



Dopamine is involved in the different patterns of copulatory behaviour of Roman high and low avoidance rats: Studies with apomorphine and haloperidol



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ABSTRACT

Outbred Roman high- (RHA) and low-avoidance (RLA) rats, originally selected for rapid vs. poor acquisition of active avoidance in a shuttle box, show differential copulatory patterns when exposed to a receptive female. Indeed, in the first copulation test male RHA rats show more mounts, intromissions and ejaculations than RLA rats. Such differences do not disappear in subsequent copulation tests, with sexually experienced RHA rats always showing higher levels of sexual motivation and performance than their RLA counterparts. This study shows that the different copulatory patterns of sexually experienced RHA and RLA rats are differentially facilitated by apomorphine, a mixed D1/D2-like dopamine receptor agonist, and impaired by haloperidol, a D2-like dopamine receptor antagonist, given at doses which facilitate and impair, respectively, copulatory behaviour in Sprague Dawley rats used as an external reference strain. Accordingly, apomorphine-induced facilitation and haloperidol-induced impairment of copulatory behaviour were more robust in RLA than RHA rats, as indicated by their effects on several copulatory parameters including mount, intromission and ejaculation latencies, mount, intromission and ejaculation frequencies, post ejaculatory interval, inter-intromission interval and copulatory efficacy. Pretreatment with haloperidol also reduced the facilitatory effect of apomorphine more effectively in RLA than RHA rats. These results suggest that the different copulatory patterns of RHA and RLA rats are mainly due to a lower dopaminergic tone at level of the mesolimbic and incerto-hypothalamic dopaminergic systems of RLA vs. RHA rats, which play a key role in sexual behaviour.

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1. Introduction

The outbred Roman high- (RHA) and low-avoidance (RLA) rat lines were psycho-genetically selected from a Wistar stock for rapid (RHA) versus extremely poor (RLA) acquisition of active avoidance in a shuttle-box (Bignami, 1965; Broadhurst and Bignami, 1965; Driscoll and Bättig, 1982; Fernández-Teruel et al., 2002a; Giorgi et al., 2007). A large body of evidence indicates that emotional rather than learning characteristics are responsible for their divergent performances in this test (Driscoll and Bättig, 1982; Steimer and Driscoll, 2003). Indeed, RLA rats are hyperemotional and display hypomotility and freezing when exposed to foot shock, whereas the hypoemotional RHA rats display a proactive coping behaviour with a rapid acquisition of the

avoidance response (Escorihuela et al., 1995). However, despite their poorer performance in the active avoidance task, RLA rats are superior to RHA rats in an appetitive working memory task (Willig et al., 1991; Guenaine and Delacour, 1985) and perform better than RHA rats in reference memory tasks (Willig et al., 1991). The two Roman lines differ also in other behavioural traits. For instance, when compared to RLA rats, RHA rats display a more robust sensation/novelty seeking profile (Siegel et al., 1993; Escorihuela et al., 1999), a higher baseline level of impulsivity (Moreno et al., 2010; Coppens et al., 2012), and a marked preference for and intake of natural and drug rewards (Zeier et al., 1978; Giorgi et al., 1997; Fernández-Teruel et al., 2002a; Fattore et al., 2009). Conversely, RLA rats show more anxious and depressive behaviour than RHA rats (Piras et al., 2010, 2014), and also a greater increment in adrenocorticotropin (ACTH), corticosterone and prolactin levels when exposed to a novel environment and stress than RHA rats (Fernández-Teruel et al., 2002b; Carrasco et al., 2008; Diaz-Morán et al., 2012). These neuroendocrine changes in RLA rats occur concomitantly with a higher expression of the prolactin gene and a higher

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neuronal density in the amygdala and hippocampus (brain areas strongly related to anxiety and fear) than in RHA rats (Sabariego et al., 2011; Gómez et al., 2009; García-Falgueras et al., 2012).

The different behavioural profiles of RLA and RHA rats may be related at least in part to differences in the functional properties of brain neurotransmitters, mainly dopamine (Driscoll et al., 1986; Durcan et al., 1984; D'Angio et al., 1988; Giorgi et al., 1994, 2003a, 2005; Lecca et al., 2004; Fattore et al., 2009; Corda et al., 1997), although a role of other neurotransmitters cannot be ruled out (Giorgi et al., 1994, 2003b). In line with such hypothesis, differential dose-related response gradients in motility, stereotypy, and yawning induced by the D1/D2-like mixed dopamine receptor agonist apomorphine have been reported between the inbred Roman lines (Giménez-Llort et al., 2005). Moreover, in outbred Roman rats the pro-yawning and pro-erectile effects of apomorphine and the pro-erectile effect of PD 168,077, a selective D4 receptor agonist, were found to be much more pronounced in RLA rats when compared to RHA rats and even more to SD rats (Sanna et al., 2013). In line with the above mentioned differences in dopamine neurotransmission between RHA and RLA rats, a lower D2 receptor availability (measured by dopamine receptor binding and mRNA assays) has been found in the substantia nigra/ventral tegmental area, caudate putamen and nucleus accumbens of RHA vs. RLA rats (Tournier et al., 2013). These findings suggest a more robust functional tone of nigrostriatal and mesolimbic dopamine neurons in RHA than RLA rats, secondary to the lower availability of inhibitory D2 autoreceptors in the cell bodies of nigrostriatal and mesolimbic dopaminergic neurons of RHA rats (Tournier et al., 2013).

Recently, we found that outbred RHA and RLA rats display a different copulatory pattern when put together with a receptive female rat, with RHA rats showing higher sexual motivation and a better copulatory performance than RLA rats (Sanna et al., 2014). Accordingly, more than 80% of RHA rats vs. only 40% of RLA rats engaged in mounts, intromissions and reached ejaculation in the first copulation test. These differences occurred with marked changes in copulatory parameters and persisted, although attenuated, even after repeated copulation tests, with RHA rats always showing higher mount, intromission and ejaculation frequencies and shorter mount, intromission and ejaculation latencies and post-ejaculatory intervals than RLA rats (Sanna et al., 2014). Since dopamine facilitates both the anticipatory (sexual motivation/arousal) and the consummatory (penile erection and copulation) phases of sexual behaviour not only in laboratory animals, but also in humans, by acting in the hypothalamus (Pfaus and Phillips, 1991; Argiolas and Melis, 1995, 2005; Melis and Argiolas, 1995; Hull et al., 1995, 1999; Melis et al., 2003; Succu et al., 2007) and mesolimbic brain areas (Pfaus et al., 1990; Everitt, 1990; Hull et al., 1991; Pfaus and Everitt, 1995; Melis and Argiolas, 2011; Pfaus, 2010), a differential dopaminergic tone may be responsible for the different copulatory patterns of the Roman lines. In order to verify such possibility, the effect of apomorphine and haloperidol, a classic dopamine D2-like receptor antagonist, given alone or in combination, on the copulatory behaviour of sexually experienced RHA and RLA rats was studied. For comparison, the effect of these two drugs on copulatory behaviour in genetically heterogeneous sexually experienced SD rats is also reported.

2. Materials and methods

2.1. Animals

Outbred Roman high- (RHA) and low-avoidance (RLA) male rats (300–350 g at the beginning of the experiments) were from the colony established in 1998 at the University of Cagliari, Italy (Giorgi et al., 2007). These animals are direct descendants of RHA/Verh and RLA/Verh rats that have been selected and bred in Switzerland since 1972 for rapid vs. extremely poor acquisition of two-way active avoidance behaviour (Driscoll and Bättig, 1982). The procedures used for the selective breeding of the Sardinian colony have been described in detail elsewhere (Giorgi et al., 2005). Sprague Dawley (SD) male rats (300–350 g

at the beginning of the experiments) were obtained from Charles River (Como, Italy). Ovariectomized SD female rats (250–330 g at the beginning of the experiments) used in all the experiments, were also obtained from Charles River (Como, Italy).

Animals were kept 4 per cage (38 cm × 60 cm × 20 cm) and were acclimated to the housing facilities of the Department of Biomedical Sciences of the University of Cagliari for at least 10 days before the beginning of the experiments under controlled environmental conditions (24 °C, 60% humidity, reversed 12 h light/dark cycle, with lights off from 08:00 to 20:00 h) and with water and standard laboratory food *ad libitum*. To limit the stress due to manipulation during the experiments, each animal was daily handled for approximately 1–2 min throughout the habituation period; in addition, contact with the animal house maintenance personnel was limited to a single attendant and bedding in the home cages was never changed either the day before or on the day of the experiment. The experiments were performed between 14:00 and 18:00 h and strictly followed the guidelines of the European Communities Directive of 24 November 1986 (86/609/EEC) and the Italian Legislation (D.P.R. 116/92).

2.2. Drugs

Apomorphine-HCl and haloperidol were purchased from Sigma (S. Louis, MO, USA). All other reagents were from available commercial sources.

2.3. Copulatory behaviour

RLA, RHA and SD rats never exposed to a receptive female before ($n = 45$ for each group) first underwent five consecutive 45 min copulation tests at three day intervals, each time with a different oestrous female rat, as already described (Sanna et al., 2014). Briefly, each RLA, RHA and SD male rat was put individually into a mating cage (45 cm × 30 cm × 24 cm) for 120 min during the dark phase of the cycle in a room lit by a dim red light. At the end of this habituation period an oestrous ovariectomized female rat (see below) was introduced in the mating cage. Oestrus condition was induced when required by subcutaneous injections of oestradiol benzoate (200 µg/rat in peanut oil) and progesterone (0.5 mg/rat in peanut oil) 48 and 6 h before the behavioural tests, respectively. The oestrus condition was ascertained by May–Grunwald–Giemsa coloration and microscopical examination of vaginal smears 1 h before the experiments. During these copulation tests, no data of copulatory activity were recorded except for the number of ejaculations reached during the whole test, as they were used only to make male rats of the three lines/strains sexually experienced, e.g., able to show a steady-state level of copulatory activity when put together with a receptive female. Five days after these preliminary copulation tests, sexually experienced male RHA, RLA and SD rats that satisfied the criterion of at least one ejaculation reached in each of the last two tests were randomly divided into three groups of 12 animals for each line/strain, the first group was used to study the effect of apomorphine, the second the effect of haloperidol and the third the effect of haloperidol + apomorphine on copulatory behaviour.

Since two doses of apomorphine and of haloperidol were used, the groups used with apomorphine or haloperidol given alone underwent three copulation tests at weekly intervals. On the other hand, the group used to study the effect of haloperidol + apomorphine, underwent four copulation tests at weekly intervals. Within each group, rats received all treatments in a latinized, repeated measures design.

The following measures of copulatory behaviour were recorded for 60 min by an observer who was not aware of the line/strain of rats used and of the treatments done: mount and intromission latency (ML and IL, the time from the moment in which the female was introduced into the experimental cage until the first mount and/or the first intromission, respectively); mount and intromission frequency (MF and IF, the number of mounts and intromissions in a series of copulatory

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