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Research report

Slower extinction of responses maintained by intra-cranial self-stimulation (ICSS) in an animal model of attention-deficit/hyperactivity disorder (ADHD)

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Abstract

Children with attention-deficit/hyperactivity disorder (ADHD) show performance deficits and excessive motor activity during extinction and in situations where no reinforcer can be identified, suggesting an extinction deficit in ADHD possibly linked to dopamine dysfunction.

The present study examined extinction of responding previously maintained by intra-cranial self-stimulation (ICSS) in spontaneously hypertensive rats (SHR), an animal model of ADHD using three different extinction procedures. Delivery of electrical pulses were terminated altogether or presented independently of responding using two different current intensities.

The results showed that more responses were retained in the SHR, especially during the initial transition from ICSS-maintained responding to response-independent delivery of electrical pulses with current reduced relative to that given during reinforcement.

Slower extinction of previously reinforced behavior is suggested as an alternative explanation for the frequently observed increased behavioral output that has previously been interpreted as "disinhibition" of behavior in ADHD.

Keywords: Catecholamine; Reward; Hyperkinesis; Hyperkinetic disorder

1. Introduction

ADHD is characterized by developmentally inappropriate levels of attention, activity, and impulsivity, usually appearing before the child is 7 years old [2,4]. The disorder affects 3–5% of school-age children; thus, making it one of the most common behavioral disorders of childhood [39] and leads to social or occupational maladjustment in 50–70% of adolescents and young adults diagnosed with ADHD in childhood [5].

Twin-, adoption-, and family studies have estimated heritability to be ∼80% in ADHD. Because of the assumed primary site of action of the stimulant drugs, dopamine genes have been the initial candidates in the search of the genetic basis of ADHD (e.g. [7,8,19]). Research on pharmacology, genetics, neurobiology, neuroanatomy, and behavior frequently indicate dopamine as central in the etiology of ADHD.

Several studies have demonstrated that the behavior of children with ADHD is affected differently by reinforcement contingencies, and suggested that altered reinforcement processes is a central factor in ADHD [9,18,28,36,41].

Reinforcement is associated with dopamine release, especially in the ventral striatum. Normally, there is a tonic "background" level in dopamine activity, allowing both a phasic increase, as well as a phasic decrease in activity. Reinforcement is associated with a phasic increase in dopamine activity [34,42]. Omission of a predicted reinforcer and delivery of a reinforcer with a lower than predicted reinforcer value is associated with a short-lasting phasic decrease in dopamine activity [33].

We have suggested that reinforcement and extinction processes are altered in ADHD as results of dysfunctioning

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dopamine systems [14,30]. An abnormally low tonic dopamine activity in ADHD may cause a failing extinction signal due to a "floor" effect [14,30]. This means that elimination of previously reinforced, but no longer maintained, responses will be slower than normal in ADHD. Consistent with this view are findings of performance deficits during extinction tasks [13] and excessive motor activity during extinction and in situations where no reinforcer can be identified [25,28,40] in children with ADHD.

The present study examined extinction of behavior in spontaneously hypertensive rats (SHR). The SHR is a genetic model bred from its normotensive progenitor Wistar Kyoto rat (WKY), and has been thoroughly validated as an animal model of ADHD [26,27]. Previous results have shown that the extinction process may be slowed in the SHR [15], and that more responses are retained in the SHR during extinction [32].

In the present study, extinction of lever pressing previously reinforced and maintained by intra-cranial self-stimulation (ICSS) was tested. A bipolar electrode was surgically implanted rostral to the ventral tegmental area (VTA) aimed at the dopaminergic projection to the ventral striatum. Small electrical pulses delivered contingent on lever presses in an operant chamber served as the reinforcer.

Effects of extinction were examined using three different behavioral procedures. Experiment 1 investigated effects of discontinuing the response–reinforcer contingencies by totally terminating the electrical pulses (EXT). In Experiments 2 and 3, intra-cranial electrical pulses previously used to reinforce and maintain behavior were presented independently of responding in order to check if the mere delivery of response-independent electrical pulses, "free" reinforcers, affected the extinction process. The "free" reinforcers were administered according to a variable time (VT) schedule of reinforcement. Assuming a slowed reduction of responding during the VT compared to the EXT schedule due to fortuitous reinforcement, reducing the reinforcer value during the VT schedule may decrease the effect of this "accidental reinforcement". Thus, the conditions in experiment 3 were the same as in experiment 2, with the exception that the current of the "free" electrical pulses delivered during the VT schedule was reduced by 15% (VTre). This condition was included to test how the reduction in the current intensity (i.e., reinforcer value) used during the VT schedule affected rate of responses retained in SHR compared to controls.

Thus, the present experiments were designed to test the hypothesis that more responses are retained during extinction and response-independent reinforcer delivery in the SHR compared to normal controls.

2. General method

2.1. Subjects

Data from seven male NIH-strain spontaneously hypertensive rats (SHR) and nine male NIH-strain Wistar Kyoto (WKY) control rats bred by a commercial supplier (Harlan, UK) are reported (see [16] for details). The animals weighed between 270 and 420 g at the time of surgery.

The animals were housed individually in opaque plastic cages 425 mm × 266 mm × 280/310 mm (height) and had free access to water and food (Beekay Feeds, BK Standard RM 1, B&K Universal Limited). During weekdays, each animal was kept in a transport box located in a room adjoining the experimental laboratory. The temperature was kept at about 20 °C. During weekends, the animals stayed in temperature and humidity controlled animal quarters (20 ± 2 °C and 55 ± 10%, respectively). In both housings, lights were on between 08:00 and 20:00 h.

The experiment, with project number 99.18B, was approved by the Norwegian Animal Research Authority (NARA), and was conducted in accordance with the laws and regulations controlling experiments/procedures in live animals in Norway.

2.2. Surgery and histology

The surgical procedure is described in [16]. In short, each rat was implanted with a bipolar electrode made of two stainless steel insect pins with a diameter of 0.25 mm (Article 101a no. 000, Benifidan, Denmark) glued together with dental cement approximately 0.7 mm apart center to center. The uninsulated tip of reach electrode was approximately 0.2 mm. The insect pins were soldered to two pedestal pins (MS363 Pedestal 2298 6 pin, Plastics One, Roanoke, VA, USA). The electrode was surgically implanted aimed at the rostral dopamine projection of the ventral tegmental area (VTA) from a flat-skull position.

After testing, the rats were sacrificed, the brains were removed and kept in formalin before cut in 25 μm coronal sections and stained with cresyl violet. The histological data were examined microscopically to determine the exact locus of the electrode tip.

2.3. Apparatus

The experiment was conducted in two LeHigh Valley Electronics (LVE) one-lever Rodent Test Cages (Model 1417) and two Tech Serv (BRS/LVE) two-lever RTC-024 Rodent Test Cages located in small environment cubicles. All the levers required 15 g to close, and were programmed to operate on the release of the lever after it had been pressed down. One 2.8 W green cue light positioned 5 cm straight above the lever was lit during the experimental session (for details, see [16]).

Four Coulbourne Instruments stimulators delivered the electrical stimulation. Two of the stimulators were of model A13-65, and two of model E13-65. The electrical pulses used throughout the experiment were 0.5-s trains of 100 Hz 0.1 ms rectangular biphasic pulses. The animals were connected to the stimulator through a cable (363–363 W/SPR cable, Plastics One, Roanoke, VA, USA), which was suspended from an electrical swivel mounted in a plastic container in the center