Multiple actions of the chemokine stromal cell-derived factor-1α on neuronal activity

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Abstract

The chemokine SDF-1α and its cognate receptor CXCR4 are expressed in several neuronal populations. This review focuses on our current knowledge about the actions of this chemokine on neuronal excitability, through CXCR4 or other yet unknown pathways. In various neuronal populations (CA1 neurons of the hippocampus, granular and Purkinje cells of the cerebellum, melanin-concentrating hormone neurons of the lateral hypothalamus, vasopressinergic neurons of the supraoptic and the paraventricular nucleus of the hypothalamus, and dopaminergic neurons of the substantia nigra), SDF-1α can modulate the activity of neurons by multiple regulatory pathways including and often combining: (i) modulation of voltage-dependent channels (sodium, potassium, and calcium), (ii) activation of the G-protein-activated inward rectifier potassium current, and (iii) increase in neurotransmitter release (gamma-amino butyric acid (GABA), glutamate, and dopamine), often through Ca-dependent mechanisms. The possible mechanisms underlying these effects and their consequences in terms of modulation of neuroendocrine systems and physiopathology are discussed.

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Introduction

Chemokines are small secreted proteins with chemoattractant properties for immune cells (Luster 1998, Luther & Cyster 2001). At least 50 chemokines have been found to date and have been classified according to the number and spacing of the conserved cysteine residues at the N-terminal position (Murphy et al. 2000). Phylogenic analyses showed that the large, highly redundant CXC chemokine family is a very recent phenomenon that is exclusive to higher vertebrates. Interestingly, its ancestral role might be within the central nervous system and not within the immune system (Huising et al. 2003). Chemokines exert their biological effects through cell surface receptors that belong to the superfamily of seven-membrane domain G-protein-coupled receptors (GPCRs). At least 22 chemokine receptors have been characterized, which are designed following chemokine nomenclature. Most chemokines bind to several chemokine receptors and most chemokine receptors recognize several chemokines (Bacon & Harrison 2000). Besides their role in the immune system, chemokines and their receptors may play an important role in the central nervous system. For example, neurodegenerative and neuroinflammatory disorders, such as multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, and human immunodeficiency virus (HIV)-associated dementia are commonly associated with local chemokine release (Streit et al. 2001, Vila et al. 2001, Lee et al. 2002, McGeer & McGeer 2004, Cartier et al. 2005). However, the effects of these pro-inflammatory factors on neural activity remain elusive.

Among CXC chemokines, CXCL12/SDF-1 has attracted much attention. This chemokine was originally described as a secreted product of bone marrow stromal cell line (Tashiro et al. 1993). Three protein isoforms, SDF-1α, SDF-1β, and SDF-1γ, which arise from alternative mRNA splicing, have been characterized (Gleichmann et al. 2000, Pillarisetti & Gupta 2001, Stumm et al. 2002); most studies have focused on SDF-1α, which is the object of this review.

In the nervous system, in situ hybridization and dual immunohistochemistry revealed that SDF-1α is constitutively expressed not only in astrocytes and microglia but also in neurons, in discrete neuroanatomical regions (Stumm et al. 2002, Banisadr et al. 2003). Indeed, neuronal expression of SDF-1α is found mainly in cerebral cortex, substantia innominata and medial septum, globus pallidus, hippocampus, paraventricular and supraoptic hypothalamic nuclei, lateral hypothalamus, substantia nigra (SN), ventral tegmental
area, and oculomotor nuclei (Banisadr et al. 2003). Overall, SDF-1z appears to be expressed in cholinergic, monoaminergic, and neuropeptide-expressing neurons, raising the possibility that SDF-1z could act as a neuromodulator (Banisadr et al. 2003, 2005a).

Until very recently, CXCR4 has been thought as the sole receptor for CXCL12/SDF-1 chemokine among six CXC receptors (Bajetto et al. 2001a, Bonavia et al. 2003). Another receptor for this chemokine has recently been described in T lymphocytes and named CXCR7 (Balabanian et al. 2005), but to date, there is no evidence of its presence in the normal brain.

CXCR4, as its ligand SDF-1z, is constitutively expressed by glial and neuronal cells in the CNS (Bajetto et al. 2001a, Bonavia et al. 2003). In situ hybridization and immunocytochemistry showed that CXCR4 neuronal expression was mainly found in cerebral cortex, globus pallidus, caudate putamen and substantia innominata (where CXCR4 immunoreactivity is co-localized with choline acetyltransferase immunoreactivity; Banisadr et al. 2002), supraoptic and paraventricular hypothalamic nuclei (where it is expressed in arginine–vasopressin (AVP) neurons; Banisadr et al. 2003), lateral hypothalamus (where CXCR4 is co-localized with neurons expressing the melanin-concentrating hormone (MCH); Guyon et al. 2005b), ventromedial thalamic nucleus, and SN (where CXCR4 is expressed on dopaminergic (DA) neurons of the pars compacta; Banisadr et al. 2002), and also on GABAergic neurons of the pars reticulata (Guyon et al. 2006) and in the cerebellum (where it is expressed both in the Purkinje neurons and granule cells and in the glial radial fibers; Ragozzino 2002). It is interesting to note that there is a co-distribution of CXCL12/SDF-1 and CXCR4 proteins in a number of brain regions, which strongly suggests that they could constitute together a functional receptor/ligand system in specific neuronal pathway.

CXCR4 activation by SDF-1z activates multiple intracellular pathways (Lazarini et al. 2003). CXCR4 activation is coupled through pertussis toxin (PTX)-sensitive G proteins to at least two distinct signaling pathways. The first pathway, involving phosphatidylinositol-3 (PI-3) kinase and extracellular signal regulated kinase (ERK)1/2, has been described in rodent astrocytes, neuronal progenitors, and cortical neurons (Bacon & Harrison 2000, Lazarini et al. 2000, Bajetto et al. 2001b, Bonavia et al. 2003). The other pathway involves the phospholipase Cβ whose activation leads to an increase in the intracellular calcium in astrocytes, cortical neurons, and cerebellar granule cell, as well as in primate fetal neuron and microglia (Bajetto et al. 1999, Klein et al. 1999, Zheng et al. 1999). The increase in calcium leads to the activation of proline-rich tyrosine kinase (PYK2), which may itself lead to ERK1/2 activation (Bajetto et al. 2001b). CXCR4 stimulation can directly modulate ionic channel of the plasma membrane in neurons, particularly high-threshold calcium channels (our results and Zheng et al. 1999), and this could also result in the intracellular calcium increase and PYK2 activation (Lazarini et al. 2003). Finally, in the primary cultures of neurons, CXCR4 can also inhibit cAMP pathways through the Gi component of GPCRs (Liu et al. 2003).

Under ligand stimulation, CXCR4 undergoes a desensitization and internalization. Signaling and internalization of CXCR4 are regulated by receptor phosphorylation-dependent and -independent mechanisms. When independent of receptor phosphorylation, desensitization appears to be a consequence of the phosphorylation of phospholipase Cβ3 (Haribabu et al. 1997).

SDF-1z has been shown to exert various functions in the brain (Lazarini et al. 2003). SDF-1z has proved to be a potent chemottractant for primary mouse microglial cells, but not for astrocytes (Tanabe et al. 1997). SDF-1z does not seem directly to be a chemoattractant for neurons, but it reduces axonal responsiveness to several known repellents (Chalasani et al. 2003a). SDF-1z is synthesized constitutively in the developing brain and has an obligate role in the neuronal migration during the formation of the granule-cell layer of the cerebellum (Ma et al. 1998, Zou et al. 1998, McGrath et al. 1999) and other brain area (Tran & Miller 2003). Indeed, mice that lack SDF-1 or CXCR4 died soon after birth and showed major defects in their vascular, hemopoietic, and central nervous system, in particular, in cortex and cerebellum development (Nagasawa et al. 1998, Tachibana et al. 1998, Stumm et al. 2003). Apart from this role in angiogenesis and development, CXCR4 is a receptor for the GP120 protein of the HIV, thus being a co-receptor for HIV entry into target cells and was thus also named fusin (Feng et al. 1996, Doranz et al. 1997). Neurotoxic effects of CXCR4 activation have been extensively studied in relation to the involvement of CXCR4 in HIV-associated dementia (Kaul & Lipton 2004, Khan et al. 2004). Massive stimulation of chemokine receptors during inflammatory processes may lead to apoptosis and neurodegeneration (Glabinski & Ransohoff 1999). On the other hand, SDF-1z is neuroprotective in cultured hippocampal neurons when apoptosis is stimulated by gp120 treatment (Meucci et al. 1998). In addition, SDF-1z has strong survival-promoting effects on cultured embryonic retinal ganglion cells through an action on CXCR4 (Chalasani et al. 2003b).

The aim of this review is to summarize the recent data which show that the chemokine SDF-1z can also modulate the activity of several neuronal populations that may have a role under physiological and/or pathological conditions.
Effects on neuronal activity and neurotransmitter release

Recently, SDF-1α was shown to act in the brain as a neuromodulator (reviewed in Lazarini et al. 2003, Banisadr et al. 2005b). The effect of chemokines on neuronal activity has been studied using electrophysiological and/or calcium-imaging techniques.

SDF-1α modulates the activity of vasopressinergic neurons recorded in the rat supraoptic and paraventricular nucleus slices through CXCR4, resulting in changes in the AVP release (Callewaere et al. 2006). SDF-1α can blunt the autoregulation of AVP release in vitro and counteract angiotensin II-induced plasma AVP release in vivo. Furthermore, a short-term physiological increase in AVP release induced by enhanced plasma osmolality was similarly blocked by central injection of SDF-1α through CXCR4 and a change in water balance induced a decrease in both SDF-1α and CXCR4 parallel to that of AVP immunostaining in supraoptic nucleus (Callewaere et al. 2006).

CXCR4 and SDF-1α are expressed in MCH neurons of the lateral hypothalamus (LHA), a peptide-expressing neuronal population mainly involved in feeding intake and energy storage regulation (reviewed in Nahon 2006). SDF-1α exerts multiple effects on this neuronal system (Fig. 1A): using rat brain slices of hypothalamus in which MCH neurons were identified electrophysiologically and a posteriori by single-cell RT-PCR, we have shown that SDF-1α increases spontaneously glutamate and gamma amino butyric acid (GABA) release on these neurons and activates a G-protein-activated inward rectifier potassium (GIRK) current (Guyon et al. 2005b). SDF-1α also modulates the action potential discharge of these neurons and interestingly, the effects vary as a function of the concentration (Guyon et al. 2005b): low concentrations (0.1–1 nM) decrease the frequency of discharge (Fig. 2B1), an effect blocked by the competitive antagonist AMD 3100, suggesting that it was mediated by extrasynaptic glutamate, possibly released by surrounding glial and/or nerve cells. This current was followed by a rise in intracellular calcium sensitive to MCPG, thus mediated through metabotropic glutamate receptors, mGluRs (Limatola et al. 2000).

In rat SN (Fig. 1D), the CXCR4 receptor is expressed on both DA neurons and GABA axonal processes. Using whole-cell patch-clamp recordings in DA neurons of rat SN slices, we showed (Guyon et al. 2006 and unpublished data) that SDF-1α exerts multiple pre- and postsynaptic effects on DA neurons, including (1) an increase in the frequency of spontaneous and miniature GABAergic activity and a slow inward current, which was drastically reduced by ionotropic glutamate receptor blockers. This current developed fully in a medium in which synaptic transmission was inhibited, suggesting that it was mediated by extrasynaptic glutamate, possibly released by surrounding glial and/or nerve cells; this inward current is not blocked by the CXCR4 antagonist AMD 3100 (1 μM) consistent with the lack of CXCR4 on astrocytes under basal conditions as shown by immunocytochemistry, (2) a glutamatergic inward current resistant to tetrodotoxine (TTX), likely due to glutamate release from nonneuronal cells; this inward current is not blocked by the CXCR4 antagonist AMD 3100 (1 μM) consistent with the lack of CXCR4 on astrocytes under basal conditions as shown by immunocytochemistry, (3) an outward GIRK current, through CXCR4 activation, TTX sensitive, and prevented by the application of GABA_A antagonist CGP 55845A suggesting GABA spillover onto GABA_A receptors, and (4) SDF-1α (0–10 nM) also increases the amplitude of total high voltage-activated calcium (HVA Ca) currents through CXCR4 activation. This effect was reversibly reduced by ω-conotoxin GVIA, suggesting that SDF-1α acted on N-type Ca currents, known to be mainly involved in DA release. However, at 100 nM, SDF-1α inhibits 65% of HVA Ca currents by a CXCR4-independent mechanism. These effects of SDF-1α on dopamine neuron activity were paralleled by modulations of dopamine release by DA neurons from the rat substantia nigra pars compacta (SNpc) (Zheng et al. 1999). However, in embryonic primary cultures of rat hippocampus, SDF-1α at higher concentrations (50–100 nM) reduced the frequency of synchronized Ca spikes among hippocampal neurons through the activation of CXCR4 by inhibiting cAMP pathways (Liu et al. 2003).

In the cerebellum (Fig. 1C), SDF-1α induced calcium transient in cultured granule cells through a PTX-resistant mechanism (Limatola et al. 2000). Purkinje neurons recorded in cerebellar slices in patch-clamp applications by an increase in spontaneous GABAergic activity and a slow inward current, which was drastically reduced by ionotropic glutamate receptor blockers. This current developed fully in a medium in which synaptic transmission was inhibited, suggesting that it was mediated by extrasynaptic glutamate, possibly released by surrounding glial and/or nerve cells. This current was followed by a rise in intracellular calcium sensitive to MCPG, thus mediated through metabotropic glutamate receptors, mGluRs (Limatola et al. 2000).

SDF-1α (25 nM) can enhance the excitatory synaptic transmission in rat hippocampus (Fig. 1B). This effect was antagonized by ω-conotoxin GVIA, a N-type calcium channel antagonist, and by 12G5, a specific antibody against CXCR4, suggesting that SDF-1α acted through a CXCR4-mediated increase in intracellular calcium through N-type Ca currents (Zheng et al. 1999). However, in embryonic primary cultures of rat hippocampus, SDF-1α at higher concentrations (50–100 nM) reduced the frequency of synchronized Ca spikes among hippocampal neurons through the activation of CXCR4 by inhibiting cAMP pathways (Liu et al. 2003).
A. LHA

- SDF-1α
- CXCR4
- Pre-synaptic glutamate and/or glia
- Glutamate
- RAMPA/NMDA
- Ca2+
- HVA Ca channels (N type)
- Pre-synaptic GABA
- GABA
- RGABAA

B. Hippocampus

- SDF-1α
- CXCR4
- Pre-synaptic glutamate
- Glutamate
- RAMPA/NMDA
- Na+/Ca2+
- mGluR
- Ca2+

C. Cerebellum

- SDF-1α
- CXCR4
- Pre-synaptic glutamate and/or glia
- Glutamate
- RAMPA
- Cl–
- Na+/Ca2+
- Purkinje neuron

D. Substantia nigra

- SDF-1α
- CXCR4
- Pre-synaptic GABA
- GABA
- RGABAA
- RGABAB
- Glutamate
- RAMPA/NMDA
- Na+/Ca2+
- DA neuron

Chemokine modulation of neuroendocrine activity
nigra, measured in preparations of dissociated neurons of rat mesencephalon as well as in vivo in the striatum, a projecting site of DA neurons, when SDF-1α was injected in the SN (unpublished data of Patrick Kitabgi’s team; U732 INSERM, Paris, France). These data strongly suggest that chemokines such as SDF-1α can act as neuromodulators of DA neuronal activity.

It is interesting to note that SDF-1α has convergent presynaptic actions in the different brain structures where it has been tested: it increases glutamate and/or GABA synaptic activities in lateral hypothalamus (Guyon et al. 2005b), hippocampus (Zheng et al. 1999), cerebellum (Limatola et al. 2000), and substantia nigra (Guyon et al. 2006). However, the presynaptic mechanisms of action of SDF-1α vary from one structure to the other: for example, the increase in frequency of GABA_A postsynaptic events in response to SDF-1α occurs through an indirect mechanism involving glutamate in the cerebellum (Limatola et al. 2000), while the effect is direct through CXCR4 in the SN (Guyon et al. 2006). Similarly, the glutamate release is TTX dependent in the lateral hypothalamus (LHA) (Guyon et al. 2005b), while it is TTX independent in the SN (Guyon et al. 2006). The target effects on the postsynaptic neurons also vary depending on the structure. For example, the SDF-1α increase in presynaptic GABA release in the LHA evokes a tonic GABA_A current in MCH-expressing neurons but does not induce GIRK current through GABA_A receptors stimulation (Guyon et al. 2005b). This contrasts to what we found in DA neurons where no GABA_A tonic current was induced by SDF-1α, but a GIRK current was activated through GABA_AR stimulation through a GABA spillover (Guyon et al. 2006). This could be due to various subunit compositions of the GABA_A receptor expressed in the two neuronal populations, with different kinetics, and/or different subcellular localization of the GABA_A/CXCR4 receptors and GIRK channels. Interestingly, in MCH neurons, SDF-1α also induced the activation of a GIRK current, but this happened directly through CXCR4 stimulation. Finally, CXCR4 stimulation is able to modulate various voltage-dependent channels: Na+ and K+ channels of the action potential in MCH neurons (Guyon et al. 2005b) and HVA Ca channels, in particular of the N-type, in DA neurons of the SN (A Guyon, unpublished data) and in presynaptic glutamatergic terminals of the hippocampus (Zheng et al. 1999).

In conclusion, from one structure to another, SDF-1α has often similar consequences on neuronal membrane currents, but through different mechanisms.

How can SDF-1α have opposite effects depending on the concentration?

SDF-1α often appears to have opposite effects on neuronal function depending on the concentration. For example, in DA neurons, at low concentrations, it acts as a neuromodulator by potentiating K+-induced DA secretion and HVA calcium currents, whereas at higher concentration, it decreases DA release and HVA calcium currents. This can be paralleled to what happens in MCH neurons of the lateral hypothalamus, where SDF-1α also exerts opposite effects on the action potential discharge depending on the concentration (Guyon et al. 2005b). Moreover, this can also be observed in other contexts, for example, low levels of SDF-1 (<100 ng/ml) are attractive, whereas higher levels (>1 μg/ml) are repulsive for T cells (Zlatopolskiy & Laurence 2001). Several putative mechanisms for these opposite effects, which are not mutually exclusive, are reviewed in Fig. 3.

Two affinity sites on the CXCR4 receptor?

SDF-1α interactions with its receptor CXCR4 occur at two binding sites in amino acids 1–17 of SDF-1α (Crump et al. 1997). The initial step involves a ‘docking site’ on SDF-1α (amino acids 12–17) in the N-terminus of CXCR4 (amino acids 10–21). Subsequently, residues 1–9 of SDF-1α bind to another region within CXCR4. Although the signal appears to be transduced only when this ‘signaling site’ is bound, the occupation of
one or two sites of the CXCR4, depending on the concentration, could activate different signaling pathways. Desensitization and internalization at the highest SDF-1α concentrations could also be involved (Fig. 3A).

**Homo-heterodimerization?**

Following SDF-1α interaction, CXCR4 undergoes a dimerization which is necessary for its functionality and signaling (Mellado et al. 2001, Toth et al. 2004).

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*Figure 2* Opposite concentration-dependent effects of SDF-1α on the action potential discharge of MCH neurons of transgenic MCH-GFP mice. At the top are presented reconstructed transversal 250 µm thick hypothalamic sections obtained from a 15-day-old transgenic mouse in which GFP is under the control of MCH promoter (MCH-GFP, A1). Notice the MCH neurons detected as green fluorescence and their absence in wild-type (WT) mouse (A2). A3 shows GFP fluorescence of a MCH neuron at a higher magnification when compared with background noise in WT mouse (A4). The same neuron as in A3 is presented in A5 by infrared-differential interference contrast (IR-DIC) microscopy (arrowhead on the recording electrode tip). A6 is an immunostained section of the lateral hypothalamus at P15 obtained with an anti-MCH antibody. Note that the distribution of MCH neurons is similar to that in A1. A7 is a Nissl staining of a hypothalamic slice at the same anteroposterior level, showing the different structures: ARH, arcuate nucleus; DMH, dorsomedian hypothalamus; fx, fornix; ic, internal capsule; LHA, lateral hypothalamus; ot, optic tract; VMH, ventromedian hypothalamus; ZI, zona incerta. (B) Whole-cell patch-clamp recordings in the current-clamp mode of MCH-GFP fluorescent neurons. At a low concentration (1 nM, B1), SDF-1α decreases the frequency of action potential discharge, whereas at a higher concentration (10 nM, B2), SDF-1α does the opposite.
Dimerization is accompanied by receptor phosphorylation as well as changes in signal transduction processes (Rodriguez-Frade et al. 2001). This dimerization enables the activation of the JAK/STAT pathway, which allows the subsequent triggering of G-protein-dependent signaling events (Vila-Goro et al. 1999; (Fig. 3B)).

Furthermore, SDF-1α itself can form a dimeric structure in solution at non-acidic pH. This dimerization has been shown to be stabilized by glycosaminoglycan, and heparin-mediated oligomerization may be essential for signaling (Sadir et al. 2001, Veldkamp et al. 2005). It is therefore possible that, depending on the concentration, SDF-1α would act as a monomer or oligomer on CXCR4 monomers or homodimers, leading to different responses. Heterodimerization is known to play a role in signal transduction of other metabotropic receptors, for example, GABAB receptors interact with metabotropic glutamate receptors (Hirono et al. 2001). CXCR4 could also form heterodimers with other GPCRs, which could lead to complex responses according to the chemokines/peptides/neuromediator environment present in the extracellular medium. Indeed, we have preliminary data suggesting that CXCR4 should interact with GABA B receptors. As SDF-1α influences presynaptic GABA release, this could be another way to explain how different SDF-1α concentrations lead to different effects. Furthermore, CXCR4 and CCR2 (the receptor for the chemokine MCP-1) are co-expressed in DA neurons of the SN. As they have been shown to form heterodimers (Percherancier et al. 2005), we are currently investigating whether SDF-1α and MCP-1 can exert synergistic effects on DA neuron activity.

**Figure 3** Putative mechanisms of the opposite effects of SDF-1α at low and high concentrations. (A) Depending on the concentration, SDF-1α could bind only to the high-affinity site or to both high- and low-affinity sites, leading to distinct responses. (B) CXCR4 could induce different responses as monomer, homodimer, or heterodimer. The formation of the various complexes could depend on SDF-1α concentration (and on its dimerization), but also probably on other factors, such as the CXCR4 phosphorylation/internalization, the local concentration of heparane sulfate, and/or some synergistic transmitters/GPCRs. (C) SDF-1α could bind to another receptor than CXCR4, leading to a distinct response. (D) SDF-1α cleaved by several proteases could lead to active peptides that would induce other responses than intact SDF-1α.

**Action on receptors other than CXCR4?**

It is not excluded that SDF-1α at high concentrations could act on a receptor other than CXCR4 to exert its actions. This could explain why, in MCH and DA neurons, the effects of high concentrations of SDF-1α were not blocked by the selective CXCR4 antagonist AMD 3100 at concentrations up to 1 μM. Indeed, the T...
lymphocytes orphan receptor, RDC1, just described as a new receptor for SDF-1α and named CXCR7 (Balabanian et al. 2005) has been reported in tumor endothelial cells of the brain (Madden et al. 2004), but no data are available in the normal brain (Fig. 3C).

**Actions of SDF-1α metabolites?**

Peptide metabolites can be active in other systems. For example, AVP fragments have a biological activity distinct from intact peptide (Stoehr et al. 1992, Fujinara et al. 1997). This should also be the case for SDF-1α. SDF-1α can be cleaved by several enzymes, leading to peptides inactive on CXCR4. For example, dipeptidyl peptidase IV (DPP IV) cleaves the peptide into SDF-1 (3–68) product (Proost et al. 1998, Mentlein 1999), leukocyte elastase into SDF-1 (4–67) (Valenzuela-Fernandez et al. 2002), matrix metalloprotease (MMP)-2 into SDF-1 (5–67) (Zhang et al. 2003), and cathepsin G into SDF-1 (6–67) (Delgado et al. 2001); all proteolized fragments becoming inactive on CXCR4. Interestingly, leukocyte elastase also inactivates CXCR4 (Valenzuela-Fernandez et al. 2002). It is worth noting that the enzymes are often carried or secreted by cells attracted by SDF-1α. In the case of MMP-2, pro-MMP-2 is produced by macrophages and activated by neuronal MT1-MPP (Zhang et al. 2003). Furthermore, CXCR4 activation by SDF-1α itself has been shown to increase the secretion of MMPs (Klier et al. 2001). Thus, it appears that there may be a feedback process inactivating SDF-1α once the target cells have reached the site of infection. On the other hand, the peptide SDF-1α can be protected from DPPs cleavage by its binding with heparane sulfate present on cell membranes, which would result in concentrating it locally (Amara et al. 1999, Sadir et al. 2004). Among the metabolites of SDF-1α, some may have physiological effects. Indeed, SDF-1 (5–67) implanted into the basal ganglia of mice can produce neuronal death and inflammation, and its actions are mediated through a G-protein-coupled receptor, as yet unidentified (Zhang et al. 2005). It is therefore possible that the opposite effects observed on neuronal activity at higher SDF-1α concentrations could come from a cleavage of SDF-1α by enzymes when heparan sulfate sites have been saturated. The possibility that other SDF-1 metabolites could affect neuronal activity/survival will have to be investigated by enzyme blockers or by applying the cleaved peptides directly (Fig. 3D).

**Physiopathological considerations**

The fact that SDF-1α and its receptor CXCR4 are expressed in the same or interrelated neuronal populations suggests that SDF-1α could act as a neuromodulator and exert a tonic action on neurons. For instance, low concentrations of SDF-1α could exert a tonic inhibition on MCH neurons, which are known to have a hyperpolarized membrane potential in basal conditions, when compared with orexin neurons of the LHA, which are in an intrinsic state of membrane depolarization (Eggermann et al. 2003). In addition, the CXCR4 antagonist AMD 3100 has its own effects when applied alone, which suggests that a tonic activation of CXCR4 occurs, at least in slices preparations, and that low levels of SDF-1α are secreted under basal conditions. However, the slice preparation, in which the cells have been stressed, could also be considered as an inflammatory state (Fig. 4).

Inflammation is often accompanied with anorexia, but the mechanisms underlying this phenomenon are poorly understood (Plata-Salaman 2001). One of the pathways could involve MCH neurons. Indeed, the following acute injections of lipopoly saccharide (LPS) in mice, which induce an inflammatory response, there is a decrease in the expression of MCH mRNAs (Sergeyev et al. 2001). A decrease in MCH release from MCH neurons of the LHA could lead to anorexia. Following inflammation, cytokines are released in the blood and they can reach the brain, the blood–brain barrier permeability being increased. Cytokine stimulation could lead to higher levels of SDF-1α by activation of glial or endothelial cells that release chemokines (Meucci et al. 1998, Ohntani et al. 1998, Lee et al. 2002). The released SDF-1α could reach MCH neurons, bind CXCR4, and induce a change in the excitability of the neurons that could induce an adaptive answer to the inflammation and anorexia. One can also imagine that a prolonged inflammation, leading to higher levels of SDF-1α, could lead to neurotoxicity through one or several of the mechanisms described in Fig. 3, and to neurodegenerescence. In this context, chronic LPS injections lead to a decrease in the number of MCH neurons (Gerashchenko & Shiromani 2004).

Similarly, SDF-1α could exert autocrine effects on vasopressinergic neurons, since the chemokine as well as its receptor are present in these neurons. The known autoregulation of AVP on its own neurons and its control by apelin which is co-expressed with its receptors in these cells (De Mota et al. 2004), could be accompanied by a third autocrine system mediated by SDF-1α. SDF-1α could therefore affect the neuroendocrine circuits controlling drinking as well as feeding behaviors. We have preliminary data that sustain such hypothesis in the LHA (K. Palin and F. Moss, personal communication). It will be interesting to determine whether this is a particularity of AVP (and MCH) neurons or if most neuroendocrine cells express modulators and their receptors.
Parkinson’s disease is one of the most prevalent neurodegenerative disorders and is characterized by the progressive loss of DA neurons in the SN. In the presymptomatic state of the disease, the remaining DA neurons can compensate for the loss of DA neurons by increasing their activity (Zigmond 1997). There is increasing evidence to suggest that the brain inflammatory response contributes to Parkinson’s disease pathogenesis (Kurkowska-Jastrzebska et al. 1999, Cicchetti et al. 2002). The loss of these neurons is associated with a glial response composed mainly of activated microglial cells and, to a lesser extent, of reactive astrocytes (Liberatore et al. 1999, Vila et al. 2001). This glial response may be the source of tropic factors that can protect against reactive oxygen species and glutamate. As we proposed in our and Patrick Kitabgi’s team studies, chemokines such as SDF-1α by increasing DA release could also participate to promote compensatory mechanisms of remaining DA neurons at the early stages of the pathology. Apart from these beneficial effects, the glial response under chronic conditions can mediate a variety of deleterious events related to the production of reactive species, and pro-inflammatory prostaglandin and cytokines (Vila et al. 2001). In this context, it was recently reported that SDF-1α expression was markedly increased in the reactive astrocytes in the SN of rat treated with 6-hydroxydopamine, a neurotoxin that induces selective destruction of central DA neurons (E Apartis Communication at the 7th French Neuroscience Society meeting, Lille, France 2005). This could represent a novel pathway associated with the induction.
of DA neuronal death in Parkinson’s disease, possibly through enhanced release of SDF-1α and production of SDF-1α (5–67) in the SN. Overall, these results call for further investigations into the role of chemokines, such as SDF-1α on the activity and survival of DA neurons under normal and pathological conditions. Agents acting on CXCR4 (Heveker et al. 2001) could thus represent useful agents in neurodegenerative diseases involving neuroinflammatory disorders, such as multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, and HIV-associated dementia.

**General conclusion**

Convergent data suggest that SDF-1α could act in the central nervous system as a classical neuromediator under normal conditions and could modulate the activity of several neuroendocrine networks. However, during a pathological state (altered immune response or inflammation), abnormal concentrations of SDF-1α and/or its presence at unusual sites can be found, due to its local production by glial and/or endothelial cells and/or its diffusion and transportation through the vascular circulation. This enhanced production of SDF-1α could affect neuronal and neuroendocrine activities and modify the functioning of the brain, leading to pathological behaviors and/or neurotoxicity.

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