Pharmacological Reports 67 (2015) 78–84

Contents lists available at ScienceDirect

Pharmacological Reports

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

Original research article

Pioglitazone prevents morphine antinociceptive tolerance *via* ameliorating neuroinflammation in rat cerebral cortex

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ARTICLE INFO

Article history:
Received 3 March 2014
Received in revised form 5 August 2014
Accepted 6 August 2014
Available online 20 August 2014

Keywords:
Morphine tolerance
Pioglitazone
Neuroinflammation
Cerebral cortex

ABSTRACT

Background: Opioid induced neuroinflammation is shown to be implicated in opioid analgesic tolerance development. In the present study the effect of pioglitazone on morphine-induced tolerance and neuroinflammation in the cerebral cortex of the rat was investigated.
Materials and methods: Various groups of rats received morphine (10 mg/kg; *ip*) and vehicle (*po*), or morphine (10 mg/kg) and pioglitazone (20 or 40 mg/kg; *po*) once a day for 17 days. In order to determine the possible involvement of PPAR-γ in the pioglitazone effect, one group of rats received PPAR-γ antagonist, GW-9662 (2 mg/kg; *sc*), and pioglitazone (40 mg/kg) and morphine once daily for 17 days. Nociception was assessed using a tail flick apparatus and the percentage of the maximal possible effect was calculated as well. On 18th day, 2 h after the last morphine injection, the cerebral cortex of the animals were harvested and the tissue levels of tumour necrosis factor alpha, interleukin-1beta, interleukin-6, interleukin-10 and nuclear factor-kappa B activity were determined.
Results: Co-administration of pioglitazone (40 mg/kg) with morphine not only attenuated morphine-induced tolerance, but also prevented the up-regulation of pro-inflammatory cytokines (tumour necrosis factor alpha, interleukin-1beta, interleukin-6) and nuclear factor-kappa B activity in the rat cerebral cortex. Moreover, GW-9662 (2 mg/kg) administration 30 min before pioglitazone, antagonized the above mentioned pioglitazone-induced effects.
Conclusion: It is concluded that oral administration of pioglitazone attenuates morphine-induced tolerance. This effect of pioglitazone may be, at least in part, due to its anti-inflammatory property which suppressed the cortical pro-inflammatory cytokine and inhibited of nuclear factor-kappa B activity.

Introduction

Opiate drugs, chiefly morphine, are the main means to relieve patients from moderate to severe pain in many medical conditions; however, development of analgesic tolerance and physical dependency has restricted their usage and serviceability [1,2].

During the past two decades, many studies have been performed on the pro-inflammatory cytokines' tumour necrosis factor alpha (TNF-α), interleukin (IL)1 beta (IL-1β) and (IL-6) and inflammatory mediators' (nitric oxide and prostaglandins) roles in the development of tolerance to the analgesic effect of morphine [3–7]. It is worth nothing that morphine augments secretion of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 through glial-cell activation [5]. Glial-derived inflammatory products increase the neuronal excitability [8], sensitize the pain transmission neurons [8], up-regulate the NMDA receptors [9,10],

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http://dx.doi.org/10.1016/j.pharep.2014.08.003
1734-1140/

down-regulate the glutamate transporters [11], and oppose opioid-induced acute and chronic analgesia [4].

Accumulating evidence indicates that concurrent administration of the second agents that interrupt pro-inflammatory cytokines production [12], hampers glial-cell activation [7,13] and inhibits inflammatory pathway signals, such as nuclear factor kappa B (NF-κB) [14]. This may be a strategic approach to attenuate development of morphine analgesic tolerance. In this regard we recently reported that neuroprotective agents such as minocycline, riluzole or donepezil prevented morphine-induced tolerance and apoptosis in the rat central nervous system [15–17]. In addition, Shen et al. [18] demonstrated that the intrathecal administration of etanercept restored the antinociceptive effect of morphine by inhibiting the spinal pro-inflammatory cytokines (e.g., TNF-α, IL-1β and IL-6) expression in the morphine-tolerant rats.

Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. Three PPAR subtypes (α, β and γ) have been identified. The PPAR-γ isotype has received considerable attention for its helpful role in the management of type-two diabetes [19,20]. Moreover, PPAR-γ activation down-regulates the expression of pro-inflammatory cytokines and the inflammatory mediators [21], suppresses the NF-κB-dependent transcription [22,23], and inhibits glial-cell activity [24]. In this regard pharmacological manipulation of CNS PPAR-γ could attenuate various disorders such as inflammatory pain [25], neuropathic pain [26], Parkinson's diseases [27], and traumatic brain injury [28] due to its anti-inflammatory properties.

Pioglitazone is one of the PPAR-γ synthetic ligands and is a useful glucose-lowering medicine for patients with type-two diabetes. Treatment with pioglitazone in type-two diabetes was shown to improve insulin resistance and blood glucose levels without increasing the risk of hypoglycemia [29].

It has also been reported that pioglitazone has an incredible neuroprotective effect in various cellular and animal models of CNS disorders, particularly where inflammation is a major component of the pathogenicity of the disease [26–28]. Pioglitazone has received increasing attention for cases of drug abuse [30] and alcohol addiction [31]. The latter study showed that pioglitazone inhibits alcohol consumption and hampers alcohol-withdrawal-signs expression [31]. Recent data from our laboratory demonstrated that acute administration of pioglitazone attenuates naloxone-induced morphine-withdrawal syndrome [32]. Moreover, one portion of our recent findings demonstrates that oral daily co-administration of pioglitazone (20 and 40 mg/kg) with morphine not only attenuates morphine-withdrawal syndrome but also decreases the tolerance development, shifting the established-tolerance first day from the 17th day in the morphine + vehicle treated group to the 28th and 32th days, respectively [33].

Considering the central role of inflammation in morphine tolerance and the anti-inflammatory features of pioglitazone, in this study we investigate the role of neuroinflammation in the effect of pioglitazone on morphine antinociceptive tolerance.

Materials and methods

Animals

Male Wistar rats, weighing 200–250 (g), purchased from Razi Institute in Tehran, Iran. The animals were housed at the controlled ambient temperature (25 ± 2 °C) in the standard polypropylene cages (four rats per cage), and kept on a 12 h light/dark cycle with free access to food and water ad libitum (except for a brief time at the testing time). Afterward, the rats were randomly divided into several experimental groups consisting of 6–8 rats in each. It is worth noting that 2 days before the experiment, the animals were habituated to the testing environment including transferring to the experimental laboratory, weighing, and handling in order to adapt the animals to the manipulation and to minimize the nonspecific stress responses. All the experiments were carried out by the research affairs of Medical Sciences in Tabriz University, Guidelines for the Care of Laboratory Animals.

Drugs

Morphine sulfate (Daroupakhsh Company, Tehran, Iran) dissolved in normal saline and injected *ip*. Pioglitazone hydrochloride was also purchased from Zahravi Company (Tabriz, Iran); suspended in propylene glycol and distilled water (60:40) adding few drops of dimethylsulfoxide. It was administered orally (*po*) by a standard ball-tipped rat gavage needle 30 min before morphine injection. PPAR-γ antagonist, GW-9662 (Sigma Chemical Company, USA), dissolved in the pioglitazone vehicle and administrated subcutaneously (*sc*). The GW-9662 was administrated 30 min before the pioglitazone gavage. All utilized solutions were freshly prepared just before the administration.

Experimental groups

Male Wistar rats were divided into five experimental groups (n = 6–8) randomly. The experimental groups were consisting of one saline treated group and four morphine treated groups. The saline treated group was only treated with saline (*ip*) and the vehicle (*po*) whereas the morphine treated groups, received vehicle (*po*) only and the pioglitazone group received pioglitazone (20 or 40 mg/kg, *po*) 30 min before morphine (10 mg/kg, *ip*) injection in the morning. To evaluate the role of PPAR-γ in pioglitazone effects on morphine antinociception tolerance and the cortical pro-inflammatory cytokines change, GW-9662, a selective PPAR-γ antagonist was administered (2 mg/kg, *sc*) 30 min before pioglitazone (40 mg/kg) gavage in the GW-9662 treated group. Needless to say that the doses of pioglitazone, morphine and GW-9662 were chosen based on previous studies [32,33].

Induction of tolerance to morphine analgesic effect

In order to induce tolerance to morphine analgesic effect, rats received morphine (10 mg/kg, *ip*) once per day until the tolerance induction. Previous studies performed in our lab have been indicated that the selected morphine dose leads to profound analgesia without any side-effects in normal rats [33,34].

Assessment of nociception

The nociception was assessed by a radiant heat tail flick apparatus (model 37360; Ugo Basile, Italy). To this end, the animals were gently restrained by hands during the test and the light beam (power intensity = 5) was focused on 3–5 cm from the tail distal end. A built-in timer was automatically stopped when the animal tail flicks were out of the light beam; the results were displayed on readout to view. Tail flick latency was also considered as the time between the tail exposure and withdrawal to the radiant heat. Baseline tail flick latency was determined for each rat and designed as the baseline latency. The baseline latency was the average of three measurements and the light intensity was adjusted so that the baseline latencies were 2–3 s. A cut-off time (15 s) was imposed to prevent the tissue damage. The animals who did not respond after 15 s were excluded from subsequent experiments. The tail flick response latencies were