visual cortex. Another study also described microglial-to-neuronal soma contact in the living brain [16]. Altogether, these reports clearly proved the presence of a direct connection between neurons and microglia.

Microglia regulate neuronal activity not only by direct contact but also by influencing signalling pathways, such as complement system, Toll-like receptors (TLR), purinergic and adenosine signalling (we recommend the excellent review of Marinelli *et al.* [17], who addressed this subject in impressive detail). These mechanisms contribute to a variety of neuronal functions, including neurotransmission [18], cell survival [19], neuroprotection [20] and axonal sprouting [21, 22].

Several factors mediate the communication between neurons and microglia. Both of these cell types are able to ex-

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press molecules that bind to cognate receptors on neurons/ microglia to promote specific biological actions. This group of molecular agents consists of neuropeptides, neurotrophins, neurotransmitters, CD, anti- and pro-inflammatory cytokines and chemokines [17, 23, 24].

In the present review, we surveyed the literature data concerning the broad role of CX3CL1, CD200 and their receptors in both physiological and pathological processes within the CNS. We underlined the critical involvement of the ligand-receptor pairs (CX3CL1-CX3CR1 and CD200-CD200R) in controlling neuron – microglia communication, noting its dysfunctions as key factors that lead to severe neurological diseases, such as schizophrenia, depression and neurodegenerative conditions (Alzheimer's and Parkinson's diseases).

2. CHEMOKINES AND CLUSTERS OF DIFFERENTIATION IN THE HEALTHY BRAIN – A SHORT OVERVIEW

2.1. Chemokines

The superfamily of small (8-15 kDa) proteins, called chemokines, consists of various ligands. These factors are defined by structure and are divided into four main subgroups (C, CC, CXC, CX3C), depending on the number and spacing of their two N-terminal cysteine residues [25]. The common name of these biological factors comes from the ability to induce directed chemotaxis (chemotactic cytokines) [25]. Since the description of the first molecules with chemotactic activity, approximately 50 chemokines, as well as 25 (20 signalling and 5 non-signalling) chemokine receptors, have been recognized [26].

Typically, the chemokine system shows bilateral activation: one chemokine can bind to more than one receptor and, correspondingly, a number of different chemokines can be recognized by the same receptor [27]. The exceptions to this pattern are CX3CL1 and CX3CR1. The literature describes the basic roles of this vast and complex system of proteins within the organism, including the development and homeostasis of immune cells and also the induction or modulation of inflammation (reviewed by Rot and von Andrian [28], and Griffith *et al.* [26]).

In parallel with their well-established role in the immune system, chemokines and their receptors have multiple actions in the CNS. One of the processes regulated by these molecules is the blood-brain barrier (BBB) permeability [29-36]. Other authors documented the importance of chemokines in synaptic transmission, plasticity and spatial memory [34-36]. A continuously increasing number of reports indicate that in the CNS these molecules also take part in adult neurogenesis [37, 38], gene regulation and abnormal neural stem cell maturation [39], cell proliferation [40], neuroendocrine regulation (reviewed by Callewaere *et al.* [41]), neurotransmission [42] and neuroprotection [43].

Chemokines have a special role in controlling microglial activity and its properties. In the cortex of mice, microglia promoted the differentiation of neural progenitors in the process of frequent movement throughout the structure [44]. The migration was mediated by the interaction of the chemokine (CXCL12) with its receptor (CXCR4). With regard to promoting migration, CCL11 significantly enhanced this process in primary microglia cultures prepared from the brains of newborn mice [45]. Feng *et al*. [46] applied a rat photic injury model to the investigation of the influence of CCL2 on the activation and migration of microglia. The results provided the conclusion that the overall (particularly the spatial-temporal) expression pattern of this chemokine correlated closely with the examined properties of microglia.

2.2. Clusters of Differentiation

In general, the CD designation is used for classifying multiple cell surface proteins [47]. Since the first Human Leucocyte Differentiation Antigens Workshop in 1982, the official CD list has included more than 370 individual and unique markers in humans [48]. The surface expression of a particular CD molecule may not be specific for a single cell type or a cell lineage, yet they are commonly used as cell markers in immunophenotyping [49]. CD factors vary greatly in terms of physiological functions, which include roles in cell signalling [50], cell adhesion [51] or leucocyte migration [52]. These molecules may act as ligands (*e.g*., CD40, CD70, CD200) or receptors (CD27, CD46, CD200R, CD358) and may be expressed on the surface of a broad range of cell types within an organism, including the CNS.

In the nervous system, one of the main effects of CD proteins concerns the regulation of microglial activity. Under physiological conditions, the so-called resting microglia constitutively express certain levels of CD11a, CD11b, CD11c, CD18 [53], CD14, CD45 [54], CD68 [55, 56], *etc*. Several CD factors are considered markers of microglial phenotypes and, as a consequence, as indicators of an activated state of these cells. The M1/M2 paradigm, which is a simplified model to classify the two directions of the inflammatory responses, distinguished M1 phenotype, representing pro-inflammatory characteristics, from M2 (with M2a, M2b and M2c subtypes), highlighting the anti-inflammatory activity of microglia [57]. In addition to this early categorization, subsequent data assigned CD molecules to specific phenotypes. M1 microglia are characterized by the expression of CD14, CD16, CD32, CD40, CD45, CD68, CD74, CD86, while M2 microglia are mainly associated with CD23, CD33, CD36, CD64, CD68, CD80, CD86, CD163, CD200R, CD204, CD206, CD209 [58-60].

Multiple reports have presented the contribution of CD molecules to the process of phagocytosis in the CNS (reviewed by Fu *et al.* [61]). Other data highlighted the involvement of these factors in oestrogen-related immune signalling in the brain [62, 63]. The widely described participation of CD antigens in maintaining the CNS homeostasis also consists of their involvement in other processes, some of these are: priming of microglia [64], antigen presentation, proliferation, apoptosis, cell migration [65-67], neuroprotection [68], neurodevelopment [16], BBB stability [69], synaptic plasticity [70], mitochondria functioning [71], insulin action [72] and lipid metabolism [73].

In terms of sustaining homeostasis in the CNS, the ligand-receptor pairs CX3CL1-CX3CR1 and CD200-CD200R are the most prominent chemokines and CD, re-

spectively (Fig. **1**), because of the unique cell-type-specific localization of their components.

2.3. CX3CL1-CX3CR1 Axis in the Healthy Brain

CX3CL1 (also known as fractalkine in humans and rats or neurotactin in mice) is the only known member of the chemokine CX3C class, possessing a specific motif in which two cysteine residues are separated from each other by three amino acids [74, 75]. This transmembrane protein occurs in two isoforms: soluble and membrane-bound [76]. The level of CX3CL1 is vastly higher in the brain than in the periphery [77]. In the CNS, where the expression of fractalkine is constitutive, neurons are its predominant source [78]. Yet, it should be mentioned that the production of this chemokine on other cell types within the CNS (mostly astrocytes) remains an open question [79, 80]. In the brain, CX3CL1 is primarily expressed in the amygdala, cerebral cortex, globus pallidus, hippocampus, striatum, thalamus and the olfactory bulb, with scant expression in the cerebellum [81].

CX3CL1 appears to be the only ligand for CX3CR1 (previously named V28). CX3CR1 is a seven-transmembrane domain G-protein-coupled receptor [82]. CX3CR1 was shown to be on the surface of monocytes/macrophages, neutrophils, T lymphocytes and natural killer cells, mast cells, thrombocytes, dendritic cells and microglia [83-87].

Since the first reports on CX3CL1 [74] and CX3CR1 [82], a unique role of this signalling pathway in physiological and pathological processes in the CNS has been consistently described (Fig. **2**). The main function of CX3CL1 involves the induction of chemotaxis and cell adhesion [88, 89], but it should be noted that the importance of this protein extends beyond a typical chemotactic action. CX3CL1, as one of the factors secreted by medial ganglionic eminence interneurons, is necessary to promote cortical oligodendrogenesis [90]. This chemokine elevates oligodendroglial differentiation of embryonic and postnatal glial precursors without affecting their proliferation.

The CX3CL1-CX3CR1 axis is also associated with promoting neurogenesis *via* various mechanisms [91-96]. For example, Sellner *et al.* [95] demonstrated that microglia derived from the hippocampal dentate gyrus (DG) of *Cx3cr1*-deficient mice displayed activation of sirtuin 1 (SIRT1) and the NF-κB pathway. This process was limited to the DG and was followed by impaired neurogenesis in the hippocampus of the knockout animals.

One of the most prominent roles of the CX3CL1-CX3CR1 pathway is to control the activation and proper functioning of microglia. The first evidence for this phenomenon was delivered in the article by Maciejewski-Lenoir *et al.* [84]. *In vitro* stimulation with CX3CL1 led to changes

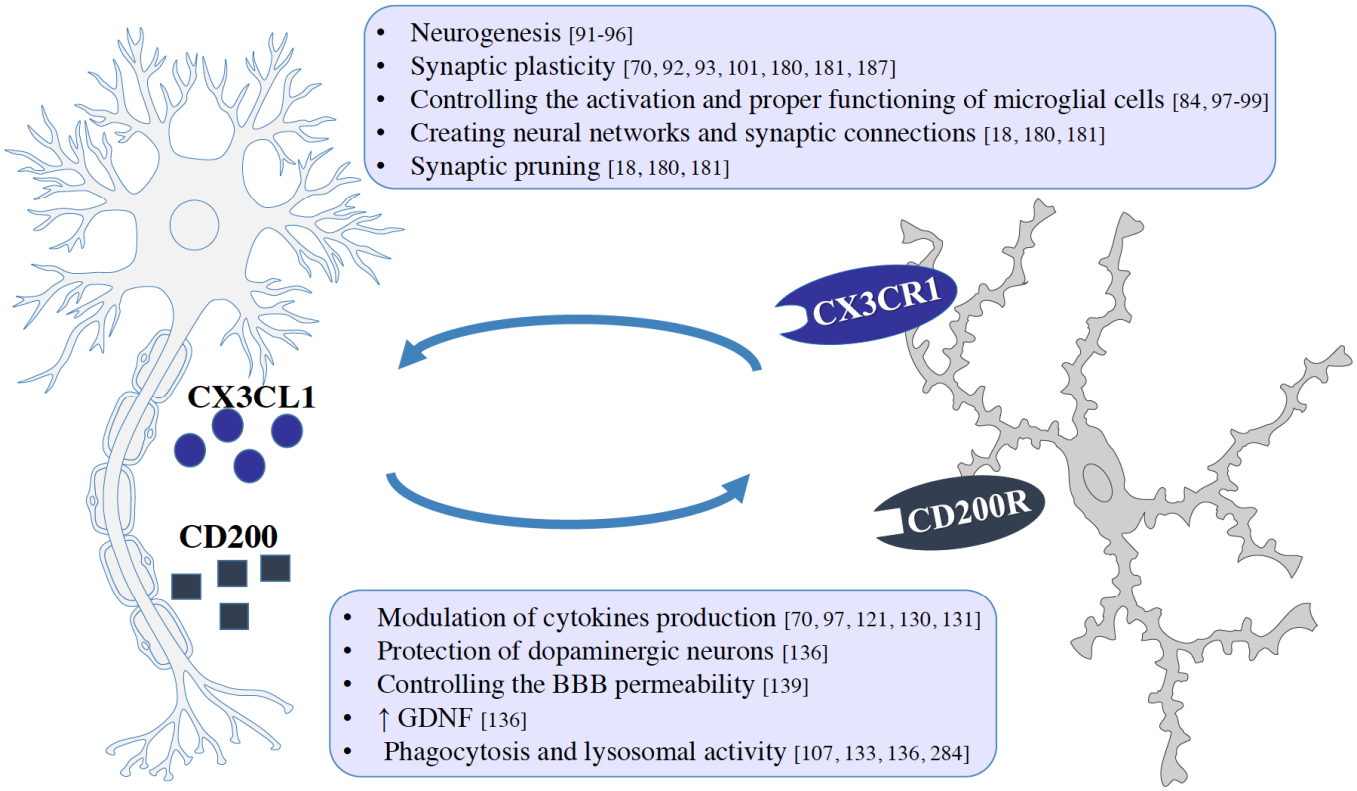

Fig. (1). Bidirectional communication between neurons and microglia is regulated by the endogenous ligand – receptor systems. Among them, the CX3CL1-CX3CR1 and CD200-CD200R axes come to the fore as they participate in the modulation of multiple processes within the healthy brain. CX3CL1 and CD200 are principally expressed on neurons, while their receptors (CX3CR1 and CD200R, respectively) are present on microglia. BBB – blood-brain barrier, GDNF – glial cell-derived neurotrophic factor. ↑ indicates an increase. Appropriate references are provided in []. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

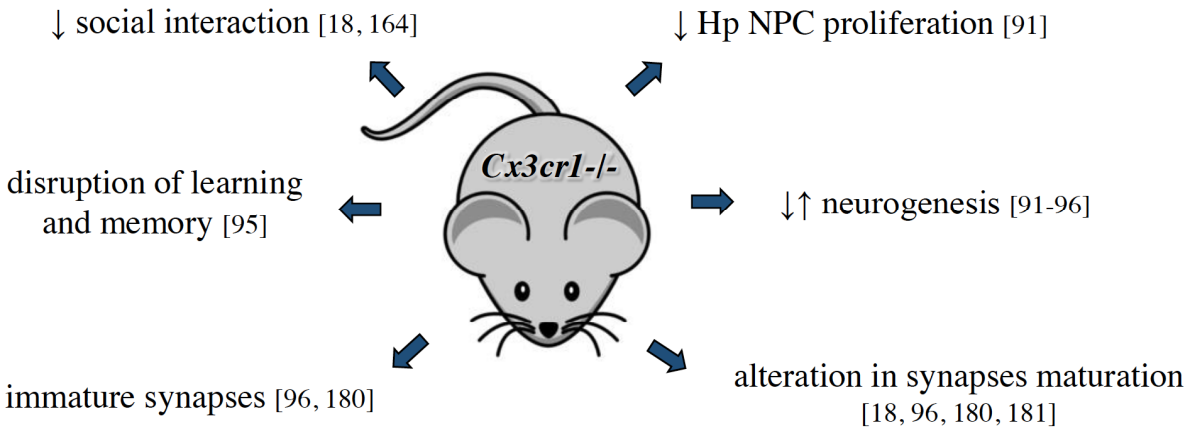

Fig. (2). Since the first reports on CX3CL1 and CX3CR1, unique roles for this network in physiological and pathological processes in the CNS has been continuously described. *Cx3cr1*-/- mice are a highly useful tool for investigating processes affected by the CX3CL1-CX3CR1 axis. To date, the literature includes reports describing the changes in the behaviour of these animals and in crucial CNS mechanisms. Hp – hippocampal, NPC – neural stem/progenitor cell. ↓ indicates a decrease and ↑↓ indicates contradictive results implicating the disturbance of the process. Appropriate references are provided in [].(*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

in microglial activity. The alteration in microglia functioning included the induction of Ca^{2+} mobilization, time- and dose-dependent activation of mitogen-activated protein kinase as well as substrate protein kinase B, extensive migratory activity, actin rearrangement and change in shape of the cells. Further, confocal imaging of retinal explants presented that CX3CL1, through its receptor, might regulate the dynamism and cellular migration of microglia and consequently the interactions between microglia and synapses [13]. This conclusion was based on results that indicated a decrease in the average velocity of spontaneous microglial process motility in *Cx3cr1*-deficient mice. The data showed that CX3CL1 had the ability to influence microglial activity through the regulation of TNF-α production [97]. The anti-inflammatory effect of CX3CL1 *via* the regulation of microglial activation was also presented in the research of Mizuno *et al.* [98], where the ligand dose-dependently suppressed the production of nitric oxide, IL-6 and TNF-α. As proposed by Ma *et al.* [99], the involvement of the CX3CL1-CX3CR1 system in microglial activation occurs, *inter alia*, in the course of receptor regulation by leucine-rich repeat kinase 2.

To investigate whether the CX3CL1-CX3CR1 axis contributes to spinal long-term potentiation (LTP), Bian *et al.* [100] used exogenous CX3CL1 and anti-CX3CR1 antibodies. As the authors concluded, CX3CL1-CX3CR1 was involved in LTP of C-fibre-induced field potentials in the rat spinal dorsal horn, and the mechanism could be regulated through IL-18/NFκB signalling. Another study showed that, in the CA1 region of the rat hippocampus, CX3CL1 negatively modulated LTP at synapses between Schaffer collaterals and pyramidal neurons [101]. The chemokine reduced the amplitude of the excitatory postsynaptic and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated currents *via* the activation of CX3CR1. The process was regulated by intracellular Ca^{2+} and synaptic activity. Comparable results regarding the engagement of the CX3CL1-CX3CR1 axis in synaptic transmission were published by Bertollini *et al.* [102]. Superfusion of the ligand to mouse hippocampal slices caused a reversible depression in the field excitatory postsynaptic potential. The mechanism of reduced efficacy in glutamatergic synaptic transmission was similar to that implicated in synaptic long-term depression.

The study of the tissues obtained from patients with drug-resistant mesial temporal lobe epilepsy revealed that the CX3CL1-CX3CR1 system affected gamma-aminobutyric acid $(GABA)_A$ currents in the human temporal lobe [103]. As shown by Heinisch and Kirby [104], CX3CL1 and serotoninergic (5-HT) neurons interact at the anatomical and functional levels in the raphe nucleus of the rat brain. The whole-cell patch-clamp recordings provided the possibility to show that CX3CL1 enhanced GABA synaptic activity at 5-HT neurons in the dorsal raphe nucleus. CX3CL1 elevated the functioning of the hippocampal N-methyl-D-aspartate receptor through mechanisms involving adenosine receptor type A2 activity and D-serine release [105]. These effects required the presence of CX3CR1 on microglia.

Several studies have reported that CX3CL1 serves as a neuroprotective factor within the CNS. As shown by the use of organotypic cerebellar slice cultures, the addition of recombinant CX3CL1, prior to H_2O_2-induced oxidative stress, significantly reduced the demyelination associated with a toxic amount of H_2O_2 and alleviated astrocyte toxicity [106]. CX3CR1 was involved in the internalization of the microtubule-associated protein – tau – by microglia [107]. These results, obtained from *in vitro* and *in vivo* experiments, suggested that the CX3CL1-CX3CR1 pathway played a key role in the phagocytosis of tau by microglia. Consistent with reports on its neuroprotective characteristics, CX3CL1 protected striatal neurons from dendritic pruning and death, which had been induced by the combined exposure to morphine and the regulatory protein necessary for an increase in HIV dsDNA transcription level, which is called Tat [108]. Similarly, the CX3CL1 protective effect was described in the context of neurotoxicity produced by another HIV-associated protein – gp120 [109]. The use of primary hippocampal neu-

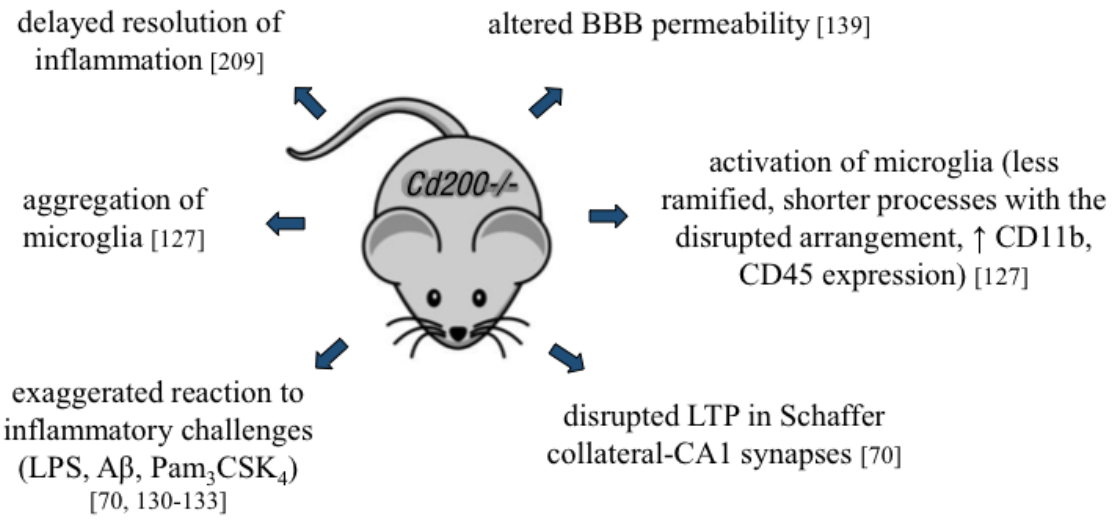

Fig. (3). Most of the data regarding the importance of CD200-CD200R signalling in sustaining homeostasis but also in pathological processes in the CNS come from studies using *Cd200*-deficient mice. These animals have been characterized by broad alterations in the immunological response (activation of microglia, changed resolution of inflammation, *etc.*), changes in the BBB permeability and LTP. BBB – blood-brain barrier, LPS – lipopolysaccharide, Aβ – amyloid-β, Pam_3CSK_4 – the TLR2/TLR1 agonist, LTP – long-term potentiation. ↑ indicates an increase. Appropriate references are provided in [].(*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ronal cultures enabled the observation of the neuroprotective effect of CX3CL1 against glutamate-produced toxicity, which was possible due to the presence of extracellular adenosine [110, 111]. The role of the CX3CL1-CX3CR1 axis in neuronal survival and neurotrophic effects in the CNS were also indicated by other research groups [43, 98, 112-114].

2.4. CD200-CD200R Axis in the Healthy Brain

CD200 (also termed OX-2 or MRC OX-2 in earlier articles) is a membrane glycoprotein, containing two extracellular immunoglobulin domains, a transmembrane region and a cytoplasmic domain. This ligand belongs to the immunoglobulin superfamily (IgSF) of cell-surface proteins [115]. Both the human and mouse forms of this antigen have a molecular weight (MW) of 32 kDa, while in rats, the MW of CD200 is origin-specific: 41 kDa in the brain and 47 kDa in thymocytes [116, 117].

CD200 is ubiquitous throughout the body. It is localized on vascular endothelial cells, follicular dendritic cells, B and T lymphocytes, placental trophoblasts, lung epithelial cells and smooth muscle cells [118]. In the brain, this glycoprotein is expressed on neurons [119] and oligodendrocytes [120] but not on microglia [121]. In the human brain, CD200 is robustly expressed in the cerebellum, cerebral cortex, hippocampus, striatum and spinal cord [122].

The only receptor for CD200, known as CD200R (or OX-2R), is also a membrane glycoprotein. In contrast to its ligand, the receptor contains an NPXY motif (with three tyrosine residues in its intracellular region), which is a signalling domain [123]. The expression of CD200R is limited principally to cells of myeloid lineage, including dendritic cells, macrophages, neutrophils, mast cells and microglia [123-125]. CD200R, similar to CD200, exists in several possible isoforms, often restricted to particular tissues [123, 126].

The specific structural characteristics and localization of CD200 and CD200R allow this axis to control the bidirectional communication between neurons and microglia. Regarding the importance of CD200-CD200R in sustaining homeostasis in the CNS, most of the *in vivo* data come from studies based on *Cd200*-deficient mice (Fig. **3**). As reported by Hoek [127], the CD200-CD200R axis maintains microglia in the quiescent state, as indicated by the ramified appearance of these cells, as well as the expression of molecules such as major histocompatibility complex class I and II, CD11b and CD45 at low or negligible levels. Lack of this signalling leads to the activation of microglia, as characterized by less ramified, shorter processes with the disrupted arrangement, an increase in CD11b and CD45 expression and the aggregation of microglia.

Multiple factors seem to be engaged in microglial activation through the pathway controlled by the CD200-CD200R system. Experiments on cortical neuronal cultures, prepared from embryos of C57BL/6 mice, highlight the functional role of N-glycosylation at Asparagine 44 of CD200R in the classical activation of microglia [128]. The *Cd200r* gene expression is regulated, in part, through the transcription factor CCAAT/enhancer-binding protein β, which binds the *Cd200r* promoter and inhibits transcription of the receptor [129].

The major role of the CD200-CD200R pathway was also described in the context of response to inflammatory challenges, generated, *inter alia*, with lipopolysaccharide (LPS) [130, 131], the TLR2/TLR1 agonist – Pam_3CSK_4 [70] or amyloid-β (Aβ) [132]. In the brains of *Cd200* knockout mice, these insults produced an exaggerated reaction, possibly due to the increased relative expression of TLR2 and TLR4 [70, 133]. Proper activation of CD200R by its ligand is also required to modulate inflammatory cytokine produc-

tion (*e.g.*, levels of IL-1β, IL-6, TNF-α) [70, 121]. Consistent with these observations, the data showed that the CD200 fusion protein (CD200Fc) reduced age-related and LPS-induced microglial activation, and also partially overcame the disruption of the LTP observed both in aged and LPS-treated rats [134]. Furthermore, slices prepared from *Cd200*-/- mice did not display LTP in the Schaffer collateral-CA1 synapses to the same degree as those slices prepared from wild type mice, which clearly indicates that CD200 is directly implicated in synaptic plasticity [70]. The use of an anti-CD200R1 blocking antibody showed that the CD200-CD200R interaction played a role in the neuroprotective action of the peroxisome proliferator-activated receptor-gamma agonist called 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 [135]. The CD200-CD200R axis is also engaged in neuroprotective properties of endocannabinoid anandamide (AEA) against LPS or interferon (IFN)-γ activated microglia-induced toxicity [68]. AEA protects neurons from inflammatory damage by upregulating CD200R through the activation of cannabinoid receptor type 2. This phenomenon was supported by data showing that AEA was unable to induce neuroprotection in microglia derived from *Cd200r*-deficient mice [68].

Another function of CD200-CD200R signalling in the CNS is the protection of dopaminergic neurons by the suppression of microglial activation and the promotion of glial cell-derived neurotrophic factor (GDNF) production [136]. GDNF is a survival factor for dopaminergic neurons. *In vitro*, it increases their size and neurite length, promotes their survival [137], and also influences the activation of microglia and protects hippocampal neurons from excitotoxic insults [138]. As shown using primary microglia culture, the expression of GDNF is increased after exposure to CD200 [136].

The data suggest that CD200-CD200R may be involved, to some extent, in controlling BBB permeability, because there was an infiltration of T cells and macrophages in the brain of *Cd200*-deficient mice, which led to the increased expression of TNF-α, IL-6, monocyte chemotactic protein-1, IFNγ-induced protein-10 and RANTES [139]. The proper interactions between CD200 and its receptor had an impact on phagocytosis and lysosomal activity, while the absence of this interplay increased Aβ engulfment [133]. As a "don't eat me" signal molecule, CD200 is associated with apoptosis. During this form of programmed cell death, the expression of CD200 is elevated on apoptotic cells, and the level of the protein remains under the control of both caspase- and p53-dependent pathways [140, 141]. However, a report from Yang *et al.* [142] stated that the expression of CD200 was affected by the combination of apoptosis, autophagocytotic cell death and necrosis, rather than by one of these processes. As shown by Webb and Barclay [143], CD200 appears on neuronal bodies and axons, where it is involved in axonal extension [143, 144]. CD200 plays a role in the process of anxiogenic sprouting and elongation, in addition to synapse formation [145] and neuritogenesis, which involves the interaction and activation of the fibroblast growth factor receptor [146]. The role of CD200 in the oligodendrogenesis recovery mechanism was also demonstrated, as the ligand may promote this process [147].

3. MALFUNCTIONS OF THE CX3CL1-CX3CR1 AND CD200-CD200R AXES AND THEIR IMPLICATIONS FOR THE PATHOGENESIS OF SCHIZOPHRENIA

Schizophrenia is a severe psychiatric disorder that affects up to 1% of the population worldwide. Statistics of the World Health Organization (WHO) [148] from 2018 inform about more than 23 million diagnosed cases of this disease. A hallmark of schizophrenia is its heterogeneity, which is manifested in the clinic, both in the aetiology and in the course of the disturbances and symptoms.

According to one of the accepted classifications, the symptoms are divided into three main groups: 1) positive, among which hallucinations, delusions or agitation are listed; 2) negative, which include: speech impoverishment, anhedonia, apathy and attention disorders; and 3) cognitive deficits: reduced ability to concentrate, impairment of various types of memory and difficulties in understanding information and using it to make decisions [149].

Factors of various origins have been indicated as the base for the symptoms and, therefore, as an aetiology of schizophrenia, often emphasizing their complicity in the final picture of the disease. This condition develops not only because of the so-called genetic predispositions [150, 151] but also because of environmental factors, which include, among others: prenatal malnutrition [152], exposure to traumatic experiences [153] and, particularly worth underlining, bacterial and viral infections [154, 155].

In the brain, the main immunocompetent cells are microglia [156]. Through interaction with neurons, under physiological conditions, microglia maintain a resting phenotype [157]. When the CNS is affected, microglia become activated, which is characterized by their increased phagocytic activity, mobility and the production of pro-inflammatory cytokines [158]. Persistent microglial activation may cause neuronal degeneration and synaptic dysfunction [159] and could lead to the subsequent development of psychiatric disorders, including schizophrenia.

Therefore, disturbances to the CX3CL1-CX3CR1 and CD200-CD200R protein systems, which are listed as key mediators of neuron – microglia communication, might be crucial in the disease course.

3.1. CX3CL1-CX3CR1 and Schizophrenia

The DBA/2 mouse strain has been suggested to be a suitable model for investigating schizophrenia-related behaviour, because of the characteristic deficits (*e.g.*, significantly reduced social interactions and prepulse inhibition) observed in these animals [160-162]. Downregulation of *Cx3cl1* gene expression in the cortices of DBA/2 mice was reported by Ma *et al.* [163]. The authors implicated CX3CL1 as a regulator of microglial activation and social behaviour in the animals. The group of Zhan *et al.* [18] indicated that *Cx3cr1*-/- mice showed alterations in social and repetitive behaviours. Zhan [164] also showed that *Cx3cr1* knockout mice displayed reduced baseline connectivity that is driven from the prefrontal cortex to the dorsal hippocampus during the habituation period in the social interaction test. A similar feature was found in schizophrenic patients, for whom severely

reduced connectivity between the hippocampus and the prefrontal cortex was observed [165, 166].

Meta-analysis performed by Bergon *et al.* [167] revealed that *CX3CR1* expression was significantly downregulated in post-mortem brains and peripheral blood mononuclear cells obtained from schizophrenic patients. The change was independent of confounding variables (*e.g.*, tobacco smoking) and was closely associated with depression – anxiety phenotype. Comparable data using integrated analysis of schizophrenia data sets were published by Li *et al.* [168]. This group discovered that *CX3CR1* level was remarkably diminished in the hippocampi of patients with schizophrenia. In another study, Ishizuka *et al.* [169] also observed a strong association between the expression of *CX3CR1* and schizophrenia. The researchers proved that the rare variant (Ala55Thr) in the gene for the receptor contributed to an increased risk for developing this severe psychiatric disorder. Ala55, which is located in transmembrane helix 1 (TM1), forms a hydrophobic core with other non-polar residues of TM1 and helix 8 in the receptor. The variant in which a hydrophobic (alanine) residue is replaced by a hydrophilic (threonine) residue may weaken the hydrophobic TM1 – helix 8 interaction and consequently destabilize the conformation of helix 8. The Ala55Thr variant in *CX3CR1* might lead to impairment in CX3CL1-CX3CR1 signalling, thereby influencing microglial function. In contrast, an overview of the schizophrenia-associated genes and transcripts presented by van Mierlo *et al.* [170] showed that the results linking *CX3CR1* expression with the disease were highly heterogeneous. The authors found the evidence insufficient to consider *CX3CR1* as the risk factor. However, as they admitted, the study included many limitations that could have differed their conclusion from the observations of others (*e.g.*, using the summary statistic information, data obtained from bulk brain tissue – not from specific structures, no control on variables that may have an impact on the immune system).

Numerous data indirectly suggested the involvement of the CX3CL1-CX3CR1 system in the etiopathogenesis of schizophrenia. Alterations in neurogenesis and cell proliferation, as well as the reduced size of the hippocampus, have been indicated as the parts of the disease pathology [171-174]. These processes must function properly for effective learning and memory, in particular, contextual and spatial learning [175-177], which are impaired in schizophrenia [178]. The age-dependent increase in the number of activated microglia can suppress neurogenesis [179]. Bachstetter *et al.* [91] evidenced that in the course of ageing, CX3CL1-CX3CR1 signalling became disrupted, leading to enhanced microglial activation and decreased neurogenesis in the hippocampus. Mice lacking the *Cx3cr1* gene were characterized by reduced hippocampal neural stem/progenitor cell (NPC) proliferation and neurogenesis. The proliferation of NPCs was also decreased when a blocking antibody for CX3CR1 was infused into the left lateral ventricle of rat brains, while the intracerebroventricular infusion of recombinant CX3CL1 reversed the disruption of neurogenesis in the aged-rat-brain [91]. The article by Sellner *et al.* [95] drew a slightly different conclusion that CX3CR1 promoted neurogenesis, but the process was independent of CX3CL1 and relied on inhibiting SIRT1 and NF-κB signalling. In that study, activation of SIRT1 alleviated cognitive impairment in *Cx3cr1*-/- mice, as manifested by disrupted learning and memory in the Morris water maze test. Another feature observed for these animals was the alteration in synaptic plasticity and synaptic pruning – the processes required for the development of neural circuits [18, 93, 180, 181]. *Cx3cr1* knockouts also exhibited a change in the number of dendritic spines and immature synapses [96, 180]. Due to the extensive literature data suggesting that schizophrenia may have a neurodevelopmental basis [182, 183], the involvement of the CX3CL1-CX3CR1 axis in controlling the mechanisms of neurogenesis, cell proliferation, synaptic plasticity and synaptic pruning may be a new target for future therapy.

3.2. CD200-CD200R and Schizophrenia

The disturbances described in schizophrenic patients comprise electroencephalogram oscillatory abnormalities, which are heritable and genetically-mediated [184-186]. Data from Narayanan *et al.* [187] showed that the theta activity of the brain was significantly correlated with and mediated by gene clusters involved in glutamic acid pathways as well as by cadherin and synaptic contact-based cell adhesion processes. In this study, *CD200* was one of the highly ranked genes moderating changes in theta activity, which, as a mainly cortical-hippocampal circuit-based process, may indicate a crucial role in the mechanisms controlling memory, spatial information and synaptic plasticity [187]. These abnormalities contribute to the heterogeneous core of the disturbances and symptoms observed in schizophrenia [188-190]. The study on lymphoblastoid cells obtained from monozygotic twins discordant for schizophrenia revealed a change in *CD200* expression, suggesting the possible pathological contribution of the CD200-CD200R axis in susceptibility to schizophrenia [191]. On the other hand, the characterization of macrophages from schizophrenic patients revealed no changes in *CD200* expression compared to those of the control [192]. However, as the authors underlined, it must be taken into account, that the data came from a small number of samples. Additionally, studies of clinical subgroups and additional screening tests used to assess the full phenotype of the macrophages are needed to confirm the conclusion described.

Maternal immune activation (MIA) produced by the systemic administration of LPS or polyinosinic:polycytidylic acid (Poly I:C) injection to pregnant dams of rodents are commonly accepted animal models of schizophrenia [193]. They are widely characterized in terms of biochemical [194-197], neuroanatomical [198-200] and behavioural [197, 200, 201] attributes, in both mice and rats. To date, no changes in CD200R level have been described in isolated microglia after a maternal immune response was induced by Poly I:C challenge in mice, regardless of the sex or age of the animal [202]. Unfortunately, the researchers did not measure the level of the ligand for CD200R, which could have been affected by the treatment. Lin *et al.* [203] accentuated that treatment with Poly I:C during pregnancy might increase embryo resorption in mice and that the mechanism involved, at least partially, direct inhibition of CD200 expression on cytokeratin 7-positive cells.

In the study by Antonson *et al.* [204], maternal infection with porcine reproductive and respiratory syndrome virus (PRRSV) tended to upregulate *CD200* expression, while *CD200R* level was unchanged in the microglia from the hippocampi of foetal piglets. The same research group reported that *CD200R* level increased in the prefrontal cortex and the striatum, and *CD200* concentration decreased in the hippocampus and the striatum of prenatally PRRSV-exposed piglets [205]. In experimental conditions, PRRSV is applied during pregnancy to induce maternal infection, which increases the risk of neurobehavioural disorders, including schizophrenia, in the offspring [204]. Comparable results were shown for young and adult mice after influenza treatment. Significantly reduced levels of *CD200* were detected in the hippocampi of these animals [206, 207]. *Cd200*-deficient mice developed more severe disease, associated with enhanced lung infiltration and lung endothelium damage after inoculation with influenza [208], and also had higher activity of macrophages, leading to the delayed resolution of inflammation [209]. The importance of CD200 during influenza infection in reference to schizophrenia results from the fact that prenatal infections with this virus are considered to confer a risk factor for the development of schizophrenia. This correlation was supported by evidence from population and epidemiological studies, which showed a higher occurrence of psychoses with schizophrenic symptoms following influenza epidemics [210, 211].

4. THE ROLES OF CX3CL1-CX3CR1 AND CD200-CD200R AXES MALFUNCTIONS IN THE DEVELOPMENT OF DEPRESSION

Depression has been reported as the leading cause of disability in terms of total years lost due to the impairments it generates [212]. According to the WHO estimations [213], the disease affects more than 300 million people worldwide. The condition is symptomatically heterogeneous, spanning cognitive, emotional, motivational and physiological alterations [214-216]. Without treatment, depressive symptoms can last for weeks, months or even a lifetime, and in severe cases may lead to suicidal attempts and death.

The aetiology of depression has a diversified nature, thus making the discovery of an exact cause challenging. As a result, alterations in multiple mechanisms have been proposed in the literature, with the following few contributors specified: monoaminergic systems [217-219], genetic background [220], circadian rhythm [221], neurotrophic factors [222], brain glucose metabolism [223], mitochondrial functioning [224-228], response of an organism to stress both during the prenatal period and early life [229-232], neuroinflammatory processes, particularly involving cytokines [233-235].

4.1. CX3CL1-CX3CR1 and Depression

To date, only a few articles have evaluated the expression of CX3CL1 in patients with depression. In those affected by moderate-severe depression, the serum level of CX3CL1 was elevated when compared to that in the control patients [236]. A similar observation was reported in plasma samples from patients diagnosed with major depressive disorder with comorbid cocaine addiction [237]. The level of CX3CL1 was thus suggested as a potential biomarker for depression and anxiety in the course of colorectal cancer, due to the raised serum level of this protein identified in patients with this condition [238].

In depression, the serotonergic pathway is a highly affected neurotransmission system. Immunohistochemical and electrophysiological studies revealed the neuroanatomical relationship between 5-HT transmission and CX3CL1 in the rat dorsal raphe nucleus [104]. Furthermore, the functional interaction linking those factors was described, showing that CX3CL1 enhanced the number and the sensitivity on 5-HT of postsynaptic GABA receptors [104]. The literature documented the participation of the CX3CL1-CX3CR1 system in the regulation of tryptophan metabolism. In mice lacking *Cx3cr1*, the induction of depressive behaviour (through the administration of LPS) was associated with the activation of the enzyme indoleamine 2,3-dioxygenase (IDO) [239]. IDO modulated the metabolism of tryptophan and led to the formation of kynurenine instead of 5-HT.

Exposure to stressful events of various types (chronic restraint, mild or acute stress, psychosocial stress, prenatal stress, *etc.*) is another widely investigated plausible cause of depression. Accordingly, experimental approaches using diverse types of stress are considered useful animal models to simulate this condition [240]. In the article by Trojan *et al.* [231], prenatal stress caused anxiety and depressive-like disturbances in the adult offspring of rats. The changes were followed by the reduction in CX3CL1-CX3CR1 expression in the hippocampi and the frontal cortices of these animals. The chronic administration of the antidepressants (tianeptine and fluoxetine) normalized the observed alterations both on the behavioural and biochemical levels [231]. Additionally, the intracerebroventricular application of exogenous CX3CL1 alleviated the changes in the behaviour and in the inflammatory processes observed in the brains of prenatally stressed rats [241]. The affected mRNA levels of *Cx3cl1* and *Cx3cr1* were detected in the prefrontal cortex and in the dorsal and ventral hippocampus of adult male rats exposed to chronic mild stress [242].

Most of the research attempts to identify the role of the CX3CL1-CX3CR1 system in the generation of depressive-like behavioural dysfunctions have been based on genetic models with a knockout of the receptor gene. *Cx3cr1*-/- mice showed prolonged depressive behaviour and social withdrawal in response to acute immune stress following a single, peripheral LPS injection [243]. The study by Milior *et al.* [244] provided evidence that disorders in neuron – microglia signalling occurred *via* the CX3CL1-CX3CR1 pathway in response to chronic unpredictable stress. Winkler *et al.* [245] showed that *Cx3cr1*-deficient mice were resilient to chronic stress-induced depression, as demonstrated by a lack of anhedonia. In another study, *Cx3cr1* knockout mice were completely unaffected by the exposure to chronic unpredictable stress in terms of emotional, cognitive, neurogenic and microglial responses to the insult, while their wild-type counterparts displayed these depressive-like characteristics [246]. Further evidence supporting this phenomenon came from the research showing that the animals with the depleted

receptor were characterized by resistance to the occurrence of depressive behaviour in a chronic despair model of depression [247]. Contrary to wild-type animals, in *Cx3cr1*-deficient mice, the lack of changes in microglial morphology was described. This observation indicated that microglial hyper-ramification is controlled by the neural-microglial CX3CL1-CX3CR1 axis.

4.2. CD200-CD200R and Depression

Nearly all the data regarding the participation of the CD200-CD200R pathway in the pathomechanisms of depression were derived from studies on animal models of this disease, with most applying different stress procedures. Wang *et al.* [248] used the early-life social isolation (ESI) model of stress to characterize the development of depressive-like behaviour in rats. The authors observed that, in the hippocampi of the ESI animals, the expression of *Cd200* receptor, which promoted microglial quiescence, was significantly decreased [248]. In turn, Bollinger *et al.* [249] found that various types of restraint stress could lead to brain region- and sex-dependent changes in CD200-CD200R signalling in corticolimbic circuitry. Acute and chronic stress increased *Cd200* mRNA level in the orbitofrontal cortex (OFC) in the female rats. In males, chronic stress increased the expression of *Cd200r* in the OFC and the basolateral amygdala (BLA), as well as *Cd200* in the dorsal hippocampus. Besides, acute stress produced an increase in *Cd200r* transcript in the BLA of male animals [249]. These changes were correlated with a decrease in the activation of microglia.

Recently published observations revealed that exposure to the acute stressor (inescapable tail shock, ITS) resulted in a reduction in *Cd200r* level in the hippocampus, the BLA and the central nucleus of the amygdala 24 hours post-stress [250]. Similar results were reported by Fonken *et al.* [251]. They observed that ITS generated a decrease in the level of *Cd200r* in the hippocampus of male and female rats. A contradictory observation was published by Blandino *et al.* [252], who suggested that inescapable footshock lowered *Cd200r* transcript in the hypothalamus but not in the hippocampus of rats. The discrepancies between these reports concerning the hippocampus might be attributed to the various protocols used by the two research groups. In turn, Lovelock and Deak [253] observed no changes in the expression of either *Cd200* or *Cd200r* in the paraventricular nucleus of the hypothalamus, the hippocampus or the prefrontal cortex after inducing chronic escalating distress, which was consistent with the data previously communicated by the same authors [254].

The outcome of the experiments on rat primary microglia cultures showed that treatment with dexamethasone for 72 hours reduced *Cd200r* level and induced the ramified form of microglia [255]. As shown by Wachholz *et al.* [256], IFN-α vulnerable mice, which are a model of immune-mediated depression, seemed to have a higher expression of CD200R in the microglia. These animals developed a depressive-like phenotype, which was manifested by an increased immobility time in the forced swim and the tail suspension tests as well as reduced explorative behaviour observed in the novel object exploration test [256].

5. THE ROLE OF CHANGES IN CX3CL1-CX3CR1 AND CD200-CD200R INTERACTIONS IN THE NEURODEGENERATION-BASED DISEASES

5.1. Alzheimer's Disease

Alzheimer's disease (AD) is recognized as the most common cause of dementia (50 – 75% cases) and, consequently, it is a growing global health concern [257]. The condition is characterized by a progressive decline in cognitive functioning (memory, language, learning and thinking), which is substantially escalated among people 65 years or older [258].

The pathophysiological picture of AD consists of the presence of Aβ plaques and neurofibrillary tangles composed of hyperphosphorylated tau but also dystrophic neurites, astrogliosis, microglial activation and consecutive neurodegeneration [259-263]. The processes associated with deleterious changes, including the death of neurons, are initiated in the cortex and then extend to the hippocampus, which are the brain regions involved in memory and learning [264, 265]. Eventually, pathology affects the entire brain [266].

Neuroinflammation is also extensively involved in the complex pathology and symptoms of AD [60]. The progressive problems centred on Aβ plaques and neurofibrillary tangles are accompanied by a number of immunological alterations, containing increased secretion of pro-inflammatory cytokines. Whether these disturbances are causes or consequences of AD remains unknown; however, inflammation within the brain of AD patients has been extensively investigated in recent years.

5.1.1. CX3CL1-CX3CR1 and Alzheimer's Disease

The importance of the CX3CL1-CX3CR1 axis in the pathology of AD seems to be undeniable, as evidenced by the enormous number of scientific articles concerning this correlation. The subject was reviewed in a few excellent articles; however, the amount of continuously emerging data elicits the need for further systematization of the findings.

As published by Strobel *et al.* [267], *CX3CL1* is highly expressed in the hippocampus, which is the main area of pathological changes, in the brains of AD patients. The elevated level of *CX3CL1* reflected the progression of the disease [267]. A similar observation was described by Bolós *et al.* [107]. The authors reported a concomitant increase in CX3CL1 protein level, phosphorylated tau and the number of microglia in post-mortem hippocampal tissue from AD patients. The disruption of the CX3CL1-CX3CR1 system and the subsequently altered neuron – microglia communication seemed to be more prominent with the progression of AD. Yet, the same research group showed a reduction in the protein level of CX3CL1 in the cerebrospinal fluid obtained from AD patients, compared to the non-demented age-matched controls [268].

A significant observation in the context of AD was also provided by Lyons *et al.* [269]. The expression of *Cx3cr1* mRNA diminished in the brains of aged rats and coincided with an age-related increase in microglial activation. The treatment of these animals with exogenous CX3CL1 attenuated the disturbances that had been observed and induced the

activation of the phosphatidylinositol-3 kinase pathway, which is required to maintain microglia in a quiescent state [269].

Recent research based on the rTg4510 mouse model of tauopathy revealed that induced overexpression of CX3CL1 resulted in the reduction of tau pathology and microgliosis, as well as the amelioration of neuronal loss in the brains of these animals [270]. Furthermore, the treatment with CX3CL1 improved cognitive performance on the novel object recognition and radial arm water maze tasks by the mice [271].

5.1.2. CD200-CD200R and Alzheimer's Disease

The analysis in the post-mortem brain tissues from patients with AD revealed that the protein level of CD200 negatively correlated with the levels of phosphorylated tau and Aβ plaques (in the temporal cortex) and neurofibrillary tangles (in the temporal and the cingulate cortices) [272]. These results suggested that the progressively increased inflammatory responses occurred with increasing severity in AD pathology. In another report from this research group [273], the expression of CD200 and CD200R (at both the mRNA and protein levels) was affected in the hippocampus and the inferior temporal gyrus in post-mortem brain tissues obtained from AD patients. The authors demonstrated that CD200R production by human microglia was elevated by the anti-inflammatory cytokines IL-4 and IL-13, which are considered to be generally lacking in elderly human brains [273].

The evidence to support these observations from the post-mortem examinations has come from the experiments applying the animal models of AD. Lyons *et al.* [121, 130] published data showing that the hippocampal activation of microglia in aged and Aβ-treated rats was followed by the perturbed expression of CD200. Treatment with CD200Fc alleviated LPS-generated microglial activation in the hippocampus of aged rats [134]. Further, the impairment of the LTP in the DG, as described for those animals, was attenuated when they were treated with CD200Fc. The result suggested that the CD200-CD200R axis might positively impact memory in AD, which was characterized as the LTP-based process [274]. In the multidimensional study by Varnum *et al.* [136], the injection of the viral vector expressing CD200 restored hippocampal neurogenesis and suppressed β-amyloidosis in APP mice, which are the transgenic model of AD. The administration of the vector weakened the inflammation represented by reduced $NOS2^+$ and the increased number of $YM1^+$ $Iba1^+$ cells. *In vitro*, CD200 expression dramatically affected microglia, causing increased neuronal maturation. CD200 stimulated and altered microglial activation, enhanced the survival of $CD11b^+$ primary microglia and also improved the ability of these cells on $A\beta_{42}$ phagocytosis and GDNF expression [136].

5.2. Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder [275]. Statistics have been used to predict that the number of people affected by PD is expected to increase by more than 50% by 2030, up to more than 9 million cases worldwide [276]. The condition is characterized by motor and nonmotor symptoms. The classical motor components of the disease include bradykinesia, muscular rigidity, rest tremor, postural and gait impairment, while nonmotor features consist of cognitive impairment, psychiatric symptoms, olfactory dysfunction, sleep disorders, autonomic dysfunction, pain and fatigue [277].

The pathophysiology of PD is complex and not fully elucidated. However, a progressive loss of dopamine-producing neurons in the substantia nigra pars compacta (SNpc) and widespread distribution of intracellular aggregates of alpha-synuclein protein (α-syn) have been reported as the core characteristics of this condition [278, 279]. α-Syn is the major component of Lewy bodies and Lewy neurites, the pathological hallmarks of PD [279].

5.2.1. CX3CL1-CX3CR1 and Parkinson's Disease

The research analysing the cerebrospinal fluid (CSF) of a large cohort of PD patients revealed that the ratio of CX3CL1 to $A\beta_{1\text{-}42}$ was positively correlated with PD severity and progression [280]. Other results from the CSF examination showed that the exosomal RNA level of *CX3CR1* was significantly reduced in the CSF of patients with PD (in that article, a similar observation was also noted for AD patients) [281]. Yet, the expression pattern of the differentially expressed microRNA for *CX3CR1* was upregulated in the peripheral whole blood obtained from PD patients [282].

Studies on the role of CX3CL1-CX3CR1 signalling in the pathomechanisms underlying PD have been widely based on *Cx3cr1* knockout mice. Castro-Sánchez *et al.* [283] analysed the contribution of the receptor to α-syn-associated degeneration and the activation and dynamics of microglia after α-syn stimulation. The injection of the vector carrying the A53T mutant of this protein ($\alpha\text{-SYN}^{A53T}$) into the SNpc of the knockout animals revealed that the lack of *Cx3cr1* enhanced the neurodegenerative and neuroinflammatory processes initiated by $\alpha\text{-SYN}^{A53T}$ treatment. The authors also proved that exposure to $\alpha\text{-SYN}^{A53T}$ in the conditions of *Cx3cr1*-deficiency shifted microglial activation towards more pro-inflammatory phenotypes [283]. What is interesting, the group of Thome [284] observed the opposite effect, showing that the receptor might be significant in disease progression of synucleinopathies. The depletion of *Cx3cr1* resulted in a decrease in microglial phagocytosis and α-syn-associated inflammation in primary microglia originating from the knockout mice.

Another approach to investigate the involvement of CX3CL1-CX3CR1 system in PD includes the use of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine neurotoxin (6-OHDA) models of the disease. The MPTP model combined with *Cx3cr1* knockout showed that, in SNpc, CX3CR1 had a protective effect against CCL2 overexpression by astrocytes, leading to dopaminergic neurodegeneration [285]. The general conclusion about the neuroprotective action of CX3CL1 was supported not only by the studies of Bickford's group, who applied MPTP [286] and 6-OHDA [287] models but also by the model with α-syn overproduction *via* recombinant adeno-associated virus [113].

The literature has also suggested other factors linked to PD. Among them, infection with *Toxoplasma gondii* might be implicated in the development of PD [288] (as well as schizophrenia [289] and AD [290]) or it may have had, at least, an influence on certain symptoms [291]. In a mouse study, the cortical neurodegeneration caused by chronic exposure to this neurotropic parasite led to increased CX3CL1 expression accompanied by microglia activation [292]. Additionally, the missense mutations in Leucine-Rich Repeat Kinase 2 (LRRK2) were proposed as significant players in PD. In the microglia derived from *Lrrk2*-/- mice, both mRNA and protein levels of CX3CR1 were increased and the cells migration towards the source of CX3CL1 was enhanced [99].

5.2.2. CD200-CD200R and Parkinson's Disease

In PD patients, disturbances in the CD200-CD200R interaction were described for the peripheral immune cells [293]. Monocyte-derived macrophages (MDMs) from young and elderly patients with PD were compared with those obtained from age-matched controls to determine any changes in CD200R expression. Basal CD200R levels were the same in all the examined groups, yet the induction of the receptor in response to various inflammatory stimuli was affected in the MDMs from the PD patients [293]. In addition, the stimulus-induced level of CD200R in the MDMs from the PD patients was inversely correlated with the level of TNF-α secretion and the age of PD onset.

Neuroinflammation, with microglial activation coming to the foreground, is among the prominent pathological features of PD. As shown by Xie *et al.* [294], the peripheral injection of LPS led to the mobilization of microglia, followed by the enhanced expression of *Cd200* and *Cd200r* in the substantia nigra of rats. The attenuation of this activation by CD200Fc protected dopaminergic neurons from the negative effect of the LPS-induced inflammation. On the contrary, blockage of signalling with anti-CD200R antibody accelerated the neuronal loss [294]. Altogether, these results suggested that the CD200-CD200R axis might be relevant to the course of PD. Comparable results were published by Xia *et al.* [295]. The authors presented that the induction of peripheral blood monocyte tolerance alleviated the neuroinflammation produced by the intraperitoneal treatment with LPS. The process was mediated by the upregulation of CD200R.

A study using an *in vivo* model of PD, based on the infusion of MPTP hydrochloride, revealed that the levels of CD200 and CD200R were reduced in mouse cerebral cortices in a time-dependent manner [296]. This observation suggested that this signalling pathway might participate in the progression of PD, due to the simultaneously obtained results showing that the dopamine level decreased similarly. The *in vitro* approach, with an injection of 1-methyl-4-phenylpyridinium ion in primary microglia cells, allowed for the determination that the protective effect of CD200 on the dopaminergic neurons was mediated through the promotion of the opening of the ATP-sensitive potassium channel

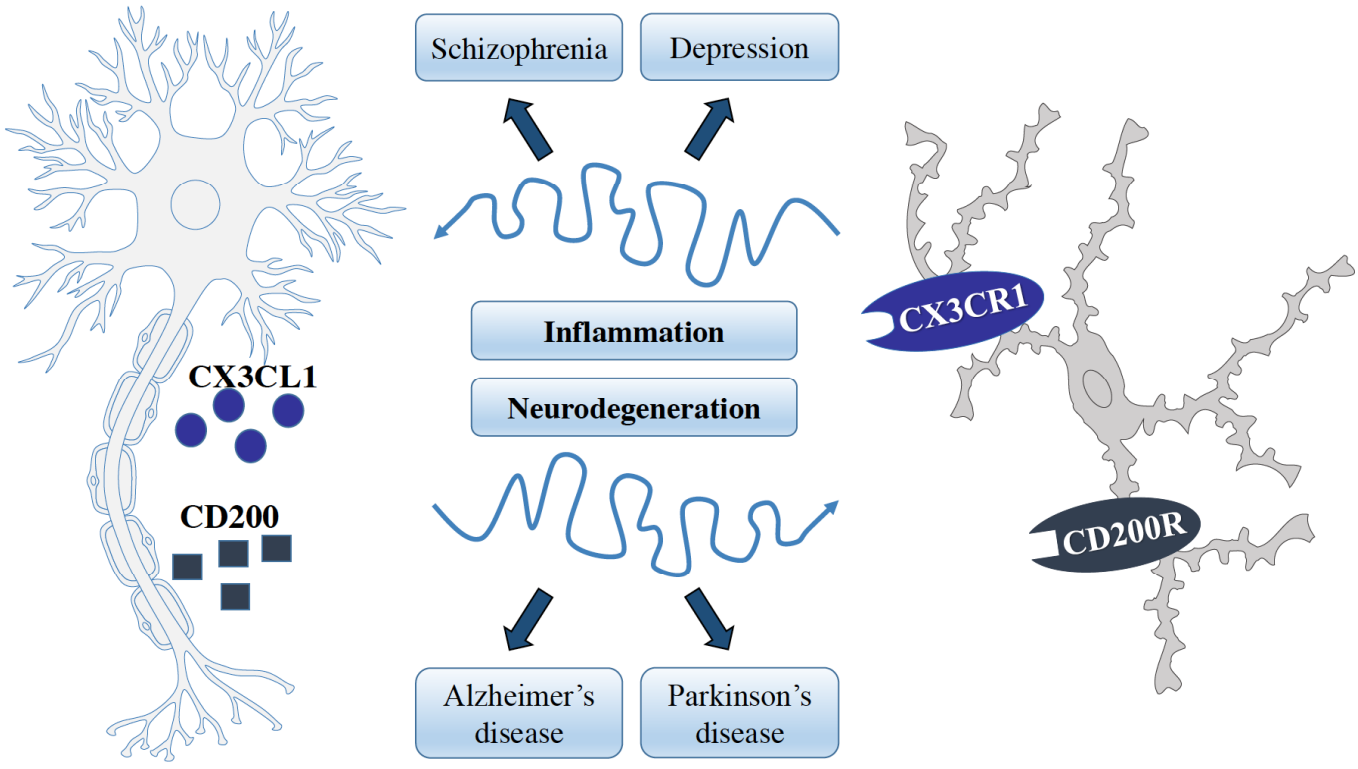

Fig. (4). The disruption of the neuron – microglia communication, specifically the CX3CL1-CX3CR1 and CD200-CD200R pathways, leads to deleterious processes, mainly neuroinflammation and neurodegeneration. The lack of this balance has been increasingly reported as the basis for the development of severe psychiatric (schizophrenia, depression) and neurodegenerative (Alzheimer's and Parkinson's diseases) conditions. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[296]. This beneficial process was accompanied by the inhibition of microglial activation and the cessation of ATP release. Besides, the ageing-related reduction in CD200 expression in the rat SNpc was reported by Wang *et al.* [297]. The suppressed levels of CD200 and CD200R were also characteristics of MPTP/probenecid-induced PD mice [298]. These animals had disturbed motor balance and coordination, likewise the declined number of dopaminergic neurons in the SNpc and lowered density of those cells in the striatum [298]. Other *in vivo* evidence was provided by Zhang *et al.* [299], who employed the 6-OHDA model combined with a CD200R-blocking antibody. In the 6-OHDA rats with moderate dopaminergic neurodegeneration in the SNpc, the administration of the antibody significantly aggravated the impairment.

CONCLUSION

In the present article, we reviewed some of the relevant data from the literature regarding the role of neuron – microglia communication both in the healthy brain and during the pathological processes within the CNS. We underlined that, in this context, both the CX3CL1-CX3CR1 and CD200-CD200R systems deserve special recognition for their specific actions and wide participation in the regulation of multiple processes (microglial activation, apoptosis, phagocytosis, neurogenesis, neuroinflammation, synaptic plasticity, *etc.*). In recent years, it has become undeniable that malfunctions in these axes are involved in psychiatric (schizophrenia, depression) and neurodegenerative (Alzheimer's and Parkinson's diseases) disorders, as the outcome of these conditions appears to rely on the processes controlled by CX3CL1, CD200 and their respective receptors (Fig. **4**). The comprehensive evidence supporting these relationships has been provided within this article. However, further research leading to a profound understanding of the signalling pathways, critical for the proper communication between neurons and microglia, is essential to determine new therapeutic directions that will enable the maintenance/restoration of homeostasis in the CNS.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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