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Antidepressants alleviate the impact of reinforcer downshift

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Abstract

Depressive disorder is associated with problems of coping with life's difficulties, including episodes of frustration and disappointment, operationally defined as an unexpected reinforcer omission or a reduction of reinforcer magnitude. In a novel model aimed at detecting potential antidepressants, rats were trained in the operant task under progressive ratio schedule of reinforcement with the break point (BP, the value of the last completed response ratio) as a behavioral endpoint. In the main experiment, a 32% sucrose solution was initially used as the reinforcer. Once the stable responding was achieved, for the following 5 days animals were treated once daily with the experimental drugs, and were offered a 4% sucrose solution instead. In vehicle-treated controls, the reduction of sucrose concentration resulted in a decrease in responding from a BP of about 40 (totaling 166 responses) to a BP of about 9 (totaling 22 responses). Chlordiazepoxide (4 and 8 mg/kg), fluoxetine (3 mg/kg), citalopram (6 mg/kg) and cocaine (2.5 and 5 mg/kg) markedly inhibited this response decrement, while fluoxetine (6 mg/kg) augmented it. Neither desipramine (1–6 mg/kg) nor morphine (1–5 mg/kg) affected responding under the reduced sucrose concentration condition. In the control experiment, the rats have never been offered 32% sucrose solution but their responding was always maintained by 4% sucrose. Under these unchanged conditions, only cocaine (5 mg/kg) affected (increased) responding. The present results suggest that the antidepressants selectively inhibiting serotonin reuptake and a benzodiazepine anxiolytic but not psychostimulant cocaine may specifically protect animals from the effects of a reinforcer downshift.

1. Introduction

The development of novel antidepressants and investigation of neurobiological aspects of depression is possible owing to the existing screening procedures and animal models. While currently used screening procedures (e.g. forced swim test,

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tail suspension test) accurately characterize antidepressants acting mostly on the monoaminergic pathways, their face and construct validity is negligible (Willner and Mitchell, 2002). It cannot be excluded that this is the reason why in recent years there is so little progress in finding novel, clinically effective antidepressants with other mechanisms of action (Sams-Dodd, 2005). In contrast to the screening procedures, animal models of depression are characterized by a much better predictive, face and construct validity. They attempt to model *all* possible symptoms of this disorder that can possibly be modeled in animals, including loss of interest or sense of pleasure (anhedonia), psychomotor changes, fatigue, loss of energy and sleep or food intake disturbances. As this is apparently a goal too difficult to be achieved in laboratory rodents, there are no ideal models of depression. Consequently, if a model does not fulfill rigorous criteria for all validities, it is regarded to have limited relevance (Willner and Mitchell, 2002).

An alternative approach is to study only an isolated symptom that is affected by antidepressants. The symptom can be common for more disorders than just the major depression, yet should be effectively relieved by antidepressants. For instance, antidepressants alleviate irritability in the rat model of the premenstrual dysphoric disorder (Schneider and Popik, 2007). While the premenstrual dysphoric disorder is obviously characterized by different symptomatology than that observed in major depression, an important observation is that antidepressants alleviate the severity of both disorders. Thus, one may hope that the development and use of novel tests based on investigating an isolated, but relevant symptom, will enhance the chance of finding active antidepressants that were "missed" by screening procedures.

One of the apparent symptoms of major depression is a low tolerance to disappointment or frustration that are manageable by healthy individuals (Klinger, 1975; Nesse, 1999; Millan, 2006). In some cases, untreated depressed patients experiencing life difficulties even do not attempt to cope with them, since they find their situation hopeless. It has been proposed that reduced responses to disappointing or frustrating events are of adaptive nature (Nesse, 2000). The efficacy of antidepressants in treating major depression is manifested by an improvement of clinical signs, including an enhancement of mood and drive, and abandonment of suicidal ideations and sense of being hopeless. However, the clinical studies specifically addressing whether antidepressants could restore the physiological reactivity to stressful events are sparse, though they have demonstrated, for instance, a fluoxetine-induced reduction of Multidimensional Anger Inventory scores (Rubey et al., 1996).

In the laboratory, one may induce a sense of frustration or disappointment by unexpectedly omitting or lowering the magnitude of the reward, i.e., by producing contrast effects between its actual postshift value with the past preshift one (Flaherty, 1999). In a variety of tests based on the so-called successive negative contrast (SNC), an anxiolytic benzodiazepine (Rosen and Tessel, 1970) and an opioid receptor agonist (Wood et al., 2005) have reduced the reactivity to a decreased reward magnitude, while an opioid receptor antagonist (Pellegrini et al., 2005) and corticosterone (Bentosela et al., 2006) potentiated the effects of reward reduction. This pharmacological profile likely suggests some stress-protecting effects of the drugs that enhance the well being of the subject, and conversely, some stress-promoting effects of the compounds producing aversive actions or increasing the stress response.

Surprisingly, the effects of antidepressants on the response to a reward downshift were hardly characterized. The only study was published by Flaherty et al. (1977) who investigated the "simultaneous" contrast in consummatory behavior, where the rats in one session were briefly offered both 32% and 4% sucrose solutions. In that study, neither imipramine nor chlordiazepoxide affected the responding. Nonetheless, the authors cited the work of Bloomfield (1972), who found that an antidepressant abolished the contrast effects in pigeons in an instrumental setting, and proposed that this could be due to the reduction of behavioral inhibition in the presence of a negative (S^-) stimulus. Similarly, Terrace (1963) has postulated that the effects of imipramine on S^- responding may operate by reducing the aversiveness of the negative stimulus.

Since the operant behavior with progressive ratio (PR) schedule of reinforcement allows for quantification of the motivation to obtain a reinforcer, we used this technique to investigate the effects of antidepressants on the response to a reinforcer downshift. We expected that antidepressants and an anxiolytic benzodiazepine would protect the animals from the purported disappointment.

2. Experimental procedures

The 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, Institute of Pharmacology.

2.1. Animals

Male Sprague–Dawley rats (Institute of Pediatrics, Prokocim, Kraków) were housed four per cage in a temperature (21 ± 1 °C) and humidity (40–50%) controlled colony room under 12/12-hour light/dark cycle (lights on at 0600 h). Behavioral testing was carried out 7 days a week during the light phase of the light/dark cycle. Animals were food-deprived starting one week before the beginning of the experiment and were maintained at 85% of their free-feeding weight by once daily feeding. The standard laboratory chow (Labofeed H, Kcynia, Poland) was offered not earlier than 30 min after the end of the daily session. Rats' weight ranged 290–350 g prior to food deprivation. Tap water was always available *ad libitum* in home cages.

2.2. Apparatus

Experiments were conducted in four identical operant chambers enclosed in sound-attenuated and ventilated cubicles (Coulbourn Instruments Inc., Lehigh Valley, PA, USA). Each chamber was illuminated by a single house light and was equipped with one lever (2.5 cm above the grid floor). A cue-light signaled the availability of the reinforcer provided by a retractable liquid dipper delivering 0.05 ml of sucrose solution for 5 s. Stimulus events and data acquisition were controlled by a personal computer.