Neuroscience Letters 548 (2013) 115–119

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

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

The dopamine agonist apomorphine enhances conditioned pain modulation in healthy humans

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HIGHLIGHTS

- Pain modulation in healthy subjects is affected by dopamine based intervention.
- Specifically, there was an enhancement in CPM after dopamine agonist administration.
- CPM was not changed following placebo administration.

ARTICLE INFO

Article history:
Received 24 January 2013
Received in revised form 16 May 2013
Accepted 20 May 2013

Keywords:
Dopamine
Apomorphine
Endogenous analgesia
Conditioned pain modulation (CPM)
Experimental pain

ABSTRACT

Although cumulative evidence suggests that dopamine plays a role in pain processing, the mechanisms by which dopaminergic transmission affects pain remain elusive. Conditioned pain modulation (CPM) is a psychophysical paradigm based on endogenous descending inhibitory pain modulation. The current study was aimed to test the effects of apomorphine, a non-specific dopamine agonist, on the magnitude of CPM in healthy subjects. One hundred and five healthy subjects participated in this randomized, double-blind study. CPM was assessed by subtracting the response to a phasic painful heat stimulus administered simultaneously with a conditioning cold pain stimulus from the response to the same heat stimulus administered alone. CPM was tested prior to and 25 min following a subcutaneous injection of either apomorphine (1.5 mg) or a placebo. CPM following apomorphine administration increased by 27.3% and by only 4% following placebo administration. RM-ANOVA revealed a significant interaction between 'session' and 'time' factors ($F = 5.316$, $p = 0.023$, $\eta = 0.054$), and significant effect for the 'session' ($F = 5.719$, $p = 0.019$, $\eta = 0.006$), but not for the 'time' ($F = 0.586$, $p = 0.446$, $\eta = 0.057$). These results suggest that dopaminergic pathways both participate in and enhance pain modulation, represented by CPM. The role of dopamine in pain processing should be further studied.

1. Introduction

Endogenous pain modulation can be demonstrated in humans by using 'dynamic' experimental pain models [24]. One such model, now termed conditioned pain modulation (CPM) [25], measures the effect of one noxious stimulus on the perception of another stimulus administered simultaneously to a remote area of the body. CPM is considered as a behavioral human equivalent to the electro-physiological phenomenon of diffuse noxious inhibitory control (DNIC) observed in animals [25]. Notably, DNIC is based on descending inhibitory pathways that reach to the dorsal horn and attenuate afferent nociceptive transmission [12,13].

The role of monoamines, particularly serotonin and norepinephrine, in descending inhibitory pain modulation is well established [2]. In contrast, relatively little is known about the involvement of dopamine in central pain processing. Clinical studies have demonstrated increased sensitivity to pain in conditions associated with dopamine deficiency, such as Parkinson's disease [14], burning mouth syndrome [10], fibromyalgia [22], and restless leg syndrome [4]. Moreover, a small number of clinical trials have shown that dopamine administration can reduce pain in conditions *not* associated with dopamine depletion, such as metastatic bone pain [5,16], painful diabetic neuropathy [6], and post herpetic neuralgia [11]. Using the PET technique with specific regard to pain modulation, Hagelberg et al. demonstrated a direct correlation between D2 binding potential in the putamen and the magnitude of CPM in healthy subjects [8]. From a neurobiological standpoint, all three major mesolimbic, mesocortical, and nigrostriatal dopaminergic pathways have been shown to be involved in

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http://dx.doi.org/10.1016/j.neulet.2013.05.041

nociceptive modulation [1,23]. The fourth dopaminergic system, the diencephalospinal dopaminergic pathway, is of special interest because of its anatomical termination [15] and its functional suppression [7] of nocicptive neurons in the dorsal horn of animals.

Based on this evidence, we hypothesized that the administration of a dopamine agonist is likely to enhance CPM. To the best of our knowledge, this hypothesis has never been tested. Therefore, the aim of this study was to examine the effect of the dopamine agonist apomorphine on the CPM magnitude in healthy subjects.

2. Methods

2.1. Subjects

Subjects were eligible for enrolment in the study if they were healthy men or women, free from chronic pain of any type, did not use any medications other than oral contraceptives, did not consume any recreational substances, and were able to understand the purpose and instructions of the study. This study, which was part of a larger pharmacogenetic study on the analgesic effects of apomorphine, was approved by both national and local ethics committees, and a written informed consent was obtained from all participants.

2.2. Instruments

Heat pain stimulation was administered using a thermal testing analyzer (TSA) thermode of 30 mm × 30 mm (Medoc TSA-II device, Ramat Ishai, Israel). For the administration of cold pain stimuli, a temperature-controlled water bath with a maximum temperature variance of ±0.5 °C, which was continuously stirred by a pump (Heto CBN 8-30 Lab equipment, Allerod, Denmark) was used.

2.3. Assessment of CPM

In order to induce CPM, the painful heat stimuli were considered as the 'test stimuli,' whereas the painful cold stimuli were used as the 'conditioning stimuli.' The TSA thermode was attached to the skin above the thenar eminence of the dominant hand. Five heat pain stimuli of 47 °C (starting from 37 °C at an increasing and decreasing rate of 10 °C/s) were delivered, with each lasting three seconds and interspersed by an interval of 12 s. The first heat stimulus was considered as the baseline test, and the subsequent four heat stimuli were marked as test 1, test 2, test 3, and test 4, respectively. After the first heat stimulus provided the baseline heat pain rating, the subjects were asked to immerse their non-dominant hand into the cold water bath (12 °C) – a stimulus which is consistently perceived as painful – for 30 s. At 15 s and again at 30 s of immersion, while the hand was still in the cold water bath, the second and third heat pain stimuli were delivered and the pain intensities were recorded (test 1 and test 2, respectively). Subjects were then asked to remove their hand from the cold water bath. Two additional heat pain stimuli were administered at 15 s and at 30 s subsequent to removal of the hand from the cold water bath, and the pain intensities were again recorded (test 3 and test 4, respectively). A numerical pain scale (NPS), ranging from 0 = "no pain" to 100 = "the worst pain imaginable," was used by subjects to rate the pain intensities experienced during each heat stimulus. The NPS was conducted verbally, since both hands were occupied by the two different devices (TSA and CPT).

2.4. Study medications

Apomorphine (1.5 mg/0.3 ml) and identical-looking placebo (normal saline) syringes were prepared by a nurse who had no contact with the subjects. Injections were given subcutaneously. In order to reduce adverse effects, the subjects were instructed to take domperidone (10 mg, oral) three times a day for three days preceding both study sessions. Domperidone is a peripheral dopamine antagonist, which does not cross the brain blood barrier and therefore is not expected to have any effect on the central nervous system.

2.5. Adverse events

Subjects were asked to self-report and to rate the intensity of adverse effects during the two hours subsequent to drug administration on a 0–3 scale (i.e., 0 = none; 1 = mild; 2 = moderate; 3 = sever). The following adverse effects were evaluated: increased sweating, dyspnea, dry mouth, sleepiness, headache, nausea, vomiting, and confusion.

2.6. Study design

The study was designed as a randomized double-blind, placebo-controlled, cross-over trial. A detailed explanation of the study design was given to all subjects, and their written informed consent was obtained. Subjects were then randomized to receive either apomorphine in the first session and a placebo in the second session, conducted one week apart from each other, or vice versa. The randomization was computer based in 27 blocks, each containing four subjects. Each session consisted of a training CPM test, followed by a baseline CPM test 15 min later. The subcutaneous injection (apomorphine or placebo) was administered 10 min after completion of the baseline test. The design of the broader study (see above) included several other pain tests. Their time course and the need for a rest period between one test to another allowed the conductance of the CPM test 25 min following drug administration. This timeframe is consistent with apomorphine pharmacokinetics, since its maximal concentration in the CSF is noticeable 10–20 min following its administration.

2.7. Statistical analyses

A power analysis was conducted by G*power 3.1.6 software. A total sample size of 32 participants was determined according to the following criteria: Effect size $f = 0.2$, alpha = .05, Power = 0.8, number of groups = 2, number of measurements = 2, Correlation among measures = 0.7. As mentioned earlier, the current manuscript describes only one aspect of a much larger study. This is the reason for the larger sample size than needed. All other analyses were conducted using the SPSS for Windows Version 17 statistical package (SPSS Inc., Chicago, IL). In many previous experiments, in which a similar method of producing CPM was used, we found that the maximal magnitude of CPM was expressed after 30 s of hand immersion in the CPT (test 2). Nonetheless, in the present CPM was measured four times. Since maximal pain reduction was found in test 2, all CPM related data and analyses were based on reduction of pain scores obtained in test 2 from the baseline pain scores. Paired *t*-tests were conducted to assess the differences in baseline CPM between the sessions. Spearman correlation was used to test the relationship between baseline CPM magnitudes, measured prior to the apomorphine and placebo injections. RM-ANOVA consisting of two within subjects factors ('session' and 'time') was conducted in order to assess the effects of apomorphine/placebo on CPM. Gender differences in baseline CPM were assessed by independent-samples *t*-testing. Multivariate Analysis of Variance (MANOVA) was used to evaluate gender differences in the response to apomorphine/placebo administration. Fisher's exact test was used to compare the number of incidence of adverse events in either treatment arm. Spearman correlations were applied to examine possible associations between the magnitudes of apomorphine induced adverse events and the magnitude of CPM before