Neuronal Chemokines: Versatile Messengers In Central Nervous System Cell Interaction

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Abstract Whereas chemokines are well known for their ability to induce cell migration, only recently it became evident that chemokines also control a variety of other cell functions and are versatile messengers in the interaction between a diversity of cell types. In the central nervous system (CNS), chemokines are generally found under both physiological and pathological conditions. Whereas many reports describe chemokine expression in astrocytes and microglia and their role in the migration of leukocytes into the CNS, only few studies describe chemokine expression in neurons. Nevertheless, the expression of neuronal chemokines and the corresponding chemokine receptors in CNS cells under physiological and pathological conditions indicates that neuronal chemokines contribute to CNS cell interaction. In this study, we review recent studies describing neuronal chemokine expression and discuss potential roles of neuronal chemokines in neuron–astrocyte, neuron–microglia, and neuron–neuron interaction.

Keywords CNS · Central nervous system · Neurons · Astrocytes · Microglia · Chemokines · Cell interaction

Introduction

Chemokines are small proteins that are able to induce a chemotactic response in cells expressing the corresponding chemokine receptors. Since the discovery of the first protein with chemotactic activity [1], the chemokine family has expanded to approximately 50 chemokines [2] and 20 receptors [3]. Chemokines have been divided into four groups based on the position of four conserved cysteine residues in the N-terminal region of the protein. The two largest groups are CXC and CC. The first two cysteines in the CXC group are separated by one amino acid residue, whereas the first two cysteines in the CC group are adjacent to each other [4, 5]. The two small groups are the C chemokines, with only one cysteine in the N-terminal region, and the CX3C chemokine, where the first two cysteines are separated by three amino acid residues [5]. Chemokine receptors are designated according to the chemokine group they preferentially bind. For example, CC chemokines bind to CC receptors and so on. There has yet only been one exception reported, namely CCL21, that, in addition to CCR7, also binds to CXCR3 [6–8]. All chemokine receptors belong to the family of G-protein coupled receptors (GPCRs). In general, GPCRs can bind many different G-proteins, allowing for a great variety of intracellular signaling pathways (for excellent review, see [9]). The majority of chemokine-induced responses are inhibited by pertussis toxin (PTX), indicating that Gαi–proteins mediate many effects [10]. Chemokine receptors can activate intracellular targets like adenylyl-cyclase, phospholipases, GTPases like Rho, Rac, and Cdc42 and pathways of major kinases like mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3-K) [11, 12]. This diversity of intracellular signaling shows that chemokine receptors, in addition to pathways involved in cell migration, also activate other pathways and may, in that way, control a great spectrum of cellular functions [13, 14].
Chemokines are well-known regulators of peripheral immune cell trafficking under both physiological and pathological conditions (reviewed by [15–17]). In addition to chemo-attraction of immune cells, chemokines have been implicated in a variety of cell functions, such as early development, formation of secondary lymphoid organs, wound healing, angiogenesis and angiostasis, regulation of adhesion molecule expression, development of Th1/Th2 profiles, tumor growth, and metastasis [5, 14, 18–24]. Thus, from being molecules thought to solely orchestrate immune cell migration, chemokines are now considered versatile messengers with the ability to control the interaction between a wide diversity of cell types.

In addition to their presence in the periphery, numerous studies have demonstrated that chemokines are also expressed in the central nervous system (CNS), where they play a crucial role in physiological and pathological conditions, such as development, synaptic transmission, homeostasis, injury, and disease-associated neuroinflammation [19, 25, 26]. Although astrocytes and microglia are the primary source of chemokines, there is evidence that neurons express and secrete chemokines as well, indicative of a neuronal contribution to chemokine signaling. In this paper, we review recent studies describing neuronal chemokine expression and discuss the potential roles of neuronal chemokines in neuron–astrocyte, neuron–microglia, and neuron–neuron interaction.

**Neuronal Chemokine Expression**

Approximately 60 studies describe chemokine expression in neurons under physiological and pathological conditions (see Table 1). These studies, of which the majority is published in the last 3 years, are reviewed in the following sections.

**CC Chemokines**

**CCL2**

CCL2 is currently the most extensively described neuronal chemokine. The majority of reports describing neuronal CCL2 expression are focused on pathological conditions. An induction of neuronal CCL2 expression was described upon ischemia [27–29], after axonal injury [30–34] and in motoneurons of patients with amyotrophic lateral sclerosis (ALS), and in mouse models for ALS [35, 36]. Interestingly, neuronal CCL2 expression in response to ischemia was detectable within 2 h, whereas CCL2 expression in astrocytes was detected only after 2 days [27]. Although most reports show induction of neuronal CCL2 expression under pathological conditions, a recent study has shown constitutive CCL2 expression in neurons throughout the rat brain [37]. This study demonstrated that, depending on the brain region, up to 100% of the neurons were positive for CCL2 [37]. CCL2 was mainly detected in neuronal cell bodies and costaining-depicted colocalization with various neurotransmitters and neuropeptides, corroborating a population-specific expression of CCL2 [37]. Constitutive neuronal CCL2 expression was also shown in a human neuronal cell line [38] and during human CNS development [39].

**CCL3, CCL4, and CCL5**

At present, there is only one study describing neuronal CCL3 expression in situ, depicting protein expression in adult human brain [40]. Further, expression of CCL3, CCL4, and CCL5 was described in cultured forebrain neurons derived from human first trimester embryos. These chemokines showed increased expression after exposure to immunological stimuli [41]. CCL3 and CCL4 expression were induced in mouse cerebellar granule neurons after infection with *Toxoplasma gondii* [42], as was CCL5 expression after viral infections [43, 44].

**CCL21**

In a middle cerebral artery occlusion (MCAO) mouse model of brain ischemia, cortical neurons rapidly expressed CCL21 in the penumbra of the ischemic core. Because control brain tissue did not express CCL21, CCL21 was assumed to be specifically expressed in endangered neurons [45]. In accordance with the in vivo findings, CCL21 expression was induced in cortical neurons in vitro within 2 h after excitotoxicity [45, 46]. The CCL21 expression in endangered neurons was rather surprising, as CCL21 is well known for its constitutive expression in secondary lymphoid organs, controlling the homing of mature dendritic cells and naïve T cells [47] and is, therefore, generally considered a homeostatic chemokine linked to the development and maintenance of secondary lymphoid organs [48]. The rapid CCL21 expression in endangered neurons after injury indicates a brain specific role of CCL21. This assumption is corroborated by findings in transgenic mice in which CCL21 was expressed ectopically in various tissues. CCL21 expression in the brain induced a massive brain inflammation that killed the animals within 3 days after the expression onset [49], whereas CCL21 expression in the skin induced the formation of secondary lymphoid structures [50].

**Other CC Chemokines**

A single study has demonstrated a constitutive and inducible expression of CCL20 in rat cerebellar granule...
**Table 1** Neuronal chemokine expression

| Chemokine | Species | Condition                  | RNA | Protein | References |
|-----------|---------|----------------------------|-----|---------|------------|
| CCL2      | h       | Brain                      | +   |         | [39]       |
|           |         | Spinal cord, ALS          | ↑1  |         | [35]       |
|           |         | Monoculture               | ↑1  |         | [41]       |
|           | r       | Brain                      | +   |         | [37]       |
|           |         | Brain, cranial nerve injury| ↑1  |         | [30]       |
|           |         | Brain, ischemia           | ↑1  |         | [28]       |
|           |         | Retina, ischemia          | ↑1  |         | [168]      |
|           |         | Spinal cord, peripheral nerve injury| ↑1 |         | [31–34]    |
|           | m       | Brain, ischemia           | ↑   |         | [27, 29]   |
|           |         | Spinal cord, ALS model    | ↑   |         | [36]       |
| CCL3      | h       | Brain, AD                  | ≈   |         | [40]       |
|           |         | Monoculture               | ↑   |         | [41]       |
|           | r       | Retina, ischemia          | ↑   |         | [168]      |
|           | m       | Monoculture               | ↑   |         | [42]       |
| CCL4      | h       | Monoculture               | ↑   |         | [41]       |
|           | r       | Retina, ischemia          | ↑   |         | [168]      |
|           | m       | Monoculture               | ↑   |         | [42]       |
| CCL5      | h       | Monoculture               | ↑   |         | [41]       |
|           | m       | Monoculture               | ↑   |         | [43, 44]   |
| CCL20     | r       | Monoculture               | ↑  |         | [51]       |
|           |         | Trigeminal neuron culture | ↓   |         | [169]      |
|           | m       | Brain, ischemia           | ↑   |         | [45]       |
|           |         | Monoculture               | ↑   |         | [45, 46]   |
|           |         | Neonatal hippocampal slice culture | ↑ |         | [46]       |
| CXCL1/2/3 | r       | Monoculture               | +   |         | [51]       |
| CXCL8     | h       | Monoculture               | +   |         | [41]       |
| CXCL9     | m       | Monoculture               | +   |         | [43]       |
| CXCL10    | h       | Brain, HIV                | ↑   |         | [54]       |
|           | mac     | Mixed brain culture       | +   |         | [54]       |
|           | r       | Brain, HIV                | ↑   |         | [54]       |
|           | m       | Brain, ischemia           | ↑   |         | [52]       |
|           |         | Brain, entorhinal cortex lesion | ↑ |         | [53]       |
|           |         | Brain, West Nile virus    | ↑   |         | [43]       |
|           | m       | Monoculture               | +   |         | [43]       |
| CXCL11    | m       | Monoculture               | +   |         | [43]       |
| CXCL12    | h       | Brain, HIV                | ↑   |         | [59]       |
|           | r       | Monoculture               | +   |         | [59]       |
|           | m       | Brain, ischemia           | ≈/↓ |       | [56]       |
|           |         | Brain, LPS injection      | ≈   |         | [56]       |
|           |         | Mixed brain culture       | +   |         | [59]       |
| CX3CL1    | h       | Brain, MS                 | ↑   |         | [113]      |
|           | r       | Brain and spinal cord, EAE| ≈   |         | [63, 65, 66, 68] |
|           |         | Spinal cord, peripheral nerve injury | ≈ |         | [171, 172] |
|           |         | Brain, LPS injection      | ≈   |         | [67]       |
|           |         | Brain, KA injection       | ≈   |         | [67]       |
neurons in vitro, which was suggested to play a role in neuronal apoptosis [51]. Expression of other CC chemokines has not yet been observed in neurons.

CXC Chemokines

**CXCL10**

CXCL10 expression was first described in cortical neurons in rat in response to MCAO-induced brain ischemia [52]. Remarkably, neuronal CXCL10 expression was transient and appeared rapidly after stroke (within 3–12 h), whereas CXCL10 expression in astrocytes was detectable later and persisted up to 15 days after MCAO [52]. Correspondingly, neurons also showed a rapid CXCL10 expression after entorhinal cortex lesion [53]. Further, neuronal CXCL10 expression and release was induced after viral infection in vitro and in vivo [43, 54].

**CXCL12**

The CXCL12 gene contains three splice variants, termed stromal cell-derived factor-1 (SDF-1) \( \alpha \), \( \beta \), and \( \gamma \). SDF-1\( \gamma \) was cloned from rat brain and showed constitutive neuronal mRNA expression with almost no change in level after peripheral nerve injury [55]. In addition, SDF-1\( \alpha \) showed neuronal mRNA expression with almost no change in level after brain ischemia or intracerebral LPS injection [56]. In contrast, SDF-1\( \beta \) mRNA expression was not detected in neurons [56]. As little is known about the role of SDF splice variants, CXCL12 is used for all SDF splice variants henceforth.

Like CCL2, but in contrast to most of the other neuronal chemokines, CXCL12 is expressed constitutively in specific neuronal populations. Neuronal CXCL12 expression in vitro was observed in cultured cortical, hippocampal, and cerebellar neurons from human, rat, and mouse [57–60]. Neuronal CXCL12 expression in vivo was studied in detail in the adult rat brain, showing CXCL12 mRNA and protein expression in cholinergic, dopaminergic, and vasopressin containing neurons throughout the brain [61, 62].

Studies describing the expression of other CXC chemokines in neurons are limited. Most notably, in vitro neuronal mRNA expression of CXCL1 [51], CXCL8 [41], CXCL9, and CXCL11 [43] has been illustrated. Expression of other CXC chemokines has not yet been described in neurons.

**CX3CL1**

CX3CL1 was the first chemokine shown to be expressed in neurons [63–66]. Because microglia were shown to express the corresponding receptor CX3CR1, a role of CX3CL1–CX3CR1 signaling in neuron–microglia interaction was suggested [63–65]. CX3CL1 is constitutively expressed in human, macaque, rat, and mouse neurons in vitro and in vivo, with high expression in cerebral cortex, hippocampus, caudate putamen, thalamus, and olfactory bulb [63, 65, 66, 68, 69]. CX3CL1 appears to be the only chemokine with a higher expression level in brain than in peripheral organs [70]. It is membrane bound and can be cleaved from the cell surface by proteases of the A Disintegrin and Metalloprotease (ADAM) family [71, 72]. The neuronal CX3CL1 mRNA expression remained relatively stable in response to both neuron-damaging stimuli in vitro [73–77] and during neuroinflammation in vivo [66], whereas in vitro neurons released CX3CL1 protein after glutamate-induced damage [73, 74, 78]. Furthermore, CX3CL1 concentrations higher than 300 pg/mg were described in aqueous extracts of the brain [79], indicating that CX3CL1 can be cleaved from the neuronal membrane and released.

Table 1 (continued)

| Chemokine | Species | Condition | RNA | Protein | References |
|-----------|---------|-----------|-----|---------|------------|
| m Monoculture | \( \approx \) | \( \uparrow/\downarrow \) | \( \uparrow/\downarrow \) | [64, 65, 73, 76, 78, 118] |
| m Brain | \( + \) | \( \approx \) | \( \approx \) | [69] |
| m Brain, prion disease | \( \approx \) | \( \approx \) | \( \approx \) | [67] |
| m Brain, LPS injection | \( \approx \) | \( \approx \) | \( \approx \) | [67] |
| m Brain, KA injection | \( \approx \) | \( \approx \) | \( \approx \) | [67] |
| m Brain, EAE | \( \approx \) | \( \approx \) | \( \approx \) | [66] |
| m Monoculture | \( \approx \) | \( \approx \) | \( \approx \) | [77] |
| m Cell line | \( \approx \) | \( \approx \) | \( \approx \) | [77] |

h Human, mac macaque, r rat, m mouse, ALS amyotrophic lateral sclerosis, AD Alzheimer’s disease, HIV human immunodeficiency virus, MS multiple sclerosis, EAE experimental autoimmune encephalomyelitis, LPS lipopolysaccharide, KA kanaic acid; + present, \( \approx \) present without change in mentioned conditions, \( \uparrow \) present with increase in mentioned conditions, \( \downarrow \) present with decrease in mentioned conditions, \( ^{a} \) Increase in soluble CX3CL1 and decrease in membrane-bound CX3CL1.
Potential Roles of Neuronal Chemokines in Neuron–Astrocyte, Neuron–Microglia, and Neuron–Neuron Interaction

Astrocytes, microglia, and neurons have been shown to express chemokine receptors in vitro under physiological and pathological conditions and in vivo. These would include CCR2 for CCL2, CXCR3 for CCL21 and CXCL10, CXCR4 for CXCL12, and CX3CR1 for CX3CL1. Studies describing the expression of these chemokine receptors on astrocytes, microglia, and neurons (see Table 2) and studies indicating a role for these chemokine–chemokine receptor pairs in CNS cell interaction are discussed in the following sections on neuron–astrocyte, neuron–microglia, and neuron–neuron interaction.

Neuron–Astrocyte Interaction

Astrocytes comprise the largest group of CNS-residing cells and are not only essential in development, homeostasis, maintenance of the blood–brain barrier, and regulation of central blood flow but are also involved in the immune defense of the CNS. Furthermore, astrocytes are considered to be involved in neuronal information processing [80].

It is becoming clear that astrocytes play an active role in the intricate chemokine network of the CNS. Not only has it been shown that astrocytes express a wide variety of constitutive and inducible chemokines in vivo and in vitro, there is also extensive evidence that they express a repertoire of chemokine receptors under physiological and pathological conditions (see reviews [81, 82]).

Neuronal Chemokines Induce Calcium Transients in Astrocytes

The activation of intracellular calcium transients is a hallmark in chemokine receptor signaling, a mechanism that also holds true for astrocytes [57, 76, 83–86]. Activation of GPCRs, including chemokine receptors, results in a rapid release of calcium from the endoplasmatic reticulum (ER) through the activation of inositol-1,4,5-triophosphate receptors on the ER membrane. One of the first chemokines described to induce calcium transients in astrocytes is CXCL12 [57, 85–87]. CXCL12 concentrations ranging from 0.1 to 100 ng/ml [85, 86] or 10–100 nM [57, 87] induced calcium fluxes in in vitro human, rat, and mouse astrocytes. In all cases, CXCL12-induced calcium mobilization was PTX-sensitive, indicating that this process is Gαi4-protein mediated. Similar results were found for CXCL10 [84], CCL2 [83, 88], and CX3CL1 [76].

In astrocytes, intracellular calcium transients not only function as a second messenger in multiple intracellular signaling pathways but are also implicated in astrocyte–astrocyte signal propagation, astrocyte–neuron synaptic transmission, and neurotransmitter release (see reviews [80, 89]). Recent findings corroborate that chemokines could also be involved in astrocyte-mediated neurotransmitter release. CXCL12 induced calcium-dependent release of glutamate from astrocytes in human and rat astrocyte cultures and rat hippocampal slice cultures [90]. Moreover, reports that investigated the effects of CXCL12 on the electrophysiological properties of neurons in brain slice cultures suggest that CXCL12-induced effects on neurons at least partly depend on astrocytic glutamate release [91–93]. Whether this astrocytic glutamate release was induced by CXCR4 activation or via other pathways was not investigated.

Neuronal Chemokines Induce Astrocyte Proliferation and Migration in Vitro: Implications for Astrogliosis?

Astrocytes respond to CNS injury or neuroinflammation by enhanced GFAP expression, proliferation, and possibly, migration, a process known as astrogliosis (see review [94]). In these reactive astrocytes, enhanced expression of chemokine receptors has been described under various pathological conditions, such as multiple sclerosis (MS), human immunodeficiency virus (HIV) infection, ischemia, and neoplasm [95–97]. Under these conditions, CXCR3 was mainly found in reactive astrocytes in the proximity of the lesion sites, suggesting that induction of CXCR3 expression in astrocytes is limited to damaged areas of the brain [95–97]. A comparable induction of CCR2 expression was found in reactive astrocytes in MS patients [97].

Interestingly, both CCL2 and CXCL10 are implicated in astrocyte proliferation in vitro [98, 99]. In addition, CXCL12 has been shown to induce astrocyte proliferation in vitro, a process that is dependent on activation of extracellular signal-regulated kinases ERK1 and ERK2 [87, 100–102]. Both CXCL12-induced astrocyte proliferation and ERK1/2 activation was inhibited by PTX and wortmannin, suggesting that they are dependent on upstream activation of Gαi4 proteins and PI3-K [87].

As chemokines are primarily known for their capacity to induce cell migration, migration assays have been used to determine chemokine receptor functionality in astrocytes [103]. Accordingly, astrocyte migration was demonstrated in vitro in response to CCL2, CXCL10, and CXCL12 [83, 84, 86, 103, 104]. Thus, reactive astrocytes express various chemokine receptors and activation of these receptors in
| Chemokine | Receptor | Cell type | Species | Condition | RNA | Protein | References |
|-----------|----------|-----------|---------|-----------|-----|---------|------------|
| CCL2      | CCR2     | astrocyte | h       | Brain, MS, HIV | ↑   | ↑       | [96, 97, 173] |
|           |          | mac       |         | Monoculture      | ↑   | ↑       | [83, 99, 174–176] |
|           |          | r         |         | Brain, EAE, LPS injection | ↑   |   | [177, 178] |
|           |          | microglia | h       | Brain, MS, HIV  | ↑   |   | [96, 173, 179] |
|           |          |           |         | Monoculture      | ↓   | +       | [173, 180] |
|           |          |           |         | Gia culture      | +   |   | [99] |
|           |          | r         |         | Brain, tumor, LPS injection, NMDA injection | ↑   |   | [177, 181, 182] |
|           |          |           |         | Monoculture      | ↑   |   |  
|           |          | neuron    | h       | Brain, HIV       | +   |   | [184] |
|           |          |           |         | Monoculture      | +   | +       | [38] |
|           |          |           |         | Cell line        | +   | +       | [38] |
|           |          |           |         | Brain and spinal cord | +   | +      | [161, 177, 185] |
|           |          |           |         | Monoculture      | +   | +       | [161, 164] |
| CXCL10/   | CXCR3    | astrocyte | h       | Brain, MS, HIV  | ↑   |   | [95, 97, 179, 186] |
| CCL21     |          | Astrocyte |         | Culture         | ↑   | ↑       | [84, 98, 175] |
|           |          | Mixed glial culture |         | +         |   |       |  
|           |          | mac       |         | Monoculture      | +   |   | [175] |
|           |          | m         |         | Monoculture      | +   |   | [84] |
|           |          | microglia | h       | Monoculture      | +   | +       | [7, 84, 98, 114] |
|           |          |           |         | Cell line        | ↑   | ↑       | [98] |
|           |          |           |         | Cell line        | ↑/↓|   | [187] |
|           |          |           |         | Brain, various infectious agents, axotomy | ≈/↑| ≈/↑| [125] |
|           |          |           |         | Monoculture      | +   |       | [45, 84] |
|           |          |           |         | Cell line        | ↑/↓|   | [188] |
| neuron    | h        | Brain, AD | +       |   |   | [95, 179, 189] |
|           |          | Monoculture | +      | +       | [38] |
|           |          | Cell line | +       | +       | [38] |
|           | mac      | Brain, HIV | +       |   |   | [54] |
|           | r        | Monoculture | +     |   |   | [163] |
| CXCL12    | CXCR4    | astrocyte | h       | Brain, HIV       | ↑   |   | [173, 190, 191] |
|           |          | Monoculture | ↑      | ↑       | [85, 90, 98, 99, 175, 192–196] |
|           | mac      | Monoculture | ↑      | ↑       | [85, 175] |
|           | r        | Brain      | +       |   |   | [197] |
|           | m        | Monoculture | ↑/↓| ↑/↓ | [57, 58, 102, 198] |
| microglia | h        | Brain and spinal cord, HIV | +       | +       | [173, 179, 190, 191, 201, 202] |
|           | bab      | Monoculture | ↑      |   |   | [98] |
|           | r        | Brain      | +       |   |   | [206] |
|           | m        | Cell line | ≈/↑    |   |   | [58, 207, 198] |
| neuron    | h        | Brain, HIV | +       | ≈/↑ |   | [179, 184, 191, 197, 202, 204, 208] |
|           |          | Monoculture | +      | +       | [38, 85] |
|           |          | Mixed brain culture | +   | +       | [202] |
|           |          | Cell line | +       | +       | [38, 191, 209] |
|           | mac      | Brain      | +       |   |   | [210, 211] |
|           | r        | Monoculture | +     |   |   | [85] |
|           |          | Monoculture | +      | +       | [57] |
vitro induces proliferation and migration, cellular reactions that are generally involved in astrogliosis. Therefore, it is tempting to speculate that chemokines are involved in the regulation of astrogliosis upon CNS injury or neuroinflammation. Whether neuronal chemokines are indeed responsible for either proliferation or migration of astrocytes in vivo is yet unknown.

Neuron–Microglia Interaction

Microglia in the healthy CNS are ramified cells that continually survey their environment by moving their processes. Upon injury, they quickly protrude their processes toward the damaged site and subsequently transform into amoeboid cells, reflecting a fast activation [105, 106]. Activated microglia form a first line of defense in CNS injury through their capacity to migrate, proliferate, secrete inflammatory and neurotrophic factors, phagocytose damaged cells and debris, and present antigens [82, 107]. Although activated microglia were initially considered to be detrimental in CNS injury, recent findings indicate a prominent neuroprotective activity as well, suggesting a balance between neurotoxic and neuroprotective microglia activity (see for recent review, [108]). Therefore, it is of particular interest to gain insight into the process of microglia activation. Until now, it is largely unknown which environmental signals mediate microglia surveillance and activation. Almost 10 years ago, chemokines were indicated as promising candidates for neuron–microglia signaling [63–65]. Because then, various studies have described constitutive chemokine expression in neurons and rapid changes in expression levels upon injury. Parallel to this, corresponding chemokine receptors were described in resting and/or activated microglia. In addition, there is increasing evidence that neurons play an important role in microglia activity, which is at least partly mediated by chemokines.

Microglia Activity Upon Neuronal Damage

Upon CNS injury, activated microglia retract their protrusions, transforming into amoeboid cells with migratory and/or proliferative capacities [109–111]. It is known that damaged neurons are accompanied by prominent activated microglia within hours after injury, suggesting that neurons emit signals that attract microglia [111]. Several findings support the notion that these signals are primarily chemokines. Microglia express various chemokine receptors, and cell migration is induced upon exposure to chemokines in vitro [7, 45, 84, 112–115]. Moreover, damaged neurons in culture express and release chemokines like CX3CL1 [73, 74, 78], CCL21 [45, 46], and CXCL10 [43, 54], all of

| Chemokine | Receptor | Cell type | Species | Condition | RNA | Protein | References |
|-----------|----------|-----------|---------|-----------|-----|---------|------------|
| CX3CL1    | CX3CR1   | astrocyte | h       | Brain, MS | ≈   | +       | [113]      |
|           |          | Monoculture | ↑     | +         |     |         | [113, 175] |
|           |          | Monoculture | ↑     |           |     |         | [175]      |
|           |          | Monoculture | ≈/↑    | ↑         |     |         | [76, 198, 212] |
|           |          | Monoculture | ↓     | ↓         |     |         | [77, 81, 200] |
|           |          | Brain, HIV | ↑     |           |     |         | [170]      |
|           |          | Monoculture | +     | +         |     |         | [75, 113]  |
|           |          | Brain, ischemia, prion disease, cranial nerve injury, EAE | ↑     | ↑         |     |         | [63, 67, 68, 213] |
|           |          | Brain, LPS injection, KA injection | ≈   |           |     |         | [67]       |
|           |          | Spinal cord, peripheral nerve injury | ↑     | ↑         |     |         | [171, 172] |
|           |          | Monoculture | ↑/↓    | ↑         |     |         | [63, 65, 198, 212, 214] |
|           |          | Cell line | ↓     |           |     |         | [187]      |
|           |          | Brain, HIV | ≈   |           |     |         | [113]      |
|           |          | Brain, LPS injection, KA injection | ≈   |           |     |         | [67]       |
|           |          | Brain, LPS injection, KA injection | ≈   |           |     |         | [170]      |
|           |          | Cell line | ≈   | ↑         |     |         | [75]       |
|           |          | Monoculture | +     | +         |     |         | [75]       |
|           |          | Brain, prion disease | ↓     | ↓         |     |         | [67]       |
|           |          | Brain, LPS injection, KA injection | ≈   |           |     |         | [67]       |

h human, mac macaque, bab baboon, r rat, m mouse, MS multiple sclerosis, HIV human immunodeficiency virus, EAE experimental autoimmune encephalomyelitis, LPS lipopolysaccharide, NMDA N-methyl-D-aspartic acid, AD Alzheimer’s disease, KA kainic acid; + present, ≈ present without change in mentioned conditions, ↑ present with increase in mentioned conditions, ↓ present with decrease in mentioned conditions
which are able to induce microglia migration [7, 45, 46, 73, 76, 84, 113, 115]. In accordance with this, inhibition of chemokine function diminished microglia migration in response to supernatants from damaged neurons [73]. Thus, in vitro results suggest a role of neuronal chemokines in neuron–microglia activation.

The issue of chemokine-mediated neuron–microglia activation has been further investigated using genetically modified mice. Mice deficient for either CX3CR1 [116] and CX3CL1 [117] have been studied in various CNS injury and neuroinflammation models. Although CX3CR1 deficiency did not influence microglia activity in response to facial nerve lesion [116], CX3CR1 deficiency was uniformly associated with higher levels of microglia activity in LPS-induced neuroinflammation, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridin-induced neurotoxicity, and in the SOD1(G93A)-model of motoneuronal death in the spinal cord [79]. Interestingly, enhanced microglia activity in the last three models was accompanied by increased neuronal death, indicating that, in wild-type mice, neurotoxic microglia activity is inhibited by CX3CL1–CX3CR1 signaling [79]. These findings are corroborated by several in vitro findings. Exposure of a neuron–microglia coculture to CX3CL1 reduced inflammation-related neuronal death, accompanied by suppressed nitric oxide and proinflammatory cytokine production [118]. In conjunction with these findings, inhibition of endogenous CX3CL1 increased neuronal cell death in cocultures [77]. Moreover, in vitro exposure to CX3CL1 supported microglia survival under basal culture conditions and reduced Fas-ligand induced apoptosis considerably [119]. Thus, exposure of microglia to CX3CL1 reduced microglia toxicity and protected microglia from apoptosis under inflammatory conditions. In contrast to these results, CX3CL1 deficiency reduced the infarct volume and mortality after transient focal cerebral ischemia [117]. However, microglia activity in CX3CL1-deficient and wild-type mice was not compared in this study, making it difficult to determine whether disturbed neuron–microglia signaling was responsible for the differences [117].

Increased microglia toxicity by CXCR3 and its ligands CXCL10 and/or CCL21 is suggested by findings derived from the entorhinal cortex lesion (ECL) model, in which CXCR3 deficiency was associated with reduced microglia activity and reduced loss of secondary neurons in the hippocampal formation [53]. An interesting aspect of chemokines in neuron–microglia signaling is acknowledged in the ECL model. In this paper, microglia activity is specifically found within the midmolecular layer of the dentate gyrus, which is the projection site of the transected neurons (see for review, [120]). The microglia activity at a site distant from the primary lesion indicates transport of the chemokine signal. Recent data reinforced this notion, showing that CCL2 that was induced in dorsal root ganglion (DRG) neurons after peripheral nerve injury was transported to afferent terminals in the spinal cord [34]. Moreover, in vitro neuronal CCL21 was sorted into vesicles, transported into neuronal processes, and even reached presynaptic terminals [46]. The finding of CCL21 protein in neuronal vesicles is a strong indication that neuronal chemokines may be the signals responsible for microglia activity at sites distant from the primary lesion, a phenomenon that has been observed also in humans [121, 122].

A role of CCL2 in microglia activity after neuronal death is suggested by a delayed microglia activity in the thalamus of CCL2-deficient mice in response to cortical injury [123]. The delayed microglia activity was accompanied by a transient improvement of neuron survival in the thalamus, which may indicate that CCL2 is involved in neurotoxic microglia activity [123]. However, it is not yet clear if this effect is due to disturbed neuron–microglia interaction. Damaged neurons are capable to express CCL2, as was found after axotomy in sympathetic ganglia [31] and facial nerve lesion [30], but cortical injury predominantly induced CCL2 mRNA expression in astrocytes [124]. Whether interference with CCL2 signaling would affect microglia activity in the first two models has not yet been investigated.

It is clear that the assumption that neuronal chemokines are involved in neuron–microglia signaling is no longer based on the finding that damaged neurons rapidly alter chemokine expression patterns and that microglia express the corresponding receptors [63–65]. Studies now show that microglia activation is reduced in mice with genetically disturbed chemokine function, indicating an important role of chemokines in microglia activation. Recent data even suggest that neurosupportive and neurotoxic microglia activity are associated with chemokine receptor expression [125]. The ultimate effects of neuronal chemokines are likely dependent on injury type, brain region, and disruption of the blood–brain barrier [53, 79, 116]. Whereas the exact role of neuronal chemokines in neuron–microglia signaling remains obscure, their importance in regulating damage responses is becoming apparent.

Neuron–Neuron Interaction

Various reports indicate that chemokines influence neuronal development, differentiation [126, 127], survival [128–130], electrophysiological properties [93, 131, 132], and synaptic transmission [26, 92, 133]. Because neurons can express numerous chemokines, autocrine and paracrine contributions of neuronal chemokines are likely.

Neuroprotection

Neuronal cell death, the ultimate consequence of all neuroinflammatory conditions, has been studied extensively in vitro.
However, there are relatively few in vitro models that can be extrapolated to pathological conditions leading to neuronal death in vivo. One of the most prominent models is glutamate or NMDA-induced neurotoxicity, a model for excitotoxicity, which is most likely involved in various neurodegenerative diseases. β-amyloid-induced neuronal death serves as a model that may explain the loss of neurons in Alzheimer’s disease, whereas exposure of neuronal cultures to HIV proteins gp120 or HIV-tat are aimed to elucidate neuronal death in HIV-dependent neurodegeneration [134–137]. Several reports indicate that neuronal chemokines may protect neurons from these toxic conditions. In vitro, CX3CL1 is known to protect neurons from glutamate-induced toxicity [78, 138], gp120-induced neuronal death [64, 139], and death induced by deprivation of trophic support [140].

Similar to CX3CL1, CCL2 exposure is shown to protect neurons from glutamate- and HIV-tat-induced neurotoxicity [141, 142]. However, CCL2 exposure was not protective in β-amyloid-dependent neuronal death [141]. As exposure of neuronal cells to chemokines is known to activate the putatively neuroprotective MEK/ERK and PI3-K/Akt signaling pathways [78, 138–140], it is reasonable to argue that chemokine-dependent protection is mediated by these pathways. Indeed, inhibition of both pathways completely abolished the neuroprotective effects of CX3CL1 in gp120- and glutamate-induced neurotoxicity in hippocampal neurons [64, 78]. Interestingly, in case of glutamate-dependent neurotoxicity, the involvement of MEK/ERK and PI3-K/Akt signaling pathways was only evident when CX3CL1 was applied together with glutamate [78]. CX3CL1 exposure was shown to be protective even when the chemokine was applied up to 8 h after the glutamate stimulus. However, an inhibition of MEK/ERK and PI3-K/Akt pathways did not affect the protective activity of delayed CX3CL1 exposure, indicating that CX3CL1 may activate additional pathways in neurons that lead to neuroprotection [78]. The effect of CXCL12 on neuronal death is contradictory. Although several reports indicate that CXCL12 exposure may protect neurons from gp120-induced neuronal death, most papers describe a toxic effect of CXCL12 in neuronal cultures (see below) [64, 143].

**Neurotoxicity**

Approximately 10% of HIV-infected patients develop HIV-1 associated dementia (HAD). It has been shown that the viral protein gp120 itself is neurotoxic [144], indicating that the neuronal loss in HAD is not only due to inflammation occurring after the virus enters the brain but also because of direct toxic effects of viral proteins (see for recent review, [145]). It was shown in 1998 that the neurotoxic effect of gp120 is mediated via the chemokine receptor CXCR4 [146], findings that have been corroborated in subsequent years by various groups [64, 102, 147, 148]. The viral protein gp120 binds and activates CXCR4, the main coreceptor utilized by HIV-1 to infect T cells. CXCR4 has subsequently become the best investigated chemokine receptor with respect to neurotoxicity, and its involvement in neurotoxic signaling has been demonstrated by use of the specific CXCR4 antagonist AMD31000 [102, 147]. The HIV-derived protein gp120 shows agonist activity on CXCR4, and therefore, it is not surprising that its ligand CXCL12 has also been described to be neurotoxic [102, 143, 146, 148, 149]. Currently, there is little information on intracellular signaling pathways that are activated by CXCR4 and subsequently lead to neuronal death. One recent report indicates the involvement of Src activity in CXCL12-induced apoptosis in a neuronal cell line, whereas gp120-induced apoptosis in these cells was independent of Src activity [149]. Interestingly, CXCL12 and gp120 had different effects on ERK activation in neurons and astrocytes [102], indicating that CXCR4 signaling exerts both ligand and cell-type specific effects. The effect of CXCL12 is further complicated by matrix metalloproteinase-2, which was shown to remove the first four amino acids of CXCL12, resulting in a truncated form of CXCL12 [150]. This truncated form was found to be highly neurotoxic compared to the full-length CXCL12, which remarkably was not mediated by CXCR4 but by a yet unknown PTX-sensitive receptor [150]. Because MMP-2 has also been described in HIV-infected patients, it is reasonable to assume that truncated CXCL12 may be a neurotoxic player in HAD [151].

CXCL12 is not the only neuronal chemokine that exerts neurotoxic effects. Neuronal cell lines and primary human neurons respond to high concentrations of CXCL10 with intracellular calcium transients, caspase activity, and apoptosis [54, 152, 153]. The direct involvement of CXCR3 was demonstrated by the use of an antibody that prevents the activation of CXCR3 and subsequently inhibited CXCL10-dependent neurotoxicity [153].

**Chemokinergic Effects on Synaptic Transmission**

Recent data show that CXCR4 activation by either gp120 or CXCL12 significantly enhanced giant depolarizing potentials (GDP) in rat neonatal hippocampus [154]. These GDPs only occur in the developing hippocampus and are involved in growth and synapse formation. These data may explain why HIV infections have a greater impact in the developing brain than in adults [152] and show that neuronal chemokines may change the electrophysiological properties of neurons, thereby corroborating earlier findings [131, 132, 155, 156].

The electrophysiological properties of neuronal chemokine receptors have predominantly been studied in cultured
primary neurons or neuronal cell lines and brain slice cultures [157]. Remarkably, in cultures of DRG, cerebellar granule or Purkinje neurons, and hippocampal pyramidal cells, chemokines induced changes in the electrophysiological properties of only 10–20% of the neurons [64, 140, 158, 159]. In addition, several effects of chemokines in neurons were not sensitive to PTX, in contrast to hematopoietic cells, suggesting that chemokine receptors in neurons, although generally accepted, are not solely coupled to Gαi proteins [128, 140, 149]. Whether these chemokinergic PTX-insensitive effects are mediated by neuronal Gαi-subunits is yet unclear [160]. Cultured cerebellar and DRG neurons respond to various chemokines with intracellular calcium transients [140]. In DRG neurons, exposure to CX3CL1 and CXCL12 also increased their excitability [158]. Although chemokinergic effects of CX3CL1, CXCL12, CCL2, and CXCL10 in neurons have been reported to modulate the frequency of both spontaneous and activity-dependent neuronal firing, a direct effect on the induction of action potentials has not yet been described [159, 161–164]. Similar to the effects on isolated neurons, CX3CL1, CXCL12, and CXCL10 also affected neuronal signaling in brain slice cultures [26, 78, 91–93, 133, 134, 165, 166]. However, the presence of glia cells (astrocytes, microglia, and oligodendrocytes) in these slice cultures makes it difficult to determine whether the electrophysiological effects of chemokines are mediated by chemokine receptors on neurons and/or on glia cells, as glia cells may also induce electrophysiological changes in neurons [26, 133, 156]. Whether the effects of CXCL12 in brain slice cultures are mediated via chemokine receptors on neurons and/or on glia cells may depend on the concentration, as concentrations up to 1 nM caused a direct decrease in peak and discharge frequency of evoked action potentials in neurons and concentrations higher than 10 nM activated an indirect GABA-mediated hyperpolarization of neurons [92].

Future Directions

As discussed here, neuronal chemokines appear to be versatile messengers in CNS cell interaction. However, several important issues need to be addressed in future studies. To begin with, neuronal CX3CR1 expression in vivo remains controversial. Immunohistochemical analysis revealed CX3CR1 positive neurons in mouse brain sections with little changes under pathological conditions [67], whereas neuronal CX3CR1 expression was never described in studies using genetically modified mice in which CX3CR1-expressing cells are also positive for EGFP [116]. Different microscopic techniques and models of neurodegeneration have been explored in these mice, demonstrating only CX3CR1 expression in resting and activated microglia [79, 105, 106, 116]. An explanation may be that neuronal CX3CR1 expression is at such a low level that detection is difficult to achieve with microscopic techniques. This may also be the case for CXCR3 expression in microglia. Although CXCR3 expression has yet not been described in microglia in vivo, functional evidence derived from CXCR3-deficient mice strongly indicates that microglia do express CXCR3 in vivo [53, 115]. Therefore, it seems appropriate that future experiments concerning the expression of chemokine receptors in CNS cells in vivo also include functional analysis.

Another issue that needs to be addressed in more detail regards cellular localization. Neurons are highly polarized cells, as their function is largely dependent on their morphology and contacts with other cells (e.g. synapses with other neurons). Although neuronal signaling molecules, such as neurotransmitters, neuropeptides, and neurotrophins, are generally found at specific sites, most reports describing neuronal chemokine expression did not address this issue. Interestingly, a few recent publications do suggest a localized expression of chemokines comparable to other neuronal signaling molecules. Our group demonstrated that neuronal CCL21 is transported in vesicles, reaching presynaptic terminals in cortical neurons in vitro [46]. In subsequent studies, these vesicles appeared to be of the large-dense core type, in which other neuronal peptides are also found (e.g. neurotrophins; Stanulovic et al., manuscript in preparation). Moreover, it has been described for several neuronal populations in vivo that CCL2 and CXCL12 colocalize with other neurotransmitters and neuropeptides in synaptic regions [37, 62]. Like neuronal chemokine expression, a site-specific expression of chemokine receptors may exist, as is suggested by CXCR4 redistribution in the axonal and dendritic compartment of hippocampal neurons after prolonged CXCL12 exposure [167]. Because a localized expression of chemokines and their receptors may have a consequence for their role in cell interaction, future studies on neuronal chemokine expression may address this issue.

At last, all reports indicating that chemokine exposure alters the excitability of neurons used exogenous chemokines, it is yet unknown whether chemokines released from neurons have similar effects.

Conclusion

Knowledge on the spatial and temporal expression of neuronal chemokines and their regulation under physiological and pathological conditions is increasing rapidly. As CNS cells can express the corresponding chemokine receptors, contribution of these neuronal chemokines to
CNS cell interaction is conceivable. This assumption is corroborated by various in vitro and in vivo studies. For example, the following effects of neuronal chemokines were observed in vitro: in astrocytes proliferation and migration, in microglia migration and neurotoxic and neuroprotective activity and in neurons electrophysiological changes, neurotoxicity, and neuroprotection. Further, the synaptic transmission between neurons seems to be influenced by the action of neuronal chemokines on neurons and/or glia cells. In vivo studies support the important role of chemokines in migration and neurotoxic and neuroprotective activity of microglia upon CNS injury and neuroinflammation. Further exploration of the roles of neuronal chemokines in CNS cell interaction is needful, as insight into the role of neuronal chemokines in CNS injury and neuroinflammation may contribute to the development of therapeutic strategies.

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