Level of response suppression and amphetamine effects on negatively punished adjunctive licking

Ángeles Pérez-Padilla and Ricardo Pellón

The purpose of the present study was to investigate whether the level of response suppression is a major determinant of the effect of D-amphetamine on negatively punished adjunctive drinking. Rats were initially exposed to a multiple fixed-time (FT) 30-s FT 30-s food delivery schedule. They were then divided into two groups and subjected to one of two different multiple schedules, FT 30-s FT 45-s or FT 30-s FT 90-s. The FT 45-s and FT 90-s components were signalled by a tone. Comparably high levels of adjunctive licking were observed in both FT 30-s components, intermediate licking levels in the FT 45-s component, and little licking in the FT 90-s component. Licking during the FT 30-s components was subsequently punished by lick-contingent signalled delays (by a blackout) in food delivery. The duration of such delays was adjusted to reduce licking to levels obtained in the FT 45-s or FT 90-s components, respectively for each of the two groups. Punished licking was increased by 0.3 and 1.0 mg/kg of D-amphetamine, an effect that was greater in the FT 30-s FT 90-s group. No increase in licking was observed in the FT 45-s component, but the 1.0 mg/kg dose also increased responding in the FT 90-s component. In general, no statistically significant differences were found between the effects of D-amphetamine on punished and unpunished schedule-induced licking. As licking decreased during the FT 90-s component when the punishment contingency was introduced in the alternate component, the punishment procedure and FT 30-s component were entirely removed. On this occasion, D-amphetamine failed to increase licking induced by the FT 90-s schedule. These results indicate that the level of response suppression might be a good indicator of the degree to which D-amphetamine shows antipunishment effects on adjunctive licking reduced by negative punishment procedures. *Behavioural Pharmacology* 17:43–49 © 2006 Lippincott Williams & Wilkins.

Behavioural Pharmacology 2006, **17**:43–49

Keywords: D-amphetamine, food delays, punishment, rat, response suppression, schedule-induced licking

Animal Behaviour Laboratories, Department of Basic Psychology I, Faculty of Psychology, National University for Distance Learning, Madrid, Spain

Correspondence and requests for reprints to Ricardo Pellón, Departamento de Psicología Básica I, Facultad de Psicología, Universidad Nacional de Educación a Distancia, C/ Juan del Rosal 10, Ciudad Universitaria, 28040-Madrid, Spain Tel: +34 91 3986223; fax: +34 91 3987972; e-mail: rpellon@psi.uned.es

Sponsorship: Research was supported by Grant BSO2002-04322-C02-02 from McyT:DGI (Spain) and preparation of manuscript was aided by financial support from Universidad Nacional de Educación a Distancia.

Received 1 June 2005 **Accepted as revised** 6 October 2005

Introduction

Food-deprived rats exposed to intermittent presentations of food develop robust patterns of water intake as an adjunctive behaviour (Falk, 1961). This behaviour has been named schedule-induced polydipsia, in that there is no explicit contingency between drinking and food delivery (see reviews by Falk, 1971; Wetherington, 1982; Reid and Staddon, 1990; Pellón *et al.*, 1998). Water intake tends to occur in small quantities after, rather than before, presentation of each food pellet (see, however, Gilbert, 1974; Avila and Bruner, 1994; López-Crespo *et al.*, 2004).

Schedule-induced polydipsia is sensitive to environmental consequences. The amount of adjunctive drinking can be increased or decreased, respectively, by arranging on licking explicit contingencies of reinforcement or punishment (Bond *et al.*, 1973; Flory and Lickfett, 1974; Reberg, 1980; Pellón and Blackman, 1987). For example, Pellón and Blackman (1987) observed that schedule-induced polydipsia can be punished by presentation of lick-contingent delays in the reinforcer, an effect that can be modulated by the duration of the delay, the length of the inter-reinforcement interval and the level of food deprivation (Flory and Lickfett, 1974; Lamas and Pellón, 1995; Pellón and Castilla, 2000).

Pellón and colleagues (1992) exposed rats to a fixed-time (FT) 60-s food delivery schedule, and observed that D-amphetamine increased schedule-induced polydipsia, which was reduced by a negative punishment procedure such as that described above, in which each lick initiated a 10-s delay in the delivery of the next food pellet. This antipunishment effect was not observed after the administration of benzodiazepine diazepam. Furthermore, D-amphetamine did not show antipunishment effects when adjunctive drinking was reduced by a positive punishment procedure that entailed presentation of electric shocks contingent upon licks (Flores and Pellón, 1998). In these circumstances, however, diazepam proved

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effective in increasing punished behaviour. Thus, there seems to be a certain pharmacological specificity according to the type of punishment procedure used to reduce schedule-induced polydipsia (for comparable results in operant behaviour, see Miczek, 1973; Branch *et al.*, 1977).

So far, nothing is known about the specific behavioural mechanisms that might underlie the unusual effect of D-amphetamine on adjunctive drinking that is punished by delays in food presentation. Pérez-Padilla and Pellón (2003) demonstrated that such an effect could not be attributed to changes in reinforcement frequency, temporal discrimination or food reinforcer value. D-Amphetamine failed to increase adjunctive drinking, both in yoked-control rats that received the same delays as the experimental rats but non-contingently with their own licks, and in experimental rats to which the delays were applied from the onset of training rather than once the behaviour had developed.

It has also been reported that, in certain circumstances, amphetamine can increase punished operant behaviour (Foree *et al.*, 1973; Miczek, 1973; McKearney and Barrett, 1975). For instance, D-amphetamine increased operant behaviour when response rates were low and shock intensity was mild, or when responses produced electric shocks intermittently (Foree *et al.*, 1973).

The purpose of the present study was to investigate whether the level of response suppression is a major determinant of the effect of D-amphetamine on negatively punished adjunctive drinking. To this end, rats were subjected to a multiple FT 30-s FT 30-s food schedule that induced high levels of licking in both components. Thereafter, one of the components was changed to FT 45-s or FT 90-s, which, being lower reinforcement frequencies, led to lower adjunctive licking levels. At a later phase of the experiment, licks in the unchanged FT 30-s component were punished by delays in food delivery, until behaviour had been reduced to the levels obtained in the FT 45-s or FT 90-s schedules. The effects of D-amphetamine on licking punished by contingent delays and on similar although unpunished licking rates were then evaluated.

Methods

Subjects

Sixteen experimentally naive male Wistar rats, obtained from Charles River (Lyon, France) were used. All animals were monitored and fed daily, and began the experiment at 70 days of age. They were individually housed and placed in a room with controlled environmental conditions (21°C ambient temperature, 60% relative humidity and an 08.00/20.00 h light/dark cycle). The rats were gradually reduced to and maintained at 80–85% of their ideal free-feeding weight through food restriction, on the basis of a growth curve. Mean weight at the beginning of the experiment was 354 g (range 331–370 g). Animals were weighed daily at the beginning of each experimental session, had their diet calculated and were fed a minimum of 30 min after the end of the session. Water was freely available in the home cages. All animal care procedures were in accordance with the European Communities Council Directive.

Apparatus

The experiment was conducted in eight, $29 \times 24.5 \times 35.5$ cm, Letica Instruments LI-836 rodent-conditioning chambers (Barcelona, Spain). The chambers were enclosed in soundproofed housing, equipped with a ventilation system and a small observation window in the left panel. The front panel of each chamber was made of aluminium, the left-hand wall and roof of transparent Plexiglas and the remaining sides of black Plexiglas. Levers were permanently withdrawn during the course of the experiment. A water bottle was attached to the external side of the right wall of each chamber, with its spout accessible to the rat through a 3.2×3.9 cm aperture, located 20 cm from the front wall and 7 cm above the floor. The spout was positioned 2 cm from the wall aperture, in such a way that the rat could lick but not maintain permanent contact with it. Licks at the spout were detected when the electric circuit between the 16 parallel metal bars comprising the grid floor and the drinking bottle spout was completed via contact with the animal's tongue. The chambers were illuminated by two internal 3-W bulbs, placed on the upper part of the front panel to either side of the food hopper, and a 25-W ambient light fitted to the external housing. The ambient noise produced by the ventilation fan was 60 dB, which served to mask any other possible external sounds. With the aid of a Letica Instruments dispenser fitted to the outside of the front panel of each chamber, 45-mg food pellets (Bio-Serv, Frenchtown, New Jersey, USA) could be dropped into a small internal receptacle, situated on the front wall at a height of 3.7 cm above the floor, which served as a food tray. Events were scheduled and recorded using an IBM Pentium 133 personal computer installed with the MED-PC for Windows software package (MED Associates Inc., Georgia, Vermont, USA).

Behavioural procedure

On being stabilized at 80–85% of their free-feeding weight, all rats were subjected to a water-ingestion test in their own home cages. For two consecutive days, 120 45-mg food pellets were deposited at once in a tray and the amount of water consumed was recorded for a total period of 65 min. This procedure provided a baseline against which to compare the level of schedule-induced drinking observed subsequently in the 65-min experimental sessions, which called for intermittent delivery of the same number of food pellets as had been received by the animals in their home cages over the test period (Roper,

1981; Cohen and Looney, 1984; Pellón and Blackman, 1987).

The rats were then exposed to an adaptation session in the test chambers for 30 min, with 60 food pellets previously deposited in the food hopper, and with ventilation and illumination provided, but with no experimental contingency in operation. During this session, no water bottles were installed.

Thereafter, the rats were exposed to a multiple FT 30-s FT 30-s schedule of food pellet presentation over 25 sessions (phase A). Each component lasted 30 min, during which a food pellet was regularly delivered into the food tray at 30-s intervals, regardless of the animal's behaviour. Prior to each session, bottles containing 100 ml of fresh water were installed in each test chamber as described above. Lights were turned on at the beginning and turned off at the end of each session, with the chambers being darkened for 5 min to separate the two components (a time-out period). In addition, the second component was signalled by a tone.

Animals were then divided into two groups on the basis of the amount of water consumed and licks recorded at the end of phase A, in such a way that the groups were equivalent. The first group was exposed to a multiple FT 30-s FT 45-s schedule, while the second group was exposed to a multiple FT 30-s FT 90-s schedule (phase B). The tone signalled the FT 45-s and FT 90-s components. Food was delivered at the specified time intervals, regardless of the animal's behaviour. This experimental phase lasted 10 sessions.

In a third phase (phase C), licking by the animals in the FT 30-s component was punished by lick-contingent delays in the delivery of the next food pellet. Each lick initiated a delay, which was signalled by a blackout, the duration of which was adjusted to reduce licking to levels obtained in the FT 45-s and FT 90-s components, respectively, for each of the two groups of the experiment. The duration of the delay varied from 5 to 10 s for the group of rats subjected to the multiple FT 30-s FT 45-s schedule, and from 10 to 25 s for the group of rats subjected to the multiple FT 30-s FT 90-s schedule. When the punished and unpunished licking rates were stabilized (which happened after 15 experimental sessions), animals received administrations of different doses of D-amphetamine as described under Pharmacological Procedure below.

As lick rates decreased during the FT 45-s and FT 90-s components when the punishment contingency was introduced, the punishment procedure and the FT 30-s component were removed entirely during the final phase of the study (phase D). Accordingly, only the FT 45-s or the FT 90-s schedules were maintained for each of the two groups during 10 sessions. Subsequently, solely the animals of the FT 90-s condition were tested again with doses of D-amphetamine, as the lick rate increased during the last phase of the study and D-amphetamine led to unusual results the first time it was administered.

The number of licks at the bottle spout, volume of water consumed and number of food pellets delivered were measured for each session during each experimental phase.

Pharmacological procedure

Each rat from both groups was exposed to administration of *S*(+)-amphetamine sulphate (dextroamphetamine sulphate) at doses of 0.1, 0.3, 1.0 and 3.0 mg/kg; rats of group FT 30-s FT 90-s were then exposed for a second time to doses of D-amphetamine of 0.1, 0.3 and 1.0 mg/kg. The drug was dissolved in 0.9% saline solution and administered intraperitoneally at a volume of 1 ml/kg, 10 min prior to the experimental session. Drug doses were administered in random order, but all rats received the same dose on the same day. Drug sessions (Tuesdays and Fridays) were preceded by a control session, during which the animals were either not injected (Mondays), or were injected with saline at a volume of 1 ml/kg, 10 min prior to the experimental session (Thursdays). Wednesdays were control sessions without injection, but were not taken into account for data analysis.

For each rat and each experimental session, the same measures were taken as during the Behavioural procedure. The number of licks was converted into licks per minute, and the percentage of change was calculated for the rate of licking under each drug dose in comparison to that of control sessions without injection. The percentage of the control rate was calculated using the following formula: rate of response in the presence of any given drug dose divided by mean response rate in control sessions, multiplied by 100.

Statistical analysis

Licks per minute were subjected to separate two-factor analyses of variance (ANOVA) for the two groups of the experiment the first time D-amphetamine was administered, with a between-group factor (schedule component) and a within-subject factor (drug dose). The effect of the second administration of D-amphetamine in the licks per minute of group FT 30-s FT 90-s was analysed by a one-way ANOVA with drug dose as the within-subject factor. When necessary, post-hoc comparisons were calculated by Newman–Keuls tests. All these analyses were performed using the Statistica 5.0 package. The significance level was set at a minimum $P < 0.05$.

Results

Table 1 shows the data for the licks per minute at the end of each of the four experimental phases to which animals

were exposed over the course of the experiment. Not only did the two groups of rats develop comparably high lick rates in each of the two components of the multiple FT 30-s FT 30-s schedule during phase A, but within each group lick rates were also similar across the components. When, during phase B, one of the FT 30-s components was changed to FT 45-s or FT 90-s, the licking induced by those schedules declined sharply. This reduction was more marked in the FT 90-s (group 2) than in the FT 45-s component (group 1). Slight decreases were also observed in the unchanged FT 30-s components, although to a much lesser extent than in those that were changed.

The introduction of lick-contingent signalled delays in the unchanged FT 30-s component (phase C) led to reductions in the lick rate to levels close to those obtained in the FT 45-s and FT 90-s components, respectively, for groups 1 and 2. The percentage reduction in licks was 60% for the first group and 75% for the second. A slight fall-off in licks was likewise observed in the unpunished components, a decline that was proportionally more marked in the FT 90-s component of group 2 than in the FT 45-s component of group 1.

Table 1 Mean licks per minute (± standard error) during the last five sessions of each experimental phase

	Group 1		Group 2	
Phase A	FT 30-s	66.1 ± 0.8	FT 30-s	67.1 ± 0.4
	FT 30-s	60.8 ± 0.5	FT 30-s	60 ± 0.2
Phase B	FT 30-s	44.3 ± 0.9	FT 30-s	53.2 ± 0.1
	FT 45-s	27.5 ± 0.6	FT 90-s	7.5 ± 0.6
Phase C	FT 30-s (+ delays)	17.7 ± 0.5	FT 30-s (+ delays)	13.1 ± 0.7
	FT 45-s	20.7 ± 0.4	FT 90-s	4.9 ± 0.1
Phase D	FT 45-s	19.9 ± 0.2	FT 90-s	18.9 ± 0.1

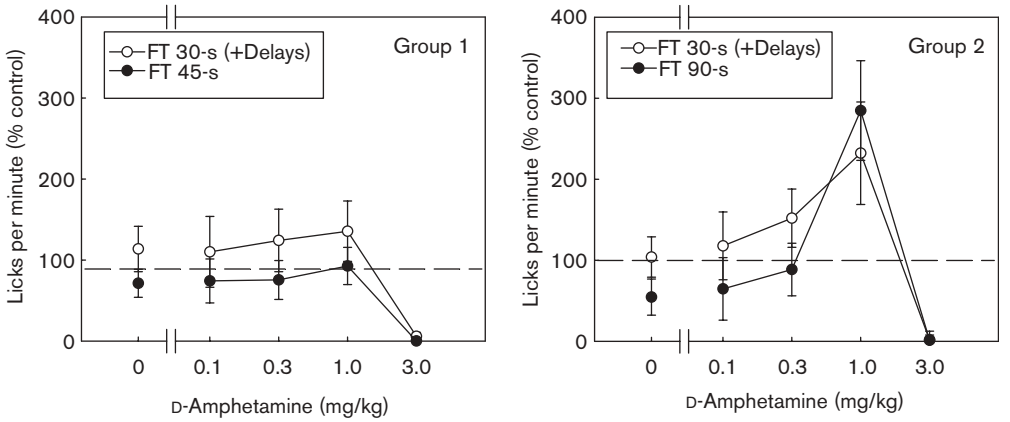
FT, fixed time.

In the last phase of the experiment (phase D), the punishment procedure and FT 30-s component were removed from both groups. Whereas for group 1 no changes in the lick rate were observed during the FT 45-s schedule, relative to the previous phase, for group 2, an increase in the response rate was observed for the FT 90-s schedule versus the previous phase (around 75% less licking during phase C than during phase D).

Figure 1 depicts the effects of the different doses of D-amphetamine on schedule-induced licking when the multiple FT 30-s (+ delays) FT 45-s schedule was in operation in the case of group 1 or the multiple FT 30-s (+ delays) FT 90-s schedule in the case of group 2 (phase C). The drug's effect on behaviour is expressed as the mean and standard error of the percentage change with respect to control rate without injection. Vehicle data (0 on the *X*-axis) correspond to the mean for licks per minute in sessions preceding the drug sessions in which saline was administered.

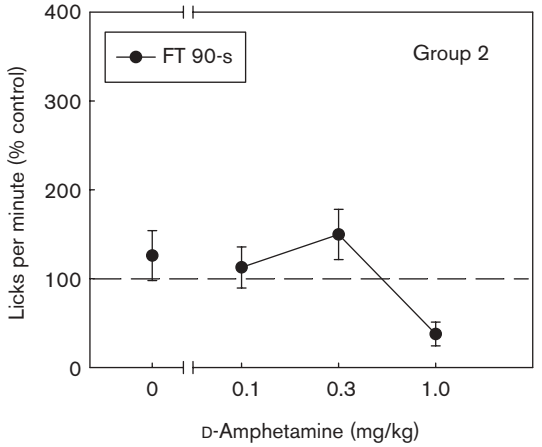
D-Amphetamine produced a dose-dependent effect in the licking rate, both in group 1 exposed to the FT 30-s (+ delays) FT 45-s schedule [$F(5,70) = 8.19$, $P < 0.01$], and in group 2 exposed to the FT 30-s (+ delays) FT 90-s schedule [$F(5,70) = 8.99$, $P < 0.01$]. No component effect was found in either of the two groups ($P > 0.05$), meaning that the drug affected equally the licking induced by the punished and unpunished components. Administration of vehicle had no effect on punished or unpunished licking rates in either group. Likewise, the dose of 0.1 mg/kg failed to alter adjunctive licking in either group. No significant effects were observed after the dose of 0.3 mg/kg in group 1, but in group 2 the licking rate was slightly increased ($P < 0.05$). The 1.0 mg/kg dose led to a significant increase in licks per minute in

Fig. 1



Effects of different doses of D-amphetamine on the licking rate of the two groups of the experiment, in the fixed time (FT) 30-s component punished with lick-contingent signalled delays in the presentation of the next food pellet (open circles), and in the unpunished FT 45-s or FT 90-s component (filled circles).

Fig. 2



Effects of different doses of D-amphetamine on the licking rate induced by the fixed time (FT) 90-s food schedule in group 2.

group 2 ($P = 0.01$), but this increase was not statistically significant in group 1 ($P = 0.06$). The dose of 3.0 mg/kg almost entirely suppressed licking in both groups ($P < 0.01$). No statistically significant interaction ($P > 0.05$) between drug dose and component was found for either group.

Figure 2 depicts the effect of the second administration of D-amphetamine on adjunctive licking, in this case, when animals of group 2 were exposed to a single FT 90-s schedule (phase D). As in the previous figure, data are shown as the mean and standard error of the percentage change in the licking rate with respect to the control sessions without injection. D-Amphetamine resulted in a dose-dependent effect on licks per minute [$F(4,28) = 5.47$, $P < 0.01$]. Neither vehicle nor doses of 0.1 and 0.3 mg/kg had any statistically significant effect. The dose of 1.0 mg/kg led to a significant decrease in licks per minute ($P < 0.05$).

Discussion

Animals developed schedule-induced licking when exposed to intermittent food delivery schedules, amount of licking being a function of inter-food interval length (Falk, 1966; Flory, 1971). The highest licking rate was induced with exposure to an FT 30-s schedule, a rate that was successively lower after exposure to FT 45-s and FT 90-s schedules. The FT 45-s schedule induced 55% fewer licks per minute than did the FT 30-s schedule, and the FT 90-s schedule induced 88% fewer licks. This relationship between licking rate and food frequency is in line with previous results reported by our laboratory (Pellón, 1992; Flores and Pellón, 1995).

The licking induced by the FT 30-s schedule was substantially reduced when each lick was punished by the initiation of a signalled delay in the presentation of the next food pellet. Comparable results have been obtained previously, in studies of both acquisition and maintenance of the behaviour (Flory and Lickfett, 1974; Moran and Rudolph, 1980; Pellón and Blackman, 1987, 1991). The suppression of licking depends critically on the duration of the delay for any given inter-food interval (Pellón and Castilla, 2000). In this study, therefore, the duration of the delays was adjusted so that the rate of licking induced by an FT 30-s schedule was reduced to values similar to those induced when FT 45-s or FT 90-s schedules were used. The duration of such delays in the second condition was more than double that in the first one, which somehow also led to reductions in the unpunished rates of licking induced by the FT 90-s schedule.

Schedule-induced drinking reduced by negative punishment procedures, such as the introduction of lick-contingent delays in food delivery, can be selectively increased by acute administration of D-amphetamine (Pellón *et al.*, 1992; Pérez-Padilla and Pellón, 2003). The purpose of the present study was to evaluate whether the level of response suppression might be an important determinant of this D-amphetamine-generated antipunishment effect. Support for this hypothesis is provided by the observation that the more the introduction of contingent delays reduced the rate of licking, the greater the effect of the drug. D-Amphetamine doses of 0.3 and 1.0 mg/kg served to increase punished adjunctive licking the most when behaviour was most reduced, as with the FT 30-s (+ delays) FT 90-s condition in group 2 versus the FT 30-s (+ delays) FT 45-s condition in group 1.

In a wide variety of circumstances, the behavioural effects of amphetamines may be described as dependent on the baseline response rate. Thus, although moderate doses of amphetamine mainly increase low response rates, they have a lesser effect on moderate rates and reduce high rates (Sanger and Blackman, 1976; Dews and Wenger, 1977). While this result may at times explain the effect of drugs on punished operant behaviour (Foree *et al.*, 1973; McMillan, 1973), the general principle of rate dependency would not seem to be able to account for the present results. Low rates of unpunished schedule-induced licking, comparable to punished licking rates, were not increased by D-amphetamine. Indeed, the rate-dependency effect on adjunctive behaviour appears to follow an inverse pattern, whereby high rates are less reduced than low rates after administration of D-amphetamine (Robbins *et al.*, 1983; Flores and Pellón, 1995). This was not the result obtained, however, for punished and unpunished licking alike.

Somewhat surprisingly, D-amphetamine was also observed to increase adjunctive licking during the unpunished FT 90-s component, when presented in the context of a multiple schedule, with the other component involving a punishment contingency. Amphetamines, far from increasing unpunished adjunctive drinking, normally lead only to decreases at high doses (McKearney, 1973; Smith and Clark, 1975; Sanger, 1978; Williams and White, 1984; Pellón *et al.*, 1992; Flores and Pellón, 1995). In view of the finding that the licking rate declined in the FT 90-s component when the punishment contingency was introduced in the FT 30-s component, this could be indicative of a generalized punishment effect. When the punishment contingency and FT 30-s component were removed, rats' behaviour recovered in the FT 90-s schedule. In this case, D-amphetamine failed to increase schedule-induced licking. These results obtained with the FT 90-s schedule can be explained by reference to the suppression-rate hypothesis. If rats experienced a generalized punishment, the degree of such indirect punishment was similar to that directly caused by delays in the FT 30-s component. The percentage of behavioural suppression during phase C was similar for both components of the multiple FT 30-s FT 90-s schedule (around 75%) and greater than for the FT 30-s component of the multiple FT 30-s FT 45-s schedule (around 60%), which would appear to indicate that, in this case, the degree of response suppression could also be a good predictor of the antipunishment effect of D-amphetamine.

Amphetamine effects on punished adjunctive licking depend on the type of punishment procedure used to decrease behaviour (Pellón *et al.*, 1992; Flores and Pellón, 1998), resulting in increases only after suppression by lick-dependent delays in food delivery. Although there remains a need for a better characterization of the effect of amphetamine on operant behaviour punished by the withdrawal of positive reinforcers (as opposed to punishment by the contingent presentation of aversive events), amphetamine effects on operant behaviour also seem to depend on the type of event that maintains the behaviour (Johanson, 1978). Such similar modulation of the behavioural effects of amphetamine on operant and adjunctive patterns of behaviour suggest that common behavioural mechanisms might be involved in the maintenance of all behavioural patterns sustained by intermittent reinforcement schedules (for a fuller discussion, see Pellón and Flores, 2005).

Acknowledgement

We thank M.A. Villajos for technical support.

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