Opioid antagonists and the sexual satiation phenomenon

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Abstract This study evaluates the effects of the IP injection of naloxone (0.3, 3 and 30 mg/kg) and naltrexone (0.2, 2 and 20 mg/kg) on the sexual satiation phenomenon. It was found that both antagonists exert a dose-based biphasic effect on the proportion of sexually exhausted rats displaying copulation. The intermediate doses of both opioid antagonists were more effective than the low and high doses in increasing the percentage of animals engaged in copulation. The analysis of the specific sexual behaviour parameters revealed that naloxone produces a slight inhibitory effect at the lowest dose, evidenced as an increase in the intromission number. The higher doses of this compound facilitated copulation reflected as a shortening of the ejaculation latency and the interintromission interval (III) and an increase in the copulatory rate. Naltrexone treatment had only facilitatory effects at the lower doses by reducing the III. The higher doses of naloxone (3 and 30 mg/kg) and the intermediate dose of naltrexone (2 mg/kg) decreased the spontaneous ambulatory behaviour of sexually satiated rats without impairing sexual behaviour execution. Data suggest a participation of the endogenous opioid systems in the sexual inhibition resulting from sexual exhaustion.

Key words Male sexual behaviour • Sexual exhaustion • Naloxone • Naltrexone • Opioid antagonists • Rats

Introduction

Long term opioid use has been usually associated with a progressive deterioration of human sexual function, which includes delayed ejaculation, decreased ejaculation volume, anorgasmia and impotence. Withdrawal from opioids is characterized by a gradual restoration of sexual function (Jones and Jones 1977; Greenberg 1984).

The role of endogenous opioids in the modulation of the hormonal and neurotransmitter systems that may be involved in the regulation of sexual behaviour has been a matter of laboratory research in the last years. The specific behavioural effects of opioid agonists and antagonists on rodent male sexual behaviour have, however, rendered controversial results (for review see Pfaus and Gorzalka 1987). There is general agreement that systemically administered opiate agonists impair male copulatory behaviour (Mumford and Kumar 1979; McIntosh et al. 1980; Agmo and Paredes 1988). Thus, low doses of morphine (5 mg/kg), which do not retard motor activity, decrease the proportion of intact males copulating, increase mount and intromission latencies, but decrease the frequency of mounts and intromissions (Hetta 1977; Kumar et al. 1977; Meyerson and Terenius 1977; Mumford and Kumar 1979; McIntosh et al. 1980; Pfaus and Gorzalka 1987). As doses are increased, a successive inhibition of ejaculation, intromissions and mounts occurs (Pfaus and Gorzalka 1987). There is, however, less agreement concerning the effects of opiate antagonists on copulation. Naloxone and naltrexone appear to facilitate male sexual behaviour by increasing the percentage of intact males copulating (Hetta 1977; Gessa et al. 1979; McIntosh et al. 1980) or ejaculating (Myers and Baum 1979), by decreasing the mount, intromission (McIntosh et al. 1980) and ejaculation latencies (Hetta 1977; Pellegrini-Quarantotti et al. 1978; Myers and Baum 1979) and/or the number of intromissions preceding ejaculation (Myers and Baum 1979). Conversely, naloxone and naltrexone also appear to have inhibitory effects, since they increase the duration of the postejaculatory interval (Szechman et al. 1979; Sachs et al. 1980; McConnell et al. 1981). An increase in the intromission frequency and in the ejaculation latency have also been reported after naloxone injection (Fernández-Guasti and Saldívar 1991). However, several authors have failed to find an effect of naloxone and naltrexone on measures of copulatory behaviour in males with a high degree of sexual experience (Gessa et al. 1979; Sachs et al. 1980; Agmo and Paredes 1988).
It has been suggested that copulation may indeed be a biological stimulus for the release of endogenous brain opioids, since during sexual behaviour, the physiological mechanisms of analgesia and reward are concurrently activated (Szechtman et al. 1981). Both phenomena, ejaculation-induced reward (Agmo and Berenfeld 1990) and hypoalgesia (Forsberg et al. 1987), can be blocked by naloxone. Thus, there is evidence suggesting that opioid peptides are released during sexual activity.

In a previous paper (Rodríguez-Manzo and Fernández-Guasti 1994), we analysed the development of sexual satiation. This state, resulting from uninterrupted copulation, consists of a prolonged copulatory behaviour inhibition that takes approximately 2 h to develop, after which sexual performance may be inhibited for up to 72 h. Four to 6 days after the satiation session a restoration of copulatory behaviour occurs, but complete recovery is only observed after a 15-day period of sexual rest (Beach and Jordan 1956; Larsson 1956). We reported that sexually exhausted rats either did not copulate or showed only one ejaculatory series when tested 24 h after a 4-h session of ad libitum copulation (Rodríguez-Manzo and Fernández-Guasti 1994). Interestingly, we also demonstrated that the sexual inhibition resulting from constant copulation can be surmounted by the administration of serotonergic or noradrenergic drugs (Rodríguez-Manzo and Fernández-Guasti 1994). Thus, administration of the \( \alpha_2 \) adrenergic antagonist, yohimbine, and the 5-HT\(_{1A} \) agonist, 8-OH-DPAT, increase the proportion of sexually sated rats that show copulatory behaviour and reinitiate copulation after ejaculation in the postexhaustion test. Pfaus and Gorzalka (1986) pioneered the pharmacological manipulation of sexual exhaustion. These authors suggested that endogenous opiate systems might be involved in this phenomenon, since naloxone, administered 30 min before exposing rats to a sexual exhaustion paradigm, delayed the onset of this state.

The purpose of the present study is to examine whether the blockade of the opioid transmission, by naloxone or naltrexone injection, can reverse the already established sexual satiation state.

### Materials and methods

#### Animals

Sexually experienced adult male Wistar rats (300–350 g body weight) were used for this study. They were housed, six per cage, in a room under controlled, inverted light:dark cycle conditions (12 h light/12 h dark; lights on at 2200 hours). Animals had free access to commercial rat chow and tap water. Male rats were rendered sexually experienced by three previous sexual behaviour tests. The sexually active subjects (those showing ejaculation latencies shorter than 15 min) were selected for the study.

#### Sexual behaviour tests

Sexual behaviour observations were conducted 2 h after the onset of darkness. Male rats were introduced in a cylindrical observation cage in the presence of a receptive stimulus female. Females’ receptivity was induced by the sequential SC administration of oestradiol valerianate (4 µg/rat) followed 44 h later by progesterone (2 mg/rat). The experimental subjects were submitted to a previously reported sexual exhaustion paradigm (Rodríguez-Manzo and Fernández-Guasti 1994). Briefly, animals were allowed a 4-h session of ad libitum copulation. Twenty-four hours later, the satiated rats were tested for sexual behaviour, preceded by the pharmacological treatments. The criterion to establish sexual exhaustion at the 24-h test was the absence of copulation along 30 min or the execution of one ejaculatory series without reinitiating sexual behaviour. The sexual behaviour parameters registered were: intromission latency (IL), defined as the time that elapses from the introduction of the female to the initial intromission; mount number (M) and intromission number (I); ejaculation latency (EL), the time from the first intromission to ejaculation; interintromission interval (III), the mean interval that separates one intromission from the other calculated as the EL divided by the I and copulatory rate (CR), indicating how many I per minute occur, this parameter is derived from the reciprocals of the III. All these data were expressed as means±SE. The percentage of animals mounting, intromitting, ejaculating and reinitiating sexual behaviour after ejaculation was also determined.

#### Experimental design

All animals included were previously submitted to the sexual exhaustion paradigm (Rodríguez-Manzo and Fernández-Guasti 1994; vide supra). Twenty-four hours later, rats received the pharmacological treatments and sexual behaviour was registered. The experimental tests were ended after either a copulatory series or a 30-min period of sexual inactivity. Rats were considered nonresponders if during this test they did not intromit within a 30-min period or an interval longer than 30 min elapsed from the first intromission without achieving ejaculation.

In the first part of this experiment the opioid antagonist naloxone hydrochloride (Research Biochemicals, Natick, USA), dissolved in a volume of 2 ml/kg physiological saline, was injected IP 30 min before the behavioural test. Initially, two independent groups receiving 3 mg/kg (n=11) or 30 mg/kg (n=28) naloxone were tested. The high dose was chosen on the basis of the data reported by Pfaus and Gorzalka (1996); the dose of 3 mg/kg corresponds to the range used in several rodent male sexual behaviour studies (Hetta 1977; Gessa et al. 1979; Myers and Baum 1979; Szechtman et al. 1979; Agmo and Paredes 1988). In an attempt to establish a dose-response relationship, a low dose of 0.3 mg/kg (n=15), one order of magnitude below, was run at a later time.

In the second part of the experiment, two independent groups were initially tested after the IP administration of 0.2 mg/kg (n=8) or 20 mg/kg (n=20) of the opioid antagonist, naltrexone hydrochloride (purchased from Research Biochemicals, Natick, USA). This drug was dissolved in a volume of 2 ml/kg physiological saline and injected 30 min before the behavioural observations. Again, another dose (2 mg/kg, n=8) was included at a later time in order to complete a dose-response curve. The high dose of naltrexone (20 mg/kg) has been tested on sexual behaviour by several authors (Murphy et al. 1979; Myers and Baum 1979). The other two were selected by decreasing one and two orders of magnitude.

#### Motor activity

A set of rats (n=6–15) from each pharmacologically treated group was selected at random and tested immediately after the sexual behaviour experiment, for spontaneous ambulatory behaviour. Each group included both copulating and non-copulating rats. This was recorded in a box measuring 43x36x19 cm, placed over a sensitive plaque (48x40 cm) of an activity meter (Stoelting Co., Chicago, Ill.) connected to a counter (Stoelting Co., Chicago, Ill.). Each rat was placed in the cage and the number of counts recorded over a 10-min period. Between each test, the cage was carefully cleaned. Data are expressed as counts per minute.