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Research report

The effects of cocaine and mazindol on the cognitive judgement bias of rats in the ambiguous-cue interpretation paradigm

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HIGHLIGHTS

- We tested the effects of cocaine and mazindol on cognitive judgement bias in rats.
- Cognitive judgement bias was measured by the ambiguous-cue interpretation test.
- Cocaine treatment did not change the cognitive judgement bias in rats.
- Mazindol treatment made rats more 'pessimistic'.

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ABSTRACT

Recent research has shown that pharmacological enhancement of dopaminergic function increases an optimism bias in humans. The present study investigated whether acute dopaminergic system stimulation through the administration of two dopamine-mimetic drugs, cocaine and mazindol, have similar effects in rats. To accomplish this goal, after initial behavioural training, two groups of rats received single injections of either cocaine or mazindol and were subsequently tested with the ambiguous-cue interpretation (ACI) paradigm. Both drugs were administered in three doses using the fully randomised Latin square designs. Cocaine (1, 2 and 5 mg/kg) had no significant effect on the interpretation of the ambiguous cue. Mazindol at all three doses (0.5, 1 and 2 mg/kg) significantly biased animals towards negative interpretation of the ambiguous cue. The results are discussed in relation to pharmacological and behaviourally evoked actions of tested compounds.

1. Introduction

According to popular folk wisdom, some people see their glass half full, and other people see their glass half empty. In fact, it is true that people vary in their interpretation of ambiguous events and the extent to which they react to negative or positive information. These cognitive judgement biases termed pessimism and optimism have been recently linked with negative and positive affective states. Specifically, negative emotions are associated with a tendency for pessimistic judgements [1,2], and positive emotions are associated with greater optimism [3]. In 2012, the first neurochemical substrate for optimism was reported. Sharot and colleagues [4] demonstrated that administration of a drug that enhances dopaminergic function (dihydroxy-L-phenylalanine; L-DOPA) increases optimism bias in humans by impairing their ability to update their beliefs in response to undesirable information about the future. Despite these findings, the information about the possibility of pharmacological manipulation of cognitive judgement bias is meagre.

The recent development of the ambiguous-cue interpretation paradigm [5,6] has created a unique opportunity for studying the pharmacological correlates of cognitive judgement bias in animals. In this paradigm, rats are trained to press a lever in an operant chamber to receive a food reward that is contingent on one tone and to press another lever in response to a different tone to avoid punishment by mild electric foot-shock. The tones acquire positive and negative valence, and the training continues until the rats accomplish a stable, correct discrimination ratio. After attaining stable discrimination performance, the animals are tested. Ambiguous cue testing is composed of a discrimination task, as described above, with the presentation of additional tones with intermediate frequencies (between positive and negative tones). The lever press

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response pattern to the ambiguous cue is considered an indicator of the rat's expectation of a positive or negative event, in other words, as 'optimism' or 'pessimism', respectively (for details, see [5,7–9]).

Using this paradigm, we recently demonstrated that the valence of the rats' judgements can be changed not only by positive and negative emotions but also by acute pharmacological stimulation of the serotonergic (5-HT), noradrenergic (NA) and dopaminergic (DA) systems using citalopram, desipramine and amphetamine, respectively [10]. Considering the optimism-inducing effects of L-DOPA in humans [4] and similar effects of amphetamine observed in animals [10], the present study was designed to investigate whether other dopamine-mimetic drugs, with different mechanism of action, cocaine and mazindol, could exert similar, pro-optimistic effects in rats. As cocaine is not only DA but also 5-HT and NA re-uptake inhibitor and mazindol, apart from its dopamine-mimetic profile, is a potent NA re-uptake inhibitor [11–14], we hypothesised that the serotonergic and noradrenergic components of the tested drugs might affect and modulate the DA-derived optimistic bias.

To verify this hypothesis, after initial behavioural training, two groups of rats received single injections of either cocaine or mazindol and were subsequently tested on the ACI paradigm. Each drug was administered in three doses using fully randomised Latin square designs.

2. Material and methods

2.1. Ethics statement

These experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee for Animal Experiments at the Institute of Pharmacology, Polish Academy of Sciences.

2.2. Subjects and housing

In total, 48 (16 in experiment with cocaine and 32 in experiment with mazindol) male *Sprague Dawley* rats (Charles River, Germany) that weighed 175–200 g upon arrival (±6 weeks old) were used in this study. The rats were group-housed (4 rats/cage) in standard type IV makrolon cages (59 × 38 × 20 cm), in a temperature-controlled room (21 ± 1 °C) with 40–50% humidity under a 12/12-h light/dark cycle (lights on at 06:00 h). During all of the experiments, the rats were mildly food restricted to approximately 85% of their free-feeding weights. This goal was achieved by providing 15–20 g of food per rat per day (standard laboratory chow). The food restriction started 1 week prior to training. Water was freely available, except for during the test sessions. The behavioural procedures and testing were performed during the light phase of the light/dark cycle, between 09:00 and 17:00 h.

2.3. Apparatus

The behavioural tasks were performed in 8 computer-controlled Skinner boxes (MedAssociates, St Albans, Vermont, USA), where each box was equipped with light, a speaker, a liquid dispenser (set to deliver 0.1 ml of 5% sucrose solution), a grid floor through which scrambled electric shocks (0.5 mA) could be delivered, and two retractable levers. The levers were located at opposite sides of the feeder. All of the behavioural protocols, including the data acquisition and recordings, were programmed in Med State notation code (Med Associates). The experimental procedures for the ACI test used in this study were modified versions of the procedures previously described by Enkel and colleagues [5] and have been described elsewhere [7–9].

2.4. Behavioural training

2.4.1. Positive tone training

During this phase, the rats were trained to press the lever located on the left side of the feeder to receive the sucrose solution when a tone (50 s, 2000 Hz at 75 dB) signalled the availability of a reward. Because of its association with a palatable reward, this tone acquired a positive valence and was referred to as the "positive tone," and the associated lever was referred to as the "positive lever." A reliable active lever pressing for the reward was achieved in three training steps: (a) presentation of the positive tone (lasting 50 s) co-occurred with a constant delivery of the sucrose solution and was followed by a 10 s intertrial interval (ITI); (b) presentation of the positive tone co-occurred with a left lever extension and was followed by a 10 s ITI (each lever press during the tone was continuously rewarded by sucrose solution delivery); and (c) was similar to (b) with the exception that after the first lever press and reward delivery, the tone was terminated and followed by a 10 s ITI. During the ITIs, the levers retracted. Each training session lasted for 30 min, and the training sessions continued until the animals attained a stable performance on each of the training steps (more than 200 responses maintained over three consecutive training sessions during step (b)); a minimum of 90% successful responses to the positive lever following a positive tone presentation maintained over three consecutive sessions during step (c). Positive tone training was followed by negative tone training.

2.4.2. Negative tone training

During this stage, the rats were trained to press the lever located on the right side of the feeder to avoid an electric shock [0.5 mA, 10 s) when another tone (50 s, 9000 Hz at 75 dB) signalled a forthcoming punishment. Because of its association with a concomitant punishment, this tone acquired a negative valence and was referred to as the "negative tone." The associated lever was referred to as the "negative lever". A reliable active lever press avoidance response was achieved in two training steps: (a) the presentation of the negative tone was accompanied by the occurrence of electric shocks unless the rat pressed the right (negative) lever, which terminated the shock and tone presentation; (b) the presentation of the negative tone preceded the occurrence of the electric shocks. The delay from the tone onset to the electric shock occurrence was progressively increased from 1 s to 40 s. Pressing the negative lever before the shock onset terminated the tone and began a 10 s ITI, which was designated the "prevention response." Pressing the negative lever after the shock onset terminated the tone and shock and was referred to as the "escape response." The maximum duration of the tone/shock application was 50 s (i.e., 40 s of tone presentation followed by 10 s of a tone/shock co-occurrence), and the tone presentations were separated by 10 s ITIs. During the ITIs, the levers retracted. Daily training sessions contained 40 tone presentations. The animals had to accomplish at least 60% correct prevention responses maintained over three consecutive training sessions before they were allowed to proceed to the discrimination training. The performance criterion for the prevention responses was set lower than that for the reward responses because during the negative tone training the animals had to additionally overcome their natural tendency to freeze after the conditioned stimulus (negative tone) presentation.

2.4.3. Discrimination training

During this phase, the rats were trained to discriminate between positive and negative tones by responding to the appropriate levers (as learned in previous training stages) to maximise reward and minimise punishment delivery. The tones, which were composed of 20 positive and 20 negative tones, were presented pseudo-randomly and separated by 10 s ITIs, during which the levers