LESIONS OF THE MESOLIMBIC Dopamine SYSTEM DISRUPT SIGNALLED ESCAPE RESPONSES IN THE RAT

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Abstract. Classically conditioned shuttling and escape responses of 14 rats with 6-hydroxydopamine lesions of the ventral tegmental area (VTA) were compared with those of 16 sham-lesioned control rats in an aversive classical conditioning paradigm. Although the 6-OHDA lesion did not enhance classically conditioned shuttling, it eliminated the facilitation of escape responses by the conditioned stimulus. Thus, whereas the classically conditioned sham-lesioned rats were faster to escape shock than were the pseudoconditioned sham-lesioned rats, the 6-OHDA classically conditioned and pseudoconditioned rats were equally slow to escape. This suggests that the ability of the rat to respond appropriately to the motivational or informational content of the warning signal was disrupted following damage to the mesolimbic dopamine system.

Electrolytic lesions of the ventral tegmental area (VTA) in the rat enhance signalled active avoidance performance (3, 5). Using a procedure developed by Izquierdo (1), we have previously demonstrated that this enhancement results from the facilitation of classically conditioned fear responses to the signal (8). Based on earlier studies involving dopamine infusion, or damage to the nucleus accumbens (7, 9), we proposed that this effect was due to damage to the mesolimbic dopamine system, rather than to damage to other neural systems present at the site of the lesion.
We tested this hypothesis in the present experiment by infusing 6-hydroxydopamine into the VTA, then examining the behavior of the rats in a classical conditioning procedure similar to that used by Wilson and Baeske (8).

Thirty-two female Sprague-Dawley rats obtained from Harlan Sprague-Dawley, Indianapolis, IN, USA served as subjects. The rats were housed individually with ad lib. access to food and water, and were maintained on a reversed 12 h light-dark cycle. Rats were approximately 100 days old at the time of surgery.

Bilateral lesions of the mesolimbic dopamine system were produced in 16 rats by the infusion of 2 μg 6-OHDA (Sigma Chemical Co., St. Louis, MO, USA) in a volume of 1 μl isotonic saline + mg/ml ascorbic acid (4). The 6-OHDA solution was prepared immediately before surgery on a group of 3 rats, and was kept on ice until infusion. Infusion was done manually via a 10 μl Hamilton microsyringe mounted in the stereotaxic device, at a rate of 1 μl/min. Stereotaxic coordinates used were 4.8 mm posterior to Bregma, ±1.0 mm lateral to the midline, and 8.4 mm ventral to skull surface, from the atlas of Paxinos and Watson (6). Vehicle alone was infused into 16 additional rats, using the same procedure.

Rats were anesthetized during surgery with sodium pentobarbitol (Nembutal, 45 mg/kg), and were allowed at least one week to recover following surgery.

Behavioral testing was conducted in two identical plastic shuttleboxes, as described previously (8). Briefly, the shuttleboxes measured 44.3 × 22.5 × 21.5 cm, had floors consisting of stainless steel bars, and were housed in sound-attenuating chambers. Movement of the rat from one side to the other caused the box to tilt slightly, constituting a response. A Sonalert speaker, mounted above the shuttlebox, provided a tone that served as the conditioned stimulus (CS). A 1.5 mA shock scrambled through the floor bars served as the unconditioned stimulus (US).

Presentation of stimuli and the timing and recording of responses were carried out by IBM-compatible microcomputers through locally developed hardware interfaces and software.

Beginning at least 1 week after surgery, 8 Lesion and 8 Control rats received 8 daily Classical Conditioning sessions in which a 5 s tone CS was paired with a 1.5 mA scrambled foot shock US. The remaining rats received Pseudoconditioning sessions in which the tone and shock were explicitly unpaired. Each session consisted of 50 presentations of both tone and shock, with tones occurring randomly every 10 to 40 s. The shock remained on until the rat shuttled, or for a maximum of 5 s in the absence of a shuttle response. Responses during the tone and during the inter-tone interval were recorded, as was the latency to escape
At the conclusion of the experiment, the rats were euthanized with an overdose of sodium pentobarbital, then perfused transcardially with isotonic saline and formalin. The brains were removed, embedded in gelatin, and sliced into 80 μm sections for verification of the site of injection.

In 14 of the 16 6-OHDA rats, injections occurred bilaterally within the VTA. In two rats the injections missed the VTA on both sides. Data from these two subjects (one Classically Conditioned and one Pseudo-conditioned) were not included in the data analysis.

Very few classically conditioned shuttle responses occurred in either the 6-OHDA- or the Sham-lesioned groups in each session over the 8 days (Means ± SEM: 6-OHDA Classical, 1.18 ± 0.29; 6-OHDA Pseudo, 1.09 ± 0.23; Sham Classical, 1.93 ± 0.54; Sham Pseudo, 1.32 ± 0.45). These numbers are comparable to those reported for unlesioned rats in our study of the effects of electrolytic lesions in this apparatus (8). Unlike the electrolytic lesion employed in that study, the 6-OHDA lesion failed to enhance the classically conditioned responses.

Overall responsiveness in the inter-tone interval was similarly unaffected by the 6-OHDA lesion (Means ± SEM: 6-OHDA Classical,
20.63 ± 2.31; 6-OHDA Pseudo, 16.45 ± 4.02; Sham Classical, 11.91 ± 1.65; Sham Pseudo, 16.27 ± 5.85; all differences nonsignificant).

However, the lesion did affect latency to escape the shock: whereas Classically Conditioned Control rats tended to escape the shock more rapidly than the Pseudoconditioned Control rats ($F_{1,14} = 7.37, P < 0.05$), 6-OHDA Classically Conditioned and Pseudoconditioned rats were equally slow to escape ($F_{1,12} = 0.13$ (see Fig. 2), responding with latencies comparable to those of the Pseudoconditioned controls. Thus the 6-OHDA lesion disrupted the rats' ability to respond to the signal for shock by preparing to escape. Pain sensitivity or threshold was not affected by the lesion, as indicated by the similarities in the latencies to escape of the lesioned rats and the Pseudoconditioned controls.

Two important conclusions can be drawn from the results of this experiment. First, the failure of the 6-OHDA lesion to enhance classically conditioned shuttling responses suggests that the enhancement that is produced by electrolytic lesions does not involve the mesolimbic dopamine system in any critical way. Further studies with discrete chemical lesions will be necessary to determine the system or systems responsible for the effect of the electrolytic lesion.

Second, because lesioned classically conditioned rats escaped as slowly
as lesioned and unlesioned pseudoconditioned rats, the results indicate that the ability of a warning signal to facilitate escape responses is disrupted by this lesion. Thus, although Koob et al. (2) have suggested that lesions of both the mesolimbic and nigrostriatal dopamine systems are necessary to disrupt avoidance performance, damage to the mesolimbic system alone is not without its effect in aversively motivated behavior. Perhaps the nigrostriatal and mesolimbic dopamine systems play complementary roles in aversively motivated behaviors, with the mesolimbic primarily involved in affective or motivational aspects, and the nigrostriatal in motor components of the behavior.

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