Can the DRL 72s schedule selectively reveal antidepressant drug activity?

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Abstract The effects of three antidepressants, desipramine (2.5–20 mg/kg), tranylcypromine (0.63–2.5 mg/kg), mianserin (1.25–10 mg/kg) and three non-antidepressants, chlordiazepoxide (CDP; 1.25–10 mg/kg), haloperidol (0.02–0.16 mg/kg), d-amphetamine (0.31–1.25 mg/kg) were evaluated in rats responding for water reinforcement under a DRL 72s schedule. The antidepressants all produced dose-related decreases in overall response rates, but no significant changes in reinforcement frequency. In contrast, the anxiolytic CDP did increase the number of reinforcers obtained. Haloperidol decreased both reinforcers and responses whilst d-amphetamine stimulated responding, thereby decreasing reinforcement frequency. An analysis of the modes of inter-response times (IRTs) revealed no significant shifts in the peaks of the IRT distributions for most of the drugs tested. Amphetamine, however, (0.31 and 0.63 mg/kg) decreased the modal values in correspondence with the shift to the left of the peak of responding caused by this compound. These results are discussed in the context of the use of the DRL 72s procedure as a screening test for antidepressant drugs.

Key words Antidepressants • DRL 72s schedule Water reinforcement • Chlordiazepoxide d-Amphetamine • Haloperidol • Rat

Introduction

Under differential reinforcement of low-rate (DRL) schedules, animals are trained to respond at low rates, only being reinforced when responses are separated by a specified time period. The schedule is defined by what is said to be the waiting period, for example, DRL 15s, DRL 20s etc. A variety of different psychoactive drugs have been studied using DRL schedules and many have been found to disrupt timing behaviour either by increasing response rates with a concomitant reduction in the number of reinforcers obtained (e.g., Segal 1962) or by simply decreasing responding (e.g., Kelleher et al. 1961). In some cases, a detailed analysis of the behaviour enabled a differentiation between classes of drug with apparently similar effects on response rates. For example, Sanger et al (1974) showed that whilst chlordiazepoxide (CDP) and d-amphetamine both decreased the efficiency of temporal discrimination in a DRL 15s schedule, a study of the inter-response time (IRT) distributions revealed that only CDP increased response bursting. More recently, Seiden and colleagues have developed a DRL 72s schedule of water reinforcement, in rats, as a model for the behavioural effects of antidepressant drugs (Seiden and O’Donnell 1985). In order to validate the procedure, Seiden and colleagues have studied the effects of many antidepressant treatments on the DRL 72s schedule. The tricyclics (O’Donnell and Seiden 1983), the monoamine oxidase inhibitors (O’Donnell and Seiden 1982; Marek and Seiden 1988) and atypical antidepressants (Seiden et al. 1985) have all been reported to show a similar profile, in that they increased the rate of reinforcement whilst decreasing responses, thus temporal discrimination appeared to be more efficient. Electroconvulsive shock treatment was also found to have an antidepressant-like profile (Seiden et al. 1985). Other categories of psychoactive drugs could be differentiated, since antipsychotics such as chlorpromazine and haloperidol decreased both response and reinforcement rates (O’Donnell and Seiden 1983; Seiden et al. 1985). These findings appear to provide support for the idea that a DRL 72s schedule can function as a behavioural test for antidepressant drugs. However, others have
not always obtained such a clear differentiation between therapeutic classes (Pollard and Howard 1986).

There is a clear need for procedures characterising antidepressant drug effects and operant schedules offer the possibility of obtaining objective data under conditions of good behavioural control. In addition, models based on timing behaviour might be of interest in the light of hypotheses of depression set in the context of dysrhythmia (Healy 1987). We therefore undertook an independent evaluation of drug effects on behaviour under control of a DRL 72s schedule of water reinforcement, in rats. We studied three known antidepressant drugs (mianserin, tranylcypromine, desipramine) and three non-antidepressants (haloperidol, CDP, d-amphetamine). In order to maximise the possibility of differentiating between these compounds, in addition to overall measures of responding and reinforcers obtained, data on IRT distributions were also collected. Our analyses were particularly aimed at detecting enhanced performance following drug administration.

Materials and methods

Subjects

Animals were male Wistar rats (Ifa Credo, France) weighing 200–220 g on arrival at the laboratories. They were housed individually in grid floor cages and maintained on a 12-hour light-dark cycle with lights off at 1900 hours. Rats had free access to standard laboratory food at all times but water was restricted to 20 min access on weekdays, following the experimental session. At weekends, water was available ad libitum until Sunday afternoon. Water was withdrawn on Sundays, such that a similar amount of deprivation time elapsed before the Monday session, as it did every other day of the week.

Apparatus

The experimental apparatus consisted of four standard operant conditioning boxes housed in sound-attenuating chambers and which were fan-ventilated. In each of the boxes, a house-light was mounted on the right-hand wall above a combination pellet-dipper trough. A response lever was located to the right of the pellet-dipper, 2.5 cm above the grid floor. Water reinforcement was delivered by raising the dipper (containing 0.02 ml water) from the water trough to the access port for four seconds. The scheduling of contingencies and recording of data were controlled using a SKED-11 system (State Systems, Kalamazoo, Mich., USA) implemented on a PDP-11 computer (Digital Equipment Corporation, France).

Procedure

The rats were trained and tested during daily 1 h sessions in the operant conditioning chambers. They commenced under a fixed-ratio 1, fixed-time 30-s schedule for water reinforcement, until they had completed 100 lever presses during a session. Following this they were placed on a DRL 18 s schedule where IRTs of 18 s or longer were required for a lever press to result in the delivery of a reinforcer. After 3 weeks (15 sessions) the schedule was changed to DRL 72s; thus the IRT requirement was raised to 72 s.

The rats continued to be trained under the DRL 72s schedule until they met the following criterion: the standard error of the mean (SEM) was less than 10% of the mean of response rates during the last five consecutive sessions (excluding data collected on Mondays) and the number of reinforcers obtained during each of these sessions was not less than seven. Following this, pre-session saline (0.9%) injections were initiated and the rats continued to be trained under the DRL 72s schedule until they reached the same criterion again. The total number of sessions required to achieve both criteria was designated the session to criterion (STC) for training.

When rats had reached STC for training, studies of drug effects on DRL 72 s performance began. The animals continued to be tested during daily 1 h sessions, but once or twice weekly, test compounds were administered in place of pre-session saline injections. Drug tests were only carried out on days following a stable performance during the preceding saline session (excluding data collected on Mondays). The criteria for stable performance were that the number of session responses should not be greater than two standard deviations from the mean of response rates during the last five training sessions and that the number of reinforcers should not be less than seven. It should be noted that throughout training and testing, any data obtained on Monday sessions were excluded and the subjects were required to reach criteria for stable responding independently of their performance on the first day of the week. This was done to ensure that baselines were stable for drug testing.

Data Analysis

Data collected for the number of reinforcers obtained and the total session responses were subject to within subjects Analysis of Variance (ANOVA) followed by Dunnetts t-tests. These data were also used to calculate efficiency ratios (responses/reinforcers) which were analysed in the same way. Thus smaller ratios represented a more efficient performance (i.e. fewer lever presses emitted per reinforcer) and larger ratios correspond to a less efficient performance (more presses per reinforcer). For desipramine, reinforcer and response rate data were also expressed as a percentage of baseline values obtained on the day before the test session, prior to the same analysis.

Inter-response times (IRTs) were collected during the test sessions and allocated to ten 12-s time bins (<12 s, 12–24 s, 24–36 s, 36–48 s, 48–60 s, 60–72 s, 72–84 s, 84–96 s, 96–108 s, >108 s). These data were first expressed as a percentage of total and then subjected to a two-way ANOVA using treatment and bin as within-subject factors. An estimate of the peak position of the IRT distributions was calculated. This was done by first determining the modal IRT for each rat (excluding data from the first and the last time bins) and then averaging these values per treatment group. Data from the first and last time bins were excluded from the calculation since the IRT distributions were typically trimodal, and a measure of the central peak of responding was required. Preliminary analyses including these data revealed inaccurate measures. The modal values were analysed by within subjects ANOVA followed by Dunnett’s t-tests.

Drugs

The drugs used in these experiments were desipramine hydrochloride (Sigma, France; six rats per treatment group), d-mianserin hydrochloride (Organon; n = 8), tranylcypromine sulphate (SKF, France; n = 8), d-amphetamine sulphate (Coop. Pharm. Francaise; n = 10) chloridiazepoxide hydrochloride (CDP, Sigma, France; n =10) and haloperidol (Research Biochemicals, France; n = 8). They were each dissolved in distilled water, except for haloperidol which was prepared in distilled water plus a minimal amount of lactic acid (8.5%). The drugs were administered subcutaneously (SC) 30 min before the test session in a volume of 10 ml/kg. In a separate experiment, desipramine was injected intraperitoneally (IP) 60 min before the test (n = 10). All doses of drugs are expressed in terms of the base.