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The effects of acute pharmacological stimulation of the 5-HT, NA and DA systems on the cognitive judgement bias of rats in the ambiguous-cue interpretation paradigm

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Abstract
In the present study, we investigated the effects of acute pharmacological stimulation of the serotonergic (5-HT), noradrenergic (NA) and dopaminergic (DA) systems on the valence of cognitive judgement bias of rats in the ambiguous-cue interpretation (ACI) paradigm. To accomplish this goal, after initial behavioural training, different groups of rats received single injections of citalopram, desipramine or *d*-amphetamine and were subsequently tested with the ACI paradigm. Each drug was administered in 3 doses using a fully randomised Latin square design. Citalopram at the dose of 1 mg/kg significantly biased animals towards positive interpretation of the ambiguous cue, while at higher doses (5 and 10 mg/kg), the animals interpreted the ambiguous cue more negatively. Desipramine at all 3 tested doses (1, 2 and 5 mg/kg) significantly biased animals towards negative interpretation of the ambiguous cue, while *d*-amphetamine at the dose of 1 mg/kg induced positive bias, having no effects at lower doses (0.1 and 0.5 mg/kg). Our results indicate that cognitive bias in rats can be influenced by acute pharmacological intervention.

1. Introduction

Why is it that for some people, the glass is half full, whereas for others, it is half empty? Which neurobiological mechanisms determine the way that we predict the consequences of our actions? How can expectations of the potential outcomes of our actions be altered? Answers to these

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questions are crucial for understanding the mechanisms that underlie human decision-making. Cognitive bias is an endophenotype also associated with stress-related disorders wherein anxious individuals tend to adopt more pessimistic judgments and depressed individuals tend to adopt not only more pessimistic but also less optimistic judgments of the ambiguous stimuli (MacLeod and Byrne, 1996; Wright and Bower, 1992). In animals, cognitive bias is observed in approach/avoidant behaviour to a range of ambiguous stimuli intermediate of an appetitive stimulus and an aversive stimulus in several animal models of stress and depression (Bateson and Matheson, 2007; Doyle et al., 2011; Enkel et al., 2010; Matheson et al., 2008; Papciak et al., 2013; Rygula et al., 2013; Salmeto et al., 2011). Cognitive bias has been shown to be pharmacologically sensitive in humans (Harmer et al., 2009; Mogg et al., 2004; Stein et al., 2012) and recent research suggests that reduced negative outcome predictions, which result in 'optimistic' processing bias, can be induced by pharmacological enhancement of the dopamine function (Sharot et al., 2012). Studies in animals revealed that stress-induced negative cognitive bias can be reversed by antidepressant treatment with imipramine (Hymel and Sufka, 2012) and recent research suggested an important role for serotonin (Anderson et al., 2013); however, apart from these pioneering reports, the neurochemical background of cognitive judgement bias and the possibility of its pharmacological modulation remain poorly understood.

The monoaminergic neurotransmitters serotonin (5-HT), noradrenaline (NA) and dopamine (DA) have been long associated with emotional regulation (Daw et al., 2002; Dayan and Huys, 2009; Harmer et al., 2009; Sharot et al., 2012; Willner et al., 2012). For instance, the "monoamine hypothesis" of depression, which involves imbalances in 5-HT, NA and DA functions (Schildkraut, 1965), has dominated notions and explanations of the pathophysiology of depression since the empirical discovery of the antidepressant properties of monoamine oxidase inhibitors (MAOIs) and tricyclics about fifty years ago. Although currently this theory is regarded as not sufficient to explain the mechanism of action of antidepressants due to the lag in therapeutic effects, selective serotonin and noradrenaline re-uptake inhibitors have been shown to modulate emotional processing also in healthy volunteers following acute and short-term treatment (Harmer et al., 2004).

The recent development of the ambiguous-cue interpretation paradigm (Enkel et al., 2010; Harding et al., 2004) has created a unique opportunity for studying the neurochemical correlates of cognitive judgement bias in animals. In this paradigm, the 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 ready to be tested. Ambiguous cue testing is composed of a discrimination task, as described above, with the presentation of additional tone(s) that have a frequency that is intermediate between positive and negative tones. The pattern of lever press responses to this ambiguous cue is taken as an indicator of the rats' expectation of a positive or negative event, in other words, as 'optimism' or 'pessimism', respectively (for details, see Enkel et al. (2010), Papciak et al. (2013), Rygula et al. (2012, 2013)).

The present study has been designed to investigate the effects of acute pharmacological stimulation of the 5-HT, NA and DA systems on the valence of the cognitive judgement bias of rats and to further validate the ambiguous-cue interpretation paradigm by using drugs that are known to change emotional states. To accomplish this goal, after initial behavioural training, different groups of rats received single injections of the selective serotonin reuptake inhibitor (SSRI) citalopram, the noradrenaline reuptake inhibitor desipramine or the DA (and to a lesser extent NA and 5-HT) releaser *d*-amphetamine, and they were subsequently tested on the ACI paradigm. Each drug was administered in 3 doses using a fully randomised Latin square design.

2. Experimental procedures

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, sixty-eight male *Sprague Dawley* rats (Charles River, Germany) that weighed 175–200 g upon arrival were used in this study. The rats were group-housed (4 rats/cage) 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.

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 20% sucrose solution), a grid floor through which scrambled electric shocks (0.5 mA) could be delivered, and 2 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 (Enkel et al., 2010) and have been described elsewhere (Papciak et al., 2013; Rygula et al., 2012, 2013).

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 sound pressure level (SPL) or 9000-Hz at

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