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Research article

Blockade of D1-like dopamine receptors within the ventral tegmental area and nucleus accumbens attenuates antinociceptive responses induced by chemical stimulation of the lateral hypothalamus

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HIGHLIGHTS

- D1 receptors in the VTA and NAc involve in the LH-induced antinociceptive responses.
- Blockade of D1-like receptors in the VTA decreased the LH-induced antinociception.
- Blockade of D1-like receptors in the NAc attenuated the LH-induced antinociception.

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ABSTRACT

It was established that stimulation of the lateral hypothalamus (LH) can induce antinociception. Previous studies showed a role for the ventral tegmental area (VTA) and nucleus accumbens (NAc) in antinociception induced by LH stimulation through the orexinergic system. In this study, we tried to assess the involvement of dopamine D1-like receptors within the VTA and NAc in the LH stimulation-induced antinociception. Male Wistar rats were unilaterally implanted with two separate cannulae into the LH and VTA or NAc. Animals received intra-VTA or intra-accumbal infusion of SCH-23390, as a D1-like dopamine receptor antagonist (0.125, 0.25, 1 and 4 μg/rat), 2 min before intra-LH administration of carbachol (125 nM/rat). The antinociceptive effects of SCH-23390 were measured by using a tail-flick analgesiometer and represented as maximal possible effect (%MPE). Results showed that intra-VTA and/or accumbal administration of SCH-23390 could prevent carbachol-induced antinociception. These findings revealed that D1-like dopamine receptors within the VTA and NAc play an important role in antinociceptive effect induced by chemical stimulation of the LH.

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1. Introduction

Previous evidence indicated that inactivation or electrical and chemical stimulation of the lateral hypothalamus (LH) can induce antinociceptive response [13,26]. This area has an important role in the modulation of nociception at the level of the spinal cord [1]. It was established that intra-LH administration of carbachol (a cholinergic agonist) enhances response latencies in both tail-flick and foot-withdrawal (acute models of pain) tests [13]. The LH, through the orexinergic projections, is associated with many areas involved in antinociception such as the ventral tegmental area (VTA) and nucleus accumbens (NAc) [5,25]. Numerous studies clarified that the orexinergic projections from the LH to the VTA and NAc are directly/indirectly involved in antinociception induced by chemical stimulation of the LH [4,23,25,28]. In addition, there is a functional interplay between the orexinergic system and mesolimbic dopaminergic pathway [4,21,25,30] and it was shown that orexinergic projections from the LH to the VTA stimulate the release of dopamine in mesolimbic areas such as the NAc [21]. Dopaminergic neurons in the VTA are involved in both endogenous and morphine-induced antinociception. This may occur through an increase in the release of dopamine in the areas receiving the VTA projections including the NAc, medial prefrontal cortex and medial striatum [6]. Intra-accumbal microinjection of dopamine antagonists blocked the antinociception induced either by pharmacological stimulation of the VTA, or by a noxious stimulus [2,9].

Dopamine is the predominant catecholamine neurotransmitter in the mammalian brain which has been shown to play a critical role in antinociceptive process [2,19]. Last studies demonstrated

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that subcutaneous administration of non-selective dopamine agonist, apomorphine, reduced response latencies of rats to acute noxious stimuli and lesion of dopaminergic neurons in the VTA resulted in hyperalgesic responses [24]. Besides, evidence claimed that dopaminergic neurons in the mesolimbic system are mostly involved in the antinociceptive effect of amphetamine and other dopaminergic agonists [29]. Dopamine agonists such as cocaine, amphetamine, apomorphine and quinpirole produce analgesia in formalin test [3,12,31] and these effects are attenuated by either pretreatment with dopamine receptor antagonists or dopamine-depleting 6-OHDA lesions in the VTA [19]. Dopamine receptors classify into two families based on their pharmacological properties: D1-like which includes D1 and closely-related D5 receptors, and D2-like consists of D2 and closely-related D3 and D4 receptors [17]. Studies revealed that dopamine D1- and D2-like receptors mediate the inhibitory role of dopamine in persistent pain [11]. Systemic administration of selective dopamine D1- and D2-like receptor agonists attenuates formalin-induced nociceptive behaviors in rats [20]. Moreover, dopamine receptors are highly expressed in the VTA and NAc [23,29]. We previously showed that chemical stimulation of the LH by the injection of carbachol induces antinociception and VTA and NAc orexin receptors are involved in this antinociception [4,26]. In addition, another study in our lab revealed that intra-accumbal administration of D1- and/or D2-like receptor antagonists decreased the antinociceptive effects of intra-VTA orexin-A injection and administration of D2-like receptor antagonist had a more remarkable effect than D1-like receptor antagonist [30]. In that study, we administrated exogenous orexin into the VTA which resulted in the stimulation of all of the orexin receptors in this area. In the current study, we tried to examine the involvement of D1-like dopamine receptors within the VTA and NAc in antinociception induced by chemical stimulation of the LH. In fact, in this study, we triggered orexin receptors in the VTA and NAc by release of the endogenous orexin which led to the stimulation of orexin receptors located in specific synapses in these regions.

2. Materials and methods

2.1. Animals and surgery

Experiments were performed on male albino Wistar rats (230–300 g from Pasteur Institute, Tehran, Iran) which were housed on a 12 h light/dark cycle at a temperature controlled room and allowed free access to food and water. Experimental procedures were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences and conducted in accordance with the animal care and use guidelines outlined by the Committee for Research and Ethical Issues of the International Association for the Study of Pain.

Rats were deeply anesthetized with ketamine/xylazine (100/10 mg/kg). Then, by using a stereotaxic apparatus, two guide cannulae were stereotaxically implanted 1 mm above the LH (AP = 2.5 mm caudal to bregma, Lat = ±1.4 mm and DV = 8.5 mm ventral from the skull surface), VTA (AP = 4.9 mm caudal to bregma, Lat = ±0.8 mm and DV = 8.3 mm) and/or NAc (AP = 1.7 mm anterior to bregma, Lat = ±1.6 mm and DV = 7.8 mm), unilaterally. These coordinates are in accordance with the rat brain atlas of Paxinos and Watson [22]. The guide cannulae then secured in place using screws anchored to the skull and dental acrylic cement. After the surgery, animals were allowed to recover for 5–7 days before experiments.

2.2. Preparation and administration of drugs

Two drugs were used during the study which both dissolved in physiological saline on the test days: carbachol (Sigma–Aldrich, USA), as a cholinergic agonist, and SCH-23390 (Tocris Bioscience, Bristol, UK), as a D1-like dopamine receptor antagonist.

On the test days, the stylet was replaced with a microinjector connected with a polyethylene tubing (PE-20) to a 1-μl Hamilton syringe, then drug solution or vehicle unilaterally was infused over 60 s and was left for an additional 60 s to minimize backflow along the cannulae tract. The total volume of drugs or saline administration into the LH and NAc was 0.5 μl and into the VTA was 0.3 μl.

2.3. Tail-flick test

Tail-flick response latencies (TFL) were measured during 1-h period at 5, 15, 30, 45 and 60 min after microinjections using a tail-flick apparatus (Harvard, USA) [10,12]. Radiant heat from a projector lamp was applied to the dorsal surface of the rat tails at a distance of 3–7 cm from its tip to evoke the tail-flick reflex. After exposing to the heat rats removed their tails and the time of removing the tails was recorded by an automatic sensor as TFL. The equipment was calibrated in order to obtain two consecutive baseline TFLs between 2 and 4 s (light intensity 45%). If at any time the animal failed to flick its tail within 10 s (cut-off point), the tail was removed from the coil to prevent damage to the skin [12,18]. TFLs (s) were expressed as percentage of maximal possible effect (%MPE) which was calculated from the following formula:

$$\%\mathrm{MPE} = \frac{\mathrm{Post-druglatency(sec)} - \mathrm{Baselinelatency(sec)}}{\mathrm{Cut-offvalue(sec)} - \mathrm{Baselinelatency(sec)}} \times 100$$

To evaluate the sensitivity of animals to nociceptive stimulus, we considered the individual TFL before drug treatment as a baseline TFL.

2.4. Experimental protocols

In all control and experimental groups, TFLs were recorded twice at 5, 15, 30, 45 and 60 min after drug/saline administrations. In our previous studies, we examined dose-response effects of intra-LH administration of carbachol (62.5, 125 and 250 nM/0.5 μl saline) on antinociception. It was showed that intra-LH injection of carbachol induced antinociception in a dose-dependent manner [4,25] and the effective dose (125 nM/rat) was used in the current study.

2.4.1. Effects of D1-like dopamine receptor antagonist administration into the VTA or NAc on antinociception induced by chemical stimulation of the LH

In order to examine the possible role of D1-like receptors within the VTA and/or NAc on LH stimulation induced antinociception, different doses of SCH-23390 (0.125, 0.25, 1 and 4 μg) were unilaterally microinjected into the VTA or NAc, just 2 min before administration of effective dose of carbachol into the LH (125 nM/0.5 μl saline). Carbachol-control group received saline instead of SCH-23390 into the VTA or NAc before intra-LH administration of carbachol and vehicle-control group received saline in all areas. In addition, the highest dose of SCH-23390 (4 μg) was injected into the VTA or NAc to determine if SCH-23390 alone has any antinociceptive effect.

2.5. Histological verification

After completion the experiments, rats were deeply anesthetized with ketamine/xylazine and perfused with 0.9% saline and 10% formaldehyde solutions. The brains were removed and kept in 10% fresh formalin solution for 3 days and sliced coronally in

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