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BRIEF COMMUNICATION

Intraventricular Injection of Antivasopressin Serum Blocks Learned Helplessness in Rats[1]

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LESHNER, A. I., R. HOFSTEIN, D. SAMUEL AND TJ. B. VAN WIMERSMA GREIDANUS. *Intraventricular injection of antivasopressin serum blocks learned helplessness in rats.* PHARMAC. BIOCHEM. BEHAV. 9(6) 889–892, 1978.—An experiment was conducted to test further the role of vasopressin in memory processes, using the learned helplessness paradigm as the memory testing situation. Mice treated intraventricularly with control rabbit serum immediately after an initial period of inescapable preshocks showed subsequent deficits in learning an escape task, a replication of the learned helplessness phenomenon. However, mice treated intraventricularly with antiserum to vasopressin after the initial inescapable shocks did not show later escape deficits. These findings are interpreted as supporting the suggestion that endogenous vasopressin is involved in long-term memory.

Vasopressin Anti-vasopressin serum Learned helplessness Memory Mice

OVER THE PAST 15 years, evidence has been accumulated implicating the neurohypophyseal peptide vasopressin in memory processes. The basic phenomenon is that animals with very low levels of vasopressin show memory impairments, whereas those with experimentally induced increases in vasopressin levels exhibit enhanced retention of learned responses [14, 15, 16, 19]. These effects of altering vasopressin levels have been demonstrated using a wide range of biological manipulations, including hypophysectomy and replacement therapy regimens [13], studying the Brattleboro rat which is deficient in vasopressin [16], injecting exogenous peptides [16,19], and treating animals with antiserum against vasopressin [16, 17, 18]. Furthermore, these effects of vasopressin appear to be centrally mediated. First, analogues of vasopressin which have no peripheral metabolic effects are as effective as the parent compound, even if they are administered only centrally [19]. Second, antivasopressin serum is only effective if administered centrally; there appear to be no effects of systemic antivasopressin administration [17].

Most of these studies of vasopressin effects on memory have used standard learning paradigms, where acquisition and retention of the same task are studied. We report here the effects of intraventricular administration of antivasopressin serum on memory as demonstrated in a different kind of memory sitatuion, the "learned helplessness" paradigm. In this situation, an animal who first is exposed to inescapable shocks shows deficits in later escape responding [11,12]. According to most theories [3,9], the deficit in escape responding is a result of the animal's having learned during the period of inescapable shock exposure that environmental events are not contingent on its behavior; therefore, it does not respond readily in the escape situation. This paradigm, then, provides an interesting test for memory, where the animal "remembers" whether or not in its earlier experience environmental events were contingent on its behavior.

METHOD

Learned helplessness was tested using a modification [7] of the procedures outlined by Maier, Albin and Testa [8]. Half of the animals were designated as experimental rats. They receive an initial experience of 60 preshocks consisting of 3 sec 1 mA scrambled shocks (Grason-Stadler Shock

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Generator, Model E1064GS) delivered once every 15 sec for 15 min. For their initial experience, the other half of the animals, the control rats, were placed into the footshock apparatus (a 24×28 cm box with a grid floor) for 15 min but did not receive shocks. Escape performance was tested 72 hr later in a standard (20×60 cm) 2-way shuttlebox. The 72 hr interval was selected because vasopressin seems to exert its effect on long-term memory [14, 15, 16]. The two halves of the shuttlebox were separated by a divider with a rounded archway measuring 7.5 cm high and 5.8 cm wide cut out of it. During escape testing, the animal was first placed into the apparatus for a 5 min adaptation period. Each trial began when a light was presented. Five sec after light onset, a 3 mA scrambled shock (BRS/LVE Shock Generator, Model SGS-004) was delivered to the floor. On the first 5 trials, one crossing through the divider terminated both the light and the shock. On Trials 6–15, the animal was required to make two crossings through the divider in order to terminate the light and shock, and on Trials 16–30, the animal was required to make three crossings. The measure of escape performance, then, was the latency to make the correct escape response. If the rat failed to escape within 35.0 sec after the onset of the light, the trial was terminated and a 35.0 sec latency was recorded. The mean intertrial interval was 60 sec with a range of 20–120 sec.

Twenty-eight male Wistar rats (200–250 g) were fitted with permanent plastic cannulae for unilateral intraventricular injection [10] under chloral hydrate anesthesia. Half of these animals received 2 μl antivasopressin serum intraventricularly immediately after the initial experience, and the other half of the animals received normal rabbit serum. The antivasopressin serum was that used previously and described by van Wimersma Greidanus and De Wied [16], and the dosage used was capable of binding approximately 5 ng vasopressin. Thus, there were a total of four groups of 7 rats each: Group PS-Anti-VP received preshocks immediately followed by an intraventricular injection of antivasopressin serum, Group PS-Control also received preshocks but received normal rabbit serum instead of antivasopressin serum, Group NPS-Anti-VP received control exposure to the preshock apparatus followed by antivasopressin serum, and Group NPS-Control received control exposure to the preshock apparatus followed by normal serum injection.

RESULTS AND DISCUSSION

Figure 1 presents the mean escape latency for each group averaged over blocks of five trials. These data were analyzed by mixed design analysis of variance, which revealed a significant interaction of the main effects of preshock vs. no preshock and antivasopressin serum vs. normal serum treatments, $F(1,24)=12.40$, $p<0.005$. This interaction is summarized in Fig. 2, which shows the mean ± standard error escape latency for each group averaged over all trials. Examination of this interaction using tests of least significant difference showed that the preshocked rats receiving normal rabbit serum after the initial experience exhibited significantly longer escape latencies than the other three groups, which did not differ significantly from each other. That in normal serum treated animals inescapable preshock led to increased escape latencies provides a replication of the "learned helplessness" phenomenon. More importantly, the lack of a difference between the two antivasopressin serum

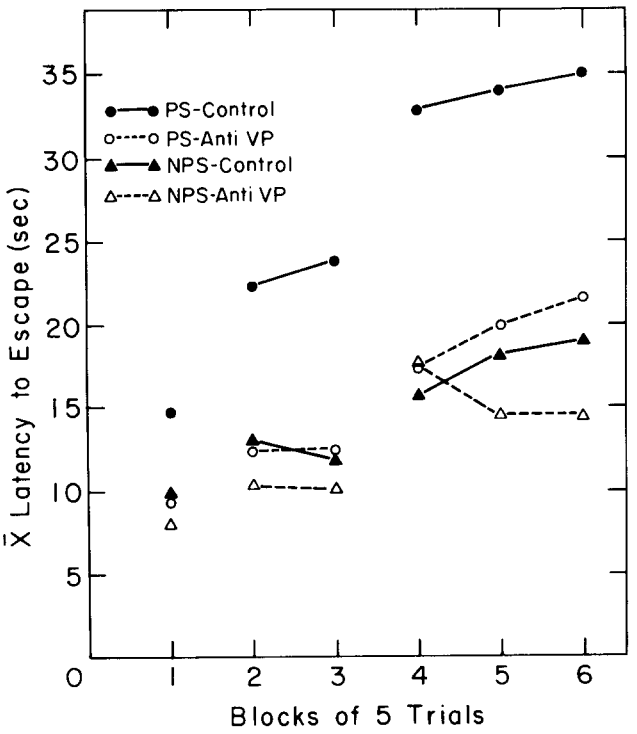

FIG. 1. Mean escape latency for each group averaged across blocks of five trials. (PS-Control: pre-shocked and treated with normal serum; PS-Anti-VP: preshocked and treated with antivasopressin serum; NPS-Control: not preshocked and treated with normal serum; NPS-Anti-VP: not preshocked and treated with antivasopressin serum.)

treated groups shows that learned helplessness does not occur in rats injected intraventricularly with antiserum against vasopressin immediately after the initial experience.

The results of this study, by showing that post-experience treatment with anti-vasopressin serum counteracts the effects of that experience on later responding, are consistent with the findings of earlier studies showing that neutralization of centrally available vasopressin leads to performance deficits in memory tests [15, 16, 18]. These findings, then, lend general support to the view [14, 16, 19] that vasopressin is a critical element in memory processes, since reducing vasopressin levels impaired memory. Furthermore, the fact that the memory impairment in the present study was evident three days after the initial experience and anti-vasopressin treatment supports the position that vasopressin's effects are on long-term memory [15,16].

By now, vasopressin's memory enhancing effects have been shown to be quite general. Vasopressin affects memory in a fairly wide range of situations, including both appetitive and aversive tasks [1,4]. In addition, vasopressin treatment has been shown to be capable of blocking amnesia produced in a variety of ways [2,6]. The present study emphasizes the generality of vasopressin's effects, since the situation studied here did not involve examining acquisition and retention of the same task.

An important question that remains concerns the mech-

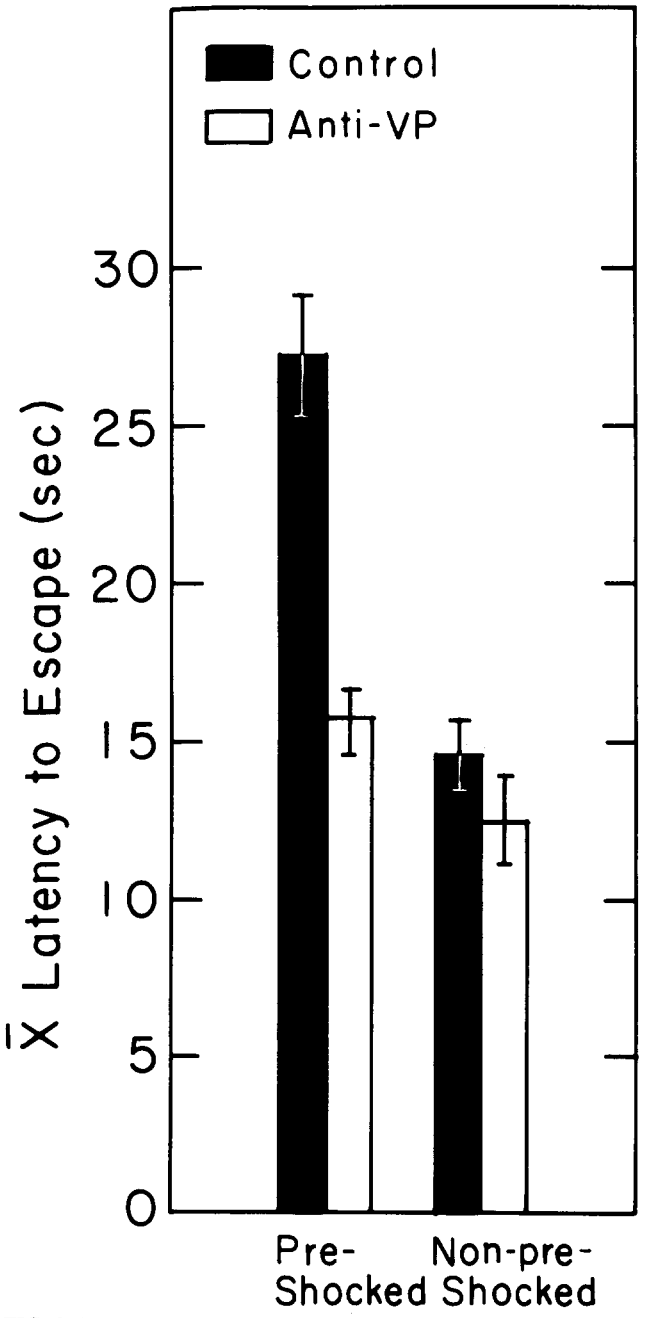

FIG. 2. Mean ± standard error escape latency for each group averaged across all trials.

anism of vasopressin's actions on memory processes. Although the precise details are not yet known [19], a likely possibility [5] is that vasopressin's effects on memory are mediated by central catecholaminergic systems.

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