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RESEARCH PAPER

Physiological evidence for interaction between the HIV-1 co-receptor CXCR4 and the cannabinoid system in the brain

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Background and purpose: The chemokine, stromal cell-derived growth factor-1α (SDF-1α/CXCL12), a member of the CXC chemokine family, and the ligand for CXCR4, the co-receptor involved in the entry of human immunodeficiency virus-1 (HIV-1), was tested for its possible interaction with a physiological response to a cannabinoid.
Experimental approach: The cannabinoid agonist, an aminoalkylindole, (+)-WIN 55,212-2 [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one], was infused directly into the preoptic anterior hypothalamus (POAH), the primary brain area involved in thermoregulation.
Key results: WIN 55,212-2 (5–15 μg) evoked a dose-related hypothermia, which was attenuated by SDF-1α/CXCL12 micro-injected directly into the POAH. The inhibitory effect of SDF-1α/CXCL12 on WIN 55,212-2-induced hypothermia was reversed by 1,1′-[1,4-phenylenebis(methylene)]bis[1,4,8,11-tetraazacyclotetradecane] octohydrobromide dihydrate, an antagonist of SDF-1α/CXCL12, acting at its receptor, CXCR4.
Conclusion and implications: This study provides the first *in vivo* evidence for a thermoregulatory interaction between the HIV-1 co-receptor and the cannabinoid system in the brain.
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Keywords: HIV; cannabinoid; hypothermia; CXCR4

Abbreviations: AMD 3100, 1,1′-[1,4-phenylenebis(methylene)]bis[1,4,8,11-tetraazacyclotetradecane]; CB, cannabinoid receptor; GPR55, orphan G protein-coupled receptor 55; HIV, human immunodeficiency virus; POAH, preoptic anterior hypothalamus; SDF-1α/CXCL12, stromal cell-derived growth factor-1α; WIN 55,212-2, [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one]

Introduction

The preoptic anterior hypothalamus (POAH) is generally considered to be the primary site for central control of body temperature (Myers, 1980; Boulant *et al.*, 1989). It contains neurons that are sensitive to subtle changes in the hypothalamus or in the body. Preoptic thermosensitive neurons also receive a wealth of somatosensory input from skin and spinal thermoreceptors. In this way, preoptic neurons compare and integrate central and peripheral thermal information. In addition, the POAH comprises an important area involved in opioid and cannabinoid thermoregulatory effects (Xin *et al.*, 1997; Benamar *et al.*, 2000; Benamar *et al.*, 2002; Rawls *et al.*, 2002; Benamar *et al.*, 2004).

Previous studies have demonstrated that [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one] (WIN 55,212-2) is highly potent and is pharmacologically active *in vivo*. WIN 55,212-2 prevents intravenous cocaine self-administration, increases tail-flick reflexes, exerts antihyperalgesic effects (Compton *et al.*, 1992; Martin and Lichtman, 1998; Fox *et al.*, 2001), and recently we have shown that it has an antipyretic action (Benamar *et al.*, 2007). The acute administration of cannabinoid agonists produces hypothermia in rats, mice and primates (Matsuzaki *et al.*, 1987; Compton *et al.*, 1992; Fan *et al.*, 1994; Spina *et al.*, 1998; Fox *et al.*, 2001). Pharmacological evidence supports a role for the POAH in cannabinoid-induced hypothermia. Δ(9)-tetrahydrocannabinol (Δ^9-THC)

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injected directly into the POAH produced dose-dependent hypothermia (Fitton and Pertwee, 1982). More recently, Ovadia *et al.* (1995) reported that HU-210, [(BaR)-*trans*-3-(1,1-dimethylheptyl)-6,7,10,10-tetrahydro-1-hydroxy-6,5-dimethyl-*H*-dibenzo[*b,d*]pyran-9-methanol], a synthetic cannabinoid agonist, induced hypothermia after injection directly into the POAH.

Growing evidence supports the idea that in addition to their well-established role in the immune system, chemokines might play a role in both normal (Bajetto *et al.*, 2001) and pathological brain function (Hesselgesser and Horuk, 1999; Mennicken *et al.*, 1999) and could be another group of substances, like the neurotransmitters and neuropeptides, involved in the regulation of brain function (Adler and Rogers, 2005; Adler *et al.*, 2006). One of the chemokine receptors thought to have important roles in the brain is CXCR4. Deletion of either the stromal cell-derived growth factor-1α (SDF-1α/CXCL12) or CXCR4 gene results in abnormal cerebellar and hippocampal development, suggesting a role for this chemokine system in neurogenesis (Zou *et al.*, 1998; Lu *et al.*, 2002). CXCR4 has also been identified as one of co-receptors for the human immunodeficiency virus-1 (HIV-1) (Feng *et al.*, 1996). HIV enters cells by a direct fusion mechanism triggered by sequential binding of the glycoprotein 120 subunit of the envelope glycoprotein, first to CD4, then to the co-receptor CCR5 or CXCR4. Increasing evidence implicates the SDF-1α/CXCL12 signalling system in the pathogenesis of tumours, and in infectious and inflammatory processes in several diseases. CXCR4 is up-regulated in HIV and simian immunodeficiency virus encephalitis, experimental allergic encephalitis and brain tumours, where its expression is increased in astrocytes, infiltrating leukocytes and/or endothelial cells on neovessels (Jiang *et al.*, 1998; Vallat *et al.*, 1998; Westmoreland *et al.*, 1998; Glabinski *et al.*, 2000). Furthermore, it has been shown that this chemokine can interact with the analgesic response to an opioid and a cannabinoid (Szabo *et al.*, 2002; Adler *et al.*, 2006; Chen *et al.*, 2007; Benamar *et al.*, 2008), at the level of the periaqueductal grey (PAG).

The purpose of the present study was to test a novel hypothesis that elevated levels of SDF-1/CXCR12 in the brain interfere with a physiological response to the cannabinoid agonist WIN 55,212-2 in the POAH.

Methods

Animals

All animal care and procedures were conducted in strict accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee. Young adult male Sprague-Dawley rats (ACE) weighing 250–300 g were used in this study. They were housed three per cage for at least 1 week before surgery and were fed laboratory chow and water *ad libitum*. Ambient temperature was 21 ± 0.3°C, and a 12 h light/12 h dark cycle was used.

Surgical procedures

Rats were anesthetized with an i.p. injection of a mixture of ketamine hydrochloride (80 mg/kg) and acepromazine maleate (0.2 $mg \cdot kg^{-1}$). An incision 2 cm in length was made along the linea alba, and the underlying tissue was dissected and retracted. A calibrated transmitter (E-mitters, series 4000, Mini-Mitter, Sunriver, OR, USA) was then inserted in the intraperitoneal space. After the transmitter was passed through the incision, the abdominal musculature and dermis were sutured independently (Benamar *et al.*, 2002). For the microinjection study, a sterilized stainless steel C313G cannula guide (22-gauge, Plastics One Inc., Roanoke, VA, USA) was implanted bilaterally in the POAH according to standard procedures (Benamar *et al.*, 2002; Benamar *et al.*, 2004). The stereotaxic coordinates for the POAH implantation of guide cannula were as follows: 0.3 mm anterior to bregma, 0.5 mm from midline and 7 mm ventral to the dura mater for POAH (Paxinos and Watson, 1998). A C313DC cannula dummy (Plastics One Inc., Roanoke, VA, USA) of identical length was inserted into the guide tube to prevent its occlusion. The animals were returned to individual cages in the environmental room.

Microinjection

After a 7 day recovery period, rats were allowed to habituate to test chambers for 1 h before testing. Either vehicle or drug was microinjected into the POAH in a volume of 0.5 µL via a C313I internal cannula (28-gauge, Plastics One Inc., Roanoke, VA, USA). The C313I internal cannula was connected by polyethylene tubing to a 10 µL Hamilton syringe. A volume of 0.5 µL of drug or vehicle was delivered at a rate of 0.5 $\mu L \cdot min^{-1}$ (manually) and the internal cannula left in place for an additional 90 s to allow diffusion. Immediately thereafter, a dummy cannula (C313DC) was inserted into the cannula guide to prevent any contamination.

Body temperature measurement

Rats were tested in an environmental room (Hotpack), maintained at 22 ± 0.3°C ambient temperature and 52 ± 2% relative humidity. After 1 h of adaptation, two readings at 15 min intervals were averaged to determine the baseline. Body temperature was measured by a biotelemetry system (Mini-Mitter, Sunriver, OR, USA) using calibrated transmitters implanted i.p. Signals from the transmitter were delivered through a computer-linked receiver. This method minimizes stress to animals during the body temperature reading. Thus, the body temperature could be monitored continuously and recorded without restraint or any disturbance to the animal. All experiments were started between 09:00 and 10:00 h to minimize the effect of circadian variation in body temperature.

Histological analysis

At the conclusion of the experiments, each rat was injected with 0.5 µL of cresyl violet, anaesthetized and perfused transcardially with 0.9% isotonic saline, followed by PBS 4% paraformaldehyde (pH 7.4). The brain was removed, stored in the same fixative for 4 h, kept in 20% sucrose overnight and cut into 20 µm sections on a freezing microtome. Each coronal section was mounted according to standard

histological procedures (Benamar *et al*., 2004), and the site of injection was verified by locating the dye and then mapping on anatomical reconstructions in the coronal planes. Only data from animals in which the site of injection was clearly located within the POAH regions were included in the studies.

Experimental protocol

Effect of intra-POAH injection of WIN 55,212-2. After a 60 min baseline interval, WIN 55,212-2, WIN 55,212-3 (inactive form) or vehicle was injected into the POAH at time zero and body temperature was measured for 90 min.

Effect of SDF-1(/CXCL12 on WIN 55,212-2-induced hypothermia. After a 60 min baseline interval, SDF-1α/CXCL12 or vehicle was injected into the POAH. Thirty min later, WIN 55,212-2 was injected into the POAH and body temperature was measured to determine whether the CXCR4 mediates the effects of SDF-1α/CXCL12 on WIN 55,212-2-induced hypothermia. We further tested the possible involvement of CXCR4 in WIN 55,212-2-induced hypothermia by giving 1,1′-[1,4-phenylenebis(methylene)]bis[1,4,8,11-tetraazacyclotetradecane] (AMD 3100), an antagonist at the SDF-1α/CXCL12 receptor. After a 60 min baseline interval, the CXCR4 antagonist was injected into the POAH. Thirty min later, SDF-1α/CXCL12 was injected into the POAH followed 30 min later by WIN 55,212-2. The body temperature was measured for 60 min.

Statistical analysis

All results were expressed as mean ± SEM. Statistical analysis of differences between groups was determined by analysis of variance (ANOVA) followed by Dunnett's post-test. A value of P less than 0.05 was considered statistically significant.

Materials

The cannabinoid agonist, WIN 55,212-2, and its inactive enantiomer, WIN 55,212-3, were obtained from Sigma-Aldrich (St. Louis, MO, USA). These drugs were dissolved in Cremophor, dimethylsulphoxide and saline (1:1:18). AMD 3100 was obtained from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in pyrogen-free saline. Recombinant rat SDF-1α/CXCL12 was purchased from R&D Systems (Minneapolis, MN, USA) and was reconstituted in sterilized artificial cerebrospinal fluid (aCSF; CMA/microdialysis AB, Stockholm, Sweden).

Results

Effect of intra-POAH injection of WIN 55,212-2 on body temperature

Consistent with a previous study (Rawls *et al*., 2002), WIN 55,212-2 microinjected directly into the POAH-evoked dose-related hypothermia (Figure 1). The lowest dose, 5 μg, did not alter body temperature. The highest doses, 10 and 25 μg 0.5 μL^{-1}, produced a significant decrease in body temperature,

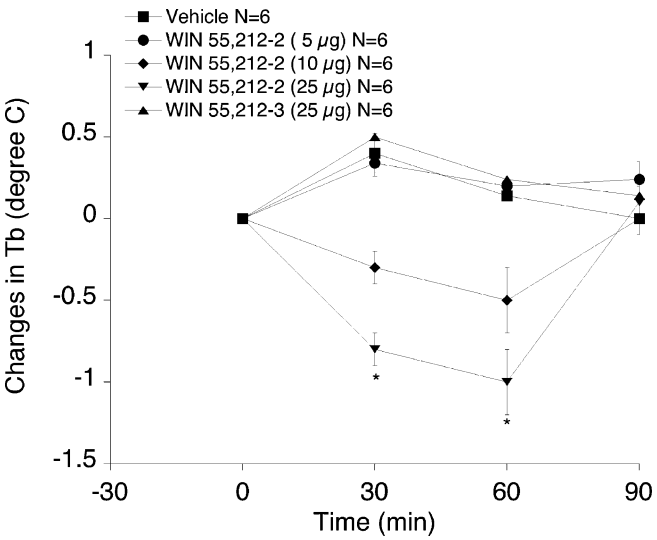

Figure 1 Effect of intra-POAH injection of WIN 55,212-2 (5–25 μg 0.5 μL^{-1}) on body temperature (Tb). WIN 55,212-2 was injected at time 0. Data are expressed as the mean ± SEM from baseline. N, number of rats; POAH, preoptic anterior hypothalamus; WIN 55,212-2, [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one]. *$P < 0.05$.

reaching a peak hypothermia of 0.5 ± 0.21 and 1.0 ± 0.2°C, respectively, between 15 and 60 min post-injection ($F_{4,16}$ = 3.01, $P < 0.05$). Body temperature returned to pre-drug levels by 90 min post-injection. Increasing the doses of WIN 55,212-2 did not result in an increase in the maximal hypothermic response (data not shown). To show that this effect was not due to a non-specific interaction with hydrophobic regions of functional proteins or their lipid surroundings in the cell membrane, and that the cannabinoid receptor (CB) has stereoselectivity, we tested WIN 55,212-3, an inactive enantiomer, on body temperature. As shown in Figure 1, WIN 55,212-3 at 25 μg had no effect on body temperature compared with vehicle ($P > 0.05$). Mean body temperature ± SEM before injection was 37.65 ± 0.19°C for the vehicle group, 37.63 ± 0.15°C for the WIN 55,212-2 (5 μg) group, 37.55 ± 0.23°C for the WIN 55,212-2 (10 μg) group, 37.59 ± 0.25°C for the WIN 55,212-2 (25 μg) group and 37.49 ± 0.14°C for WIN 55,212-3 (25 μg) group.

Effect of intra-POAH injection of SDF-1α/CXCL12 on WIN 55,212-2-induced hypothermia

First, we examined whether SDF-1α/CXCL12 itself altered body temperature. This chemokine was microinjected directly into the POAH, and body temperature was measured. During the 60 min recording period, no significant change was observed after POAH injection of SDF-1α/CXCL12 at a dose of 25 ng, 50 ng and 100 ng, compared with the effect of injection of an equivalent volume of vehicle (aCSF) (Figure 2, $P > 0.05$). Mean body temperature ± SEM before injection was 37.71 ± 0.22°C for the SDF-1α/CXCL12 (25 ng) group, 37.66 ± 0.26°C for the SDF-1α/CXCL12 (50 ng) group, 37.57 ± 0.23°C for the SDF-1α/CXCL12 (100 ng) group and 37.63 ± 0.18°C for the vehicle group.

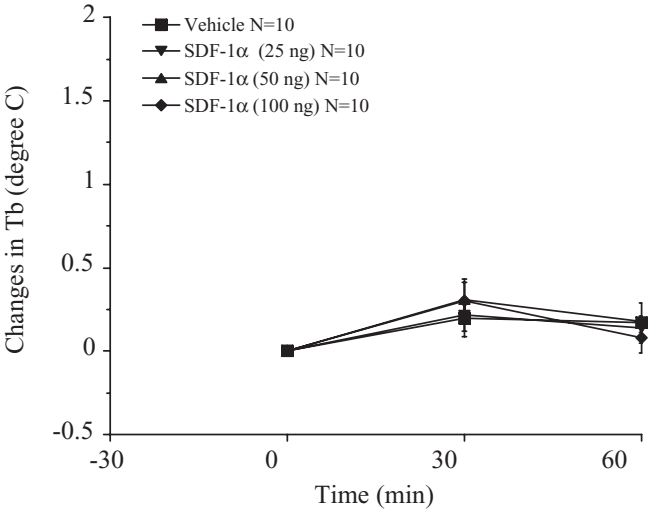

Figure 2 Effect of POAH pretreatment with SDF-1α/CXCL12 (25–100 ng, –30 min) on WIN 55,212-2-induced hypothermia. WIN 55,212-2 was injected at time 0. Data are expressed as the mean ± SEM changes in body temperature (Tb) from baseline. N, number of rats; POAH, preoptic anterior hypothalamus; SDF-1α/CXCL12, stromal cell-derived growth factor-1α; WIN 55,212-2, [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one].

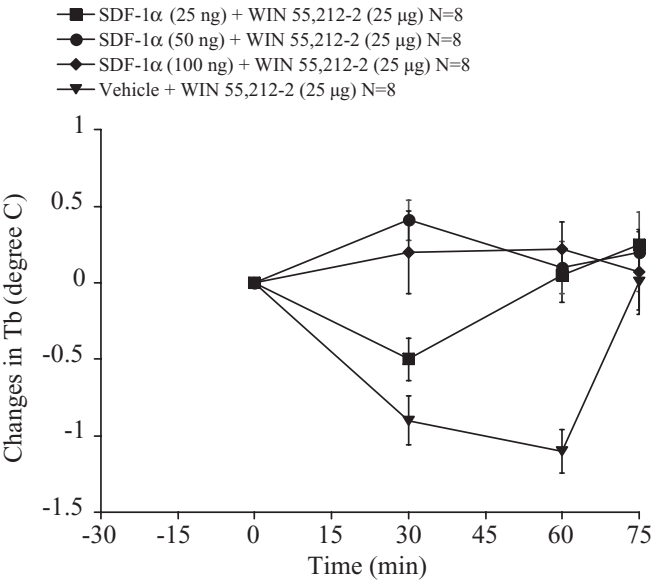

Figure 3 Effect of SDF-1α/CXCL12 (25–100 ng) on body temperature. WIN 55,212-2 was injected at time 0. Data are expressed as the mean ± SEM changes in body temperature (Tb) from baseline. N, number of rats; SDF-1α/CXCL12, stromal cell-derived growth factor-1α; WIN 55,212-2, [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one].

In separate experiments, we determined whether SDF-1α/CXCL12 would interfere with WIN 55,212-2-induced hypothermia. SDF-1α/CXCL12 was given into the POAH over a range of doses from 25–100 ng·0.5 μL^{-1}. After 30 min, WIN 55,212-2 (25 μg) was injected into the POAH and body temperature was monitored. SDF-1α/CXCL12 attenuated the WIN 55,212-2-induced hypothermia. The effect of SDF-1α/CXCL12 was dose-dependent. A dose of 25 ng·0.5 μL^{-1} partially attenuated the WIN 55,212-2-induced hypothermia (–0.5 ± 0.14°C, $P < 0.05$). At doses of 50 or 100 ng·0.5 μL^{-1}, SDF-1α/CXCL12 completely abolished the hypothermia produced by WIN 55,212-2 (Figure 3, $F_{4,15} = 3.06$: $P < 0.05$). Mean body temperature ± SEM before injection was 37.56 ± 0.17°C for the vehicle/WIN 55,212-2 group, 37.62 ± 0.20°C for the SDF-1α/CXCL12 (25 ng)/WIN 55,212-2 group, 37.65 ± 0.24°C for the SDF-1α/CXCL12 (50 ng)/WIN 55,212-2 group, 37.70 ± 0.23°C for the SDF-1α/CXCL12 (100 ng)/WIN 55,212-2 group and 37.59 ± 0.20°C for the AMD 3100/vehicle/WIN 55,212-2.

In order to prove that the SDF-1α/CXCL12 effect was mediated through its receptor, the SDF-1α/CXCL12 antagonist, AMD3100, was given directly into the POAH (10 to 100 ng·0.5 μL^{-1}). The results showed that when the AMD3100 was given 30 min before the injection of SDF-1α/CXCL12 at doses of 10, 50 or 100 ng, it reversed the effect of SDF-1α/CXCL12 on WIN 55,212-2-induced hypothermia (Figure 4, $F_{4,15} = 3.06$, $P < 0.05$). However, the intra-POAH injection of AMD 3100 had no effect on the WIN 55,212-2-induced hypothermia (Figure 4, $P > 0.05$). AMD 3100 (100 ng) by itself had no effect on body temperature (data not shown).

A composite anatomical map of some individual sites of microinjection is presented in Figure 5. The tips of the injector needles were distributed in coronal planes anterior-posterior –0.26, –0.40, –0.92 and –1.40 from bregma (Paxinos and Watson, 1998).

Discussion

Our present data provide the first *in vivo* evidence of a thermoregulatory interaction between chemokine and cannabinoid systems in the brain, and show that elevated levels of SDF-1α/CXCL12 in the brain diminish the thermoregulatory response to a cannabinoid.

Consistent with previous studies (Rawls *et al.*, 2002), the injection of WIN 55,212-2 into the POAH evoked dose-dependent hypothermia. The selective CB_1 antagonist, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride, prevented the WIN 55,212-2-evoked hypothermia, indicating that a CB_1 receptor mechanism mediated the hypothermic effect (Rawls *et al.*, 2002). The selective CB_2 antagonist, [*N*-{(1*S*)-*endo*-1,3,3-trimethyl bicyclo heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide}, did not affect WIN 55,212-2-induced hypothermia, suggesting that CB_2 receptor activation is not involved (Rawls *et al.*, 2002). Recently, it has been shown that the orphan G protein-coupled receptor 55, GPR55, is a novel CB with an ability to interact with and be modulated by endogenous, plant and synthetic cannabinoid ligands (Ryberg *et al.*, 2007). Thus, the involvement of CB_1 receptors in WIN 55,212-2-induced hypothermia does not discount the possibility of GPR55 being also involved.

To determine whether SDF-1α/CXCL12 interacts with the cannabinoid system in the POAH, we investigated the

ability of this chemokine to alter the hypothermic function of WIN 55,212-2. Pretreatment with SDF-1α/CXCL12 (10–100 ng) significantly attenuated the hypothermic effect of the WIN 55,212-2, indicating that this chemokine is able to interfere with the pathway involved in the mechanisms that control the development of hypothermia induced by a cannabinoid.

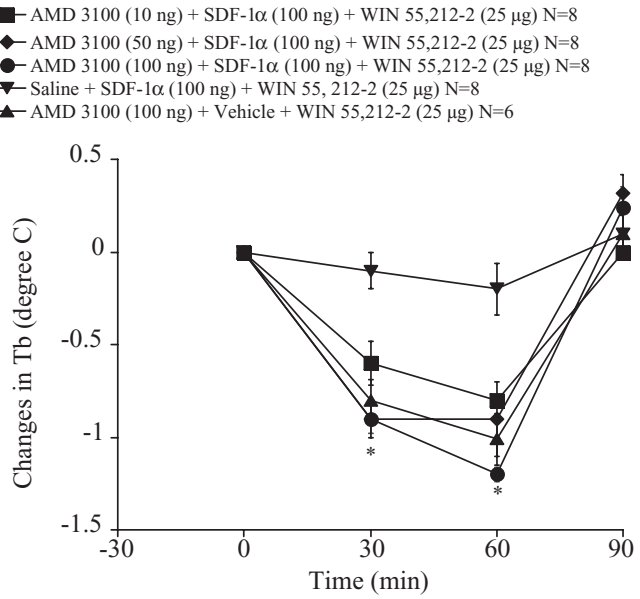

Figure 4 Antagonism of the effects of SDF-1α/CXCL12 on WIN 55,212-2-induced hypothermia by AMD 3100. Rats were injected into POAH with SDF-1α/CXCL12, 30 min before WIN 55,212-2. SDF-1α/CXCL12 was given to rats at a dose of 100 ng 1 h before WIN 55,212-2 (at 0 min). Data are expressed as the mean ± SEM changes in body temperature (Tb) from baseline. AMD 3100, 1,1′-[1,4-phenylenebis(methylene)]bis[1,4,8,11-tetraazacyclotetradecane; N, number of rats; POAH, preoptic anterior hypothalamus; SDF-1α/CXCL12, stromal cell-derived growth factor-1α; WIN 55,212-2, [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one]. *$P < 0.05$.

In an attempt to establish that the SDF-1α/CXCL12 effect was mediated through its receptor, the SDF-1α/CXCL12 antagonist, AMD 3100, was given directly into the POAH. The results showed that when AMD 3100 was given 30 min before the injection of SDF-1α/CXCL12 at 100 ng·0.5 μL^{-1}, the blockade of WIN 55,212-2-induced hypothermia by the chemokine was prevented. This finding indicates that the inhibitory effect of SDF-1α/CXCL12 on WIN 55,212-2-induced hypothermia was mediated by CXCR4. In addition to CXCR4 (Bleul *et al.*, 1996), SDF-1α/CXCR12 also binds to CXCR7 (Schönemeier *et al.*, 2008). The possibility therefore exists that CXCR7 may also contribute to the SDF-1α/CXCR12 effect on WIN 55,212-2-induced hypothermia.

An accumulating body of evidence points to CB_1 cannabinoid receptors as being located in the hypothalamus (Pettit *et al.*, 1998; Tsou *et al.*, 1998), including the POAH (Herkenham *et al.*, 1991; Mailleux and Vanderhaeghen, 1992; Moldrich and Wenger, 2000). Furthermore, CB_1 receptors within the POAH are the primary mediators of cannabinoid-induced hypothermia (Rawls *et al.*, 2002). On the other hand, the SDF-1α/CXCL12 protein is constitutively and regionally expressed in specific neuronal populations throughout adult rat brain (Banisadr *et al.*, 2003), particularly in discrete nuclei of the hypothalamus (such as the paraventricular and supraoptic nuclei). Because both chemokines and cannabinoids are found in the POAH, and their receptors are members of the G protein-coupled receptor family, one likely explanation for the antagonistic effect of SDF-1α/CXCL12 on WIN 55,212-2 is interference with CB_1 receptor function in the POAH probably via activation of CXCR4. It is possible that a heterologous desensitization mechanism may occur at the G protein-coupled receptor level. Indeed, such an effect has been found between

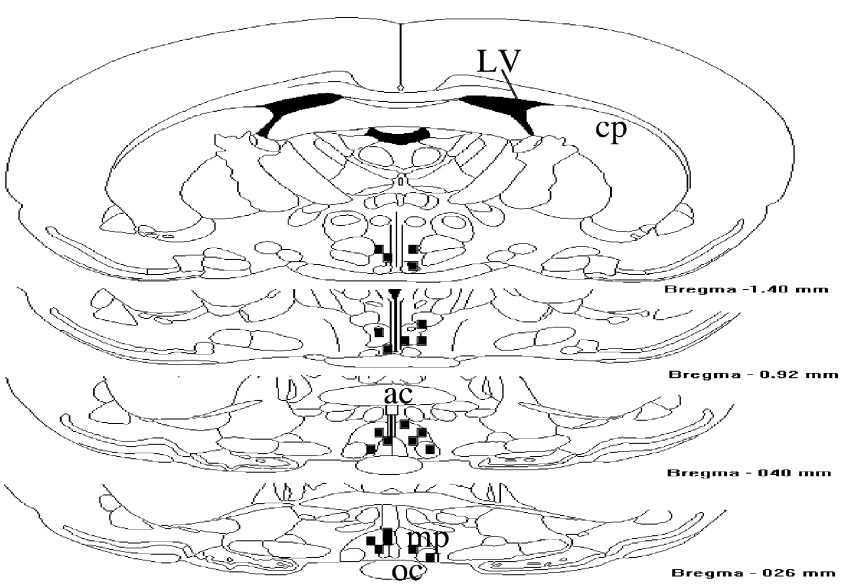

Figure 5 Anatomical mapping in successive frontal sections. illustrating the distribution of some individual sites of microinjection in the POAH. ac, anterior commissure; cp, caudate putamen; LV: lateral ventricle; mp, medial optic area; oc, optic chiasma; POAH, preoptic anterior hypothalamus.

SDF-1α/CXCL12 and the opioid system in the PAG (Szabo *et al*., 2002; Adler *et al*., 2006; Chen *et al*., 2007), where pretreatment with SDF-1α/CXCL12 desensitized the analgesic effects of opioids.

In summary, we have previously shown that analgesic activity of the cannabinoid agonist WIN 55,212-2 in the brain can be overcome in situations in which there are elevated levels of SDF-1α/CXCL12 in the brain (Benamar *et al*., 2008). The present data support the idea of a functional interaction between chemokine and cannabinoid systems in the brain and show that a thermoregulatory action of the cannabinoid agonist WIN 55,212-2 can be antagonized by elevated levels of SDF-1α/CXCL12. Taken together, it seems that conditions associated with elevated level of chemokines may result in reduction of cannabinoid functions, as is the case with most neuroinflammatory diseases (such as multiple sclerosis and HIV encephalitis). In addition, the fact that the pretreatment with AMD 3100 was able to restore the thermoregulatory (our present data) and analgesic (Benamar *et al*., 2008) effects of a cannabinoid, suggests the use of chemokine blockers might be used as a strategy to restore cannabinoid functions, particularly in neuroinflammatory conditions.

Both drugs of abuse and HIV represent serious public health threats. HIV and drugs of abuse are not isolated problems, but they interact and influence each other (Burdo *et al*., 2006; Bruce and Altice, 2007). Because SDF-1(/CXCL12 as well as the HIV-1 coat protein 120 can bind to CXCR4, the full significance of the interaction of HIV-1 infection and cannabinoids may not yet be fully appreciated. However, the intriguing possibility of functional links between the co-receptor involved in the entry of HIV and the physiological efficacy of cannabinoids is completely novel and may present new dimensions to the study of HIV and drugs of abuse.

Acknowledgements

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Conflicts of interest

None.

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