



Quantitative analysis of performance on a progressive-ratio schedule: effects of reinforcer type, food deprivation and acute treatment with Δ^9 -tetrahydrocannabinol (THC)

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ABSTRACT

Rats' performance on a progressive-ratio schedule maintained by sucrose (0.6 M, 50 μ l) and corn oil (100%, 25 μ l) reinforcers was assessed using a model derived from Killeen's (1994) theory of schedule-controlled behaviour, 'Mathematical Principles of Reinforcement'. When the rats were maintained at 80% of their free-feeding body weights, the parameter expressing incentive value, a , was greater for the corn oil than for the sucrose reinforcer; the response-time parameter, δ , did not differ between the reinforcer types, but a parameter derived from the linear waiting principle (T_0), indicated that the minimum post-reinforcement pause was longer for corn oil than for sucrose. When the rats were maintained under free-feeding conditions, a was reduced, indicating a reduction of incentive value, but δ was unaltered. Under the food-deprived condition, the CB1 cannabinoid receptor agonist Δ^9 -tetrahydrocannabinol (THC: 0.3, 1 and 3 mg kg⁻¹) increased the value of a for sucrose but not for corn oil, suggesting a selective enhancement of the incentive value of sucrose; none of the other parameters was affected by THC. The results provide new information about the sensitivity of the model's parameters to deprivation and reinforcer quality, and suggest that THC selectively enhances the incentive value of sucrose.

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1. Introduction

In ratio schedules of reinforcement, the subject is required to emit a specified number of responses, N , to obtain a reinforcer. In progressive-ratio schedules, N is systematically increased, usually from one reinforcer to the next (Hodos, 1961; Stafford and Branch, 1998), but sometimes after batches of two or more reinforcers (Baunez et al., 2002; Randall et al., 2012) or between successive sessions (Griffiths et al., 1978; Czachowski and Samson, 1999). Performance on progressive-ratio schedules is characterised by rapid responding under low ratios which peters out as N is increased. The ratio at which the subject stops responding, the breakpoint,

is widely regarded as a measure of the subject's motivation or the incentive value of the reinforcer (Hodos, 1961; Hodos and Kalman, 1963 for review, see Ping-Teng et al., 1996; Killeen et al., 2009).

Despite its widespread use, several authors have expressed doubts about the specificity of the breakpoint (Arnold and Roberts 1997; Killeen et al., 2009; Bradshaw and Killeen, 2012), pointing out that it is sensitive not only to changes in the incentive properties of reinforcers (Rickard et al., 2009; Gosnell et al., 2010) but also to non-motivational manipulations such as changes in the response requirement (Skjoldager et al., 1993; Aberman et al., 1998) and the ratio step size (Covarrubias and Aparicio, 2008). It has also been noted that the breakpoint shows considerable variability, being derived from a single point in time while data from the rest of the session are ignored, and that its definition is arbitrary, there being no consensus as to the time that must elapse without a response before responding may be said to have stopped (Arnold and Roberts, 1997; Killeen et al., 2009).

Many of the shortcomings of the breakpoint may be avoided by the use of quantitative models of performance on progressive-ratio schedules, for example the model recently proposed by Bradshaw and Killeen (2012). This model was derived from Killeen's (1994) general theory of schedule-controlled behaviour, the Mathematical

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Principles of Reinforcement (MPR), according to which schedule-controlled responding is determined by an excitatory effect of reinforcers on behaviour, biological constraints on responding, and the efficiency with which schedules couple responses to reinforcers. In addition, the progressive-ratio model invokes the linear waiting principle (Wynne et al., 1996) to predict the escalating duration of the post-reinforcement pause in successive ratios, thereby yielding a dynamic account of performance on this schedule. The linear waiting principle expresses the finding that the post-reinforcement pause on trial i , $T_{P,i}$, is linearly related to the total inter-reinforcement interval on trial $i-1$, $T_{TOT,i-1}$:

$$T_{P,i} = T_0 + kT_{TOT,i-1} \quad (1)$$

where the parameters T_0 and k represent the minimum post-reinforcement pause and the slope of the linear waiting function. The progressive-ratio model contains two key equations that define running response rate, R_{RUN} , and overall response rate, $R_{OVERALL}$:

$$R_{RUN,i} = \frac{1}{\delta(1 + T_{TOT,i-1}/a)} \quad (2)$$

$$R_{OVERALL,i} = N_i/T_{TOT,i} \quad (3)$$

The parameter a ('specific activation'), which is defined as the duration of behavioural activation induced by a single reinforcer, is regarded as an index of incentive value. δ is the minimum time needed to execute a response (the reciprocal of the maximum response rate), and is regarded as a measure of the biological limitations on responding (Killeen, 1994; Reilly, 2003; Covarrubias and Aparicio, 2008; Sanabria et al., 2008; Bradshaw and Killeen, 2012).

Several lines of evidence support these interpretations of a and δ . Consistent with the notion that a is an index of incentive value, it has been found that this parameter is monotonically related to the volume of a sucrose-solution reinforcer (Rickard et al., 2009; data re-analysed by Bradshaw and Killeen, 2012). Recently, Olarte-Sánchez et al. (2013) compared the values of a for corn oil and sucrose reinforcers; their findings were consistent with extant evidence that sucrose is less efficacious than corn oil on a volume-for-volume basis, but more efficacious on a calorie-for-calorie basis (Naleid et al., 2008). Valencia-Torres et al. (2014) found that diabetes induced by systemic treatment with streptozotocin was associated with a reduction of a , consistent with an antihedonic effect of this treatment (Nefs et al., 2012). D_1 and D_2 dopamine receptor antagonists also reduce a , consistent with the purported antihedonic effect of these drugs (Olarte-Sánchez et al., 2012; data re-analysed by Bradshaw and Killeen, 2012; Olarte-Sánchez et al., 2013). Some drugs with known sedative properties, including clozapine and cyproheptadine, have been found to increase the response-time parameter δ (Olarte-Sánchez et al., 2012; data re-analysed by Bradshaw and Killeen, 2012).

The experiment described in this paper further explored the utility of the progressive-ratio model. The aims were firstly to examine the sensitivity of the parameters of the model to the food deprivation condition and the type of reinforcer used, and secondly to examine the effect of Δ^9 -tetrahydrocannabinol (THC), a principal constituent of cannabis resin with high affinity for CB1 cannabinoid receptors (Gaoni and Mechoulam, 1964; Howlett, 2002; Ledent et al., 1999; Matsuda et al., 1990), on the parameters of the model. Since, ex hypothesi, a represents the incentive value of a reinforcer, it was expected that the value of this parameter would be greater under conditions of food deprivation than under free-feeding conditions. Moreover, in view of the known orexigenic effect of THC (Abel, 1975; De Luca et al., 2012; Higgs et al., 2003; Williams et al., 1998; Williams and Kirkham, 2002a,b), it was expected that this drug would induce an increase in the value of a . However, in apparent conflict with the latter prediction, Olarte-Sánchez et al. (2012) recently reported that THC had no effect on the value of a for food-

pellet reinforcers. The present experiment extended these findings by examining the effect of THC on performance on progressive-ratio schedules maintained by sucrose and corn oil reinforcers. In addition, since Olarte-Sánchez et al. (2012) analysed their data using an earlier model derived from MPR, designed to account for performance on fixed-ratio schedules (Killeen, 1994), a re-analysis of their data was carried out using the new progressive-ratio model.

2. Methods

The experiment was carried out in accordance with UK Home Office regulations governing experiments on living animals.

2.1. Subjects

Twenty-four female Wistar rats (Charles River, UK) approximately 4 months old and weighing 250–300 g at the start of the experiment were used. They were housed individually under a constant cycle of 12 h light and 12 h darkness (light on 0600–1800 h), and were maintained at 80% of their initial free-feeding body weights (see below) by providing a limited amount of standard rodent diet after each experimental session. Tap water was freely available in the home cages.

2.2. Apparatus

The rats were trained in operant conditioning chambers (CeNeS Ltd. Cambridge, UK) of internal dimensions 25 × 25 × 22 cm. One wall of the chamber contained a central recess covered by a hinged Perspex flap, into which a peristaltic pump delivered the liquid reinforcer (see below). An aperture located 5 cm above and 2.5 cm to one side of the recess (left for half the subjects; right for the other half) allowed insertion of a motorised retractable lever (CeNeS Ltd. Cambridge, UK) into the chamber. The lever could be depressed by a force of approximately 0.2 N. The chamber was enclosed in a sound-attenuating chest with additional masking noise generated by a rotary fan. No houselight was present during the sessions. An Acorn microcomputer programmed in Arachnid BASIC (CeNeS Ltd. Cambridge, UK) located in an adjacent room controlled the schedule and recorded the behavioural data.

2.3. Behavioural training

Two weeks before starting the experiment the food deprivation regimen was introduced and the rats were gradually reduced to 80% of their free-feeding body weights. They were randomly allocated to two groups that underwent training with different reinforcers: 50 μ l of a 0.6 M solution of sucrose in distilled water ($n = 12$), and 25 μ l of undiluted corn oil ($n = 12$). The rats were first trained to press the lever for the liquid reinforcer, and were then exposed to an fixed-ratio 1 schedule for 3 days followed by fixed-ratio 5 for a further 3 days. Thereafter, they underwent daily training sessions under the progressive-ratio schedule. The progressive-ratio schedule was based on the exponential progression: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, ..., derived from the formula $(5 \times e^{0.2n}) - 5$, rounded to the nearest integer, where n is the position in the ratio sequence (Roberts and Richardson, 1992). Sessions took place at the same time each day during the light phase of the daily cycle (between 0800 and 1300 h) 7 days a week. At the start of each session, the lever was inserted into the chamber; the session was terminated by withdrawal of the lever 40 min later.

2.4. Drug treatment

Injections of THC were given on Tuesdays and Fridays, and injections of the vehicle alone on Mondays and Thursdays; no injections

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