Pharmacological Reports 68 (2016) 686–691

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Opioid-induced redistribution of 6TM and 7TM μ opioid receptors: A hypothesized mechanistic facilitator model of opioid-induced hyperalgesia

Wei Wang [a,1], Yan Wang [b,1], Wei Zhang [c,1], Xiaoju Jin [d,1], Yusheng Liu [a], Shiqin Xu [a], Liming Lei [a], Xiaofeng Shen [a], Xirong Guo [e], Xiaoqiong Xia [b,*], Fuzhou Wang [a,f,*]

[a] Department of Anesthesiology, Nanjing Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University, Nanjing, China
[b] Department of Anesthesiology, Affiliated Chaohu Hospital, Anhui Medical University, Chaohu, Anhui, China
[c] Department of Anesthesiology, Nanjing T.C.M. Hospital, Nanjing, China
[d] The First Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, China
[e] Pediatric Institute, Nanjing Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University, Nanjing, China
[f] Division of Neuroscience, The Bonoi Academy of Science and Education, Chapel Hill, NC, USA

ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form 30 January 2016
Accepted 2 March 2016
Available online 19 March 2016

Keywords:
Opioids
Hyperalgesia
μ-opioid receptor
G-protein coupled receptor
Receptor redistribution

ABSTRACT

Opioids are still the most popular form of pain treatment, but many unavoidable side effects make opioids a big challenge in effective pain management. Opioid-induced hyperalgesia (OIH), a paradoxical phenomenon, portrays an increased sensitivity to harmful stimuli caused by opioid exposure. Changes in the neural modulation are considered a major contributor to the development of OIH. Activation of opioid receptors (ORs) and corresponding downstream molecules are the vital composition of functional performance of opioids. Increasing interests were proposed of the interaction between ORs and other neural transmitter systems such as glutamatergic, GABAergic and adrenergic ones to the genesis of OIH. G protein coupled μ-opioid receptor (MOR) was studied comprehensively on its role in the development of OIH. In addition to the relationship between MOR and other neurotransmitter receptors, a new intracellular MOR that has six transmembrane (6TM) domains was identified, and found to perform a pro-nociceptive task in contrast to the counterpart 7TM isoform. A mechanistic model of OIH in which both 6TM and 7TM MORs undergoing membrane redistribution upon opioid exposure is proposed which eventually facilitates the neurons more sensitive to nociceptive stimulation than that of the preceding opioid exposure.

Contents

* Corresponding authors.
E-mail addresses: 2366833@sina.com (X. Xia), zfwang50@njmu.edu.cn (F. Wang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.pharep.2016.03.003
1734-1140/

Introduction

Pain is one of the major reasons for seeking medical service, and it is considered a key symptomatic composition of most pathological disorders as well. However, in-depth mechanistic studies are increasingly revealing the somatic property of pain, which indicates that pain is not only a symptom of diseases, but also a sign with physical basis [1]. As thus, pain is defined as "the fifth disease" in consideration of its somatic characteristics. In consideration of the distinction between acute and chronic pain in their pathogenesis and prognosis, the therapeutic interventions on both types of condition also display significant difference correspondingly [2].

Opioid, the earliest finding for pain relief in the history of human being, is still the therapeutic mainstay of pain even we have made great progress in developing other kinds of non-opioid analgesics [2,3]. Compared with the acute pain, chronic pain is still the major reason for prescribing opioid as the treatment no matter of the etiologies. Cancer is a large composition of chronic pain, of which about half patients suffer pain at the time of cancer being diagnosed, and in up to 80% patients with advanced cancer stage, moderate to severe pain was reported [4]. For these patients, the World Health Organization (WHO) recommends strong opioids as the initial choice in the pain ladder treatment [5]. In all patients undergoing surgeries, approximately 15% reported chronic post-surgical pain (CPSP) with moderate to severe intensity [6], and opioidergic analgesics are considered as the second line drugs backing up the failure of the first line non-opioid therapy [7]. However, close investigations have revealed that using opioids tends to induce changes in pain sensitivity including hyperalgesia or tolerance [8]. The changes brought about by these unforeseen sensitivity therapy has made opioid be a huge stumbling block in effectively reducing pain. Opioid-induced hyperalgesia (OIH) works by proving that the level of pain perceived is greatly enhanced paradoxically by administering opioid. As opposed to OIH, tolerance to analgesics implies that there will be reduced response to analgesic drugs after opioid use over time. Changes in the central nervous system (CNS) brought about by pain is regarded as pain-related neuronal plasticity, which can later result in sensitization of the nervous system, *i.e.* allodynia and hyperalgesia [9]. With the escalation of opioid therapy of non-cancer pain in recent years, the incidence of OIH also increased substantially in accompanying with the increasing use of opioids [10–12]. Three types of opioid-administration procedures were identified so far indicating that OIH was resulted from: persistent dose [13], high dose [14], and ultra-low dose [15]. Whereas significant development has been made in exploring the underlying mechanisms of OIH over the past decade, it has been impossible to find ways to control over the over sensitized state or to prevent its occurrence prophylactically.

Definitive data have confirmed the primary role of μ-opioid receptor (MOR) in opioid analgesics. As the target of opioid, MOR induces pain relief by inhibiting the second messenger pathways and modulating ion channel activities [16]. Of recent, scientific discoveries suggested the six transmembrane (6TM) subclass of MORs play a contradistinctive role in taking function from opioid binding through a very different signaling pathway, *i.e.* excitatory effect, in contrast to the conventional 7TM isoforms that majorly show up an inhibitory effect [17]. In this perspective hypothesis, we highlighted the recent development in OIH studies and focused on the up-to-date recognitions of its underlying mechanisms. Based on the newly emerged knowledge, we present an opioid-induced MOR redistribution model that may contribute to the development of OIH.

History and epidemiology

In the year 1943, Dr. Andrews was the first to present the findings of reduction in pain threshold after morphine administration in patients with post-addition [18]. Things were the same until 1973 that the first report regarding opioid induced hyperalgesia in animals was published [19]. With the aid of these findings, researchers found that the pain threshold in those who is addicted to opioids was much higher than the healthy [20], and patients who received high doses of opioids or long-course maintenance with opioid therapy had improved responsiveness to lower threshold stimulation [21,22].

Even though there are no studies that are directly focusing on the prevalence of OIH, some researchers believed that the occurrence of OIH is not that rare compared with other opioid-associated complications and considered that it was under-recognized by current clinical practice [23]. Interestingly, the opioid-sensitized pain condition needs higher doses of opioids. In an observatory study in which about 200 patients received long-standing opioid therapy for chronic pain, and finally over 25% patients required more opioids even though no definite evidence showed that was due to OIH [24]. If both cancer and non-cancer pain was considered, the total incidence of OIH reaches to 12% [10–12].

Neural modulation of OIH

Tissue injury and other pain provoking factors tend to fuel neuroplasticity changes within the nervous system, which in the long run result in hypersensitivity of both peripheral and central neural processing. During this neural modulating process, opioid administration produces three types of OIH formats under different drug delivering situations. The mostly focused OIH is those with chronic opioid addiction or opioid maintenance [13]; the second form of OIH occurs in patients receiving extra high or escalating doses of opioids [14]; and another form of OIH observed in animal studies when an extra low dose of opioid was given [15,22]. Neural modulation was considered as the common underlying mechanism of OIH induced by these three different types of opioid use [25].

Glutamate serves as a major excitatory neurotransmitter in the CNS. A body of evidence suggests that the activation of glutamatergic pathways largely through N-methyl-D-aspartate (NMDA) receptor is a key mechanism for promoting OIH. The NMDA-specific antagonist MK-801 prevented the development of OIH in animals [26], and ketamine, a NMDA receptor antagonist widely used in clinical settings, alleviated fentanyl-induced hyperalgesia [27,28]. The on- and off-neurons in the rostro-ventral medulla (RVM) plays an essential role in contributing to the development of OIH *via* mediating NMDA system as evidenced that the overbalanced on- and off-cell activation prompts OIH occurrence to be much easier after opioid administration [29].

Beside the high rate excitatory activity of glutamatergic transmission, the low rate activity of inhibitory neural transmission was also considered as an important composition of the pathogenesis of OIH. Gamma-aminobutyricacid (GABA) is the key mediator of inhibitory neural transmission. Activation of the declined GABA transmission with gabapentin, a GABA agonist anticonvulsant, produced significant analgesic effect especially in the context of neuropathic pain [30,31], from which gabapentin even was considered as the first-line medication for chronic pain treatment [32,33]. Attributed to its pain-relieving role, the prophylactic gabapentin prior to surgical procedures was found possessing an opioid-sparing effect during the post-operative pain management [34]. For the condition of OIH, gabapentin could prevent its occurrence in a dose-dependent manner [35]. These