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# The participation of nitric oxide in the facilitator effect of arginine vasopressin on memory

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**Abstract.** In this study we tested the hypothesis that nitric oxide (NO), which function as a novel type of inter-cellular messenger in the central nervous system (CNS) participated in the facilitator effect of arginine vasopressin (AVP) on learning and memory. Recent investigations have provided evidences that inhibition of NO synthesis attenuated the vasodilatation caused by AVP, and inhibited the improvement of learning and memory evoked by angiotensin II. AVP as well as pharmacologically produced increase in endogenous NO facilitates the consolidation of shock avoidance learning. We evaluated the behavioural effects of AVP at dose 1 μg after the inhibition of NOS by $N^G$-nitro-L-arginine methyl ester (L-NAME) at dose 10 μg, and after the injection of endogenous donor of NO -L-argnine- 10 μg in the retrieval of passive avoidance situation, and in consolidation of active avoidance responses. The locomotor activity of all investigated drugs was tested in the open field test. AVP facilitated the recall of passive avoidance responses and consolidation of active avoidance responses. Neither the increase of NO concentration after the injection of L-arginine nor the decrease of NO after the inhibition of NOS by L-NAME changed the behavioural effects of AVP. L-arginine increased the psychomotor behaviour and L-NAME decreased the activity of animals in the "open field" test. L-arginine itself improved the consolidation of active avoidance responses. Our results indicate that central action of AVP is probably independent of NO concentration in the brain.

**Key words:** vasopressin, nitric oxide, L-arginine, learning and memory, rat

## INTRODUCTION

The neurohypophyseal hormone arginine vasopressin (AVP) exerts antidiuretic, vasopressor and behavioural effects. It is well known, that AVP facilitates memory in laboratory animals and in humans (for review see De Wied 1983, Legros and Timsit-Berthier 1988). It is considered that behavioural effects of AVP are mainly mediated by the $V_1$ type of vasopressinergic receptor coupled to the formation of inositol 1,4,5-triphosphate and diacylglycerol, however, there is evidences strongly suggesting an important role for the $V_2$ type of vasopressinergic receptor and receptors for oxytocin (De Wied et al. 1991). Interestingly, Hirasawa et al. (1994) using a reverse transcription-polymerase chain reaction method have not detected the presence of the $V_1$ receptor type, while showing the existence of $V_2$ receptors in the hippocampus. Therefore, the existence of a novel AVP receptor subtype has been proposed. Taken together, the mechanism of action of AVP in cognition is unclear.

The discovery of nitric oxide (NO) as a novel type of inter-cellular messenger raised the issue of its role in the function of the central nervous system (CNS) (Garthwaite et al. 1988, Knowles et al. 1989). NO generated enzymatically from L-arginine by nitric oxide synthase (NOS) appears to be unique in its abilities as a neuromodulator or neurotransmitter (Wood and Garthwaite 1994). The release of NO strictly bound with the stimulation of N-methyl-D-aspartate (NMDA), a subtype of excitatory amino acid receptor, suggested an important role in cognition. At first, NO seemed to be involved at least in some form of learning and memory (Böhme et al. 1993), because inhibitors of NOS attenuated the acquisition of spatial memory, and were ineffective in shock avoidance learning. However closer investigation has shown that the process of consolidation of memory in shock avoidance learning also seemed to be sensitive to NO. Interestingly, both NO donors (Fin et al. 1995) and AVP improve the consolidation of memory for affect (fear caused by electric shock).

Recent investigation carried out in our laboratory indicate that the inhibition of NOS attenuated the facilitator influence of angiotensin II on performance of the rats in shock avoidance learning (Hoły and Wiśniewski 1994). This suggests suggests that NO is probably involved in the central action of some neuropeptides.

AVP causes a biphasic effect in vascular resistance: vasoconstriction at lower doses and endothelium dependent vasodilatation at higher doses (Hirsch et al. 1989, Suzuki et al. 1989). Recent reports have shown that vasodilatation evoked by AVP was abolished by pre-treatment with NOS inhibitors. This indicates that some effects of AVP are mediated by NO (Katušič 1992).

Therefore, we decided to test the hypothesis that NO participated in the central action of AVP in the learning and memory in rats. We evaluated the central effects of AVP after the inhibition of NOS by $N^G$-nitro-L-arginine methyl ester (L-NAME), and after the injection of endogenous donor of NO -L-arginine in the retrieval of passive avoidance situation, and in consolidation of active avoidance responses.

## METHODS

### Subjects

Male Wistar rats, laboratory strain, weighing 160-180 g were used. They were housed in cages (55 x 40 x 20cm), 8 animals per cage, at room temperature with a 12 h light--dark cycle beginning at 7.00 a.m. Food and water were freely accessible.

### Surgery

Under light ether anaesthesia, two burr holes, 0.5 in diameter, were drilled in the skull 2.5 mm laterally and 1 mm caudally from the point of intersection of a bregma and the superior sagittal suture on the both sides of the head. After 48 h of recovery, intracerebroventricular (icv) injections were made manually at volumes 5 µl into both ventricles. It was relatively nontraumatic as the animal, gently fixed in the left hand of the experimenter, was usually quiet and no vocalization occurred. Arginine vasopressin (Calbiochem) at a dose of 1 µg was injected into the left lateral cerebral ventricle in saline solutions, L-arginine at a dose 10 µg, and $N^G$nitro-L-arginine methyl ester (RBI) at a dose of 10 µg, freshly prepared in saline solution were administrated into the right ventricle. The control rats received 0.9% NaCl solution into both ventricles. The intracerebral injections were given 15 min before testing in the open field, and before the retrieval session in the passive avoidance response, and immediately after the learning trial on the 5-th day in conditioned avoidance responses (CAR). At the end of each experiment rats were sacrificed and the sites of injections were verified after brain sectioning. The data from animals with incorrect injections were not included in the final analysis.

### Behavioural studies

All behavioural experiments were carried out in a quiet, diffusely lit room (25 W bulb, 2 m away from animal, light indirect) between 11.00 and 16.00 h with each group equally represented at the times of testing. Each test was carried out twice; in the first protocol L-NAME was used, and in the second one L-arginine. Locomotor and exploratory activity was measured in an "open field", which was a square 100 cm x 100 cm of white floor divided by 8 lines into 25 equal squares and surrounded by 47 cm high walls. Four plastic bars, 20 cm high, were located at four intersections of the lines in the central area of the floor. Following 1 min of adaptation, crossings, rearings and bar approaches were counted manually for 5 min.

CARs were studied in a shuttle-box (60 x 28 x 24 cm) divided in two equal parts by a wall 6 cm wide and 8 cm high, opening in the middle of its length. A buzzer (45 dB, 2,000 Hz) was sounded for 5 s and simultaneously a dim light was emitted by a 2 W bulb located in a rear wall of each part of the box creating together a conditioned stimulus (CS). If the rat did not make a positive (+) CAR, i.e. move to the other compartment within 5 s, a 1 mA AC scrambled electric shock (unconditioned stimulus, US) was delivered through the box floor, which was made of stainless steel rods 4 mm in diameter and spaced at 18 mm intervals. The US was terminated when the animal escaped to the other compartment of the box. CAR acquisition training consisted of 5 daily 20-trial sessions. To assess the memory consolidation, the responses to the conditioned stimulus (without unconditioned reinforcement) were tested on days 12 and 19 after the beginning of acquisition training. The rats used in this experiment were preselected: each rat was tested for 3 days with 10 trials per day. The rats with greater ability to acquire the CAR (more than 3 crossings within 3 days) were taken to the proper experiment. The number of (+) CARs was recorded every day and expressed as percent of the total number of trials. The intertrial interval was 10 s. The grid floor was kept clean throughout training sessions.

Passive avoidance behaviour was studied in a one trial learning, step-through situation (Ader et al. 1972), which utilizes the natural preference of rats for a dark environment. After 2 min of habituation to the dark compartment the rat was placed on an illuminated platform and allowed to enter the dark compartment. On the second day, the guillotine door was closed behind the animal once it entered the dark compartment and the animal received electric footshock (0.25 mA, AC, 2 s) *via* the grid floor (learning trial). The rat was then returned to its home cage and placed back into the holding room. Retention of the passive avoidance response was tested 24 h later by placing the animal on the platform and measuring latency to re-enter the dark compartment to a maximum of 300 s.

### Statistics

Statistical analysis was carried out using the program Systat for Windows version 5.0 for IBM and compatible computers. Statistical comparisons were made by an analysis of variance (ANOVA) followed by Tukey tests, when multiple means were compared (active avoidance situation and open field test). The medians (passive avoidance situation) were compared by the Kruskal-Wallis nonparametric analysis of variances, and in the subsequent analysis of differences between groups a nonparametric Mann-Whitney U test was used.

## RESULTS

The administration of AVP, L-NAME, and AVP with L-NAME in comparison with control group receiving 0.9% NaCl into both ventricles decreased the exploratory activity of the rats in the "open field" test (Fig. 1). There were not any significant differences between the groups in the number of crossings, however, the number of rearings were decreased ($F_{3,51} = 4.085$; $P<0.05$). Subsequent analysis of differences by Tukey test showed significant differences between control group and AVP ($P<0.05$), control and L-NAME ($P<0.05$), and control and combining group ($P<0.05$). There was significant difference for the number of bar approaches. Further analysis of differences by Tukey test revealed significant differences between control and AVP ($P<0.05$), control and L-NAME ($P<0.05$), control and combining group ($P<0.01$).

We observed an increase in locomotor activity in the rats injected with L-arginine in comparison with control group and combining group (Fig 2). In the second protocol there was significant difference between groups only in number of crossings ($F_{3,35} = 7.337$, $P<0.01$). The analysis by Tukey test showed significant differences between control and L-arginine ($P<0.05$), and between the combining group in comparison with L-arginine ($P<0.01$). We noticed a tendency to inhibition of the psychomotor behaviour in rats injected by AVP.

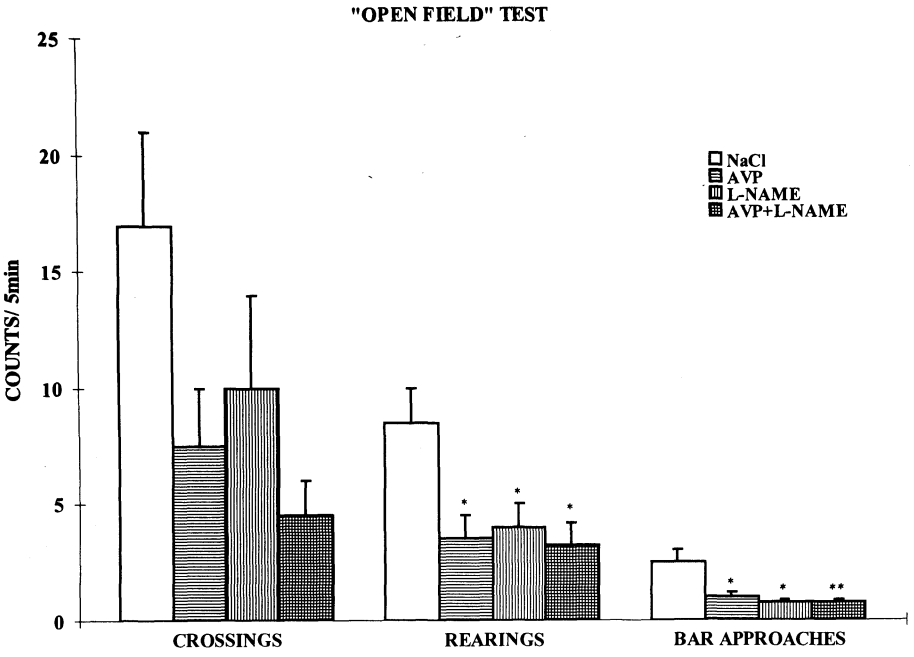


Fig. 1. Effect of AVP and L-NAME on the locomotor behaviour in the open field test. Columns represent means ± SEM of the results. NaCl - 0.9% NaCl; AVP - 1 μg AVP; L-NAME - 10 μg of L-NAME. *$P$<0.05; **$P$<0.01 vs. control group (NaCl + NaCl).

As shown in Table I AVP alone and AVP combined with L-NAME facilitated retrieval of passive avoidance responses. The analysis of differences by Kruskall--Walis nonparametric test gave $\chi^2$ = 12.575; $P$<0.01 for 47 cases and $df$ = 3. Subsequent analysis by Mann-Whitney nonparametric U test showed that AVP alone (U = 35.50; $P$<0.05) and AVP combined with L-NAME (U = 24.50 $P$<0.05) considerable delayed re-entering the dark compartment of cage in comparison with the control.

L-NAME did not display a significant difference in comparison with control.

The data shown in Table II indicate that AVP, L-arginine, and AVP combined with L-arginine delayed re-entering to the dark compartment of the cage in comparison with the control group in the passive avoidance situation. Kruskal-Walis nonparametric test statistic showed significance between groups ($\chi^2$=9.354; $P$<0.05 for 46 cases, $df$ = 3), whereas Mann-Whitney U test revealed that rats injected by AVP (U = 18.00;

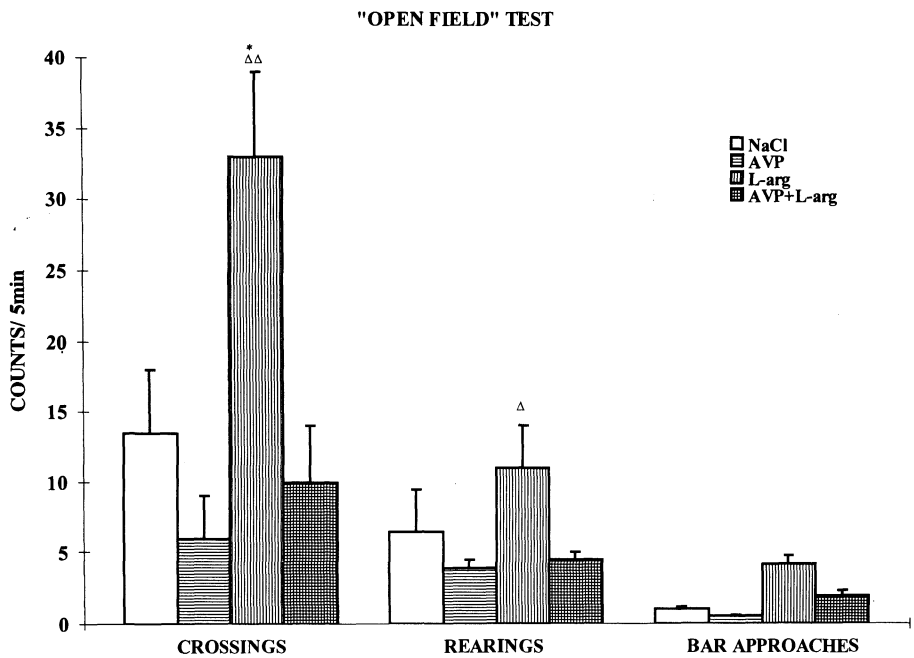


Fig. 2. Effect of AVP and L-arginine on the locomotor behaviour in the open field test. Columns represent means ± SEM of the results. NaCl - 0.9 % NaCl; AVP - 1 μg AVP; L-arg - 10 μg of L-arginine. *$P$<0.05 vs. control group (NaCl + NaCl); Δ $P$<0.05 vs. AVP + L-arginine; ΔΔ $P$<0.01 vs. AVP + L-arginine.

TABLE I

Effect of AVP and L-NAME on the retrieval of the passive avoidance response. Median latencies are given with the, in paratheses, the 25-75 percentiles. N - number of subjects in each group. NaCl - 0.9% NaCl; AVP - 1 μg of AVP; L-NAME - 10 μg of L-NAME. *$P$<0.05 vs. control group (NaCl + NaCl)

| Treatment | N | Latency (s) |
|---|---|---|
| NaCl + NaCl | 11 | 13 (7-18) |
| AVP + NaCl | 13 | 37 (13-112)* |
| NaCl + L-NAME | 13 | 9(7-13) |
| AVP + L- NAME | 11 | 36 (17-103)* |

TABLE II

Effect of AVP and L-arginine on the retrieval of the passive avoidance response. Median latencies are given with the, in paratheses, the 25-75 percentiles. N - number of subjects in each group. NaCl - 0.9% NaCl; AVP - 1 μg of AVP; L-arg - 10 μg of L-arginine. *$P$<0.05 vs. control group (NaCl + NaCl)

| Treatment | N | Latency (s) |
|---|---|---|
| NaCl + NaCl | 10 | 10.5 (7-54) |
| AVP + NaCl | 10 | 60 (13-300)* |
| NaCl + L-arg | 13 | 48 (16-113)* |
| AVP + L- arg | 13 | 39.5 (20-300)* |

$P$<0.01), L-arginine (U = 27.50; $P$<0.05), and AVP with L-arginine (U = 25.50; $P$<0.05) entered the dark compartment later than the control group. Accordingly, neither L-arginine nor L-NAME changed the performance of the rats injected with AVP in the passive avoidance situation.

The injection of AVP and AVP combined with L-NAME delayed the extinction of active avoidance responses in rats (Fig. 3). There were significant differences between groups on day 12 ($F_{3,40}$ = 5.912; $P$<0.01) and day 19 ($F_{3,40}$ = 3.480; $P$<0.05). However, further analysis by Tukey test revealed differences between control and AVP ($P$<0.05), and control in comparison with AVP combined with L-NAME ($P$<0.05) only on the 12th day.

As shown in Fig. 4, AVP, L-arginine and AVP with L-arginine delayed the extinction of active avoidance responses ($F_{3,36}$=6.544; $P$<0.01) for day 12, $F_{3,36}$=5.845;

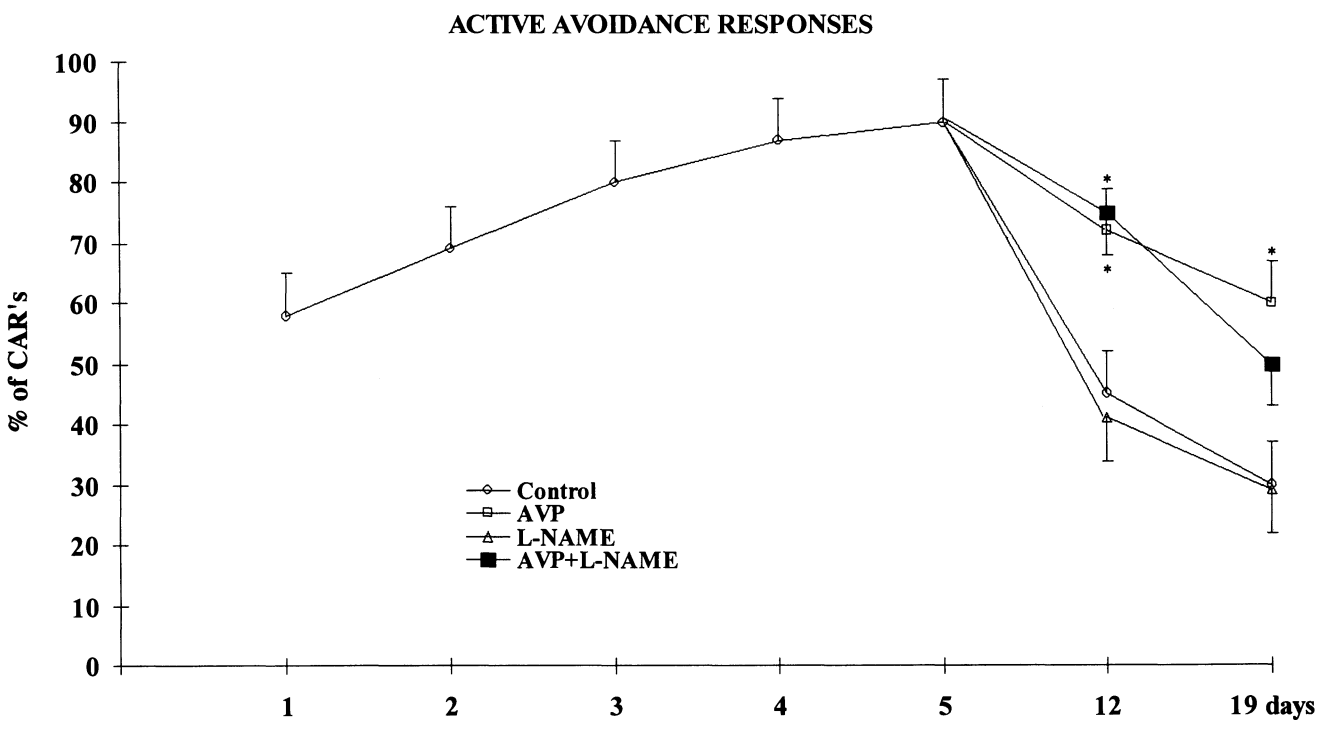


Fig. 3. Effect of AVP and L-NAME on the consolidation of active avoidance responses. All compounds were injected on the 5th day immediately after the learning session . NaCl - 0.9 % NaCl; AVP - 1 μg of AVP; L-NAME - 10 μg of L-NAME. *$P$<0.05 vs. control group (NaCl + NaCl).

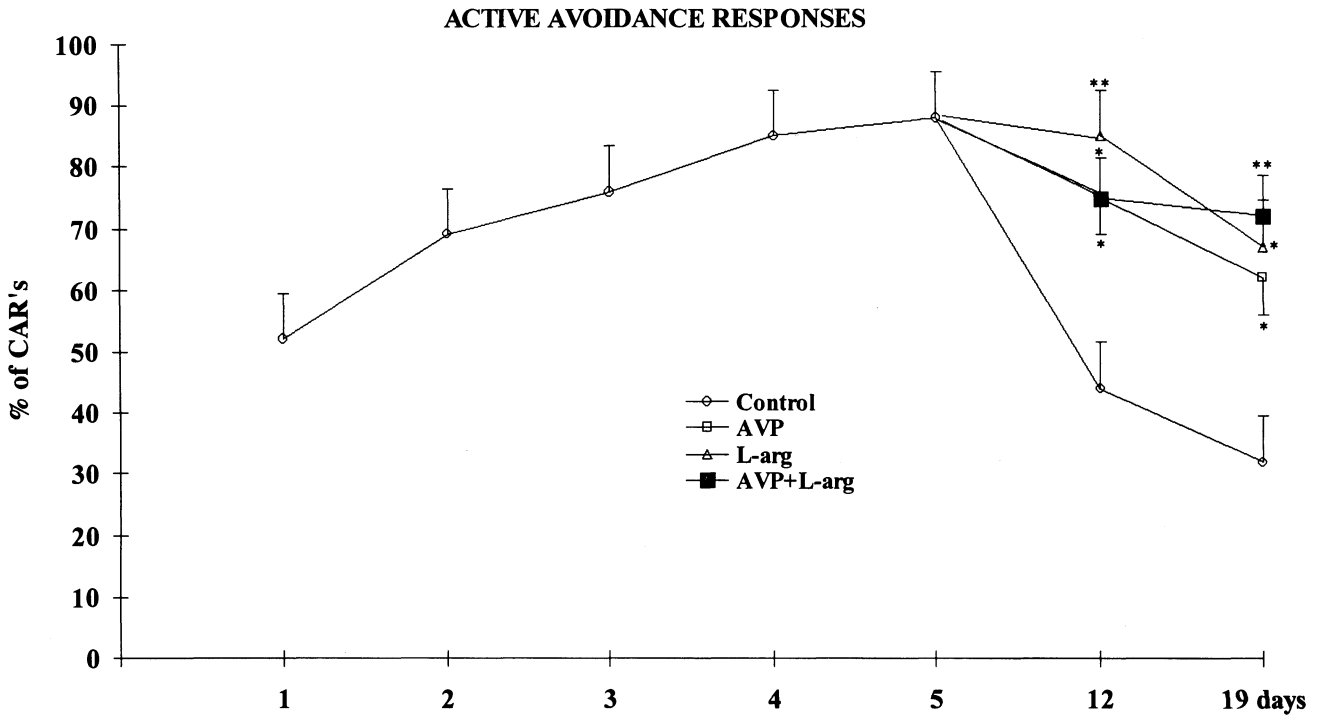


Fig. 4. Effect of AVP and L-arginine on the consolidation of active avoidance responses. All compounds were injected on the 5th day immediately after the learning session. NaCl - 0.9% NaCl; AVP - 1 μg of AVP; L-arg - 10 μg of L-arginine. *$P$<0.05; **$P$<0.01 vs. control group (NaCl + NaCl).

$P$<0.01 for day 19). Subsequent analysis by Tukey test revealed significant differences in comparison with the control on day 12 (AVP $P$<0.05, L-arginine $P$<0.01, AVP with L-arginine $P$<0.02), and on day 19 (AVP, $P$<0.05; L-arginine, $P$<0.05; AVP with L-arginine, $P$<0.01).

## DISCUSSION

The present study demonstrates that the improvement of memory in passive and active avoidance situations produced by AVP is probably independent of NO concentration in the brain. Neither the increase of NO concentration after the injection of L-arginine, nor the decrease of NO after the inhibition of NOS by L-NAME, changed the behavioural effects of AVP. In agreement with previous works (De Wied 1976), Bohus et al. 1978, Baranowska et al. 1983, Car et al. 1993), we have observed the facilitation of retrieval and consolidation of shock avoidance memory induced by icv administrated AVP. Considering that the control group latency was very low in the passive avoidance retrieval test, this may suggest that the positive effect of vasopressin in this study could be achieved in a nonspecific manner. Although Sahgal et al. (1982) failed to find any effect on passive avoidance after icv AVP administration and subscribes it to an arousal (alertness, central excitable state) theory, which suggests that vasopressin affects cognitive processing by way of increasing the arousal level of the organism, further studies showed that the AVP administered icv was effective in this paradigm (Engelamann et al. 1996). Moreover, stimulation of AVP release by ip injection of hypertonic saline improved the retention of the avoidance tasks and this effect was blocked by $V_1$ antagonist treatment (Baratti et al. 1989). The response latencies of animals that were not given a foot-shock on the training trial were unaffected by any of the doses of hypertonic saline that were given after training. This finding contradicts the suggestion that AVP may act indirectly in this behavioural test. It is unlikely that L-arginine and L-NAME significantly changed the psychomotor activity of the rats, which made the interpretation of the results, especially in the passive avoidance situation, much more complicated.

Several studies support the hypothesis that NO mediates the vasodilatatory effect caused by higher doses of AVP (Katušič 1992). It seemed that the activation of $V_1$ -like receptors (Katušič et al. 1984), which are functionally different from $V_1$ receptor in smooth muscles

(Yamada et al. 1993), caused the stimulation of NO synthesis. On the other hand, it has been shown that the central action of AVP at least partially is dependent on the $V_1$ receptor (De Wied et al. 1991). However, according to our results, the increase of NO synthesis is not necessary due to? The behavioural action of AVP in the passive and active avoidance situations.

The inhibition of NOS attenuated the acquisition of passive and active avoidance responses produced by A II (Hoły and Wiśniewski 1994). Recent research has indicated the existence of the dual angiotensin II / AVP receptor coupled to the same second messenger in kidney (Ruiz-Opazo et al. 1995), however, present data suggest a separate mechanism for the central action of angiotensin II and AVP in cognition. Several conclusions can be drawn from the observed differences between AVP and A II, which seem to be consistent with other experimental data (Baranowska et al. 1983). First, Winnicka et al. (1988) have shown that bilateral lesion to the dopaminergic innervation of the central amygdala, a structure playing a crucial role in memory motivated affectively (Kesner et al. 1993), abolished the improvement of recall of the passive avoidance behaviour caused by A II. The same lesion of the dopaminergic projection to the central amygdala did not affect the facilitator effect of AVP on retrieval process in a step-through passive avoidance situation. It seemed that the inhibition of NOS acted mainly on learning and memory dependent on dopamine release. Next, it has been shown that the inhibition of NMDA receptor complex prevented the facilitator effect of A II (Wiśniewski and Lutostańska 1995) and its 3-7 fragment (Braszko and Wiśniewski 1995), and only partially attenuated the behavioural effect of AVP (unpublished data). Accordingly, A II seemed to be more sensitive to the block of the glutaminergic transmission than AVP in the CNS. Finally, it has been shown that AVP plays a role in the consolidation and retrieval of newly acquired information, and that A II influences mostly the process of acquisition of memory. This seems to be agreement with previous work (Böhme et al. 1993) showing that NO is involved only in some forms of learning and memory.

To the best of our knowledge, this is the first experiment showing the facilitator effect of L-arginine on consolidation of active avoidance responses. There is some evidence indicating that exogenous NO donors, e.g., S-nitrosoacetylpenicillamine (SNAP) or sodium nitroprusside (SNP) (Wiśniewski and Hoły 1995) improve the retrieval and consolidation of passive avoidance response. This raises the questions whether the observed influence of L-arginine depends on NO synthesis, and what mechanism is responsible for this effect. L-arginine is considered to be a precursor of kyotorphin, an endogenous Met-enkephalin releaser (Kawabata et al. 1992) and agmatine (Gen et al. 1994), an agonist of adrenergic $\alpha_2$ receptors in the CNS. According to Kawabata et al. (1992), exogenously administrated L-arginine mainly activates kyotorphin synthesis, because the $K_m$ value of constitutive NOS from cerebella (Bredt and Snyder 1992) is much lower than the $K_m$ value of kyotorphine synthetase in the brain (Ueda et al. 1987). Additionally, several reports have shown that NO donors potentiate neurotransmitters release in separate brain regions *in vitro* (Dickie et al.1992, Prast and Philippu 1992, Zhuo and Luo 1992, Lonart et al. 1992) and *in vivo* (Guevara-Guzman et al. 1994). Accordingly, L-arginine as an NO donor may stimulate glutamate, acetylcholine, and dopamine release from different regions of the CNS. In addition, L-arginine given icv, probably through the stimulation of dopaminergic transmission, significantly increased the stereotypy induced by apomorphine and amphetamine (unpublished data). In addition, L-arginine stimulates release of two hormones: AVP (Ota et al. 1993) and corticotropin-realising hormone (Costa et al. 1993) from hypothalamus. Therefore, the explanation of the facilitator effect of L-arginine requires more evidence. However, recent research has shown that L-arginine administered icv in doses in a similar range to ours decreases numbers of trials to learning criterion, increases retention indexes and memory retrieval in newborn rats (Mysliveček et al. 1996).

L-NAME did not affect the performance of rats in the passive and active avoidance situation. The effect of NOS inhibitors on performance of rats in shock avoidance learning remains controversial. At first it was shown that $N^G$-nitro-L-arginine (L-NNA), another NOS inhibitor, did not act on learning and memory in passive avoidance response (Böhme et al. 1993). Recent evidence has suggested that L-NNA hindered the retention test performance (Fin et al. 1995). It seemed that NOS inhibitors disturb the learning and memory dependent on hippocampal function. However, it is possible that the action of NOS inhibitors on learning and memory could result from unspecific influence on the behaviour, which refers to a more general disturbance (Bannerman et al. 1994). It is unlikely that L-NAME possesses some side effects, e.g., muscarinic-receptor antagonist properties (Buxton et al. 1993).

It seemed that decreased psychomotor behaviour evoked by L-NAME was caused by the influence on dopamine release in striatum. Has been shown that NOS inhibitors significantly changed DA release in the striatum (Yamada et al. 1995). In addition, the injection of L-NAME caused the inhibition of apomorphine and amphetamine induced stereotyped behaviour in rats.

In conclusion, it can be suggested that NO does not play an important role in the facilitator action of AVP on learning and memory in rats. L-arginine facilitates consolidation of active avoidance responses, however, the mechanism of action remains unclear.

## ACKNOWLEDGEMENT

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