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The effect of vasopressin analogue [d$(CH_2)^1_5$, Tyr$(Me)^2$]AVP on memory process in rats with experimental amnesia

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Short communication

Abstract. We investigated the effect of a single 2 μg dose of vasopressin (AVP) analogue [$(CH_2)^1_5$,Tyr$(Me)^2$]AVP on the processes of retrieval of conditioned reflexes in rats with experimentally induced amnesia. The models used were: electroconvulsive shock (ECS) and hypoxia. It severely impaired the memory processes. The AVP analogue [d$(CH_2)^1_5$,Tyr$(Me)^2$]AVP facilitated retrieval of passive avoidance in all animals.

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There have been reports in the literature which suggest that vasopressin (AVP) and its analogues can affect learning and memory processes in the central nervous system. The majority of this evidence was obtained from studies using the conditioned avoidance paradigm (Mundy et al. 1987). DeWied and his associates showed that hypophysectomized rats were deficient in the acquisition of a shuttlebox avoidance task and less resistant to extinction (DeWied 1965). Subcutaneous administration of vasopressin reversed the acquisition deficit and restored resistance to extinction (Bohus et al. 1973). The effect of AVP on learning and memory seems not to depend on hormonal function, as it has been shown that the AVP analogues, having only minimal endocrine effects, improve memory consolidation and retrieval (Bohus et al. 1978).

$[d(CH_2)^1_5,Tyr(Me)^2]AVP$ is an analogue of vasopressin which is virtually devoid of endocrine and pressor activity (Manning et al. 1987), and it is one of the most potent and specific V_1 vasopressin receptors antagonists. Our previous studies have shown a facilitatory effect of this AVP analogue in passive and active avoidance situations and also that it abolishes memory defects caused by ethanol (Car et al. 1993). We also observed a beneficial effect in the lever-touch autoshaping model of memory in rats (Car et al. 1994).

Based on these observations we investigated the effect of the AVP analogue $[d(CH_2)^1_5,Tyr(Me)^2]AVP$ on retrieval of passive avoidance response in rats with experimentally induced amnesia.

Subjects were white, male Wistar rats weighing 160-180 g. The animals were fed on a standard diet and housed in group cages in an air-conditioned room with a 12 h light/12 h dark cycle beginning at 7 am.

AVP and analogue $[d\ CH_2)^1_5, Tyr(Me)^2]$ AVP were administered into the lateral ventricle of the brain (icv) (Herman 1970). Under ether anaesthesia, a burr hole of 0.5 mm in diameter was drilled in the rat's skull, 2.5 mm laterally and 1 mm caudally from the point of intersection of bregma and the superior sagittal suture on the right side of the head. Icv injection was made to a depth of 4.5 mm with a Hamilton microsyringe. After termination of each experiment, all animals were killed by decapitation, their brains were removed and the site of injection was verified macroscopically. The animals with inappropriate site of injection were deleted from the calculations. Passive avoidance response training. The response was induced using the one-trial learning method of Ader et al. 1972. The apparatus consisted of a 6 x 25 cm platform illuminated with a 25 W electric bulb connected through a 6 x 6 cm opening with a dark compartment (40 x 40 x 40 cm). The floor of the cage was made of metal rods of 3 mm in diameter, spaced at 1 cm. The investigation took advantage of the natural preference of rats to stay in dark compartments. The test lasted for 3 days. On the 1st day, after 2 min of habituation in the dark compartment, the rats were placed on the illuminated platform and were allowed to enter the dark compartment, from which they were immediately removed. Two similar trials, at an interval of 2 min, were carried out on the 2nd day. After the first trial the rats were allowed to stay in the dark compartment for 10-15 s. In the second trial when the rat entered the dark compartment it received a foot shock (0.25 mA, 3 s) delivered through the metal rods. The presence of the passive avoidance was checked 24 h later. The rats were placed on the illuminated platform once more and the latency to enter the dark compartment was measured, with the cut time of 300 s. According to the protocol proposed by Matthies (1980), to determine the effect of AVP and $[d(CH_2)^1_5, Tyr(Me)^2]AVP$ on retrieval these analogues were administered on the 3rd day, 15 min before the test for preservation of the passive avoidance response.

Amnesia produced by electrogenic convulsions. Electroshock was induced using a UGO BASILE ECT UNIT. After attaching ear clip electrodes moistened with saline the body resistance of animals was measured to select rats with low resistance. In the selected animals the electroconvulsive shock (ECS) (50 mA, 0.4 s, 50 Hz) (Woltarius 1971) invariably produced tonic and clonic convulsions. Retrograde amnesia (Squire 1986) was induced by a single ECS administered on the 2nd day

of training, 15 min after the completion of induction of passive avoidance according to Ader et al. 1972.

Amnesia produced by hypoxia. Hypoxia was produced by placing rats in a glass chamber flushed with a mixture of 2% O_2 in N_2 (Allweis et al.1984) until the respiratory occurred, after which they were immediately removed. The hypoxia was induced on the 2nd day, 15 min after the training for passive avoidance.

The statistical comparison of the results was carried out by analysis of variance (ANOVA) followed by modified *t* statistics and Bonferroni's procedure (Wallenstein et al. 1980) when multiple means were to be compared.

The influence of AVP and analogue [$d(CH_2)^1_5$, $Tyr(Me)^2$]AVP on retrieval of the passive avoidance response in control rats and those subjected to ECS is shown in Fig. 1. AVP in a dose of 2 μg did not significantly change the latency, while [$d(CH_2)^1_5$,$Tyr(Me)^2$]AVP significantly prolonged the latency to enter the dark compartment, and facilitated the painful stimulus in the control group.

The rats receiving ECS displayed a significant shortening of the latency; this effect was considerably reversed by AVP and [$d(CH_2)^1_5$,$Tyr(Me)^2$]AVP (Fig. 1). The influence of AVP and [$d(CH_2)^1_5$,$Tyr(Me)^2$]AVP on retrieval of the passive avoidance response in control rats and those subjected to hypoxia is shown in Fig. 2.

The latency of enter the dark compartment was shortened in rats undergoing hypoxia. Administration of AVP and [$d(CH_2)^1_5$,$Tyr(Me)^2$]AVP significantly prolonged the latency in those subjects (Fig. 2).

The present results indicate that a single intracerebroventricular dose of 2 μg of AVP and analogue [$d(CH_2)^1_5$,$Tyr(Me)^2$]AVP not only facilitates

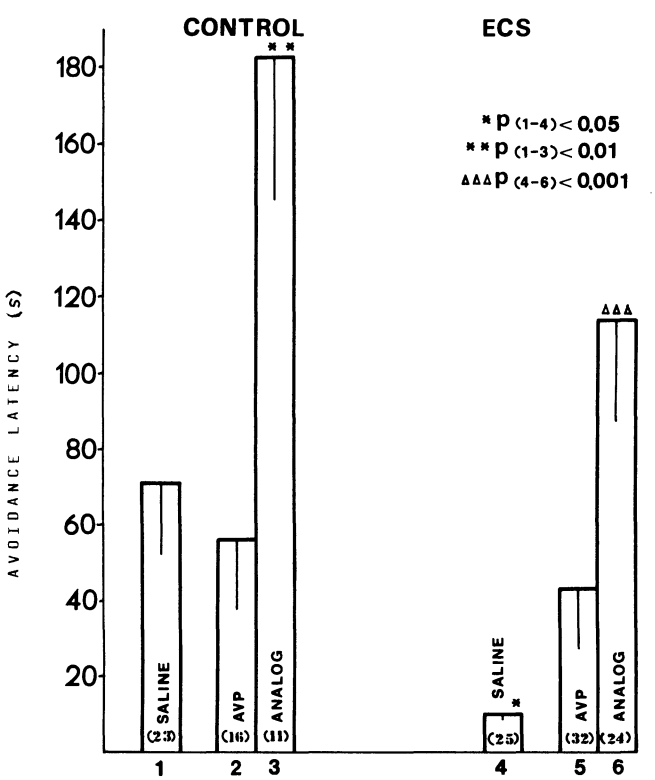

Fig. 1. The effect of AVP and [$d(CH_2)^1_5$,$Tyr(Me)^2$] AVP (2 μg, icv) on retrieval of the passive avoidance response in control and ECS-treated rats. Columns represent means ± SEM of the number of animals indicated in the columns.

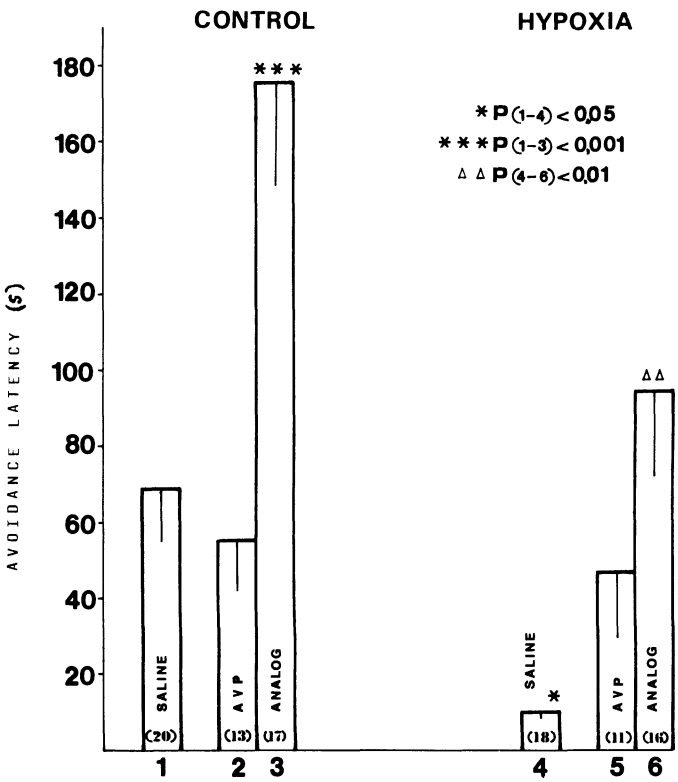

Fig. 2. The effect of AVP and [$d(CH_2)^1_5$,$Tyr(Me)^2$]AVP (2 μg, icv) on retrieval of the passive avoidance response in control and hypoxia-treated rats. Columns represent means ± SEM of the number of animals indicated in the columns.

the retrieval of painful stimulus in the control rats, but also facilitates the retrieval in rats with amnesia induced by single ECS, and by a single episode of hypoxia.

$[d(CH_2)^1_5,Tyr(Me)^2]AVP$ investigated in this study, having no vasopressor action, may be classified as an antagonist of peripheral V_1 receptors (Legros and Timsit-Berthier 1988). Various analogues of AVP appear to have an effect similar to AVP on memory (Legros and Timsit-Berthier 1988). Pfeifer and Bookin (1978), using a passive avoidance paradigm, found that vasopressin reduces retrograde amnesia caused by ECS in rats. Hypoxia and ECS produce amnesia and several changes in the central nervous system, including disruption of synthesis and release of neurotransmitters (Gibson et al. 1981, Vetulani 1984a,b, Miva et al. 1986). It is well established that ECS can induce a number of neuroendocrine responses. It is interesting that ECS induces both acute increases in plasma vasopressin and more prolonged increases persisting up to 8 days after a course of ECS (Mattes et al. 1990). The magnitude of these increases is relatively small, and the relationship of this to ECS--induced memory impairment is unknown (Mattes et al. 1990). Similar to ECS, hypoxia increases plasma vasopressin (Gibson et al. 1981, Miwa et al. 1986). Taking into account that analogue AVP is an antagonist of V_1 receptors and vasopressin may affect memory processes in an unspecific manner, Jolles (1987) and Legros and Timsit-Berthier (1988) emphasize the effect of AVP on perception, attention and concentration, and on elevation of mood, which may change motivational processes and arousal. We suggest a non-receptor mechanism of action in memory processes with the investigated analogue.

This is of considerable theoretical interest, while the practical aspect of this study is the possibility of reducing memory impairment using $[d(CH_2)^1_5,Tyr(Me)^2]AVP$. This will need to be investigated by further clinical studies.

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