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Sumatriptan effects on morphine-induced antinociceptive tolerance and physical dependence: The role of nitric oxide

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ABSTRACT

Sumatriptan, a 5HT (5-hydroxytryptamine)$_{1B/1D}$ receptor agonist, showed neuroprotection in different studies. The aim of the present study was to investigate the effect of sumatriptan on morphine-induced antinociceptive tolerance and physical dependence. We also investigated the possible role of nitric oxide (NO) on sumatriptan effects.

Tolerance was induced by morphine injection (50, 50, 75 mg/kg) three times daily for five days. Antinociceptive latency after acute and chronic treatment with sumatriptan (0.001, 0.01, 0.1 and 1 mg/kg) was measured by hot plate test in morphine-dependent animals. To investigate the possible involvement of NO, different isoforms of nitric oxide synthase (NOS) inhibitors including L-NAME, aminoguanidine and 7-nitroindazole were co-administered with sumatriptan. Nitrite level in mice hippocampus was quantified by Griess method. To examine the role of sumatriptan on physical dependence, three parameters of withdrawal signs were recorded after injection of naloxone (4 mg/kg).

Acute treatment with sumatriptan (0.01, 0.1 and 1 mg/kg) attenuated the antinociceptive tolerance ($P < 0.001$). Chronic injection of sumatriptan (0.001, 0.01 and 0.1 mg/kg), as well, decreased the antinociceptive tolerance ($P < 0.001$). Moreover, co-administration of NOS inhibitors prevented the effects of sumatriptan. Sumatriptan significantly increased the level of nitrite only after chronic administration. Sumatriptan administration showed no alteration in naloxone-precipitated withdrawal signs.

Acute and chronic administration of sumatriptan attenuated morphine antinociceptive tolerance; at least in chronic phase via nitrergic pathway. Our data did not support beneficial effects of sumatriptan on morphine-induced physical dependence in mice.

1. Introduction

The long-term administration of morphine and related opioids remains limited in pain management due to its adverse effects such as tolerance and dependence phenomena (Mao et al., 1995; Trujillo and Akil, 1991). Tolerance occurs when the efficacy of drug diminishes by continued usage; therefore, dose increasing is required to maintain the same therapeutic effect. Dependence consists of psychological and physical components. Psychological dependence is an obsessive need for seeking the drug while physical part develops when drug cessation causes withdrawal signs (Bläsig et al., 1973; Way et al., 1969).

To obtain a solution to prevent these two issues, it's essential to study the probable mechanisms involved in morphine-induced tolerance and dependence. Among all the studies investigated the

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mechanisms contributed to opioid-induced tolerance and dependence, the majority of evidence verified the involvement of nitric oxide (NO) pathway (Herman et al., 1995; Mao, 1999; Marek et al., 1991; Nestler, 2004).

Sumatriptan, a selective $5HT_{1B/1D}$ receptor agonist, is a well-known drug for treatment of migraine and cluster headache. It's a well-tolerated drug with minor, rare and transient adverse effects (Dechant and Clissold, 1992; Ikeda et al., 2002). Although the mechanisms of action of sumatriptan need to be clarified, growing body of evidence presumed NO-dependent pathway as one of the probable mechanisms involved in its beneficial effects. Sumatriptan protective effects are mediated by inhibition of NO-induced calcium gene-related peptide (CGRP) synthesis, altering the balance of NO and superoxide in brain, and modulating the bioavailability of NO in central nervous system (CNS) (Dechant and Clissold, 1992; Ikeda et al., 2002; Stepień et al., 1999).

Nitric oxide, which is derived from amino acid L-arginine by the enzyme nitric oxide synthase (NOS), is an essential agent to produce cyclic guanosine monophosphate (cGMP). There are three identified isoforms of NOS, including inducible (iNOS), neuronal (nNOS) and endothelial (eNOS), expressed in different organs (Förstermann and Sessa, 2011). Nitric oxide plays an important role in numerous physiological and pathological conditions of CNS (Buisson et al., 1993; Montague et al., 1994; Szabó, 1996). A great body of evidence supported the involvement of NO/cGMP pathway on the morphine-induced tolerance and dependence. It has been shown that the suppression of NO by NOS inhibitors could suppress both the tolerance to morphine-induced antinociception and the withdrawal symptoms induced by naloxone (Babey et al., 1994; Elliott et al., 1994; Homayoun et al., 2003; Mao et al., 1995).

The purpose of our study was to test the hypothesis of sumatriptan effects on the morphine-induced antinociceptive tolerance and physical dependence in mice. We also examined the involvement of NO pathway in the possible effects of sumatriptan.

2. Materials and methods

2.1. Animals

The experiment was carried out on male NMRI mice (Naval Medical Research Institute), 6–7 weeks old, weighing 25–30 g. Animals were housed in cages under standard laboratory conditions (12-h light/dark cycle with an average temperature of 22 ± 2 °C and humidity of 55 ± 2%) with free access to food and tap water except for the time of experimental procedures. Each experimental group consists of 6–8 mice and each mouse was used once during the study. All the experiments were performed at the same time of every day. All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978) with the approval of Research and Medical Ethics Committees of Tehran University of Medical Science. The study consists of different experimental groups as follows: group 1: morphine alone, groups 2–5: acutely received four different doses of sumatriptan, groups 6–9: chronically received four different doses of sumatriptan, groups 10–13: morphine + four different acute doses of sumatriptan, groups 14–16: morphine + sumatriptan + three different isoforms of acute NOS inhibitors, groups 17–20: morphine + four different doses of chronic sumatriptan, groups 21–23: morphine + sumatriptan + three isoforms of chronic NOS inhibitors, groups 24–27: morphine + acute sumatriptan + naloxone, groups 28–31: morphine + chronic sumatriptan + naloxone.

2.2. Chemicals

The drugs that were used throughout this study were: sumatriptan, a $5HT_{1B/1D}$ receptor agonist; morphine sulfate, an opioid receptor agonist; L-NAME [L-NG-Nitro-L-arginine methyl ester hydrochloride], a non-specific inhibitor of NOS; aminoguanidine, a selective inhibitor of iNOS; 7-NI [7-nitroindazole], a selective inhibitor of nNOS; naloxone hydrochloride, an opioids receptor antagonist. Drugs were administered intraperitoneally (i.p.) in the volume of 10 ml/kg of mouse body weight. All drugs were dissolved in normal saline (NaCl 0.9%) freshly for use except for 7-NI which was dissolved in a 1% aqueous solution of dimethyl sulfoxide (DMSO), followed by sonication. Morphine sulfate was purchased from TEMAD, IRAN, naloxone was provided from Tolid Daru, Co Ltd, Tehran Iran, and all other drugs were purchased from Sigma, USA.

2.3. Induction of antinociceptive tolerance and dependence to morphine

The experiment was performed to assess two main problems of continued usage of morphine including tolerance and dependence. To induce antinociceptive tolerance, multiple injections of morphine were administered three times daily for 4 consecutive days with the doses of 50 mg/kg (8:00 a.m.), 50 mg/kg (11:00 a.m.) and 75 mg/kg (4:00 p.m.) (the third dose was higher in order to prevent withdrawal signs during night). On the last day of each experiment (5th day), animals received a single dose of morphine (50 mg/kg). The protocol for induction of antinociceptive tolerance to morphine was based on previous studies (Javadi et al., 2013). To assess antinociceptive threshold and degree of tolerance hot plate test was conducted.

The method of utilizing hot plate test for evaluating antinociceptive property was firstly described by Eddy and Leimbach (Eddy and Leimbach, 1953). The device consists of an electrically heated surface (50 ± 2 °C) covered with a plexiglass tube (18 cm high × 22 cm diameter) (Tahghigh-Gostaran-Teb, Iran). The antinociceptive threshold was defined as a time interval (s) between placing the animal on the heated surface and pain response (licking the hind paw or jumping with all four feet). Antinociceptive effect of morphine was assessed 60 min after the first injection of morphine on first, third and fifth days of the experiment. If the animals could not respond within 90 s, they were removed from the hot plate to prevent tissue damage. The increase in a time of animal response considered as antinociceptive induction and the decrease of antinociceptive threshold was determined as the degree of tolerance.

In aim of rendering physical dependence, morphine was injected three times daily with doses of 50 mg/kg (8:00 a.m.), 50 mg/kg (11:00 a.m.) and 75 mg/kg (4:00 p.m.) (the higher dose was administered to prevent withdrawal signs overnight) for 4 days and a single dose of 100 mg/kg on the last day of the study (fifth day).

To induce withdrawal signs, naloxone (4 mg/kg, i.p.) was administered one h after the last dose of morphine (100 mg/kg). After naloxone injection, each animal was placed in separated plexiglass cylinder (40 cm long, 25 cm wide and 45 cm high). Animals were observed for one h, and signs of withdrawal including jumping and rearing were recorded throughout this time. Percentage of weight loss as another sign of withdrawal was determined by measuring animal's weight before and 60 min after naloxone injection.

2.4. Assessing the effect of sumatriptan on morphine antinociceptive tolerance and naloxone-induced withdrawal signs

To investigate the antinociceptive property of sumatriptan, these doses of the drug were administrated alone (acute and chronic with four doses of 0.001, 0.01, 0.1 and 1 mg/kg) without morphine injection 45 min before hot plate test.

We evaluated the effect of sumatriptan on morphine-induced antinociceptive tolerance based on two protocols: In the first protocol, different doses of sumatriptan (0.001, 0.01, 0.1 and 1 mg/kg) were injected 45 min only before the last dose of morphine on the last day of the experiment in order to evaluate the acute treatment with sumatriptan on morphine antinociceptive tolerance.

In the second protocol, four different doses of sumatriptan (0.001,