Spontaneous alternation and scopolamine[1]

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Rats were tested for spontaneous alternation following injections of saline, scopolamine, and atropine, using doses of 0.4 and 1.2 mg/kg. It was found that scopolamine, at the higher dose, resulted in a reduction of alternation to a rate very near chance. A possible relation between the effects of scopolamine injection and removal of the hippocampus was discussed.

The anticholinergic drugs of the belladonna family, in addition to being potent parasympathetic blocking agents, also produce marked changes in the electrical activity of the brain. Scopolamine, for example, has been found to abolish theta activity in the hippocampus (Stumpf, Petsche, & Gogolak, 1962), and to counteract or block the theta-inducing effects of eserine (Stumpf, 1964). This drug apparently effects the entire theta system, as it simultaneously reduces the synchronous firing of the septal B units which are "pacemakers" for hippocampal theta waves. It might be expected that this blocking of theta activity would be accompanied by some loss of function of the hippocampus, and that these drugs should produce some behavioral changes similar to those found after the removal of the hippocampus. The present authors, in reviewing the literature, found that many parallels do indeed exist. Whitehouse (1964) found that atropine injections interfered with the learning and performance of a successive discrimination problem, while Kimble (1963) found hippocampectomized rats to be very deficient in learning this problem. Hearst (1959) found pronounced perseverative tendencies, as well as deficits in extinction after scopolamine injection, and these effects have also been reported to occur following hippocampal removal (Kimble & Kimble, 1965; Peretz, 1965). Carlton (1961) found that scopolamine and atropine, especially the former, interfered with performance of a delayed bar press, while Clark & Isaacson (1965) reported a large deficit in learning a similar delay in hippocampally ablated rats. Carlton (1961) also found that scopolamine greatly interfered with the performance of an alternating bar press task, while Gross, Chorover, & Cohen (1965) found a similar defect after hippocampectomy.

In the present experiment this apparent parallel between the effects of these drugs and removal of the hippocampus was further investigated by testing the effects of two dose levels of scopolamine and atropine on spontaneous alternation in the rat. The term "spontaneous alternation" refers to the tendency of the rat to enter opposite alleys on consecutive unrewarded trials in the T maze (see Dember & Fowler, 1958). Normal rats alternate alley entrances at a high rate of about 80%, but this tendency is markedly reduced by even small hippocampal lesions, and apparently completely abolished by larger lesions (Roberts, Dember, & Brodwick, 1962; Douglas & Isaacson, 1964). There is probably no behavior which is changed to a greater extent by hippocampal removal than spontaneous alternation, and if these drugs interfere with hippocampal function this effect should be readily observable as a reduced rate of alternation. Both atropine and scopolamine were used because they have similar peripheral effects, but differ in their central effects, with scopolamine being more potent.

Method

Subjects Ss were 18 male hooded rats from a population bred at the University of Michigan. All were roughly 6 mos. old, and the average weight was 350 gm. All were individually housed, with food and water ad lib.

Equipment A T maze of the following dimensions was used: Length of main and side alleys, 2 ft.; alley height, 6 in.; width, 5 in. The main alley contained a 6 in. starting box which was separated from the rest of the maze by a sliding door. Sliding doors were also located at the entrances to the side alleys. The maze floor was wooden, and the maze covered with wire mesh. Illumination was provided by a 7-1/2 watt hooded light bulb placed directly over the choice point.

Procedure Testing procedure consisted of placing S in the start box and, after a 10 sec. wait, raising the door to the main alley. When S's whole body was present in one of the side alleys, the door to that alley was lowered and the response scored. After a 10 sec. wait, S was removed from that alley and replaced in the start box for the next, identical, trial. Each S was given three such trials on a given daily session, with an alternation score of 0, 1, or 2. These scores were used for statistical testing of drug effects, but for convenience the results have been presented in percent alternation form.

All Ss were first tested on one session with no injections, and were then tested on three daily sessions after injection with either atropine or scopolamine (0.4 mg/kg) or an equivalent volume of a saline solution. Each S received each drug condition, and the order of administration was varied. There are six possible sequences in which three drugs can be administered, and three animals were randomly assigned to each sequence. All injections were intraperitoneally, and testing began 25 min. after injection.

One week after completion of this first test, the experiment was repeated with a higher dose of 1.2 mg/kg.

Results

Spontaneous alternation before injection occurred at a rate of 83.3%, which is a typical rate for normal rats. At the low dosage used in the first drug test, neither atropine nor scopolamine results in significant changes in alternation scores: Atropine, 78%; scopolamine, 81%; saline, 78%. On the second test, however, when the dose was increased from 0.4 to 1.2 mg/kg, the results were different. The saline-injected rats continued to perform normally (77.8%), atropine injections had a minor but non-significant effect (72.2%), but rats injected with the high dose of scopolamine fell to a low of 52.8%, a rate which does not reliably differ from a random or chance rate, and which is significantly lower than the rates obtained after saline ($t = 2.3$, $p < .05$) or atropine ($t = 2.43$) injections.

Discussion

The present results show that scopolamine, at least at the higher dose of 1.2 mg/kg, profoundly disrupts spontaneous alternation in the rat. It is unlikely that this dose represents the threshold for this effect, but this is not known for certain, as intermediate doses were not used. The greater, though probably parallel effects of scopolamine, as compared to atropine, are probably due to the differences between the two in ability to penetrate the blood-brain barrier. The present results cannot be due to the peripheral effects of these drugs, as these are comparable for the two, but only in the case of scopolamine was the reduction in alternation pronounced.

Thus, the effects of scopolamine injections and hippocampal removal have once again been found to be similar. In both cases spontaneous alternation has been found to be reduced to rates very near the chance level. This adds further evidence to the effect that the abolition of theta activity in the hippocampus by this drug is an indicator of hippocampal malfunction. Of course, it cannot be expected that the effects of hippocampectomy and scopolamine injections on behavior will be entirely similar, as the drug does much more than simply interfering with hippocampal function.

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