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Biphasic effect of apomorphine on rat nociception and effect of dopamine D_2 receptor antagonists

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Abstract

Studies on the effect of dopaminergic agonists in behavioral measures of nociception have gathered numerous but rather conflicting data. We studied the effects of the D_1/D_2 receptor agonist apomorphine, as well as the modulatory effects of (*S*)-(−)-sulpiride (selective D_2 receptor antagonist) and domperidone (peripheral D_2 receptor antagonist), on thermal, mechanical and chemical nociception on rats. Apomorphine induced a biphasic dose–response relationship, low doses producing hyperalgesia and high doses inducing antinociception. Tonic (chemical) pain was more sensitive to apomorphine than phasic (thermal and mechanical thresholds) pain. (*S*)-(−)-sulpiride, but not domperidone, fully antagonized the antinociceptive effect of apomorphine in all three measures of nociception, pointing to a participation of D_2 dopaminergic receptors for the antinociceptive action of apomorphine. Although spinal sites for dopaminergic ligands mechanistically may account for the effects observed, involvement of dopaminergic receptors of the forebrain could probably explain better the antinociceptive effects of apomorphine, especially in chemical tonic pain.

Keywords: Pain; Dopamine; Apomorphine; (*S*)-(−)-sulpiride; Domperidone; Tail-flick; Paw pressure; Formalin

1. Introduction

Experimental studies on the participation of the central dopamine systems in antinociception have gathered numerous but rather conflicting data. For instance, pharmacological interventions that increased dopaminergic neurotransmission (i.e. administration of L-3,4-dihydroxyphenylalanine (L-DOPA), dopamine receptor agonists with D_1/D_2 selectivity or dopamine reuptake blockers) have demonstrated to produce antinociception (Paalzow and Paalzow, 1975; Michael-Titus et al., 1990; Morgan and Franklin, 1991; Frussa-Filho et al., 1996; Bittencourt and Takahashi, 1997; Gilbert and Franklin, 2001), while other similar studies have reported no effect or even hyperalgesia (Tulunay et al., 1976; Gatch et al., 1998; Malhotra et al., 2000). Contradictory results have also been obtained when studying the modulatory effects of dopamine systems on opioid-induced analgesia, since potentiation (Dunai-Kovacs and Szekely, 1977; Nazarian et al., 1999) as well as inhibition (Zetler, 1983; Kamei and Saitoh, 1996) of the antinociceptive actions of opioids has been found after administration of dopaminergic agonists. Procedures that inhibit dopaminergic transmission in the central nervous system have also led to rather inconclusive results. In fact, administration of both dopamine D_1 and dopamine D_2 receptor antagonists may produce either antinociception (Zarrindast et al., 1999) or hyperalgesia (Paalzow, 1992). In addition, knock-out mice lacking dopamine D_1 (Becker et al., 2001) or dopamine D_2 (King et al., 2001) receptors displayed enhanced opioid analgesia, while rats with chemical lesions of dopaminergic terminals in limbic areas exhibit increased nociceptive reflexes, which may represent a hyperalgesic status (Saade et al., 1997). Taken together, the previous observations indicate that there is a considerable controversy with respect to the conditions under which antinociception induced by activation of central dopamine

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receptors can be demonstrated. These include specificity and dosage of receptor agonists, type of behavioral pain testing and animal species, among other factors.

With regard to the dosage of receptor agonists, it has been suggested that low systemic doses (25–100 μg/kg) of the dopamine D_1/D_2 receptor agonist apomorphine produce hyperalgesia in the rat, whereas higher doses induce antinociception (Paalzow and Paalzow, 1983); a similar concentration-dependent opposing effect in nociception has been shown by utilizing L-DOPA as enhancer of dopamine neurotransmission (Paalzow, 1992). In contrast, other studies have shown that apomorphine significantly increased tail-flick latency only at low doses, while at high doses decreased it (Wesler and Frey, 1985). With respect to the type of behavioral pain testing, it has been reported that systemic apomorphine can induce antinociception in the hot plate test and in phenylbenzoquinone writhing, but not during testing of tail immersion in hot water, tail-flick, tail-clip, or electrical stimulation of the tail in mice (Gonzales-Rios et al., 1986), in the tail-flick and formalin tests but not in hot plate testing in rats (Dennis and Melzack, 1983), as well as in writhing, hot plate, tail-flick and inflamed tail-pinch procedures in rats and mice (Dunai-Kovacs and Szekely, 1977). Finally, with regard to the animal species, antinociceptive and hyperalgesic effects of either agonists or antagonists of dopamine receptors have been found in mice (Tulunay et al., 1976; Dunai-Kovacs and Szekely, 1977; Zetler, 1983; Michael-Titus et al., 1990; Frussa-Filho et al., 1996; Kamei and Saitoh, 1996; Bittencourt and Takahashi, 1997; Zarrindast et al., 1999; Malhotra et al., 2000) and rats (Paalzow and Paalzow, 1975; Dunai-Kovacs and Szekely, 1977; Paalzow and Paalzow, 1983; Morgan and Franklin, 1991; Paalzow, 1992; Gilbert and Franklin, 2001); the only study performed in monkeys revealed that dopamine reuptake inhibitors did not produce antinociception or increase antinociception induced by nalbuphine or morphine (Gatch et al., 1998). As a whole, these later observations show some agreement in that dopamine systems can modulate chemical tonic pain, whereas data concerning to dopaminergic modulation of phasic nociception of thermal and mechanical origin appear to be more inconsistent. Although spinal sites may account for the antinociceptive effects of dopaminergic ligands, it has recently been claimed that dopaminergic neurons of the mesolimbic system (originating from cell bodies within the ventral tegmental area and projecting to the ventral striatum/nucleus accumbens) are mostly involved in the antinociceptive effect of amphetamine and other dopaminergic agonists (see review of Wood, 2006).

In view of the various inconsistencies regarding the nature of pain that may be sensitive to acute administration of dopaminergic agonists and the dosage needed, the present study was aimed to clarify these aspects using a variety of doses of apomorphine as agonist for dopamine D_1/D_2 receptors, on rats submitted to three nociceptive tests: (a) the tail immersion test (phasic thermal nociception); (b) the hindpaw pressure test (phasic mechanical nociception); and (c) the formalin test (tonic chemical nociception). In addition, the antagonistic effects of (*S*)-(−)-sulpiride (a selective dopamine D_2 receptor antagonist) and domperidone (a peripheral dopamine D_2 receptor antagonist) on apomorphine-induced effects were also investigated.

2. Materials and methods

Sprague–Dawley juvenile male rats weighing 220–280 g were used throughout this study. Animals were housed 5 per cage under standard laboratory conditions and were given food and water ad libitum. Experiments were carried out on the afternoon (13:00 to 19:00 h) with a double blind design. The ethical guidelines for investigations of experimental pain in conscious animals recommended by the International Association for the Study of Pain (IASP) were followed (Zimmermann, 1983). In particular, the duration of the experiments was as short as possible, the number of animals involved was kept to a minimum and the animals were killed immediately after termination of each recording session.

2.1. Nociceptive tests

2.1.1. Thermal nociception

The tail immersion test was used, as described by Villanueva et al. (1985). Briefly, the rat tail was immersed into a hot-water bath at 46 °C by immobilizing the animal with both hands. Each rat had been previously adapted to this procedure, so that no fighting or tail movements occurred during 15 s (cut-off limit of hot-water immersion). When the animal reached the threshold of pain sensation, a tail-flick occurred. To repeat the stimulation in order to measure the pain threshold after drug administration, a 15-min period was allowed to elapse between two consecutive tail immersions, since drug-induced changes in tail temperature have been reported to modify tail-flick scores (Juszkiewicz-Donsbach and Levy, 1962). Tail temperature after administration of drugs was measured in a separated group of rats to assess this parameter as a potential factor in the results obtained. This was achieved by means of a thermocouple brought in contact with the dorsal surface of the tail and connected to an electrometer.

2.1.2. Mechanical nociception

The paw pressure test initially described by Randall and Sellito (1957) was used. The test consisted on the progressive application of an increasing point-pressure over the hindpaw, which evokes a pain reaction characterized by a fighting reaction (struggle) and a vocalization as manifestations of the pain sensation. These are integrated reactions with participation of supraspinal structures. To avoid injury, a cut-off value of 750 g was used.

2.1.3. Chemical nociception

The formalin test originally described by Dubuisson and Dennis (1977) was used. The procedure involved subcutaneous injection of dilute formalin (2.5%) into the plantar forepaw, after which the animal response was rated in four pain scores according to the following objective behavioral criteria: (0), the injected paw is not favored with respect to the non-injected paw; (1), the injected paw is favored but still rests in contact with the floor; (2), the injected paw is favored by lifting from the floor; (3), there is a licking, flinching or shaking of the injected paw.