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Determination of α_2-adrenoceptor and imidazoline receptor involvement in augmentation of morphine and oxycodone analgesia by agmatine and BMS182874

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ABSTRACT

Studies have demonstrated that clonidine (α_2-adrenoceptor and imidazoline receptor agonist) and BMS182874 (endothelin ET_A receptor antagonist) potentiate morphine and oxycodone analgesia. Agmatine, an endogenous clonidine-like substance, enhances morphine analgesia. However, its effect on oxycodone analgesia and its interaction with endothelin ET_A receptor antagonists are not known. The present study was performed to determine the effect of agmatine on morphine and oxycodone analgesia and the involvement of α_2-adrenoceptors, imidazoline receptors, opioid receptors, and endothelin receptors. Antinociception at various time intervals was determined by the tail-flick latency method in mice. Agmatine produced dose-dependent increase in tail-flick latency, while BMS182874 did not produce any change over the 360-min observation period. Agmatine significantly potentiated morphine as well as oxycodone analgesia which was not altered by BMS182874. BMS182874 pretreatment did not increase the analgesic effect produced by agmatine alone. Agmatine-induced potentiation of morphine and oxycodone analgesia was blocked by idazoxan (imidazoline receptor/α_2-adrenoceptor antagonist) and yohimbine (α_2-adrenoceptor antagonist). BMS182874-induced potentiation of morphine or oxycodone analgesia was not affected by yohimbine. However, idazoxan blocked BMS182874-induced potentiation of oxycodone but not morphine analgesia. This is the first report demonstrating that agmatine potentiates not only morphine but also oxycodone analgesia in mice. Potentiation of morphine and oxycodone analgesia by agmatine appears to involve α_2-adrenoceptors, imidazoline receptors, and opioid receptors. In addition, imidazoline receptors may be involved in BMS182874-induced potentiation of oxycodone but not morphine analgesia. It is concluded that agmatine may be used as an adjuvant in opiate analgesia.

1. Introduction

Opioids are one of the most potent classes of analgesics to treat severe acute as well as chronic pain. They are the favored drug of choice in clinical situations because of their high analgesic efficacy, however, a number of side effects develop after their prolonged use. The most serious adverse effects are sedation, tolerance, drug dependence, hyperalgesia, constipation, respiratory depression, and miosis (Muranyi and Radak, 2008). Mechanisms involved in these negative outcomes are very complex and involve opioid and non-opioid systems (Bailey et al., 2009). Non-opioid systems like gamma butyric acid (GABA), dopamine, nitric oxide, N-methyl-D-aspartate (NMDA), and glutamate play important roles in the development of adverse effects mentioned above (Hutchinson et al., 2007; Toda et al., 2009; Ueda and Ueda, 2009).

In order to potentiate the analgesic effects and to reduce the adverse effects of opioids, several alternative therapies have been proposed. Adjuvant analgesics are not classical analgesics, but may be useful either alone or in combination with other agents for management of pain. Anticonvulsant and antidepressant drugs can enhance the analgesic effect of opioids and can be useful in the management of neurogenic pain (Backonja et al., 1998; Gilron et al., 2005; Saarto and Wiffen, 2005; Semenchuk et al., 2001). Previous studies have demonstrated that α2-adrenoceptor agonists produce dose dependent analgesia in animals (Fairbanks et al., 2002; Pertovaara, 1993). Clonidine, an α2-adrenoceptor agonist, produces analgesia (Congedo et al., 2009) that can be blocked by yohimbine, a selective α2-adrenoceptor antagonist (Gulati et al., 2009; Sahraei et al., 2004). In addition, studies have shown, that clonidine potentiates the antinociceptive effect produced by morphine and oxycodone in rats (Gulati et al., 2009). Another endogenous clonidine-like substance, agmatine, enhances morphine-induced analgesia when given systemically (Roerig, 2003). Agmatine by itself is a weak analgesic, but studies have shown that it enhances antinociceptive action of morphine and inhibits the development of tolerance and dependence on opioids as well (Aricioglu-Kartal and Regunathan, 2002; Kitto and Fairbanks, 2006).

Endothelin-1 causes nociception and hyperalgesia by binding to endothelin ET_A receptors localized on nociceptors (Pomonis et al., 2001).

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Studies have indicated that endothelin ET_A receptor antagonists counteract endothelin-1 induced hyperalgesia and treat neuropathic pain in rats (Jarvis et al., 2000). Recent studies have shown that central endothelin mechanisms are involved in the analgesic actions of morphine, as well as the development of tolerance in mice and rats (Bhalla et al., 2002, 2003, 2005). We have shown significant potentiation of opioid analgesia and restoration of antinociceptive effect during opioid tolerance by endothelin ET_A receptor antagonists (Bhalla et al., 2002, 2003, 2005, 2010). It was also found that endothelin ET_A receptor antagonists did not bind directly to opioid receptors in the brain (Bhalla et al., 2002) and the mechanism of interaction was found to be mediated through the G-proteins (Bhalla et al., 2005). We also found that the interaction of endothelin ET_A receptor antagonist occurs at all subtypes of opioid receptors, i.e. mu, delta, and kappa receptors (Bhalla et al., 2010).

The interaction between clonidine and endothelin in cardiovascular effects of sympathetic nervous system has been studied in detail (Gulati, 1992; Gulati et al., 1997; Gulati and Srimal, 1993; Mutafova-Yambolieva et al., 1992). It is known that endothelin-1 modulates clonidine induced cardiovascular effects (Lim et al., 1998). Endothelin ET_A receptor antagonists enhance morphine and oxycodone analgesia in mice and rats (Bhalla et al., 2002, 2005, 2010; Gulati et al., 2009). Agmatine, a clonidine-like substance, has also been reported to potentiate morphine analgesia (Roerig, 2003). Since both agmatine and endothelin ET_A receptor antagonists potentiate opioid analgesia, it might be worth investigating a possible interaction between endothelin ET_A receptor antagonist and agmatine and how opioid receptor agonist induced analgesia may be affected. The interaction of endothelin ET_A receptors with agmatine has not been studied. Therefore, the aim of this study was to determine the interaction between agmatine and endothelin ET_A receptors in morphine and oxycodone analgesia in mice. In the present study, we determined: 1) the effect of agmatine on morphine and oxycodone induced analgesia; 2) the involvement of α2-adrenoceptors and/or imidazoline receptors in morphine and oxycodone analgesia; and 3) the interaction of endothelin ET_A receptors and α2-adrenoceptors/imidazoline receptors in the potentiation of morphine and oxycodone analgesia by agmatine. The present study is being conducted using both morphine and oxycodone because they are the most commonly used opioid analgesics, having different mechanisms of action (Gulati et al., 2009; Nielsen et al., 2007; Nozaki and Kamei, 2007; Ordonez Gallego et al., 2007). In addition, the effect of agmatine on oxycodone has not been studied previously.

2. Materials and methods

2.1. Animals

Male Swiss Webster mice weighing approximately 25 to 30 g were used. The animals were housed three per cage in the Animal Resources Facility at Midwestern University, Downers Grove, IL with controlled temperature (23 ± 1 °C), humidity (50 ± 10%) and 12-h light/dark cycle (6:00 AM to 6:00 PM). Food and water were made available *ad libitum*. Experiments were carried out after the animals had at least four days to acclimate to their environment. Animal care and use of experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at

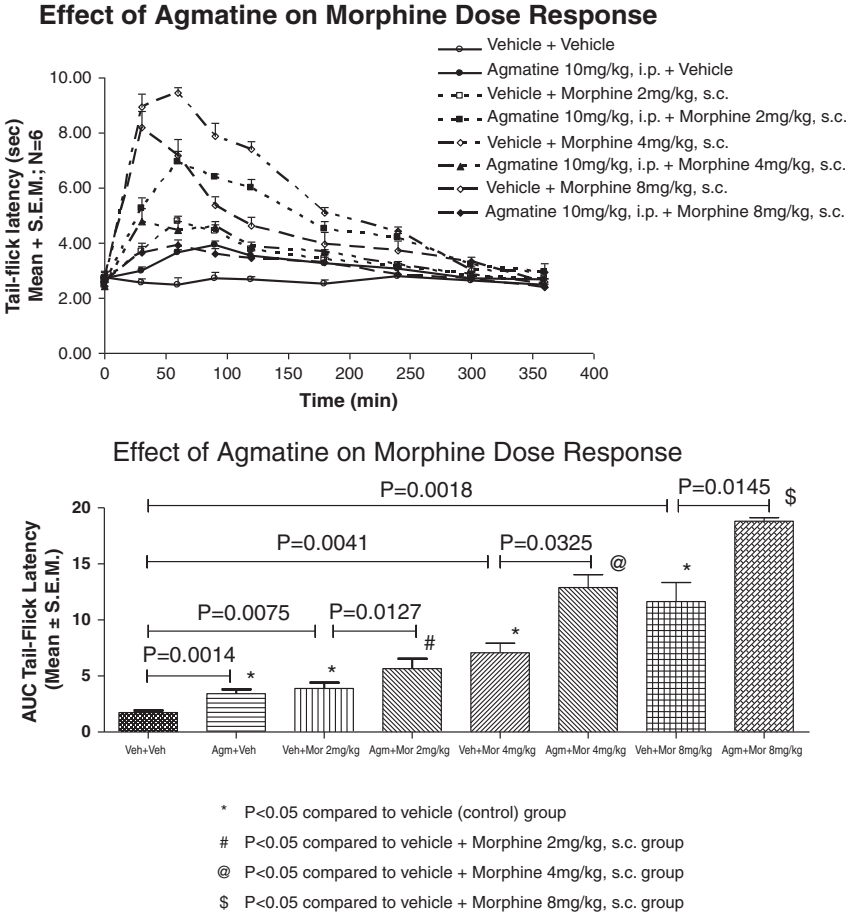

Fig. 1. Effect of agmatine on three different doses of morphine (2 mg/kg, 4 mg/kg, and 8 mg/kg, s.c.). Agmatine (10 mg/kg, i.p.) or vehicle (10 ml/kg, i.p.) was administered 30 min before morphine (2, 4, or 8 mg/kg, s.c.) treatment. Tail flick latency responses were measured at various time intervals and antinociceptive response was converted to $AUC_{0\rightarrow 360\ min}$. Values were expressed as mean ± S.E.M, N = 6 each group.