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Selective Attention Dysfunctions in Adult Rats Neonatally Treated with 6-Hydoxydopamine[1]

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OKE, A. F. AND R. N. ADAMS. *Selective attention dysfunctions in adult rats neonatally treated with 6-hydroxydopamine.* PHARMAC. BIOCHEM. BEHAV. 9(4) 429–432, 1978.—Adult rats treated intracisternally with 6-hydroxydopamine during the perinatal period were trained on a black-white discrimination. Alterations in cue shape and cue location failed to selectively distinguish differences in response patterns for the treated animals. However, when irrelevant stimuli were added to the discriminative array, the 6-hydroxydopamine group evidenced marked impairment of performance throughout the period of distraction.

Selective attention Neonatal Distractibility 6-Hydroxydopamine Brain catecholamines

THE DEPLETION of brain catecholamines by 6-hydroxydopamine (6-OHDA) has produced a variety of behavioral disruptions which implicate attentive dysfunctions. The introduction of novel stimuli to a behaving animal treated with 6-OHDA has been shown to produce exaggerated interruptions in runway performance [15] as well as increased reactivity in an open field [2]. Similarly treated animals have also demonstrated retarded habituation to novel stimulation in both familiar [15] and unfamiliar [16] environments. The phenomenon of increased responding in the absence of reward (i.e., resistance to extinction), which becomes accentuated in animals treated with 6-OHDA [10,11], has been argued to result possibly from attentional deficits [11].

A categorical distinction has been made between selective attention and attentional states resulting from increased arousal or activation [13,17]. Inherent in selective attention is the ability to select properly from an array of relevant/irrelevant stimuli. The present study investigates selective attentional deficits produced in adult rats through neonatally administered 6-OHDA. These deficits were examined in terms of the sensitivity to irrelevant stimuli during the performance of a visual discrimination task.

METHOD

Animals

Fourteen Sprague-Dawley rats received intracisternal 6-OHDA or vehicle solution 1 day post partum. Injections of 10 μl containing either 100 μg of 6-OHDA in vehicle solution (0.1% ascorbic acid in saline) (N−9) or vehicle solution (N−5) were accomplished using light ether anesthetic. Ninety days later each rat was individually housed and reduced to 80% of ad lib body weight by partial food deprivation. Maintenance of an approximate 80% deprivation level throughout the experiment required periodic adjustments in body weight by increased food allowance (ca. 7 g/week) in accordance with the normal growth curve.

Apparatus

Performance was observed in a grey T-maze with interchangeable black (non-reinforcement) or white (positive reinforcement) goal boxes placed at right angles from the arms of the maze. A guillotine door separated the start box from the maze proper and hinged doors 2 in. into each arm permitted blockage of response reversal. Overlays containing positive and negative discriminative cues extended the length of both arm segments. One end of each overlay contained white discriminative stimuli and signaled positive reinforcement. The other end contained black discriminative stimuli and signaled nonreinforcement. A grey midportion extended the width of the runway and separated the positive and negative cues (see cue illustrations, Fig. 1). Individual overlays were designed to cover the back wall and/or the floor of the T-maze arms. All floor overlays were topped with a clear vinyl covering. Olfactory cues were minimized by periodic cleaning. Solid grey overlays were substituted for cue overlays when the discriminative stimuli were removed from the wall or the floor.

Procedure

Animals were handled for a brief period daily during the induction of the desired deprivation level. Two hourly sessions were then allotted for unrewarded exploration of the apparatus followed by a 5 min session of freely available reinforcement pellets in the positive goal box.

Formal training began by placing the rat in an open start

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box and removing it from the apparatus 3 min later or following the consumption of the available food pellet. Latency measures from start box opening to food pellet contact were assessed for all trials. During the presolution period, the initial choice was always scored, although the animal was allowed to reverse directions into the positive goal box. A response was considered to be correct as long as no foot passed the demarcation of the hinged door leading to the negative goal box. When animals began responding in a manner suggesting cue discrimination, the hinged door of the opposite arm was closed following an incorrect choice. This prevented any quick reversal of choice and subsequent reinforcement of an incorrect response. Reinforcement was a 45 mg Noyes food pellet.

Animals were given 10 trials/day with visual cues placed in a quasi-random fashion to minimize ordering effects [5,7]. That is, sequential trials were used only when randomized ordering permitted: (a) 50% positive reinforcement in the right and 50% positive reinforcement in the left goal boxes; (b) no single or double alternation of cue positioning throughout the 10 trials; and (c) no more than three repetitive trials of a single cue placement. Sessions were maintained for 5 days a week throughout the experiment except for an occasionally omitted session. No alteration of cues was initiated following a weekend or an omitted session.

During the early acquisition phase of black-white discrimination, cue overlays were placed on both the wall and floor (Trials 1–130). Later, cues were retained exclusively on the wall (Trials 131–170) or on the floor (Trials 171–200) during each session. On subsequent trials, cue location was quasi-randomly placed on either the wall or the floor within each session. Each animal was required on these trials to attend to 4 possible locations for cue placement (wall right, floor right, wall left, floor left). Cues were later modified (Trials 261–380) so that the discriminative stimuli which formerly covered the total segment of the maze arm now only covered a stripe measuring 11×3/4 in. During the distraction period, 8 white circles (3/4 in. dia.) flanked the black stripe. The white stripe in the positive reinforcement arm remained unaltered. Circles were oriented in a staggered fashion so as not to simulate a straight line.

Following behavioral manipulations, the brain of each rat was quickly removed after decapitation, frozen in liquid nitrogen and stored at −70°C for later analysis. Catecholamine content was assayed by electrochemical detection following liquid chromatographic separation [9].

Behavioral data were statistically evaluated using analysis of variance and covariance including repeated measures (BMDP2V—UCLA Health Sciences Computing Facility) or *t*-test (two-tailed).

RESULTS

Despite an initial episode of unresponsiveness within the T-maze apparatus, the 6-OHDA-treated rats demonstrated equivalent rates of acquisition when compared to those of the controls for a simple black-white discrimination (see Fig. 1). During early trials, the treated animals often remained in the start box while assuming a cataleptic-like state for the designated time limit. Cautious exploration began on subsequent trials and by Trial 40 all treated animals were quickly negotiating the maze and accepting the reinforcement.

The 6-OHDA group performed equivalently to controls throughout acquisition (Trials 1–130) and an early adjustment in cue placement (Trials 131–170). Significantly superior performance, $F(1,12) = 4.96$, $p < 0.05$, was noted for the treated group when the cue overlay was restricted to the floor. When the cues were quasi-randomly positioned on the floor or wall, the 6-OHDA group quickly adapted to maintain a superior, albeit nonsignificant, $F(1,12) = 0.01$, $p > 0.9$, level of performance (Trials 201–260).

Cues were modified on Trial 261 to black and white stripes. This alteration required an adaptive shift from the utilization of brightness cues to the incorporation of stimulus configuration. Presumably, attention would focus on cue pattern as well as cue brightness. No significant difference, $F(1,12) = 0.04$, $p > 0.8$, was noted between the 2 groups for 60 trials displaying an initial impairment in performance efficiency. When irrelevant, competitive stimuli were added, the 6-OHDA-treated animals instantly demonstrated performance significantly inferior, $F(1,12) = 12.43$, $p < 0.005$, to controls for Trials 321–380. The 6-OHDA group failed to overcome the initial distraction created by the irrelevant stimuli and maintained a consistent 65% accuracy level.

Latency measures for both groups revealed a lack of significance ($p > 0.5$) for the striped discrimination (Trials 261–320). Similarly, a lack of significance ($p > 0.4$) was found for latency measures during distraction.

Analysis of brain catecholamines revealed a depletion of both norepinephrine (NE) and dopamine (DA) in the 6-OHDA-treated group. The brains of treated animals contained only 52% and 57% of NE and DA, respectively, compared to controls (Table 1).

TABLE 1

EFFECT OF NEONATAL 6-OHDA TREATMENT ON BRAIN CATECHOLAMINES IN THE RAT*

Brain CA (ng/g)	Control N=5	6-OHDA N=9	% Control
NE	274 ± 8.2	142 ± 20.9	52
DA	627 ± 19.5	355 ± 56.6	57

*Data represent mean ± SEM

DISCUSSION

The present experiments suggest a functional hypersensitivity to the distractive effects of irrelevant stimuli. Furthermore, this deficit in performance is noted long after any known disturbances related to the initial toxicity period of the 6-OHDA injection itself, and well beyond the phase of habituation to extraneous and novel stimuli in both the apparatus and total environment.

The successive phases of discrimination in this study placed increasing demands on attentional mechanisms. This is especially true in the latter phases during which each animal must locate the proper cue in one of several locations while progressing through the maze intersect. The fact that the 6-OHDA-treated animals responded in a fashion seemingly superior to controls during non-distractive phases suggests at least 2 conclusions: (1) the CA-depleted animals were not handicapped simply by motor deficits, and (2) a distinction should possibly be made between the neurochemical processes subserving such attentional functions as the orientation reflex and those underscoring the mechanisms of selective attention. This would seem plausible inasmuch as

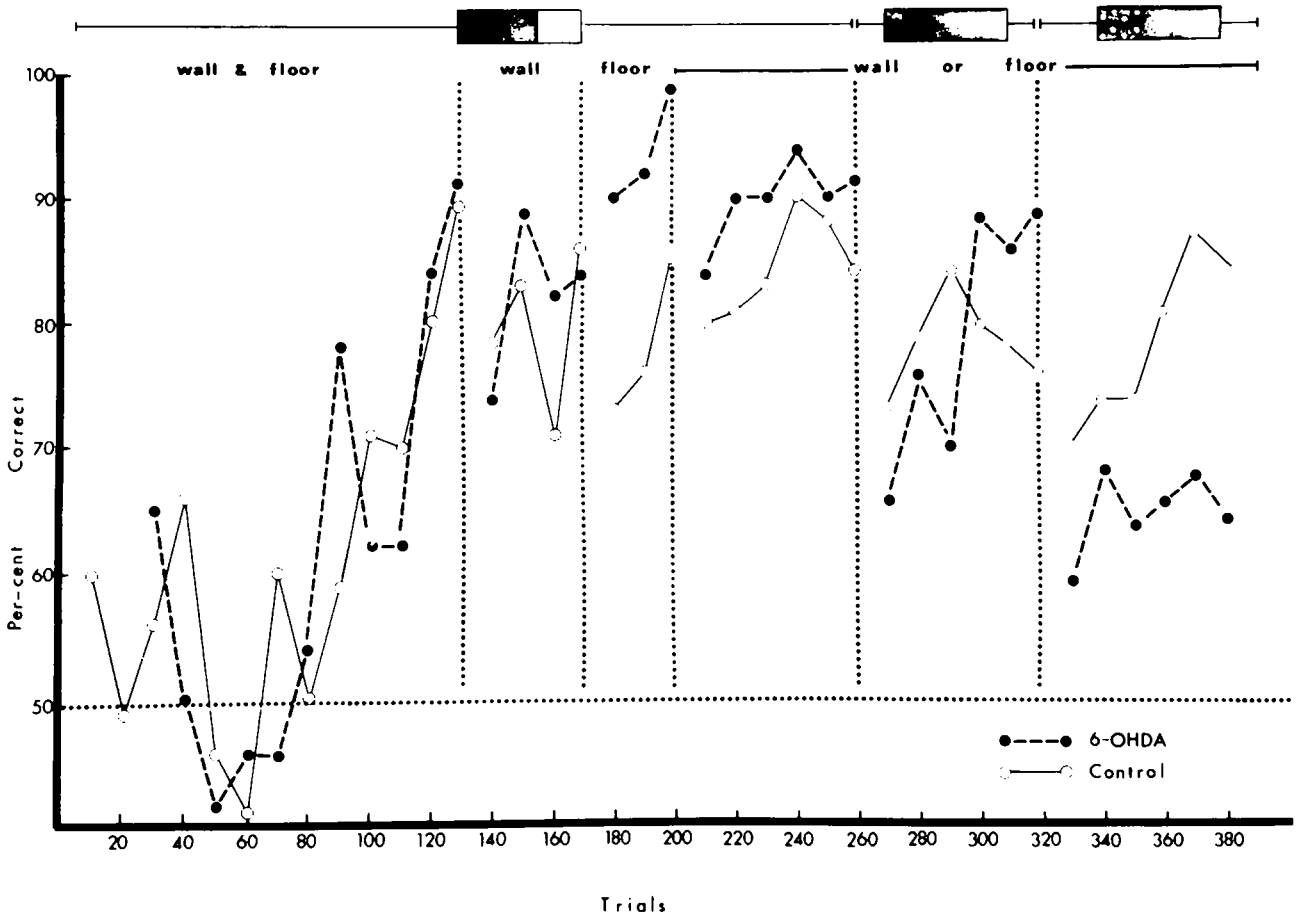

FIG. 1. Acquisition and performance on a black-white discrimination in a T-maze for control rats and those neonatally treated with 6-OHDA. Indentification of cue overlays as well as their placement in the arms of the maze are designated for each segment of the graph.

selective search and distractibility have been found to be differentially altered by testosterone regulation [1]. There was little indication that the treated animals in this study were handicapped by orienting difficulties. Performances by the treated animals equal or superior to controls suggest unimpaired adaptation to changing stimulus placements. This is especially true for Trials 201–320 which required demanding orienting capabilities.

Distinguishing between altered performance levels which are tied to improperly operating cognitive mechanisms or, alternatively, due to interferences in motor abilities becomes crucial when one attempts to interpret the behavioral functions of CNS catecholamines. Some investigators have pointed out that what at first glance might be regarded as an inability to appreciate stimulus information is more accurately accounted for by a loss of optimal engagement of motor functions necessary to complete the task [6]. In the present study, sustained performance decrements appeared in the treated animals only after the introduction of competitive irrelevant stimuli. These results are compatible with the existence of a catecholamine-influenced selective attentional mechanism which loses some functional capacity when depleted by 6-OHDA. An alternative explanation of these results might incorporate the notion of perseveration of a previously learned habit. This is a commonly reported feature of animals with a depletion of norepinephrine in the forebrain regions [7,9]. The difference in performance between groups in the present study during trials with distraction could, in fact, reflect the continuation of a now non-functional prepotent habit. Another possibility is an attraction to the arm (T-maze) of greater luminescence. The addition of 8 white circles around the black stripes more closely equalizes the general luminescence of the opposing T-maze arm (white stripe). Thus, the consequences of perseveration in this situation would be a random selection of either arm irrespective of cue configuration. Animals tested for perseveration following selective brain lesions (hippocampus) tend to exhibit faster latencies per trial when novel stimuli are added to the environment [13,17]. The fact that the 6-OHDA-treated group demonstrated latencies indistinguishable from controls for the period of distraction (Trials 321–380) as well as striped discriminative cue (Trials 261–320) is nonsupportive of a perseveration hypothesis.

The present study demonstrates that a selective attention mechanism is capable of manipulation via brain CA levels, and yet is essentially independent of motor functioning. We feel such a differentiation makes this animal model far more interesting and potentially valuable in terms of comparisons to human attentional dysfunctions. Broadbent [3] has conceptualized some limitations in attentional capacities as being a function of restricted channels in the nervous system. A filtering mechanism selects pertinent sensory infor-

mation and disregards or temporarily stores the irrelevant, thus determining the processes of selective attention. If this hypothetical filter system (which admittedly lacks any proven anatomical or neural substrate) were considered to be under the influence, however vague at present, of central CA systems, then partial destruction of these neurons might lower the threshold capacity for filtering out irrelevant inputs. Models like the one proposed by Broadbent have been used to characterize the attentional dysfunctions so common to the schizophrenic conditions and the special vulnerability of schizophrenics to distracting stimulation [12]

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