Pharmacology, Biochemistry and Behavior 90 (2008) 586–589

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Relationship between ethanol and sucrose self-administration and schedule-induced polydipsia

Claudia Alvares Toscano [a], Marcia Kameyama [a], Miriam Garcia-Mijares, Maria Teresa Araujo Silva [a], Erica Maria Machado Santarem [b,*]

[a] Experimental Psychology Department, Institute of Psychology, University of São Paulo, Avenida Professor Mello Moraes, 1721-CEP: 05508-030. São Paulo, SP, Brazil
[b] Faculdade de Psicologia, Universidade São Francisco, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 9 January 2008
Received in revised form 15 April 2008
Accepted 24 April 2008
Available online 5 May 2008

Keywords:
Oral self-administration
Schedule-induced polydipsia
Ethanol
Sucrose
Drug abuse
Compulsive behavior
Dopaminergic system

ABSTRACT

Studies have suggested a relationship between drug abuse and compulsive behaviors. The present experiments investigated the relationship between schedule-induced polydipsia (SIP) and self-administration (SA) of ethanol and sucrose. SIP served as a model of compulsive behavior, and oral self-administration on a progressive-ratio (PR) schedule of reinforcement assessed the reinforcing value of either a 10% ethanol solution or an isocaloric sucrose solution. Rats first were exposed to PR sessions in which break points were the dependent variable and then switched to SIP sessions, with number of licks as the dependent variable. Results showed a positive relationship between PR and SIP for sucrose but not for ethanol: higher and lower PRs for sucrose were associated with higher and lower SIP levels. The order of the sessions then was reversed, such that SIP sessions were run before PR sessions. An opposite relationship was observed in which high and low SIP animals exhibited low and high PR break points, respectively. The relationship between SIP and SA was dependent on the reinforcing value of the substance and on prior SIP exposure. These results may reflect a common dopaminergic substrate and suggest that prior experience in coping with stress may reduce vulnerability to substance abuse behavior.

1. Introduction

Schedule-induced polydipsia (SIP) is the excessive drinking that occurs when food-restricted subjects are exposed to intermittent food delivery. SIP belongs to the adjunctive behavior class, which includes such behaviors as running, gnawing, fighting and air-licking. From a theoretical standpoint, the origin and function of SIP are relevant issues. Regarding function, SIP may be considered an experimental analogue of the ethological concept of "displacement", since both displaced and adjunctive behaviors occur under conditions that hinder the emission of a motivated behavior. Consequently, the animal exhibits some other habitual behavior, although in a stereotyped and non-adaptive form. In doing so, part of its evolutionary history is exposed (Pitman, 1989; Timberlake and Lucas, 1991). This perspective led to the proposal of SIP as an animal model of compulsive behaviors in humans, such as those characterized in the DSM-IV description of Obsessive Compulsive Disorder (OCD) as well as other "excessive" behaviors, including excessive eating, drug abuse and alcoholism (Cantor et al., 1982; Falk and Tang, 1988; Rapoport, 1989). Thus, SIP may be part of a large behavioral class including abusive and compulsive acts, all mediated by common neurobiological substrates from the dopaminergic reward system.

In view of the possible functional similarity between abusive and compulsive behaviors, both supposedly modeled by SIP, Piazza et al. (1993) investigated the relationship between this kind of polydipsia and intravenous self-administration of an addictive drug, amphetamine. In a first experiment, rats were first exposed to the self-administration procedure and then to SIP. The authors observed that subjects developing amphetamine self-administration also developed SIP. This result was attributed to the correlation between predisposition towards dependence and emission of compulsive behaviors. However, in a second experiment, when rats were exposed first to the SIP procedure and then to amphetamine self-administration, the inverse relation was observed: polydipsic subjects did not develop self-administration. In explaining this result, the authors argued that previous exposure to SIP had generated an adaptive response of coping with the stress of intermittent food presentation, with consequent reduction in adrenal response and elicited anxiety. This reduction would account for the diminished tendency toward addiction.

The present study was aimed at verifying whether the relationship observed by Piazza et al. (1993) would be replicated if different drug (ethanol) and alternative self-administration route (oral) were used. In addition, a non-drug reinforcer (sucrose) was also introduced. Ethanol and sucrose both act via the dopaminergic reinforcement system akin to amphetamine (Hajnal and Norgren, 2001; Weiss et al., 1993). The progressive ratio model was used to assess their reinforcing value (Hodos, 1961; Richardson and Roberts, 1996).

* Corresponding author. Tel.: +55 11 3091 4176; fax: +55 11 3091 4357.
E-mail address: erica.santarem@terra.com.br (E.M.M. Santarem).

0091-3057/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.pbb.2008.04.019

2. Materials and methods

2.1. General methods

2.1.1. Subjects

Naïve male Wistar rats weighing approximately 300 g at the beginning of the experiment were used ($N=32$). They were housed singly following a 12±12-h light/dark cycle (lights off at 19:00 h) under controlled temperature (22 °C) and humidity (60%) with ad libitum access to water. Rats were given sufficient food to maintain 85% of their baseline weight. The ethical guidelines of the National Institute of Health Guide for Care and Use of Laboratory Animals (Publication NoNo. 85-23, revised 1985) were followed.

2.1.2. Apparatus

Experiments were run in four experimental chambers (32×25×21 cm), encased in sound-attenuating isolation boxes (all equipment from *Med Associates*). A ventilation fan (ENV-025F28) provided background noise and a house light was on throughout all experimental sessions. In the self-administration (SA) phase a bar was located 8 cm above the floor and a 0.01 ml dipper provided the reinforcer solution. In the schedule-induced SIP sessions, the dipper was replaced by a food tray connected to a 45 mg-pellet dispenser. Noyes pellets were used. The opposite wall was covered by a removable stainless steel wall where a graduated test tube was inserted behind it, with its spout protruding 1.5 cm into the box. Licks on the spout were detected by a lickometer circuit (ENV-250A) which accumulated responses at 5-s intervals during the food delivery intervals. Water consumption was measured through visual reading. A 486 IBM personal computer was programmed to control stimulus presentation and provide data recording. A microcamera allowed monitoring and video taping of the animal behavior.

2.1.3. Procedure

2.1.3.1. Self-administration. The experimental procedure consisted of:

(a) Bar-pressing shaping. A 20% sucrose solution was used as reinforcer for bar-pressing. The response was gradually shaped until a fixed-ratio 4 (FR 4) was reached. Subjects were then distributed into two groups, ethanol (ET) and sucrose (SUC).

(b) Habituation to ethanol drinking. Animals remained on 30-min FR 4 schedule sessions as they were submitted to the procedure of habituation to ethanol oral SA. For ET subjects ($N=16$) the procedure was as follows. ET concentration was increased and SUC concentration decreased until replacement by saccharin (SAC) according to the following sequence: 0% ET+20% SUC; 0% ET+10% SUC; 2% ET+10% SUC; 5% ET+10% SUC; 5% ET+5% SUC; 10% ET+5% SUC; 10% ET+0.25% SAC. Subjects in the SUC group ($N=16$) were submitted to the same number of SA sessions as ET subjects, but received 14.2% sucrose as reinforcer. The SUC concentration was chosen because it is isocaloric in relation to ethanol.

(c) Progressive ratio. After the habituation phase, animals were run on three 60-min FR 4 sessions, and were then exposed to five progressive ratio (PR) schedule sessions which increased daily arithmetically (FR 4, 8, 16, 20, 24...66). Sessions were terminated either after a 30-min period of non-response or after 3 h. The last ratio completed in the session was defined as the breaking point (BP).

2.2. Schedule-induced polydipsia

When subjects were run on the SIP procedure, a food pellet was delivered on a fixed time (FT) schedule. The schedule value was gradually increased until FT 60-s was reached. Subjects remained on this schedule for ten sessions, being simultaneously allowed to drink from the water bottle. Experimental sessions were all run at the same time of day and lasted until 30 pellets had been delivered.

2.3. Experimental design

2.3.1. Experiment 1

Thirty-two subjects were first exposed to ethanol ($N=16$) or sucrose ($N=16$) oral SA and later to SIP. The SIP procedure was run 2 ydays after SA termination. After SIP sessions the group was divided on the basis of median BP value into two subgroups consisting of animals presenting the highest and lowest BPs (BP+and BP−).

2.3.2. Experiment 2

Thirty-five subjects were first exposed to SIP and later to ET ($N=17$) or SUC ($N=18$) oral SA. Groups were balanced according to their SIP levels. The oral SA procedure started immediately after habituation to ethanol drinking had been terminated. After SA sessions the group was divided on the basis of median SIP value into two subgroups consisting of animals presenting the highest and lowest number of licks (SIP+and SIP−).

2.4. Statistics

Repeated measures ANOVA with $p<0.05$ as the significance level were conducted separately for ET and SUC with sessions as within-factor and group (BP or SIP) as between-factor. There were two levels for each group (BP+ /BP− and SIP+/SIP−).

3. Results

3.1. Experiment 1: Effect of oral ethanol or sucrose self-administration on subsequent schedule-induced polydipsia

Fig. 1 presents mean and standard error (+SE) of BPs attained in progressive schedule throughout SA sessions, along with mean +SE of number of licks throughout SIP sessions for Ethanol (ET) and Sucrose (SUC) groups. In the SA sessions, a small but statistically significant BP decrease can be observed for the ET group ($F_{4,60}=2.901$, $p<0.05$) and a larger significant decrease for the SUC group ($F_{4,60}=6.805$, $p<0.001$). In ensuing SIP sessions, mean number of licks increased significantly over sessions for both ET ($F_{9,135}=14.490$, $p<0.001$) and SUC groups ($F_{9,135}=18.820$, $p<0.001$).

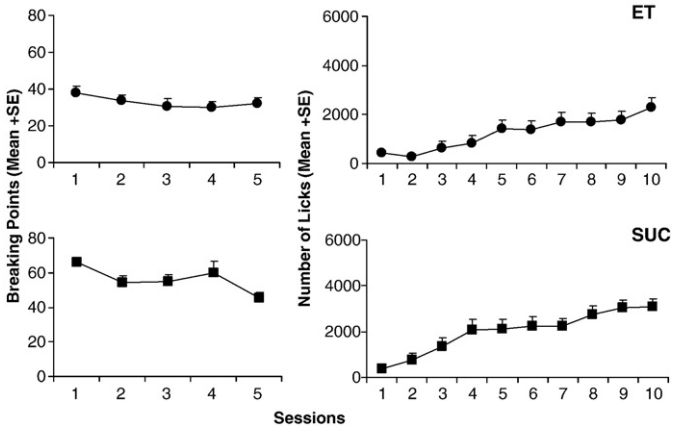

Fig. 1. Relationship between self-administration and schedule-induced polydipsia when subjects were first exposed to ethanol or sucrose oral self-administration, and later to schedule-induced polydipsia. Data are shown as mean and standard errors of progressive schedule breaking points during the self-administration sessions, and as mean and standard errors of number of licks during the schedule-induced polydipsia sessions. Data for subjects from the Ethanol (ET) and Sucrose (SUC) groups are shown in the upper and lower panels respectively.

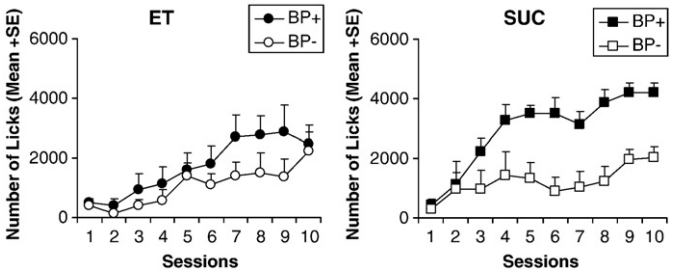

Fig. 2. Mean and standard errors of number of licks during the schedule-induced polydipsia sessions for BP+ (highest BPs) and BP− (lowest BPs) subjects. Data for subjects from the Ethanol (ET) and Sucrose (SUC) groups are shown in the left and right panels respectively.

Subjects in both ET and SUC groups were divided into subgroups according to the median value of their average BPs over the last three SA sessions. Fig. 2 presents the mean +SE of number of licks during the schedule-induced SIP sessions for BP+ and BP− (<0.001) and the SUC group ($F_{9,126}=20.066$, $p<0.001$). The ANOVA for the between-subjects factor (subgroups) showed significant differences for BP+ and BP− in the SUC group ($F_{1,14}=9.091$, $p<0.01$), but not for the BP+ and BP− in the ET group.

3.2. Experiment 2: Effect of schedule-induced polydipsia on subsequent oral ethanol or sucrose self-administration

Fig. 3 shows the development of SIP and SA when subjects were first exposed to SIP and later to ET or SUC oral SA. Mean licks during the ten SIP sessions increased significantly in both groups ($F_{9,144}=33.017$, $p<0.001$ for the ET group and $F_{9,153}=23.756$, $p<0.001$ for the SUC group). Mean BPs during the five SA sessions were significantly decreased in the ET group ($F_{4,64}=3.916$, $p<0.01$) but not the SUC group.

Subjects in both ET and SUC groups were divided into subgroups according to the median value of their average licks over the last three SIP sessions. Subjects showing SIP levels above 2800 licks formed the SIP+ sub-group ($n=9$ in the ET group, $n=9$ in the SUC group), whereas subjects scoring below this value made up the SIP− sub-group ($n=8$ in the ET group, $n=9$ in the SUC group). Figure 4 presents the mean+SE of progressive schedule BPs over the five SA sessions for SIP+ (highest SIP levels) and SIP− (lowest SIP levels) subjects in the ET and SUC groups. The ANOVA revealed a significant session effect in the ET

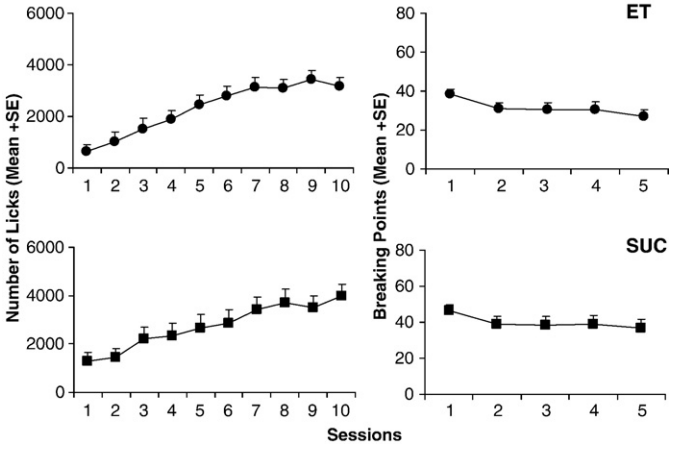

Fig. 3. Relationship between schedule-induced polydipsia and self-administration when subjects were first exposed to schedule-induced polydipsia, and later to ethanol or sucrose oral self-administration. Data are shown as mean and standard errors of number of licks during the schedule-induced polydipsia sessions, and mean and standard errors of progressive schedule breaking points during the self-administration sessions. Data for subjects from the Ethanol (ET) and Sucrose (SUC) groups are shown in the upper and lower panel respectively.

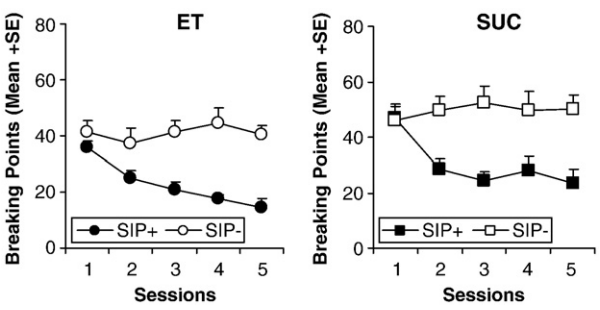

Fig. 4. Mean and standard errors of progressive schedule breaking points during the five SA sessions for SIP+ (highest SIP levels) and SIP− (lowest SIP levels). Data for subjects from the Ethanol (ET) and Sucrose (SUC) groups are shown in the left and right panels respectively.

($F_{4,60}=4.495$, $p<0.01$) and SUC ($F_{4,64}=2.505$, $p=0.05$) groups. The ANOVA also showed a significant difference between subjects in the SIP+ and SIP−(<0.001) and SUC groups ($F_{1,16}=11.310$, $p<0.01$).

4. Discussion

The relationship between schedule-induced polydipsia and intravenous amphetamine self-administration demonstrated by Piazza et al. (1993) was partially replicated in the present study for oral self-administration of ethanol or sucrose. When SA preceded SIP, BPs in a progressive schedule of reinforcement were directly proportional to the SIP level observed subsequently for sucrose but not for ethanol. When SIP preceded SA, the inverse relationship was observed: highly polydipsic subjects did not self-administer ethanol or sucrose, whereas animals exhibiting low SIP levels did so. The relationship between polydipsia and self-administration was thus confirmed for another reinforcing substance and another self-administration route.

The fact that in Experiment 1 a direct relationship was only observed between self-administration responding for sucrose and SIP but not for ethanol may be due to the weak reinforcing value of the ethanol concentration used. The direct relationship observed between polydipsia and amphetamine (Piazza et al., 1993) or sucrose (present experiment) self-administration, but not ethanol, suggests that this relationship depends not only on the nature of the substance but also on its concentration. In fact, the difference in SIP between high and low SA responding for ET, albeit not significant, followed the same trend as SA responding for ET. One could speculate that, if sucrose and ethanol concentrations could be made equipotent for reinforcing value, both substances would prove equally reinforcing, and a direct relationship between SA for ET and SIP when SA precedes SIP would eventually emerge.

Another aspect of the relationship between polydipsia and self-administration relates to the neurobiological substrate for compulsive and abusive behaviors, modeled by SIP and SA respectively. The hypothesis that brain biochemistry is similarly affected by compulsive behavior as by drugs of abuse (Holden, 2001) is supported by recent research pointing to neurochemical similarities between drug addiction and compulsive behaviors, such as reduction of dopaminergic receptors in both these disorders (Blum et al., 1996; Blum et al., 2000; Wang et al., 2004). In view of the possible relationship between drug dependence and compulsive behavior, it is perplexing that the direct relationship obtained between polydipsia and self-administration when SA preceded SIP was not observed in the reverse condition either by Piazza et al. (1993) or by the present authors. Why should animals that were first exposed to sucrose self-administration go on to develop polydipsia, whereas those that first became polydipsic did not subsequently develop self-administration? The latter result does not support the relationship between predisposition towards dependence and compulsive behavior, and was explained by Piazza et al. (1993) as an influence of the coping experience in reducing vulnerability to

addiction. However, both results may be understood in the context of the mesolimbic dopaminergic system. When the polydipsia procedure occurs first, the mesolimbic dopaminergic system is involved both in SIP acquisition and maintenance. SIP increment has been generally related to increases in dopaminergic activity (Mittleman et al., 1992; Tung et al., 1995). On the contrary, SIP disruption has been related to dopaminergic activity reduction (Abrous et al., 1993; Didriksen et al., 1993; Mittleman et al., 1990; Mittleman et al., 1994; Snodgrass and Allen, 1988; Weissenborn et al., 1996). Blum and collaborators (Blum et al., 1996; Blum et al., 2000) suggested that a "reward deficiency syndrome" characterizes drug abuse and compulsive behaviors such as gambling and excessive sex, which are facilitated in individuals with a low DA level, particularly in the accumbens. In fact, a dopaminergic deficiency is indeed present in animals and humans susceptible to drug addiction or compulsive eating (Wang et al., 2004).

From the above considerations an explanation for the seemingly conflicting results between the two experiments reported in the present work can be derived. Subjects exhibiting high SA might have started out from a "deficient reward system" and thus from a higher probability of emitting behavior leading to brain dopamine increase such as high SIP. The inverse relationship obtained when SIP preceded SA may be similarly explained. Initial exposure to SIP has been related to a greater dopaminergic response in SIP+ than in SIP− subjects. This greater dopaminergic activation makes subjects less sensitive to the subsequent effects of reinforcing substances. SIP− subjects, on the contrary, experienced a lower dopaminergic activation on SIP exposure. When later exposed to the drug, they were presumably more sensitive to its reinforcing effects, thus exhibiting high SA responding. Thus, vulnerability to substance abuse behavior may be reduced by prior experience in coping with stress.

Besides pointing to a correlative hypothesis between predisposition to substance dependence and emission of compulsive behaviors, our results corroborate the usefulness of SIP as an animal model of compulsive behavior and drug abuse (Cantor et al., 1982; Falk, 1977; Woods et al., 1993). The present data also highlight the importance of individual variability and of nature of the substance of abuse in vulnerability to addiction, and indicate that previous experience in dopaminergic activation is able to alter susceptibility to drug reinforcement. Certainly, additional studies will be necessary to clarify the behavioral and biological mechanisms influencing the effect of previous experience on vulnerability to drug reinforcement, thus contributing to advances in the management of excessive and compulsive behaviors.

References

Abrous DN, Choulli K, Rouge-Pont F, Simon H, Le Moal M, Herman JP. Effects of intracerebral dopaminergic grafts on behavioural deficits induced by neonatal 6-hydroxydopamine lesions of the mesotelencephalic dopaminergic pathway. Neuroscience 1993;54:499–511.

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 2000;32 (Suppl: i–iv):1–112.

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996; 89:396–400.

Cantor MB, Smith SE, Bryan BR. Induced bad habits: adjunctive ingestion and grooming in human subjects. Appetite 1982;3:1–12.

Didriksen M, Olsen GM, Christensen AV. Effect of clozapine upon schedule-induced polydipsia (SIP) resembles neither the actions of dopamine D1 nor D2 blockade. Psychopharmacology (Berl) 1993;113:250–6.

Falk J. The origin and fuctions of adjunctive behavior. Anim Learn Behav 1977(5): 325–35.

Falk JL, Tang M. What schedule-induced polydipsia can tell us about alcoholism. AlcoholClin. Exp Res 1988;12:577–85.

Hajnal A, Norgren R. Accumbens dopamine mechanisms in sucrose intake. Brain Res 2001;904:76–84.

Hodos W. Progressive ratio as a measure of reward strength. Science 1961;134:943–4.

Holden C. 'Behavioral' addictions: do they exist? Science 2001;294:980–2.

Mittleman G, Blaha CD, Phillips AG. Pituitary-adrenal and dopaminergic modulation of schedule-induced polydipsia: behavioral and neurochemical evidence. Behav Neurosci 1992;106:408–20.

Mittleman G, Rosner AL, Schaub CL. Polydipsia and dopamine: behavioral effects of dopamine D1 and D2 receptor agonists and antagonists. J Pharmacol Exp Ther 1994;271:638–50.

Mittleman G, Whishaw IQ, Jones GH, Koch M, Robbins TW. Cortical, hippocampal, and striatal mediation of schedule-induced behaviors. Behav Neurosci 1990;104: 399–409.

Piazza PV, Mittleman G, Deminiere JM, Le Moal M, Simon H. Relationship between schedule-induced polydipsia and amphetamine intravenous self-administration. Individual differences and role of experience. Behav Brain Res 1993;55:185–93.

Pitman RK. Animal models of compulsive behavior. Biol Psychiatry 1989;26:189–98.

Rapoport JL. The biology of obsessions and compulsions. Sci Am 1989;260:82–9.

Richardson NR, Roberts DC. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J Neurosci Methods 1996; 66:1–11.

Snodgrass SH, Allen JD. The effects of apomorphine on the acquisition of schedule-induced polydipsia in rats. Pharmacol Biochem Behav 1988;29:483–8.

Timberlake W, Lucas GA. Periodic water, interwater, and adjunctive behavior in a 24-hour multiresponse environment. Anim Learn Behav 1991;19:369–80.

Tung CS, Lu CC, Liu YP, Tseng CJ, Yin TH. Schedule-induced polydipsia increased both mesotelencephalic-dopaminergic and pontine-noradrenergic activities in the rat brain. Chin J Physiol 1995;38:57–63.

Wang GJ, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. J Addict Dis 2004;23:39–53.

Weiss F, Lorang MT, Bloom FE, Koob GF. Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants. J Pharmacol Exp Ther 1993;267:250–8.

Weissenborn R, Blaha CD, Winn P, Phillips AG. Schedule-induced polydipsia and the nucleus accumbens: electrochemical measurements of dopamine efflux and effects of excitotoxic lesions in the core. Behav Brain Res 1996;75:147–58.

Woods A, Smith C, Szewczak M, Dunn RW, Cornfeldt M, Corbett R. Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: a potential model for obsessive compulsive disorder. Psychopharmacology (Berl) 1993;112: 195–8.