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Dynamic increases in dopamine during paced copulation in the female rat

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Abstract

The role of dopamine in the rewarding aspects of sexual behaviour in female rats was investigated. This is a unique model because sexual behaviour is only rewarding when copulatory stimuli are experienced at the preferred rate of copulation for a female rat. In addition, increases in dopamine in the nucleus accumbens occur during sexual behaviour only when the female achieves this preferred rate of copulation. In this study, minute-by-minute changes in nucleus accumbens dopamine were monitored using *in vivo* microdialysis. We report here that extracellular dopamine in the nucleus accumbens increases before coital stimulation only when sexual behaviour is occurring under conditions that are rewarding to the female rat. We conclude that increases in dopamine in the nucleus accumbens are involved in anticipation, not consummation, of sexual behaviour in the female rat.

Introduction

Brain dopamine (DA) is implicated in the rewarding effects of food (Wise *et al*., 1978; Ettenberg & Camp, 1986), several drugs of abuse (Yakel & Wise, 1975; De Wit & Wise, 1977; Bozarth & Wise, 1981; Corrigal *et al*., 1992), lateral hypothalamic brain stimulation (Liebman & Butcher, 1973; Fouriezos & Wise, 1976), and sexual behaviour (Pfaus & Phillips, 1990). The DA terminals in the nucleus accumbens (NAcc) are most clearly implicated in this regard (Roberts *et al*., 1977; Taylor & Robbins, 1984; Zito *et al*., 1985).

Sexual behaviour in the female rat is unique in that it is not rewarding under traditional laboratory testing conditions (Oldenberger *et al*., 1992; Paredes & Alonso, 1997; Paredes & Vazquez, 1999; Martinez & Paredes, 2001). However, sexual behaviour is rewarding to the female rat when she achieves her preferred rate of copulation (Paredes & Alonso, 1997; Paredes & Vazquez, 1999; Martinez & Paredes, 2001), whether or not she is actively pacing the rate of copulation (Jenkins & Becker, 2003). While both male and female rats show increases in extracellular concentrations of DA in the NAcc during sexual behaviour (Pfaus *et al*., 1990; Pfaus *et al*., 1995), females only exhibit this increase if they can achieve a preferred rate of intromissions either by actively controlling or 'pacing' the rate of copulation, or by having males removed from them and returned at appropriate intervals during copulation (Mermelstein & Becker, 1995; Becker *et al*., 2001). Achieving the preferred rate of copulation is important for females to optimize the rate of vaginocervical stimulation received from a male to activate a neuroendocrine reflex that is necessary for pregnancy to occur (Adler, 1969, 1978; McClintock & Adler, 1977; McClintock, 1984; Erskine, 1989).

The conditions in which females find sexual behaviour rewarding are associated with increases in extracellular concentrations of DA in the NAcc and to a lesser extent the striatum (Mermelstein & Becker, 1995; Becker *et al*., 2001). Experiments from the Becker laboratory indicate that the striatum and NAcc play differential roles in mediating paced copulatory behaviour, with the NAcc being implicated in the motivation to engage in sexual behaviour (Xiao & Becker, 1997; Jenkins & Becker, 2001). Taken together, these findings suggest that NAcc DA is involved in rewarding properties of sexual behaviour in the female rat. However, previous studies have provided little information with regards to how changes in NAcc DA map onto the sexual interaction itself.

In the present study, the role of DA in behaviour was investigated by sampling NAcc DA by *in vivo* microdialysis at consecutive 1-min intervals while the female engaged in sexual behaviour; these were time locked with intervals in which the female received an intromission or ejaculation (hereinafter referred to as an intromission). We demonstrate that during sexual behaviour, extracellular DA in the NAcc increases before a female rat receives coital stimulation at the preferred rate of copulation but not if the same amount of coital stimulation occurs at other rates. This paradigm allows for the dissociation of the rewarding aspects of sexual behaviour and coital stimulation.

Materials and methods

Male and female adult Long-Evans rats (Charles Rivers Laboratories, MA) were maintained on a 14 h light : 10 h dark cycle (lights on at 18.30 h) with soy free rat chow (Harlan Teklad #2014) and water available *ad libitum*. All procedures were carried out under a protocol approved by the University of Michigan Committee for the Use and Care of Animals.

Ovariectomized female rats (Becker *et al*., 2001) were anaesthetized with sodium pentobarbital (45 mg/kg, i.p.) and received an implant of a guide cannula aimed at the NAcc (left/right randomized; from Bregma in mm: anterior, 1.8; lateral, 1.5; ventral, 1.0) using stereotaxic procedures. On the day prior to dialysis, microdialysis probes

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(CMA/11, CMA/Microdialysis AB, Chelmsford, MA, USA) were implanted under isoflurane (5% in O_2) anaesthesia as described previously (Becker *et al*., 2001). Probes (recovery of DA $12 \pm 4\%$) were lowered to 8.25 mm from top of skull (2 mm exposed dialysis membrane). A ringer's solution (Becker *et al*., 2001) was perfused through the probe overnight at a rate of 0.5 μL/minute. On the day of testing, the flow rate through the probe was 2.0 μL/minute, and baseline and test session samples were collected at consecutive 1-min intervals. Baseline samples were collected prior to the introduction of the male, and the male was introduced once a stable level of DA had been established. Once the male was introduced and sexual behaviour commenced, 1-min dialysate samples were collected for up to one hour of sexual interaction. The concentration of DA in dialysate was determined using high performance liquid chromatography and electrochemical detection as described previously (Becker *et al*., 2001). Comparisons were made between and within groups on the percent change from basal DA. All NAcc samples were timelocked relative to when the animal received an intromission.

Female rats were randomly assigned to one of 3 groups: preferred pacing interval (PPI), nonpacing (NP) and nonpacing-5 min (PI5). All animals were primed with 10 μg estradiol benzoate and 500 μg progesterone 48 and 4 h (respectively) prior to behavioural testing (Becker *et al*., 2001). Groups were run in parallel. In all, the data collected from the NAcc of 21 experimental females are reported here ($n = 11$ for PPI, $n = 5$ for NP, and $n = 5$ for PI5).

In the PPI group, the male was gently removed from the chamber after an intromission for 2 min and then replaced. This time interval was chosen both because it allowed dialysate samples to be collected which were associated with only one discrete sexual interaction and because this interval falls within the average range of interintromission intervals observed in female rats in our lab (Becker *et al*., 2001; Jenkins & Becker, 2001). The nonpacing group was tested with the male such that the male was never removed and had access to the female throughout the testing session. For the PI5 group, the male was gently removed for 5 min following an intromission or ejaculation before being replaced. This group was included to control the possibility that just removing the male from the chamber and returning him at a later time would influence DA in dialysate. All tests were video recorded and analysed by an experimenter blind to group membership for the number and timing of intromissions. Mean interintromission interval was calculated by dividing the sum of interintromission intervals by the total number of intromissions received during the test session. The scorer also noted the time that collection vials were changed so that it would be possible to timelock dialysate data with behavioural observations.

After testing, animals were deeply anaesthetised with sodium pentobarbitol and received an intracardial perfusion of 0.9% saline followed by 4% paraformaldehyde. Following brain sectioning, sections were stained with cresyl violet and inspected microscopically to determine probe placement. Any animals with probes outside of the NAcc, as determined with the aid of a rat brain atlas (Paxinos & Watson, 1998), were excluded from subsequent analyses. Of the 21 animals with probes within the NAcc, 16 were in the core region and five rested in the dorsomedial boundary between the shell and core. These five animals were distributed across all three groups (PPI = 3, NP = 1, and PI5 = 1).

After calculating the mean percent baseline measures of DA in dialysate for each animal, any observations falling outside two standard deviations of the mean were reassigned a maximum value of two standard deviations of the mean in order to reduce variability within animals. The percent baseline measures of NAcc DA in dialysate for the minute before, during, and after an intromission occurred were compared to baseline and analysed by a between–within repeated measures analysis of variance (ANOVA) and *post hoc* pairwise comparisons using the Tukey's HSD procedure to calculate a critical difference for multiple individual time point comparisons. For the PPI and PI5 groups, only samples that were not immediately followed by another intromission were included in the analysis in order to eliminate the potential for multiple analyses of a single observation.

The number of intromissions, interintromission intervals, and baseline concentrations of NAcc DA in the three groups were compared using one-way factorial ANOVA. All statistical tests were performed using StatView 5.0 for the Macintosh computer. Differences were considered significant if $P \leq 0.05$.

Results

There was a main effect of group on the mean percent baseline concentrations of DA in dialysate ($F_{2,18} = 5.80$, $P < 0.015$; Fig. 1). The PPI group had greater extracellular DA values than either the NP or the PI5 group ($P < 0.001$). The NP and PI5 groups did not differ from each other. There was also a significant interaction effect of group and the repeated sample variable ($F_{2,6} = 2.80$, $P < 0.02$). The Tukey's HSD procedure was used to calculate minimum critical differences for multiple pairwise comparisons within groups ($P < 0.05$). For the PPI females, only the sample preceding copulatory stimulation exceeded this critical difference when compared to baseline and the interval during which an intromission occurred. There were no within group differences for either the NP or PI5 groups. After one or two intromissions, increases in DA in dialysate came to anticipate intromisisons in the PPI group. To illustrate this point, the concentration of DA in dialysate for baseline, the minute before, minute during, and the minute after the first (Fig. 2A) and the last (Fig. 2B) intromission of the test session are presented for an individual female randomly selected from each group.

Baseline concentrations of NAcc DA did not differ among the three groups ($F_{2,18} = 0.566$, $P = 0.578$). The mean concentrations of DA in baseline dialysate samples (±SEM) were 65.3 pM (±16.0), 49.0 pM (±23.0) and 42.5 pM (±13.1) for the PPI, NP, and PI5 groups,

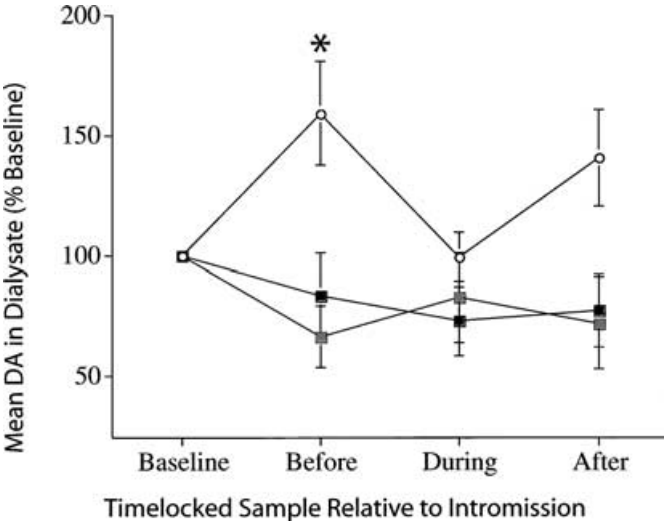

FIG. 1. Changes in NAcc DA as a function of intromission. Open circles, PPI group; black squares, NP group;grey squares, PI5 group; error bars, SEM. *indicates that the sample timelocked with the minute before an intromission occurred is greater than baseline and greater than the interval during which the intromission occurs ($P < 0.05$).

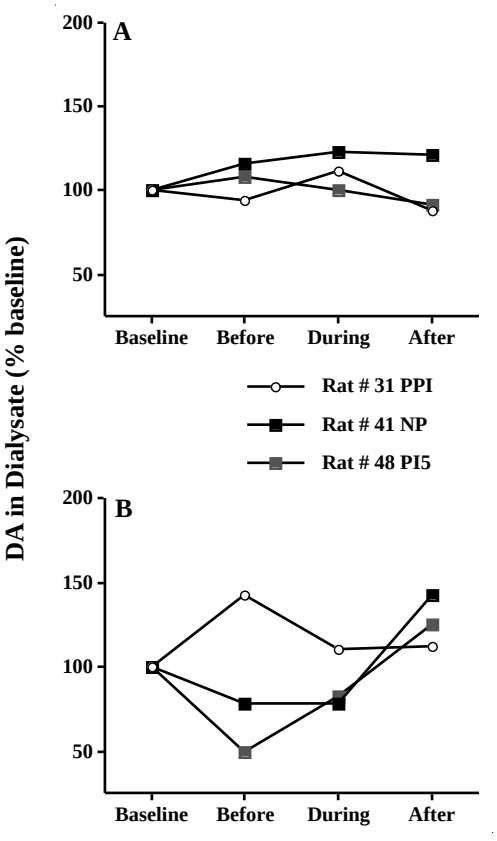

FIG. 2. The concentrations of DA in dialysate for the first (A) and last (B) intromission of the test session for an individual female from each group. White circles, an animal in the PPI group; black squares, an animal in the NP group; grey squares; an animal in the PI5 group.

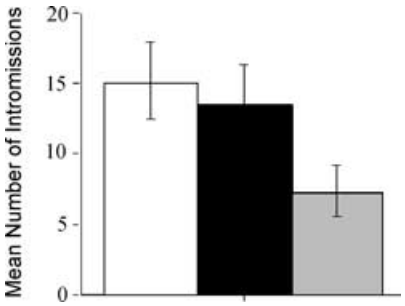

FIG. 3. Amount of coital stimuli received during the test session. White bar, PPI group; black bar, NP group; grey bar, PI5 group. There were no differences among the three groups in terms of the number of intromissions received. However, there was a trend for fewer intromissions in the PI5 group compared to the PPI and NP groups. Error bars, SEM.

respectively. There were no significant differences in the number of intromissions received during the test session among the three groups ($F_{2,18} = 1.70$, $P = 0.21$); however, there was a trend for fewer intromissions in the PI5 group compared to the PPI ($P = 0.08$) and NP ($P = 0.2$) groups (Fig. 3). The mean (±SEM) interintromission interval was 132.8 (±3.7) seconds for the PPI group, 46.8 (±10.3) seconds interval for the NP group, and 349.3 (±43.3) seconds for the PI5 group. There was a main effect of group on this measure ($F_{2,18} = 54.9$, $P < 0.0001$). The PI5 group had significantly longer intervals than did the PPI or NP group, and the PPI group had significantly longer intervals than did the NP group (all $P < 0.0003$).

Discussion

Females engaged in sexual behaviour that occurred at their preferred interval exhibited increased concentrations of DA in dialysate from the NAcc compared to animals engaged in sex at other rates. Furthermore, DA increases in the NAcc occurred prior to coital stimulation if intromissions were received at the female's preferred pacing interval, but not when coital stimulation occurred under other conditions. These data support the hypothesis that DA increases in the NAcc signal the impending receipt of coital stimulation at the female's preferred pacing interval.

As demonstrated here, female rats that have males removed for 5-min intervals do not show increased NAcc DA concentrations relative to nonpacing animals, nor do those that have the males removed from them for 10-min intervals (Becker *et al*., 2001). Thus, changes in NAcc DA are not associated with coital stimulation or removal of the male rat, but coital stimulation that occurs at a specific interval. It is possible that the female is sensitive to cues that the male provides about his readiness to engage in copulatory behaviour or cues that the experimenter provided about the male's return. Therefore, increases in DA just prior to the receipt of coital stimulation observed here may encode the anticipation of sex at the female's preferred interval as a function of those cues.

While not reaching statistical significance, the interval following the intromission is also associated with an increase in concentrations of DA in dialysate. It is possible that the DA pattern observed here simply reflects a relative decrease in DA that is a function of the receipt of the intromission itself. However, it is unlikely that such a decrease is due to any aversive properties associated directly with coital stimulation, as there is no evidence that female rats find nonpaced sex or coital stimulation aversive. In fact, female rats develop a conditioned place preference for vaginal lavage (Walker *et al*., 2002). Furthermore, aversive stimuli such as tail pinch induce an increase in extracellular concentrations of NAcc DA and reactivity of DA neurons in the NAcc (Louilot *et al*., 1986; Rouge-Pont *et al*., 1993).

It is also possible that the lordotic posture assumed during the receipt of coital stimulation is associated with decreased DA. This might explain the consistent low levels of DA in the NP group as they often received multiple intromissions in analysed sample intervals. However, the PI5 group shows no change in DA during the interval associated with the intromission relative to intervals that immediately precede or follow. Furthermore, intracranial infusions of DA antagonists have been shown to attenuate the female rat's lordotic responsiveness, while DA agonists actually facilitate the response (Apostolakis *et al*., 1996; Frye & Vongher, 1999). Therefore, it seems likely that the increase in DA occurs in anticipation of the receipt of coital stimuli. This idea is supported by the data presented in Fig. 2, which suggests that the differences seen between the PPI and other two groups emerge after the animals have experienced the pattern of intromissions typical for a group.

Whatever the case, it is clear that sex, if it approximates the female's preferred rate, is associated with dynamic changes in DA at the level of the NAcc. The data reported here are consistent with other studies investigating the role that NAcc DA plays in the anticipation of sexual behaviour of both male and female rats (Pfaus *et al*., 1990; Pfaus *et al*., 1995; Robinson *et al*., 2001). Bilateral lesions of the medial shell and core of the NAcc in female rats dramatically increase the latency to make an approach toward male rats (Jenkins & Becker, 2001), and

female rats develop conditioned place preferences for sex at their PPI (Jenkins & Becker, 2003). Coupled with these data, it appears the NAcc and DA activity in the NAcc are important for the female's approach towards a sexually active male and the anticipation of sexual behaviour that occurs under conditions that are rewarding to the female rat. In addition, it clarifies the role of DA in the NAcc in female sexual behaviour. While previous research indicates that DA in the NAcc increases both before and during sex (Pfaus *et al*., 1995), we report here that DA is only elevated when the female has sex at her preferred interval, and this elevation is almost entirely due to the anticipation of receiving properly spaced intromissions. Future studies employing methods that allow even more precise temporal resolution will be invaluable in fully understanding the relationship between NAcc DA and paced sexual behaviour in the female rat.

It has been argued that DA encodes reward directly (Wise, 1985; Koob & Le Moal, 1997), becomes associated with cues that predict reward (Schultz *et al*., 1997), or is involved in the desire to approach incentives (Robinson & Berridge, 1993; Berridge & Robinson, 1998). Sexual behaviour of the female rat requires new considerations and interpretations of the role of DA in reward. Female rats find sexual behaviour rewarding and have increased NAcc DA when they engage in sex at their preferred interval (Mermelstein & Becker, 1995; Paredes & Alonso, 1997; Becker *et al*., 2001; Martinez & Paredes, 2001). Sex that is rewarding has been shown to be associated with the triggering of a neuroendocrine reflex necessary for pregnancy (Adler, 1974; Gilman *et al*., 1979; Erskine *et al*., 1989). One could posit therefore that the changes in DA observed here represent a coupling of the sexual interaction and its physiological consequences, both of which may be necessary for sexual behaviour to be rewarding. In other words, increases in DA predict the receipt of coital stimulation, but only if it is occurring at such a rate that facilitates the triggering of the neuroendocrine reflex necessary for successful pregnancy to occur. In this way, only paced sexual behaviour, or sex that occurs at a rate that approximates the female rat's PPI, would be rewarding even though sex that occurs at other rates may ultimately lead to the same physiological endpoint.

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Abbreviations:

Intro, intromissions/ejaculations; DA, dopamine; NP, nonpacing; NAcc, nucleus accumbens; PI5, pacing interval of 5 min; PPI, preferred pacing interval of 2 min; SEM, standard error of the mean.

References

Adler, N.T. (1969) Effects of the male's copulatory behavior on successful pregnancy of the female rat. *J. Comp. Physiol. Psychol*, **69**, 613–622.

Adler, N.T. (1974) The behavioral control of reproductive physiology. *Adv. Behav. Biol.*, **11**, 259–286.

Adler, N.T. (1978) On the mechanisms of sexual behavior and their evolutionary constraints. In Hutchison, J.B. (Ed), *Biological Determinants of Sexual Behavior*. Wiley and Sons Ltd., New York, pp. 657–694.

Apostolakis, E.M., Garai, J., Fox, C., Smith, C.L., Watson, S.J., Clark, J.H. & O'Malley, B.W. (1996) Dopaminergic regulation of progesterone receptors: D5 dopamine receptors mediate induction of lordosis by D1-like agonists in rats. *J. Neurosci.*, **16**, 4823–4834.

Becker, J.B., Rudick, C.N. & Jenkins, W.J. (2001) The role of dopamine in the nucleus accumbens and striatum during sexual behavior in the female rat. *J. Neurosci.*, **21**, 3236–3241.

Berridge, K.C. & Robinson, T.E. (1998) What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.*, **28**, 309–369.

Bozarth, M.A. & Wise, R.A. (1981) Heroin reward is dependent on a dopaminergic substrate. *Life Sci.*, **29**, 1881–1886.

Corrigal, W.A., Franklin, K.B.J., Coen, K.M. & Clarke, P. (1992) The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology*, **107**, 285–289.

De Wit, H. & Wise, R.A. (1977) Blockade of cocaine reinforcement in rats with dopamine receptor blocker pimozide, but not with noradrenergic blockers phentolamine or phenoxybenzamine. *Can. J. Psychol*, **31**, 195–203.

Erskine, M.S. (1989) Solicitation behavior in the estrous female rat: a review. *Horm. Behav.*, **23**, 473–502.

Erskine, M.S., Kornberg, E. & Cherry, J.A. (1989) Paced copulation in rats: Effects of intromission frequency and duration on luteal activation and estrus length. *Physiol. Behav.*, **45**, 33–39.

Ettenberg, A. & Camp, C.H. (1986) Haloperidol induces a partial reinforcement extinction effect in rats: Implications for a dopamine involvement in food reward. *Pharmacol. Biochem. Behav.*, **25**, 813–821.

Fouriezos, G. & Wise, R.A. (1976) Pimozide-induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. *Brain Res.*, **103**, 377–380.

Frye, C.A. & Vongher, J.M. (1999) $GABA_A$, D1, and D5, but not progestin receptor, antagonist and anti-sense oligonucleotide infusions to the ventral tegmental area of cycling rats and hamsters attenuate lordosis. *Behav. Brain Res.*, **103**, 23–34.

Gilman, D.P., Mercer, L.F. & Hitt, J.C. (1979) Influence of female copulatory behavior on the induction of pseudopregnancy in the female rat. *Physiol. Behav.*, **22**, 675–678.

Jenkins, W.J. & Becker, J.B. (2001) Role of the striatum and nucleus accumbens in paced copulatory behavior in the female rat. *Behav. Brain Res.*, **121**, 119–128.

Jenkins, W.J. & Becker, J.B. (2003) Females develop conditioned place preference for sex at their preferred interval. *Horm. Behav.*, **43**, 503–507.

Koob, G.F. & Le Moal, M. (1997) Drug abuse: hedonic homeostatic dysregulation. *Science*, **278**, 52–58.

Liebman, J.M. & Butcher, L.L. (1973) Effects of self-stimulation behavior of drugs influencing dopaminergic neurotransmission. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **277**, 305–318.

Louilot, A., Le Moal, M. & Simon, H. (1986) Differential reactivity of dopaminergic neuronsin the nucleus accumbens to different behavioral situations: An in vivo voltammetric study in free moving rats. *Brain Res.*, **397**, 395–400.

Martinez, I. & Paredes, R.G. (2001) Only self-paced mating is rewarding in rats of both sexes. *Horm. Behav.*, **40**, 510–517.

McClintock, M.K. (1984) Group mating in the domestic rat as context for sexual selection: consequences for the analysis of sexual behavior and neuroendocrine responses. *Adv. Study Behav.*, **14**, 1–50.

McClintock, M.K. & Adler, N.T. (1977) The role of the female during copulation in wild and domestic norway rats. *Behaviour*, **67**, 67–96.

Mermelstein, P.G. & Becker, J.B. (1995) Increased extracellular dopamine in the nucleus accumbens and striatum of the female rat during paced copulatory behavior. *Behav. Neurosci.*, **109**, 354–365.

Oldenberger, W.P., Everitt, B.J. & De Jonge, F.H. (1992) Conditioned place preference induced by sexual interaction in female rats. *Horm. Behav.*, **26**, 214–228.

Paredes, R.G. & Alonso, A. (1997) Sexual behavior regulated (paced) by the female induces conditioned place preference. *Behav. Neurosci.*, **111**, 123–128.

Paredes, R.G. & Vazquez, B. (1999) What do female rats like about sex? Paced mating. *Behav. Brain Res.*, **105**, 117–127.

Paxinos, G. & Watson, C. (1998) *The Rat Brain in Stereotaxic Coordinates*. Academic Press, San Diego, CA.

Pfaus, J.G., Damsma, G., Nomikos, G.G., Wenkstern, D.G., Blaha, C.D., Phillips, A.G. & Fibiger, H.C. (1990) Sexual behavior enhances central dopamine transmission in the male rat. *Brain Res.*, **530**, 345–348.

Pfaus, J.G., Damsma, G., Wenkstern, D. & Fibiger, H.C. (1995) Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats. *Brain Res.*, **693**, 21–30.

Pfaus, J.G. & Phillips, A.G. (1990) Differential effects of dopamine receptor antagonists on the sexual behavior of male rats. *Psychopharmacology*, **98**, 363–368.

Roberts, D.C., Corcoran, M.E. & Fibiger, H.C. (1977) On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacol. Biochem. Behav.*, **6**, 615–620.

Robinson, T.E. & Berridge, K.C. (1993) The neural basis of drug craving: an incentrive-sensitization theory of addiction. *Brain Res. Rev.*, **18**, 247–291.

Robinson, D.L., Phillips, P.E.M., Budygin, E.A., Trafton, B.J., Garris, P.A. & Wightman, R.M. (2001) Sub-second changes in accumbal dopamine during sexual behavior in male rats. *Neuroreport*, **12**, 2459–2452.

Rouge-Pont, F., Piazza, P.V., Kharouby, M., Le Moal, M. & Simon, H. (1993) Higher and longer stress-induced increase in dopamine concentrations in the nucleus accumbens of animals predisposed to amphetamine self-administration. A microdialysis study. *Brain Res.*, **602**, 169–174.

Schultz, W., Dayan, P. & Montague, P.R. (1997) A neural substrate of prediction and reward. *Science*, **275**, 1593–1599.

Taylor, J.R. & Robbins, T.W. (1984) Enhanced behavioural control by conditioned reinforcers following microinjections of d-amphetamine into the nucleus accumbens. *Psychopharmacology (Berl)*, **84**, 405–412.

Walker, Q.D., Nelson, C.J., Smith, D. & Kuhn, C.M. (2002) Vaginal lavage attenuates cocaine-stimulated activity and established place preference in rats. *Pharmacology, Biochem. Behav.*, **73**, 743–752.

Wise, R.A. (1985) The anhedonia hypothesis: Mark III. *Behav. Brain Sci.*, **8**, 178–186.

Wise, R.A., Spindler, J., deWit, H. & Gerberg, G.J. (1978) Neuroleptic-induced 'anhedonia' in rats: Pimozide blocks reward quality of food. *Science*, **201**, 262–264.

Xiao, L. & Becker, J.B. (1997) Hormonal activation of the striatum and the nucleus accumbens modulates paced mating behavior in the female rat. *Horm. Behav.*, **32**, 114–124.

Yakel, R.A. & Wise, R.A. (1975) Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. *Science*, **187**, 547–549.

Zito, K.A., Vickers, G. & Roberts, D.C.S. (1985) Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. *Pharmacol. Biochem. Behav.*, **25**, 1029–1036.