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Indices of extinction-induced "depression" after operant learning using a runway vs. a cued free-reward delivery schedule

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ABSTRACT

Loss of reward is one of the etiological factors leading to affective disorders, such as major depression. We have proposed several variants of an animal model of depression based on extinction of reinforced behavior of rats. A number of behaviors emitted during extinction trials were found to be attenuated by antidepressant treatment and, thus, qualified as indices of extinction-induced "despair". These include increases in immobility in the Morris water maze and withdrawal from the former source of reward as well as biting behavior in operant chambers. Here, we assess the effects of reward omission on behaviors after learning of (a) a cued free-reward delivery in an operant chamber and (b) food-reinforced runway behavior. Sixty adult male Wistar rats were either trained to receive food reinforcement every 90 s (s) after a 5 s lasting cue light (FI 90), or to traverse an alley to gain food reward. Daily drug treatment with either the selective serotonin reuptake inhibitor citalopram or the tricyclic antidepressant imipramine (each 10 mg/kg) or vehicle was begun either 25 days (operant chamber) or 3 days (runway) prior to extinction. The antidepressants suppressed rearing behavior in both paradigms specifically during the extinction trials, which indicates this measure as a useful marker of depression-related behavior, possibly indicating vertical withdrawal. In the operant chamber, only marginal effects on operant learning responses during extinction were found. In the runway, the operant learned responses run time and distance to the goal, as well as total distance moved, grooming and quiescence were also influenced by the antidepressants, providing a potential set of markers for extinction-induced "depression" in the runway. Both paradigms differ substantially with respect to the anticipation of reward, behaviors that are learned and that accompany extinction. Accordingly, antidepressant treatment influenced different sets of behaviors in these two learning tasks.

1. Introduction

Loss of reward and reinforcement in the onset and maintenance of affective disorders, especially major depression (MD), have been implicated in psychopathological theories of depression (Ferster, 1973). The episodes of depression are often triggered by the loss of positive reinforcer, such as loss of employment, partnership, health, and physical abilities (Hammen, 2005), resulting in avoidance behavior, such as escape and withdrawal, which represent a critical precursor predisposing to as well as contributing to the maintenance of depression (Ferster, 1973; Trew, 2011). Besides feelings of despair, helplessness as well as psychomotor agitation or slowness of movement (American Psychiatric Association, 1994), avoidance and withdrawal behaviors as a result of loss of reinforcement, represent core symptoms of depression (Ferster, 1973; Trew, 2011).

Given the close relationship between absence of reward and the occurrence of affective disorders, particularly MD, we set out to examine the effects of operant extinction on rodent behavior. In our earlier studies, we focused on the extinction of negatively reinforced behavior and provided evidence that the behavioral effects of the extinction procedure resemble those found in other animal models of depression. In the Morris water maze, where rodents learn to escape from the aversive water onto an invisible platform (negative reinforcement), the amount of immobility displayed increased over trials, when the platform was no longer present (loss of negative reinforcement – extinction) (Schulz, Buddenberg, & Huston, 2007a; Schulz, Huston, Buddenberg, & Topic, 2007b; Schulz, Topic, de Souza Silva, & Huston, 2004). This extinction-induced immobility was attenuated by the antidepressant desipramine (Schulz et al., 2007a) and correlated with a number of anxiety-related behaviors (Schulz et al., 2007a, 2007b), mimicking the co-morbidity with anxiety disorders found in human patients (Mineka, Watson, & Clark, 1998). Furthermore, a number of neurobiological alterations also seen in major depression, including stress markers of the hypothalamus-pituitary adrenal (HPA) axis,

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changes in monoamine neurotransmitters as well as neurotrophins in specific regions of the brain involved in MD, were accompanied by the behavioral alterations found after extinction (Schulz et al., 2004; Topic, Oitzl, Meijer, Huston, & de Souza Silva, 2008b; Topic et al., 2008a; for review see Huston, Schulz, & Topic, 2009), supporting the hypothesis that the procedure of operant extinction in rodents leads to depressive-like behaviors.

Given the important role of the loss of positive reinforcer in human depression (Carvalho, Trent, & Hopko, 2011; Ferster, 1973), we also started to employ the extinction-induced depression model on the basis of positive reinforcement derived from food reward (Huston, van den Brink, Komorowski, Huq, & Topic, 2012; Komorowski et al., 2012). Operant extinction results in elevated levels of corticosterone in rodents (Coover, Goldman, & Levine, 1971; Kawasaki & Iwasaki, 1997), indicating that the loss of reinforcement represents stress for the animal. Furthermore, during operant extinction rats exhibit a greater spatial variability (Devenport, 1984) and respond to it with an increase in aggressiveness (Azrin, Hutchinson, & Hake, 1966; Dantzer, Arnone, & Mormede, 1980), motor activation (Flaherty, 1982; Flaherty, Troncoso, & Deschu, 1979), anxiety-like behavior (Komorowski et al., 2012; Schulz et al., 2007a) or escape responses (Bentosela, Barrera, Jakovcevic, Elgier, & Mustaca, 2008; Daly, 1974; Huston et al., 2012; Komorowski et al., 2012; Norris, Pérez-Acosta, Ortega, & Papini, 2009). We hypothesized, that withdrawal from positive reward during extinction could serve as a behavioral marker of a depressive-like state and examined this question by using a cued fixed-time reward delivery paradigm in an elongated operant chamber as well as food-reinforced lever-pressing response in a Skinner-box, which was connected to a withdrawal chamber (Huston et al., 2012; Komorowski et al., 2012). We found an attenuating effect of antidepressants on rearing and aggressive biting behavior during extinction in the two-compartment chamber (Huston et al., 2012). Also the withdrawal behavior shown by vehicle-treated rats, assessed by the number of entries and sojourn time in the lever-pressing paradigm and the distance gradient in the elongated operant chamber, was reduced by antidepressant treatment (Huston et al., 2012; Komorowski et al., 2012). Furthermore, the extinction procedure induced anxiogenic-like effects in the open field, which were alleviated by antidepressant treatment (Komorowski et al., 2012). These results indicated that withdrawal and avoidance behavior, common symptoms of MD, may serve as behavioral markers for extinction-induced depression.

Besides the spatial horizontal withdrawal and avoidance behavior, animals also exhibit so called exploratory-related behavior during extinction, usually interpreted as being emitted in the service of information gathering (e.g. Fowler, 1965). In our previous study with the two-compartment chamber, we found indication that also rearing behavior may be sensitive to antidepressant treatment and, thus, qualify as a behavioral marker for depression (Huston et al., 2012). However, also a reducing effect on general activity levels upon imipramine treatment was found, which may have confounded the results. Here, the selective serotonin reuptake inhibitor (SSRI) citalopram and the tricyclic antidepressant (TCA) imipramine were applied chronically in a lower dose of 10 mg/kg, which was derived on the basis of our previous study (Komorowski et al., 2012). Treatment was administered during the final acquisition trials and subsequent extinction trials. Furthermore, in order to assess, whether the behavioral markers for extinction-induced depression found upon extinction in variants of the operant chamber also hold in other operant paradigms, we also investigated the effects of antidepressants on extinction behavior in a straight runway. We expected to find a set of operant as well as other behaviors, such as rearing, to be sensitive to antidepressant treatment in both task situations.

2. Materials and methods

2.1. Subjects

In total 60 male outbred Wistar rats (weight: 303.60 g ± 2.07 SEM) with an age of 3 months and derived from the animal breeding facility of the University of Düsseldorf, were used. They were housed in standard Macrolon cages of type IV in groups of five animals per cage and maintained under standard laboratory conditions with a reversed light/dark cycle (lights off from 7:00 AM to 7:00 PM). Animals had free access to water, but were food deprived for 5 days before beginning of the experiment during which they received 10 g of standard laboratory food chow (Ssniff Spezialdiät) per rat and day between 4:00 and 6:00 PM. Upon feeding, care was taken that each animal ate something of the chow and they were weighed daily. The experiments were carried out during the active period of the rats between 8:30 AM and 2:00 PM. Experiments were performed in accordance with the German law on protection of the animals and approved by the state authority (Bezirksregierung Düsseldorf).

2.2. Drug administration

The SSRI citalopram (Cipramil, Lundbeck, Germany) or the TCA imipramine (10,11-Dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine hydrochloride, 5-[3-(Dimethylamino)propyl]-10, 11-dihydro-5H-dibenz[b,f]azepine hydrochloride; Sigma–Aldrich, Germany) was diluted in distilled water, which was used as the vehicle. According to the random group assignment, animals received an intraperitoneal (i.p.) injection of either vehicle or citalopram or imipramine in a dosage of 10 mg/kg with an injection volume of 1 ml/kg body weight.

2.3. Operant chamber and procedures

2.3.1. Apparatus

Two standard modular operant chambers (12″W × 10″D × 12″H; Habitest; Coulbourn Instruments, USA), made of two clear transparent and two stainless steel walls placed opposite to each other and having a grid floor, were used. In the middle of one side of the steel walls a triple cue light (yellow, green, red) was positioned in a height of 8 cm. The opposite wall was equipped with a house light mounted in the middle near the top, providing illumination of about 1 lux during the whole testing session. A food cup with an integrated photo detector was located in a height of 5 cm from the bottom of the chamber below the house light. This food cup was connected to a food magazine outside of the operant chamber containing BioServ® Dustless precision pellets. The operant chambers were situated separately in dark, sound attenuating boxes, equipped with a masking white noise generator and two video cameras (Sony, CCD), one at the top and one at one side of the chambers, to allow observation of behavior. The cameras were connected to a TV screen and a DVD recorder for video recording and post hoc analysis of the behavior, which was carried out via the manually recorded behavior module of the Any-Maze Software (Version 4.5, Stoelting, USA). All modules from the operant chambers were connected to a computer and controlled by the related GraphicState program (Version 3, Coulbourn Instruments, USA). The operant chambers were cleaned with an ethanol solution (70%) after each trial.

2.3.2. Procedure

For the operant chambers 40 animals were used. They were brought to a holding room located next to the experimental room at least 30 min before beginning of testing to allow acclimatization.