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Copulation is reactivated by bromocriptine in male rats after reaching sexual satiety with a same sexual mate

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HIGHLIGHTS

- Bromocriptine reactivates copulation after sexual satiety with the same female.
- Stimulation of D2 receptors may reverse the sexual satiety state.
- Bromocriptine can mimic the Coolidge effect with a same sexual mate.

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ABSTRACT

Male sexual satiety has been associated with a decrease in dopamine levels. Spontaneous recovery of copulatory behavior begins at least 72 h after sexual satiety is reached or in the condition in which a sexually-satiated male is exposed to a new receptive female distinct from the one with which sexual satiety was reached. The aim of the present study was to explore whether dopaminergic activation by bromocriptine (BrCr) can reactivate copulatory behavior with the same sexual mate immediately after sexual satiety is reached. Male rats were divided into three groups exposed to one of the following three conditions: 1) administration of 2 mg/kg s.c. of BrCr and exposure to the same female with whom sexual satiety was previously reached; 2) administration of 0.3 mL s.c. of the vehicle solution with exposure to the same female with whom sexual satiety was reached; and, 3) exposure to a new receptive female after sexual satiety was reached. Results showed that BrCr significantly reactivated copulatory capability in sexually-satiated males with the same receptive female. In contrast, no males in the vehicle group ejaculated with the same female after reaching sexual exhaustion. Copulation was reactivated by BrCr in a way similar to that observed in untreated males exposed to a new receptive female (*i.e.*, the Coolidge effect). The reversal of sexual satiety in the males treated with BrCr could be explained by its action on D2 family receptors, which promotes a reactivation of sexual motivation at a level sufficient to allow renewed copulation with the same female mate.

1. Introduction

Male sexual satiety is a state of prolonged sexual inhibition that, in the case of the rat, occurs as a result of constant copulation with the same receptive female, during which several ejaculatory series are achieved (average = 7), but after which the males are unable to resume their sexual activity. Spontaneous recovery of copulatory capacity begins 72 h after sexual satiety is reached [34, 37, 39, 40, 41, 43].

Different criteria have been described to establish the state of sexual satiety in the male rat [3,29]. Rodríguez-Manzo and Fernández-Guasti [41], for example, elaborated a procedure to study the development of sexual satiety in male rats that consisted in allowing sexually-experienced males to copulate *ad libitum* during a period of approximately 4 h with the same receptive female until an interval of 90 min passed with no ejaculation. In their model, once the male is incapable of initiating another copulatory series after this interval it is considered to have reached sexual satiation.

At 24 h after reaching sexual satiety, 2/3 of males show a complete absence of sexual behavior, while the other third is able to perform a copulatory series and ejaculate, but only once, without an ensuing recovery period within an interval of 30 min [39,41]. The hypothesis that the state of sexual satiety is caused by such factors as motor inability and fatigue has been discarded [37,41], so it is now thought that this condition is a consequence of reduced sexual motivation due to repeated ejaculations that is manifested as an inhibitory state which affects mechanisms of motivation and sexual performance [37,39,40,43]. This explanation posits the possibility that the state of sexual satiety can be reversed and reactivation of sexual behavior achieved through behavioral or

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pharmacological manipulations that are capable of reestablishing sexual motivation.

Studies have described that treatments may reverse sexual satiety when they produce a significant increase in the proportion of males capable of ejaculating more than once at only 24 or 48 h after copulating *ad libitum* to satiety [37]. Indeed, various studies provide support for the idea that the sexual inhibition which occurs under conditions of satiety can be reversed pharmacologically, such that the animals resume sexual behavior 24 h after reaching satiety and, in some cases, achieve more than one copulatory series. The drugs that have been tested and found to have this capacity are naloxone and naltrexone [18,42], 8-OH-DPAT [41], yohimbina [40,41], and apomorphine [39].

Another means of reversing sexual satiety without pharmacological methods was described in 1963, based on the finding that a male that is capable of copulating to satiety with the same female can be induced to copulate again if that female is replaced by a new receptive female. This phenomenon, known as the "Coolidge effect", has been observed in a wide range of mammalian species [8,15,31,37,39,47,50]. It is believed that the Coolidge effect is caused by an increase in sexual motivation due to renewed interest based on the notion that the new female represents a sexually-significant incentive stimulus [37].

Numerous studies seem to suggest that sexual motivation and performance are also strongly influenced by dopamine, and that drugs which affect this neurotransmitter's activity in the central nervous system have a clear effect on sexual behavior [12,15,16,20,25,27,30,35,37,40,49]. This effect has been demonstrated in various studies that evaluated the role of different dopaminergic receptors by administering agonistic drugs. Those studies found an increase in the percentage of male rats – intact or castrated – that are able to copulate and ejaculate during tests of sexual behavior that did not involve sexual satiety [1,16,23,35], and a greater ability to achieve erections *ex copula* [20]. More specifically, they emphasized the role of D2 post-synaptic receptors as the principal candidates that may facilitate male sexual behavior [12,16,35].

Similarly, there are reports that bromocriptine (BrCr), a selective dopaminergic agonist for D2 family receptors [2,46], exerts a facilitating effect on male sexual behavior, reflected in a greater facility to achieve erection and an increase in sexual desire in humans [4], higher hit-rates and more numerous ejaculations in rats [9], and a reduction in the number of mounts required to ejaculate in sheep [22]. In all these cases the effect of bromocriptine was associated with a decrease in levels of prolactin, a hormone that is known to inhibit sexual behavior [10,11,20,28].

The Coolidge effect, meanwhile, manifests a male's potential to reactivate copulation during the period immediately after reaching sexual satiety, thus suggesting a neurofunctional change provoked by the new female that leads to restored copulation. However, no experimental strategy has yet studied the possible reactivation of copulatory behavior using the same sexual partners immediately after satiety is reached.

Given these antecedents, the objective of the present study was to determine whether dopaminergic activation *via* administration of bromocriptine fosters resumption of copulation with the same sexual mate immediately after the state of sexual satiety is reached. Also, the study was designed to evaluate spontaneous copulatory activity 24 h after this condition begins. Finally, we analyzed the characteristics of the copulatory behavioral pattern observed during the possible reactivation of copulation with the same sexual mate, and compared it to the patterns observed under the Coolidge effect protocol.

2. Materials and methods

2.1. Animals

From a total of 90 adult male Wistar rats (300–400 g body weight), we selected 30 sexually-experienced subjects that met the criterion of presenting ejaculatory latencies equal to or less than 30 min in three sessions of sexual experience acquisition with a minimum interval of 72 h between sessions. This previous testing of sexual performance was necessary because it is well-known that a large proportion of males do not show appropriate sexual behavior. Animals were housed in home cages in a room under controlled conditions of temperature 23° ± 2° C and a normal light:dark cycle (12 h light/12 dark, lights on at 08:00 h). The animals were placed in collective cages from weaning to 74 days of postnatal age. At 75 days of age (10 days before assessing sexual behavior) each subject was placed individually in a home cage that measured 30 × 40 × 15 cm. They had free access to commercial rat chow and tap water throughout the study. The experiment was performed in accordance with the guidelines established in the guide for the care and use of laboratory animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, 1996).

2.2. Sexual behavior assessment

Recording of sexual behavior was conducted 2 h after onset of the light phase. In each recording session male rats were placed in a test cage (50 × 40 × 30 cm; length, width, height) and allowed a 10-min adaptation period before a receptive female was introduced. The parameters of sexual behavior recorded were: mount latency (ML), mount frequency (M), intromission latency (IL), frequency of intromissions (I), ejaculation latency (EL), hit-rate (HR), number of ejaculations before reaching sexual satiety, time to reach sexual satiety, percentage of rats that copulated after reaching sexual satiety, and percentage of copulating rats capable of ejaculating after reaching sexual satiety.

2.3. Sexual experience acquisition test

Prior to testing for sexual satiety, at 85 days of age all the male rats were exposed to 3 sessions of sexual behavior separated by intervals of 72 h. The males considered sexually active (*i.e.*, those with ejaculation latencies below 30 min in the three sessions) were selected for the study. Receptive female rats were used as stimuli. Receptivity in the females was induced by subcutaneous administration of estradiol valerate (400 μg/rat once a week) and 500 μg of progesterone 2 h before each session.

2.4. Sexual satiety test (sexual exhaustion paradigm)

Seventy-two hours after the final session of the sexual acquisition phase, all the sexually-experienced male rats were allowed to copulate *ad libitum* with a single receptive female during sufficient time to reach satiety, according to the criteria described by Rodríguez-Manzo and Fernández-Guasti [41]; *i.e.*, satiety was considered to have been reached when the male had no ejaculations during a period of 90 min after several copulatory series.

2.5. Copulatory reactivation test immediately after reaching sexual satiety

Once the males satisfied these criteria of sexual satiety they were randomly assigned to one of three experimental treatment groups: 1) BrCr group (n = 10), administration of a single s.c. dose of 2 mg/kg of bromocriptine mesylate (Sigma-Aldrich Inc.) 30 min before exposure to the same receptive female with which they had achieved sexual satiety; 2) Veh group (n = 10), administration of a single s.c. dose of 0.75 mL/kg of the vehicle composed of saline solution and ethanol (99.5 purity), (ratio 2:1) 30 min before exposure to the same receptive female with which they achieved sexual satiety; 3) Coolidge group (n = 10), 30 min after reaching the sexual satiety criteria these males were exposed to a different receptive female. All of the aforementioned sexual behavior parameters were recorded.