Published in final edited form as:

Neuropharmacology. 2010 January ; 58(1): 35–37. doi:10.1016/j.neuropharm.2009.07.012.

Opiate-induced Hypernociception and Chemokine Receptors

Fletcher White¹ and Natalie Wilson²

¹ Departments of Cell Biology, Neurobiology and Anatomy, and Anesthesiology, Loyola University, Chicago, Illinois, USA

² Department of Pharmacology, Loyola University, Chicago, Illinois, USA

Abstract

Opiates, such as morphine, are typically employed to alleviate acute or chronic pain states. However, there are a myriad of side effects including constipation, nausea, respiratory depression, cough suppression, vomiting, sedation, addiction and tolerance. It has also been reported experimentally and clinically that exposure to opioids can elicit paradoxical pain (opiate-induced tactile hyperalgesia; OIH) in regions of the body unrelated to the initial pain complaint. Several mechanisms have been suggested to be responsible for OIH such as sensitization of peripheral nociceptors, enhanced production/release of glutamate and neuropeptides in the spinal cord, protein kinase C γ -induced signaling, and/or enhanced descending facilitation of nociceptive pathways from the rostral ventromedial medulla; however signaling pathways known to lead to directly to OIH remain undiscovered. Recent publications from our laboratory and others have discovered a potentially important link to OIH that involves the chemokine (chemotactic cytokine chemokines), stromal-derived factor 1 (SDF1 also known as CXCL12) and its cognate receptor CXCR4.

Introduction

Opiates, such as morphine, currently represent the best option for the management of moderate to severe trauma-induced, perioperative and cancer pain. Opiate compounds are also increasingly being used for non-cancer chronic pathological pain. However, prolonged administration of opiates is associated with significant problems including the development of antinociceptive tolerance, wherein higher doses of the drug are required over time to elicit the same amount of analgesia. These higher doses are also thought to be increasing pain sensitivity, a concept known as opiate-induced tactile hypernociception (OIH). This increased pain is usually experienced at a location separate from the original site of injury (Ossipov et al., 2004).

OIH has been observed both clinically (Angst et al., 2003; Arner et al., 1988; Singla et al., 2007) and experimentally (Laulin et al., 1999; Woolf, 1981). Many explanations for this phenomenon have been suggested. For example, OIH was once believed to occur as a result of “mini withdrawals”, however OIH still occurs when opiates are constantly infused (Vanderah et al., 2000; Vanderah et al., 2001). Some investigators will even go so far as to suggest that OIH is actually a form of tolerance, in which patients require a greater opiate dose in order to receive the same analgesic effect (Guignard et al., 2000; Luginbuhl et al., 2003). Yet another explanation is that the hyperalgesic response to morphine is caused by a compensatory response to the inhibition produced by activation of the mu opioid receptor

(mOR), causing a hyperactivity of the system (Gutstein, 1996). In fact, higher doses are suggested to precipitate this effect largely because the hyperactive state becomes more dominant (Colpaert, 2002).

OIH has previously been shown to be blocked by a number of different methods such as glutamate antagonism (Celerier et al., 2000; Laulin et al., 1998). The involvement of glutamate receptors is not surprising because the long lasting effects that are witnessed in OIH would require neural plasticity, changes that likely require glutamate receptors. However, the ability of glutamate blockade to effectively treat OIH is questioned. This is because neural plastic changes that are occurring are present in two parts; i) the sensitivity of the glutamate receptor, and ii) the perceived decreased responsiveness of the mOR. Blockade of the glutamate receptor would transiently reverse the nociceptive behavior however, it does not address the changes that have occurred in the mOR-bearing cell (Mao et al., 1995). Despite a considerable amount of work on the topic little is known about the underlying mechanism.

Role of Chemokines/Receptors in OIH

Chemokines (chemotactic cytokines) are a family of small proteins involved in leukocyte trafficking under normal physiological and pathological conditions as well signaling in the developing and injured adult nervous system. Chemokines are typically classified by the presence of a cysteine motif in the N-terminal region of the protein. Initial characterization of chemokines divided the family into α - and β -chemokines. In α chemokines, one amino acid separates the first two cysteine residues (cysteine-X amino acid-cysteine or CXC), whereas in β -chemokines, the first two cysteine residues are adjacent to each other (cysteine-cysteine, or CC). Two additional classes were added for the chemokines, lymphotactin (single cysteine, XC) and fractalkine (first two cysteines are separated by three amino acids, CX3C). The chemokine nomenclature herein utilizes both the original ligand name and the systematic name. The systematic name uses XC, CC, CXC and CX3C, indicating the class to which the chemokine belongs, followed by the letter "L" (for ligand) and then a number. The numbering system corresponds to that already in use to designate the genes encoding each chemokine.

All chemokines exert their biological effects through the activation of an extended family of seven transmembrane G-protein-coupled receptors (GPCRs). Nineteen chemokine receptors have been cloned including six CXC receptors (CXCR1-6), 10 CC receptors (from CCR1-10) and two single receptors each for lymphotactin (XCR1) and fractalkine (CXCR3). Chemokine receptors are notoriously promiscuous, i.e. single chemokines can activate several different chemokine receptors. There are, however, instances when a chemokine receptor is uniquely activated by a single chemokine. For example, the CXCR4 receptor has only one known ligand, stromal-derived factor-1 (SDF1/CXCL12).

Stromal derive factor 1 alpha and CXCR4

SDF1 was first identified in 1993 from murine bone marrow, hence the name (Li and Ransohoff, 2008; Tashiro et al., 1993). SDF1 is highly conserved between mice and humans, is widely expressed throughout the body, and exhibits a broad range of actions affecting stromal cell migration, leukocyte chemotaxis, vascularization of multiple organ systems, metastatic tumor formation, neural development and chronic pain (Miller et al., 2008; White et al., 2007).

The molecular structure of this chemokine exhibits an amino acid sequence that contains four cysteine residues conserved by most CXC chemokines with the N-terminus of SDF-1 particularly important for activity. The monomer form of SDF1 is known to produce internalization of its receptor, CXCR4, and intracellular Ca^{2+} mobilization. Recent studies using nuclear magnetic resonance structure analysis of the SDF1: CXCR4-N-domain complex

have also determined that the structural basis of the recognition of receptor residues by the chemokine is indicative of a constitutively active dimeric form of SDF1. Importantly, this dimeric form serves only to activate intracellular Ca^{2+} mobilization (Lynch and Banks, 2008). The differential effects on CXCR4-bearing cells by either the monomeric or dimeric forms reveal the latter to be a potent partial agonist (Lynch and Banks, 2008).

Chemokine/Opiate Receptors

It is known that some chemokines, including SDF1, potentially alter neuronal signaling in the nervous system via heterologous desensitization between chemokines and opiate receptors. This phenomenon was first discovered in vitro and confirmed in vivo (Szabo et al., 2002; Zhang et al., 2004). Initial injections of the chemokine SDF1 into the PAG 30 minutes alone produced no change in the animal response to a cold water challenge (Szabo et al., 2002). However, when the chemokine was administered prior to morphine or DAMGO administration, it effectively blocked the expected analgesic effect on a rodent tail subjected to a cold water bath (Szabo et al., 2002). Szabo and colleagues further determined that the effects of the SDF1 were both dose- and time-dependent.

A key discovery regarding CXCR4 and the mOR is the documented interaction between mOR agonists and lymphocytes. Steele and colleagues (Steele et al., 2003) determined that exposure of monocytes and lymphocytes to mOR agonists produced an increase in the expression of CXCR4. The importance of this finding is that components of the HIV-1 virus, such as the coat protein gp120, uses CXCR4 to infect CD4+ T cells. Subsequently, the clinical relevance of this finding is that intravenous heroin users, in addition to risky lifestyle choices (sharing needles and having unprotected sex (Donahoe and Vlahov, 1998)), are more susceptible to HIV-1 infection as a result of the effects of heroin on chemokine receptor upregulation.

If increased chemokine signaling is indeed a central feature of opiate-induced hypernociception then it is also essential to know what cell type is involved in the development and maintenance of the paradoxical nociceptive behavior—the glial cell or the neuron? Most proposed mechanisms involve changes in the mOR bearing neurons. However, any cell type within the nervous system that bears the mOR can conceivably serve as a potential source of chemokine receptor signaling following chronic morphine treatment, including non-neuronal cells (i.e. leukocytes fibroblasts and endothelial cells (White et al., 2007)). Detailed analysis by a number of groups demonstrate that CXCR4-receptor-bearing cells in the CNS are largely restricted to neurogenic regions (Schonemeier et al., 2008; Tran et al., 2007) and expression of SDF1 and CXCR4 in the normal peripheral nervous system is largely localized to nonmyelinating satellite glial cells in the naive dorsal root ganglia (DRG) (Bhangoo et al., 2007). In addition, recent publications suggest that peripheral nerve injury, the use of NRTIs and repeated administration of morphine, can lead to *de novo* CXCR4 in sensory neurons and CXCR4 dependent nociceptive behaviors (Bhangoo et al., In press; Bhangoo et al., 2007; Wilson et al., 2008). Whether similar outcomes occur in the CNS is unknown.

The mechanism responsible for increased signaling of SDF1/CXCR4 following repeated administration of morphine is unknown. As such, it is reasonable to identify the signaling components that are responsible for the increased chemokine/receptor interaction. There are a myriad of signaling pathways that are affected by morphine treatment, however, one family of intracellular signaling compounds that plays an important role in transcription and post-translational modification of a number of different proteins is the mitogen-activated protein kinases (MAPK) family. One of the members of this pathway is ERK (extracellular signal-regulated protein kinase) which is activated through phosphorylation. Previous studies have demonstrated that repeated morphine treatment leads to increases in neuronal p-ERK levels (Chen et al., 2008; Ma et al., 2001; Narita et al., 2002; Patel et al., 2006). Furthermore, increases

in p-ERK have been observed specifically in the DRG and corresponding to increases in pain-related neuropeptides and receptors and can be reversed by specific inhibitors of ERK (Chen et al., 2008; Ma et al., 2001). Perhaps more importantly, the MAPK family has also been shown to play a role in pain hypersensitivity (Ji et al., 2009).

SUMMARY

Morphine currently represents the best option for the management of severe pain and chronic pain states. Prolonged use of opiates often produces a heightened state of pain (OIH). The mechanisms associated with OIH are thought to be due to morphine-induced cellular adaptations leading to cellular hypersensitivity. Recent studies suggest that opiates acting via the mOR can modulate the expression of chemokines and their receptors on immune cells. Similar changes may be occurring in the nervous system and a better understanding of these chemokine/receptor-mediated events may provide the necessary framework for the design of agents that counteract deleterious opiate-induced neuronal adaptations.

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