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BRIEF COMMUNICATION

Vasopressin Potentiation in the Performance of a Learned Appetitive Task: Reversal by a Pressor Antagonist Analog of Vasopressin

AARON ETTENBERG,[1] MICHEL LE MOAL, GEORGE F KOOB AND FLOYD E. BLOOM

Arthur V. Davis Center for Behavioral Neurobiology, The Salk Institute, P.O. Box 85800, San Diego, CA 92138

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ETTENBERG, A., M. LE MOAL, G. F. KOOB AND F. E. BLOOM. *Vasopressin potentiation in the performance of a learned appetitive task: Reversal by a pressor antagonist analog of vasopressin.* PHARMACOL BIOCHEM BEHAV **18**(4) 645–647, 1983.—Rats were tested in a simple one-trial water-finding task for the effects of arginine vasopressin (AVP) on performance of an appetitive task. On the training day, each animal was exposed for 5 min to a novel open-field environment that contained a water-tube located in an alcove set into one of the walls of the enclosure. Immediately upon removal from the enclosure, the animals received a subcutaneous injection of either AVP (1 μg/rat) or vehicle solution. When water-deprived and tested 48 hr later, vasopressin-treated rats found the water tube reliably faster than controls. In other groups of animals, this potentiation in learned performance was prevented by concurrently treating the rats with a vasopressin analog having potent pressor antagonist properties. These results are consistent with the notion that vasopressin may play a role in memory consolidation, but peripheral visceral factors may mediate this action.

Arginine vasopressin Learning and memory Vasopressin antagonist peptide Appetitive conditioning
Neurohypophyseal hormones Anti-diuretic hormone

SEVERAL lines of evidence suggest an involvement of the neurohypophyseal hormone, vasopressin (AVP), in memory consolidation. Hypophysectomized animals are impaired in the acquisition of a number of conditioned responses [4,5]. These deficits can reportedly be reversed by the administration of AVP [2, 8, 9].

When applied to intact animals, AVP has been observed to increase the resistance to extinction of various learned avoidance behaviors [6, 7, 16, 20]. Furthermore, healthy animals administered anti-vasopressin agents demonstrate effects on such learned behaviors either opposite to, or preventing those observed with AVP itself [16, 20, 25, 26]. In clinical studies, AVP and its analogs reportedly produce increases in attention and performance of memory related tasks as well as reductions in the severity of memory deficits having alcoholic, post-traumatic and pathological origins [13, 18, 19, 22, 27].

In the animal literature, positive results with AVP have come almost exclusively from paradigms employing aversively motivated tasks (i.e., conditioned passive or active avoidance experiments). Recently, however, we have reported that post-training administration of AVP also potentiated the performance of rats in a simple appetitive water-finding task [11, 12, 17]. In other work from our laboratory, the behavioral effects of peripherally administered AVP in conditioned avoidance studies, occurred at doses that produce substantial increases in systolic blood pressure [1,20]. Injection of a potent peptide analog that prevented AVP's pressor response, concurrently prevented its behavioral actions [20]. These results suggest that peripheral visceral factors may be important for demonstrating apparent memory improvements with AVP and/or that similar receptors are involved in both the pressor and behavioral responses to AVP. The present experiment was devised to determine whether AVP's effects in an appetitive learning paradigm would also be prevented by administration of this pressor analog.

METHOD

Male Wistar rats (150–175 g) were housed under standard

[1]Requests for reprints should be addressed to Dr. Aaron Ettenberg, Department of Psychology, University of California, Santa Barbara, CA 93106.

laboratory conditions with a 12 hr light/dark cycle and ad lib access to food and water. The animals were allowed one week to adapt to their home cage environment during which time each animal was handled for several minutes a day on three different days. Training began one week after arrival.

The test apparatus was constructed to the specifications described by Major and White [21]. It consisted of an open rectangular box (37×64×46 cm) with a steel rod floor (rods spaced 1.5 cm apart). Recessed into the middle of one of the long walls of the enclosure was an alcove (11×13×46 cm) that contained a standard metal drinking tube 8.5 cm above the floor. The drinking tube and the metal floor were connected to a drinkometer circuit that indicated licking.

Pure arginine vasopressin (AVP) and an analog of vasopressin [1-deaminopenicillamine, 2-(0-methyl) tyrosine] arginine vasopressin (abbreviated as dPTyr (Me) AVP) were synthesized at the Salk Institute by Dr. Jean Rivier (Peptide Biology Laboratory). The AVP analog has been characterized as a specific potent antagonist of the pressor actions of AVP [1,20]. Both compounds were prepared in 50 μl solutions of 0.01 M hydrochloric acid which was subsequently diluted in 0.9% physiological saline. All injections were administered subcutaneously behind the neck in a volume of 0.5 ml per animal.

Training consisted of placing a non-water deprived rat individually into one corner of the test apparatus and leaving the animal to explore the enclosure for 5 min. Observation indicated that while all subjects found and inspected the drinking tube none consumed any measureable amount of water during their 5 min in the box. Upon removal from the apparatus, half the rats (n=18) were immediately injected with the saline vehicle solution. Two minutes later, these animals received another injection of either saline (a SAL/SAL group, n=9) or a 1.0 μg dose of AVP (constituting a SAL/AVP group, n=9). Of the remaining 18 rats, half were initially administered a 5.0 μg dose of the antagonist peptide, dPTyr (Me) AVP, and the other half a dose of 25.0 μg of antagonist. Two minutes after the antagonist was injected these same animals each received a 1.0 μg dose of AVP thereby producing another two groups: a dPYyr (ME)AVP$_5$/AVP group (n=9) and a dPTyr(Me) AVP$_{25}$/AVP group (n=9). Following this injection regimen each animal was immediately returned to its home cage without water for 48 hrs. The rats were then individually returned to the test apparatus for a single test trial conducted with a dry drinking tube. The latency to make contact with the drinking tube was recorded for each subject.

RESULTS

As reported in preliminary studies [11,17], AVP reliably reduced the latency of rats to find the drinking tube on test day. This potentiation in learned performance was prevented by pretreating with 25.0 μg but not with 5.0 μg of the antagonist analog. These results are shown in Fig. 1. A one-factor Analysis of Variance was computed on the log-transformed data from Fig. 1 revealing a reliable difference across groups, $F(3,32)=2.80$, $p<0.05$. Post hoc analysis confirmed that both the SAL/AVP and dPTyr(Me)AVP$_5$/AVP groups were reliably different from SAL/SAL controls, $t(16)=2.18$, $p<0.05$ and $t(16)=2.28$, $p<0.05$, respectively. The large dose of the antagonist, however, completely blocked the behavioral actions of AVP (SAL/SAL group versus dPTyr(Me)AVP$_{25}$/AVP: $t(16)=0.45$, n.s.).

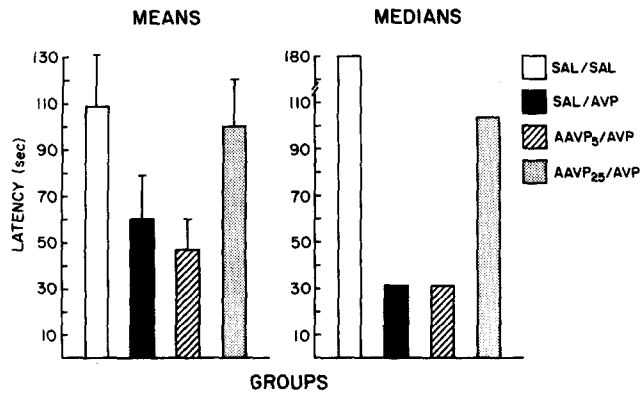

FIG. 1. Mean (±S.E.M.) and Median latencies to contact a dry drinking tube on test day. Vasopressin potentiated the learned performance of treated animals compared to control animals. This effect was reversed by a 25 μg (but not a 5 μg) dose of the pressor antagonist peptide, dPTyr (Me) AVP.

DISCUSSION

In previous work, animals administered AVP following exposure to the same open-field environment but without a water-tube present during training, did not demonstrate any reductions in test day latencies [11, 12, 17]. AVP also produced no evidence of increased activity 48 hr post-injection that might account for the present data [12,17]. It would seem, therefore, that these results are consistent with the notion that AVP may play a role in memory consolidation. However, the precise nature of that role remains unclear. Arousal, for example, has long been known to alter an animal's ability to learn. Low levels of arousal are generally thought to yield less effective performance than moderate levels and very high levels disrupt test performances [15]. One might view the visceral effects of peripherally-administered AVP as an arousing event that only indirectly acts to improve learned performance. The present data and those from avoidance conditioning studies in our laboratory [16,20] support this interpretation: when a major source of AVP's visceral action is prevented by pretreatment with the pressor antagonist peptide, the behavioral response is also prevented.

In the previous study [16] less dPTyr(Me)AVP (5 μg/rat) was required to block the prolongation of active avoidance observed with the same dose of AVP. The reason for this difference in sensitivity of the antagonist in the two tasks is not clear. Water deprivation would be a logical explanation, particularly since such a deprivation does reliably increase plasma AVP levels in rats (Deyo, Koob and Bloom, unpublished observations); however, in the present study the rats were not deprived when injected with AVP and dPTyr (Me) AVP. Thus a more probable explanation would be related to the nature and design of the task. Current ongoing studies with an inhibitory avoidance task should clarify whether the nature of the motivation (appetitive vs. aversive) is the critical variable.

Neuroanatomical studies [3, 10, 14] have identified non-pituitary AVP fibers originating in the hypothalamus and innervating such areas as amygdala and hippocampus, both implicated in memory processing [23,24]. It may be that the correlation reported here between the behavioral and

pressor effects of AVP does not stem from some peripherally-induced arousal, but rather from a common receptor found in the viscera (i.e., blood pressure) and in the CNS (i.e., behavior). Current research in our laboratory is aimed at characterizing the role of central and peripheral AVP action with respect to the peptide's role in learning and memory.

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