

## ROLE OF NEUROPEPTIDES IN ANTIDEPRESSANT AND MEMORY IMPROVING EFFECTS OF VENLAFAXINE

*Elżbieta Nowakowska<sup>#</sup>, Krzysztof Kus, Teresa Bobkiewicz-Kozłowska, Hanka Hertmanowska\**

Department of Pharmacology, Karol Marcinkowski University of Medical Sciences, Rokietnicka 5A, PL 60-806 Poznań, Poland, \*Neurology Department of Regional Hospital of Poznań, Juraszów 7/19, PL 60-479 Poznań, Poland

*Role of neuropeptides in antidepressant and memory improving effects of venlafaxine.* E. NOWAKOWSKA, K. KUS, T. BOBKIEWICZ-KOZŁOWSKA, H. HERTMANOWSKA. Pol. J. Pharmacol., 2002, 54, 605–613.

The aim of this study has been to investigate the effects of vasopressin and oxytocin on antidepressive and memory improving effects of venlafaxine. Male Wistar rats weighing 180–200 g were used in the study. Venlafaxine (20 mg/kg) was administered *po* 30 min before the test once, and for 7 and 14 days in the chronic experiments. Oxytocin (1 µg/kg) *ip* and vasopressin (1 µg/kg) *sc* were administered only once on the test day, 60 min before the tests. The animals were subjected to Porsolt's test for testing antidepressant activity, and their memory functions (working and spatial memory) were evaluated in the maze test and Morris Water Maze test. Antidepressant effects of venlafaxine could be observed already after single drug administration and the effect was maintained during 7 days of drug administration. Oxytocin also exhibited antidepressant activity, and concurrent administration of venlafaxine and oxytocin helped to maintain antidepressant activity of venlafaxine. Vasopressin was devoid of antidepressant action, yet concurrent administration of vasopressin and venlafaxine did not suppress antidepressant activity of the latter. In the chronic experiment, there was no shortening of passive swimming time. Venlafaxine improved memory in the labyrinth test and in the spatial memory test, whereas oxytocin did not affect memory of the tested animals. Joint administration of venlafaxine and oxytocin did not produce memory improving effect observed after administration of venlafaxine only. Vasopressin improved memory and joint administration of venlafaxine and vasopressin maintained the memory improving effect induced by vasopressin.

The regulatory role of neuropeptides and new antidepressant drugs, e.g. venlafaxine in mood status and memory functions may depend on the interactions between monoaminergic and neuropeptidergic systems.

**Key words:** *venlafaxine, oxytocin, vasopressin, behavioral effects, rats*

---

<sup>#</sup> *correspondence*

## INTRODUCTION

Venlafaxine (VEN) is a novel, nontricyclic antidepressant agent, thought to produce its therapeutic effects by inhibiting the neuronal uptake of serotonin, norepinephrine and, to a lesser extent, dopamine [21]. In our earlier studies, VEN exerted antidepressant action even after single administration which may have been related to prolonged noradrenergic desensitization of the neural system [23, 25]. VEN was also found to improve working memory, both after single and multiple administration [25], and this effect may have been related to the rise in monoamine concentration in the synaptic cleft.

Studies on animals have demonstrated that neuropeptides modulate nervous system functions [9]. The two neuropeptides, arginine vasopressin (AVP) and oxytocin (OXY), seem to play a pivotal role as neurotransmitters/neuromodulators in behavioral processes. The results of numerous anatomical, biochemical and behavioral studies indicate the existence of interactions between neuropeptides and monoamines, thus providing background for explaining the role of neuropeptides in the pathogenesis of affective disorders [24].

Vasopressin and related peptides improve memory processes in animals [31] and in humans [7]. The impact of OXY on memory processes is opposite to that of vasopressin [17, 18, 31, 32] and the effects are dose-dependent, as well as dependent on the gender of the tested animals and route of administration [7].

The aim of the present study was to investigate the effects of vasopressin and OXY on antidepressive and memory improving effects of VEN.

## MATERIALS and METHODS

### Animals

Male Wistar rats (180–200 g) bought from a licensed breeder (licence of the Ministry of Agriculture Warszawa, Poland) were used in this study. The animals were housed in standard laboratory conditions under a 12 h light/dark cycle, light on at 6 a.m., in a temperature controlled room at  $21 \pm 2^\circ\text{C}$ , 60% humidity, with free access to granulated standard food and tap water. The rats were kept four per cage ( $30 \times 30 \times 20$  cm). Each experimental and control group consisted of 8 animals. All the tests were carried out between 10:00 a.m. and 2:00 p.m.

The study protocol was approved by the Ethics Commission for Research on Humans and Animals at the University of Medical Sciences in Poznań.

### Drugs

VEN (hydrochloride, Effectin) was from Wyeth-Ayerts Laboratories Princeton NJ, USA), AVP was from Bachem (Switzerland), OXY was from Fluka AG (Switzerland) and carboxymethyl cellulose sodium salt (CMC) pure B.P.C. was from Koch-Light Laboratories Ltd., (London, England).

VEN (20 mg/kg) was suspended in the solution containing CMS sodium salt and administered *po* 30 min before the tests. In the chronic experiments, VEN was administered for the period of 2 weeks. Each week, after one drug-free day to wash out the remnants of the last dose, the test was performed after administering the usual dose of the drug. OXY (1  $\mu\text{g}/\text{kg}$ ) was dissolved in saline and administered *ip* at a single dose 60 min before the tests. The controls were given only saline (2 ml/kg *ip*) according to the same schedule. Vasopressin (1  $\mu\text{g}/\text{kg}$ ) was dissolved in saline and injected *sc* at a single dose 60 min before the tests. The controls received saline *sc* (0.25 ml) according to the same schedule.

## BEHAVIORAL STUDIES

### Forced swimming test

Measurement of immobility according to Porsolt et al. [27].

a) Pre-test: 24 h before the experiments, the rats were placed individually in plexiglas cylinders (height 40 cm, diameter 18 cm) filled with water at  $25^\circ\text{C}$  up to 17 cm of a height of the cylinder, and 15 min later they were removed to a drying room ( $30^\circ\text{C}$ ) for 30 min.

b) Test: the drugs were administered 24 h after the pre-test, 30 min after the administration of VEN or 60 min after OXY and AVP. The animals were placed once again in the cylinders and immobility was measured for 5 min. A rat was judged to be immobile when it remained floating in the water, in an upright position, making only very small movements necessary to keep its head above water level. The total duration of immobility during 5 min was recorded by the observer unaware of which treatment the rats had received.

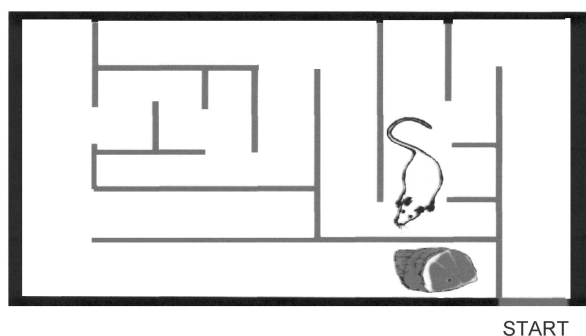
c) After prolonged administration (7 and 14 days) of VEN, the drug action was tested as described in b).

Water was changed after observation of each rat.

## Memory assessment

### *The maze test*

Rats were subjected to a maze test (Scheme 1) according to the procedure developed by Chodera (unpublished data).



Scheme 1. Maze structure

Before the test, the animals were deprived of food (rats were individually housed with limited access to food – 3 pellets per day) but had unlimited access to water. During 2 weeks, the rats were trained in the maze, with food placed in the endpoint of a complex route. The food was the reward for finding the way. The animals were put always in the same place of the maze (start place), only one animal at a time. Every two days, the rats were fed without limitations (after test) for 30 min. After a 2-week training only those rats were selected for the test which needed less than 30 s for finding the way to the food. The rats were divided randomly into groups. The mean time in the groups before starting the experiment (without drugs) was similar ranging between 22 and 25 s. CMC, VEN, OXY and AVP were administered during the tests.

### *Morris water maze test (according to Morris [22])*

The apparatus was a circular basin (diameter = 180 cm, height = 50 cm) filled with water (approximately 22–24°C) to the depth of 24 cm, with pieces of styrofoam hiding an escape platform (diameter = 8 cm) placed 1 cm below the water surface (learning place, invisible condition). Many extra-maze

visual cues surrounding the maze were available, and the observer remained in the same location for each trial.

The rats were placed in the water close to and facing the midpoint section of the wall at one of four equally spaced locations: North (N), East (E), South (S) and West (W). The pool was divided into 4 quadrants: NW, NE, SE and SW. The rats were allowed to swim freely until they found the platform on top of which they could climb. If a rat failed to locate the platform within 60 s it was placed on the platform where it remained for 5 s. Each rat was submitted to 6 trials per day and at each trial the starting position was changed (starting on the N side, followed by E, S, and W sides in that order). The inter-trial interval was 5 min between trials 1–3 and 4–6 and 10 min between trails 3 and 4. For the first 3 days of maze testing, the submerged platform was placed in the NW quadrant and then in the SE quadrant for the following 2 days. After those 5 testing days, there was a period of 7 days without any testing. On day 6, the rats were retested with the platform located as on day 5. On day 7 day (one day later), the platform was lifted above water level and placed in the SW quadrant. On the test day, each rat was subjected to a single probe trial swim (6 trials). The total number of times each rat crossed the probe target area and the time of probe trial swim were recorded by the observer. The time of each of the 6 trials was noted and a mean value for each rat was calculated. The same procedures were followed in the chronic experiments.

## Statistics

The data are shown as means  $\pm$  SEM. Statistical analysis of the data from antidepressant activity test and memory test was carried out using non-parametric Kruskal-Wallis' test for unpaired data and by Friedman test for paired data. Statistical significance was then tested by post-hoc Dunn's test for memory test and Dunnett's test for antidepressant test.

## RESULTS

### Immobility time

Both after single administration and 7-day treatment, the dose of 20 mg/kg of VEN shortened the passive swimming time, as shown in Table 1, but

after 14 days, the passive swimming time was only slightly reduced, without statistical significance. OXY at the dose of 1 µg/kg administered 60 min before the test significantly reduced immobility time on the 1st, 7th and 14th day of its administration. After joint administration of OXY + VEN, the passive swimming time was reduced after 7 days and 14 days of the treatment (Tab. 1). Vasopressin at a dose of 1 µg/kg administered 60 min before the test produced no antidepressant effects on the 1st and on the 7th day, but after 14 days, the passive swimming time was significantly increased. Concurrent administration of vasopressin and VEN did not mask antidepressant effects of the latter after single administration and there was no shortening in the passive swimming time after multiple administration (Tab. 2).

## Oxytocin and venlafaxine effect on memory

### Maze test

VEN administered only once 30 min before the test improved memory in a statistically significant manner. Significant shortening of food finding time in rats was observed both after single and after multiple administration (for 7 and 14 days) of VEN (Tab. 3). OXY at the dose of 1 µg/kg given 60 min before the test did not affect working memory in rats (Tab. 3). Joint administration of VEN + OXY both after single administration and in chronic treatment counteracted memory improving effect observed after administration of VEN alone (Tab 3). Vasopressin at the dose of 1 µg/kg administered 60 min before the test shortened food finding time both after single and multiple administration (me-

Table 1. Effect of venlafaxine and oxytocin on immobility time in the forced swimming test in rats

Compounds	Single administration	Chronic treatment		Friedman H [2.23]
	IT [s] [ $\bar{x} \pm \text{SEM}$ ]	7 days IT [s] [ $\bar{x} \pm \text{SEM}$ ]	14 days IT [s] [ $\bar{x} \pm \text{SEM}$ ]	
Control 0.5% CMC <i>po</i> 0.5 ml/rat	236.2 ± 6.1	231.3 ± 4.7	234.2 ± 5.1	1.5
Control saline 2 ml/kg <i>ip</i>	231.4 ± 8.1	229.8 ± 3.1	238.1 ± 6.2	1.7
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test	202.1 ± 5.9*	211.9 ± 6.5*	217.1 ± 7.0	2.5
Oxytocin 1 µg/kg <i>ip</i> 60 min before the test	175.3 ± 9.6 <sup>#</sup>	168.4 ± 12.4 <sup>#</sup>	199.5 ± 11.1 <sup>#</sup>	2.6
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test + oxytocin 1 µg/kg <i>ip</i> 60 min before the test	220.2 ± 10.9 <sup>x</sup>	210.3 ± 7.02 <sup>*#x</sup>	213.0 ± 7.5 <sup>**</sup>	2.3
Kruskal-Wallis H [4.39]	11.8	13.4	8.6	

\* Statistically significant difference ( $p < 0.05$ ) vs. control (CMC), <sup>#</sup> statistically significant difference ( $p < 0.05$ ) vs. control (saline), <sup>x</sup> statistically significant difference ( $p < 0.05$ ) vs. oxytocin-treated group, IT – immobility time

Table 2. Effect of venlafaxine and vasopressin on immobility time in the forced swimming test in rats

Compounds	Single administration	Chronic treatment		Friedman H [3.31]
	IT [s] [ $\bar{x} \pm \text{SEM}$ ]	7 days IT [s] [ $\bar{x} \pm \text{SEM}$ ]	14 days IT [s] [ $\bar{x} \pm \text{SEM}$ ]	
Control 0.5% CMC <i>po</i> 0.5 ml/rat	236.2 ± 6.1	231.3 ± 4.7	234.2 ± 5.1	1.5
Control saline 0.25 ml <i>sc</i>	234.2 ± 7.1	230.2 ± 3.9	236.6 ± 5.7	0.9
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test	202.1 ± 5.9*	211.9 ± 6.5*	217.1 ± 7.0	2.5
Vasopressin 1 µg/kg <i>sc</i> 60 min before the test	222.9 ± 10.8	247.0 ± 7.9	269.5 ± 2.8 <sup>#</sup>	9.8
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test + vasopressin 1 µg/kg <i>sc</i> 60 min before the test	189.9 ± 8.0 <sup>*#+</sup>	225.0 ± 13.8	247.0 ± 12.9	7.0
Kruskal-Wallis H [4.39]	11.8	7.9	14.9	

\* Statistically significant difference ( $p < 0.05$ ) vs. control (CMC), <sup>#</sup> statistically significant difference ( $p < 0.05$ ) vs. control (saline), <sup>+</sup> statistically significant difference ( $p < 0.05$ ) vs. vasopressin-treated group, IT – immobility time

**Table 3.** The influence of acute and chronic treatment with venlafaxine and oxytocin on the food finding time in the maze test. Each test was performed 30 min after venlafaxine and 60 min after oxytocin administration in 8 rats

Compounds	Food finding time [s]			Friedman H [2.23]
	Single administration [ $\bar{x} \pm \text{SEM}$ ]	Chronic treatment		
		7 days [ $\bar{x} \pm \text{SEM}$ ]	14 days [ $\bar{x} \pm \text{SEM}$ ]	
Control 0.5% CMC <i>po</i> 0.5 ml/rat	21.4 ± 3.4	23.2 ± 4.1	20.0 ± 2.3	1.4
Control saline 2 ml/kg <i>ip</i>	20.9 ± 2.8	23.9 ± 3.9	19.5 ± 1.9	1.9
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test	12.8 ± 1.5 <sup>#</sup>	10.5 ± 1.3 <sup>#</sup>	13.0 ± 1.4 <sup>#</sup>	0.4
Oxytocin 1 µg/kg <i>ip</i> 60 min before the test	17.2 ± 2.4	19.2 ± 2.6	15.2 ± 2.8	0.3
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test + oxytocin 1 µg/kg <i>ip</i> 60 min before the test	20.7 ± 2.7 <sup>z</sup>	25.3 ± 3.3 <sup>z</sup>	19.0 ± 2.2 <sup>z</sup>	2.9
Kruskal-Wallis H [4.39]	3.8	6.5	5.1	

\* Statistically significant difference ( $p < 0.05$ ) vs. control (CMC), # statistically significant difference ( $p < 0.05$ ) vs. control (saline),  
<sup>z</sup> statistically significant difference  $p < 0.05$  vs. venlafaxine-treated group

**Table 4.** The influence of acute and chronic treatment with venlafaxine and vasopressin on the food finding time in the maze test. Each test was performed 30 min after venlafaxine and 60 min after vasopressin administration in 8 rats

Compounds	Food finding time [s]			Friedman H [2.23]
	Single administration [ $\bar{x} \pm \text{SEM}$ ]	Chronic treatment		
		7 days [ $\bar{x} \pm \text{SEM}$ ]	14 days [ $\bar{x} \pm \text{SEM}$ ]	
Control 0.5% CMC <i>po</i> 0.5 ml/rat	21.4 ± 3.4	23.2 ± 4.1	20.0 ± 2.3	1.4
Control saline 0.25 ml <i>sc</i>	20.7 ± 1.9	22.9 ± 2.8	20.5 ± 2.5	1.2
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test	12.8 ± 1.5 <sup>#</sup>	10.5 ± 1.3 <sup>#</sup>	13.0 ± 1.4 <sup>#</sup>	0.4
Vasopressin 1 µg/kg <i>sc</i> 60 min before the test	10.7 ± 1.0 <sup>#</sup>	11.3 ± 1.1 <sup>#</sup>	12.5 ± 1.4 <sup>#</sup>	1.7
Venlafaxine 20 mg/kg <i>po</i> 30 min before the test + vasopressin 1 µg/kg <i>sc</i> 60 min before the test	15.3 ± 1.6 <sup>#+</sup>	10.2 ± 1.4 <sup>#</sup>	10.5 ± 1.2 <sup>#</sup>	6.3
Kruskal-Wallis H [4.39]	8.2	11.3	9.9	

\* Statistically significant difference ( $p < 0.05$ ) vs. control (CMC), # statistically significant difference ( $p < 0.05$ ) vs. control (saline),  
<sup>+</sup> statistically significant difference ( $p < 0.05$ ) vs. vasopressin-treated group

memory improving effect). The memory improving effect could still be observed after joint administration of VEN and vasopressin (Tab. 4).

### Morris water maze

After single and chronic administration of VEN, lower values of escape latencies and lower number of crossed quadrants were noted, which indicates performance improvement (Fig. 1–4). After administration of OXY, no changes in the number of crossed quadrants and escape latencies, compared to the control group, were observed (Fig. 1, 2). Joint administration of VEN and OXY did not affect memory processes evaluated in the Morris test

(Fig. 1, 2). Administration of vasopressin 60 min before the Morris memory test shortened both escape latencies and the number of crossed quadrants. Similar effect of improvement of spatial memory was observed after joint administration of vasopressin and VEN (Fig. 3, 4).

## DISCUSSION

VEN is a novel antidepressant which selectively inhibits the uptake of serotonin and norepinephrine [13] but, in contrast to tricyclic antidepressants, its antidepressant effect can be observed already after single administration [25, 28].

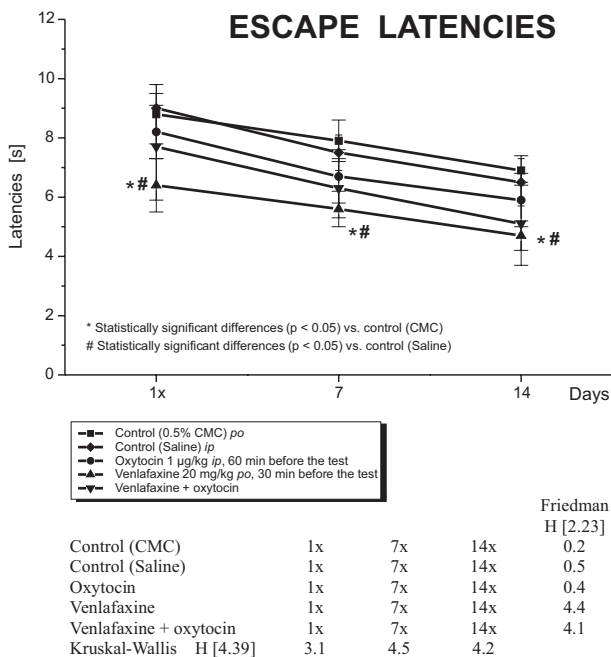


Fig. 1. The influence of venlafaxine and oxytocin on the spatial memory (Morris water maze test)

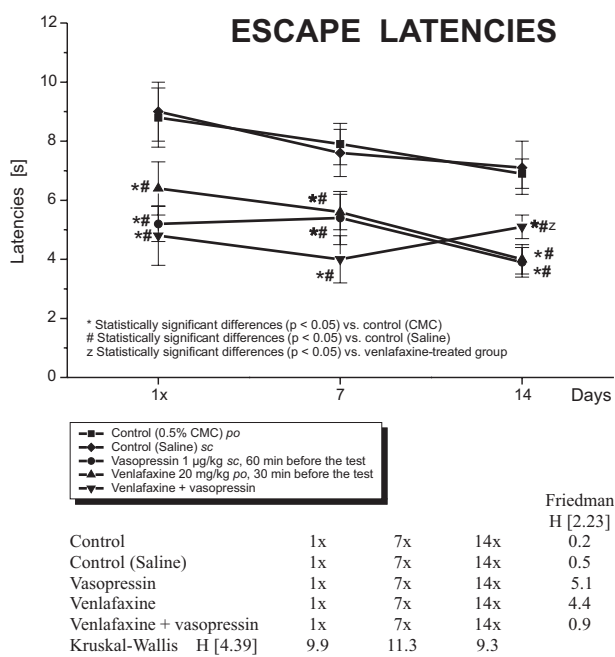


Fig. 3. The influence of venlafaxine and vasopressin on the spatial memory (Morris water maze test)

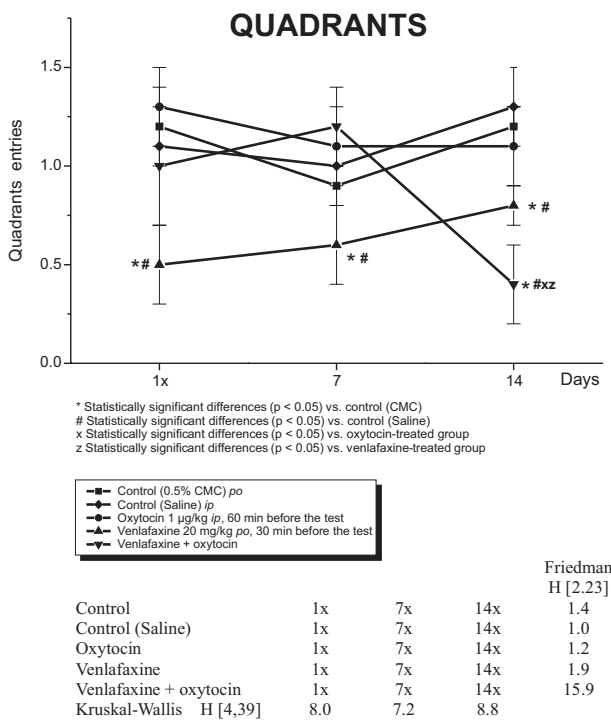


Fig. 2. The influence of venlafaxine and oxytocin on the spatial memory (Morris water maze test)

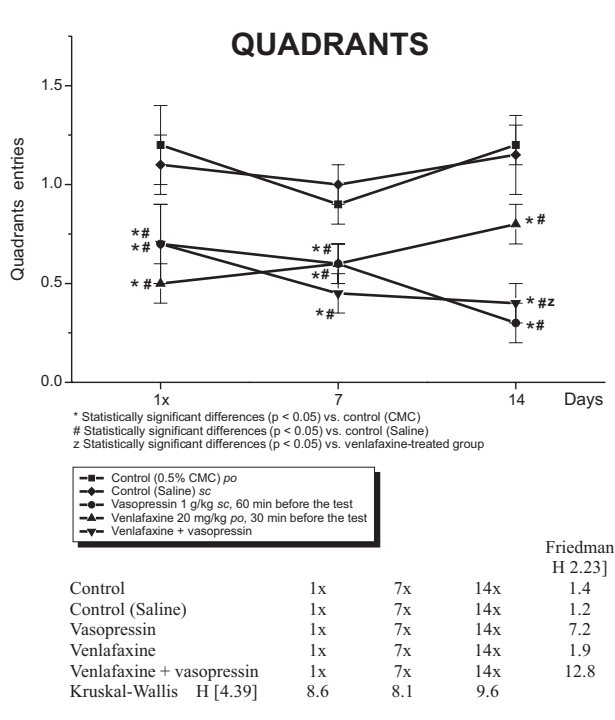


Fig. 4. The influence of venlafaxine and vasopressin on the spatial memory (Morris water maze test)

Both single and 7-day administration of VEN shortened immobility time in Porsolt's test, but after 14 days of its administration, immobility time did not differ significantly in comparison with the control group. Similar results were obtained by other authors [28, 29]. VEN appears to produce a rapid desensitization of  $\beta$ -adrenergic receptors which may have potential relevance to the time course of antidepressant response [21, 23]. As shown in another study, VEN induced prolonged desensitization of neuronal noradrenergic receptors already after single administration [23, 25]. There is both clinical and experimental evidence which suggests a role of neuropeptides in affective disorders, and some of the neuropeptides, e.g. vasopressin and its derivatives, may have beneficial effect in some depressed patients [1, 5]. Other studies point to a major role of OXY as an endogenous antidepressant hormone [2].

Previous experiments in animals have demonstrated antidepressant-like effects of OXY in mice [2, 19, 20]. Other studies revealed that citalopram, belonging to SSRIs, produced increased plasma OXY levels, and probably OXY release is an important aspect of the pharmacological actions of SSRIs [30]. In our study, OXY at 1  $\mu$ g/kg administered 60 min before the test displayed antidepressant activity of the potency similar to that of VEN. Similar results were obtained by Arletti and Bertolini [2] who administered OXY at 0.25–1 mg/kg to mice, and demonstrated that OXY was characterized by antidepressant activity of the potency similar to that of imipramine. Therefore, OXY may be postulated to act as a regulatory neuropeptide in the central nervous system.

No antidepressant activity was observed after the administration of vasopressin, yet joint administration of vasopressin and VEN enhanced antidepressant effects of VEN after single administration. Nalepa and Vetulani [24] have found that vasopressin produces down-regulation of  $\beta$ -adrenoreceptors similar in extent and character to that induced by chronic treatment with imipramine. The authors suggested that due to a similar biochemical effect, vasopressin might have antidepressant properties.

Enhancement of antidepressant effect of VEN by vasopressin seems to support the view that vasopressin may be involved in the pathogenesis of depression symptoms as vasopressin deficiency in the central nervous system is observed in endogenous depression [14]. VEN improved both spatial memo-

ry in Morris test and working memory in the maze test. As shown in our earlier work [25], the memory improving effect of VEN may be related to antidepressant efficacy of the drug which is indirectly related to the rise in monoamine concentration in the synaptic cleft. OXY did not affect memory processes in rats and, similarly, joint administration of VEN and OXY did not improve memory in the tested animals. On the contrary, vasopressin improved working memory and spatial memory, and the effect could be observed also after joint, both single and multiple, administration of VEN and vasopressin. Also other authors [11] observed improvement of short-term olfactory memory performance after a narrow range of concentrations of endogenous OXY in female rats. However, these data were discussed in the context of sexual dimorphism in brain development and support the hypothesis of a variation in the recognition performance of female rats according to the stage of their estrous cycle [16]. Generally, OXY produces effects which are opposite to those of vasopressin, and it has been suggested that OXY may be an amnesic neuropeptide [31].

Interestingly, in contrast to OXY, peripherally and centrally administered vasopressin seems to improve the memory performance not only in males [12] but also in females [3]. It should be remembered that AVP is a neuropeptide which, in addition to its hormonal function, improves memory processes in animals and humans [7, 9], although the mechanism of vasopressin-induced memory improvement remains unknown. Possibly, the behavioral memory improving effect of vasopressin in the central target structures is mediated not only by vasopressin  $V_1$  receptors but also by OXY receptors [8, 26] which indicates that the influence of the two neuropeptides on memory improving processes is obviously complex [11]. Sustained memory improving effect after joint administration of VEN and vasopressin may be linked to noradrenergic mechanisms *via*  $\beta$ -adrenergic receptors [4, 17]. It must also be emphasized that vasopressin exerts positive effects on memory impairment observed in depression syndrome [6, 10, 15].

The present results support the hypothesis that such neuropeptides as OXY and vasopressin modulate nervous system functions and play an important role in antidepressant and memory improving effect of venlafaxine. Some memory improving neuropeptides, e.g. vasopressin, may prove thera-

apeutically beneficial during the early stage of dementia.

## REFERENCES

1. Altemus M., Pigott T., Kalogeras K.T., Demitrack M., Dubbert B., Murphy D.L., Gold P.W.: Abnormalities in the regulation of vasopressin and corticotropin releasing factor secretion in obsessive-compulsive disorder. *Arch. Gen. Psychiat.*, 1992, 49, 9–20.
2. Arletti R., Bertolini A.: Oxytocin acts as an antidepressant in two animal models of depression. *Life Sci.*, 1987, 41, 1725–1730.
3. Bluthé R.M., Dantzer R.: Social recognition does not involve vasopressinergic neurotransmission in female rats. *Brain Res.*, 1990, 535, 301–304.
4. Brinton R.: Neuromodulation: associative and non-linear adaptation. *Brain Res. Bull.*, 1990, 24, 651–658.
5. De Bellis M.D., Gold P.W., Geraciotti T.D., Listwak S.J., Kling M.A.: Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine-vasopressin in patients with major depression. *Amer. J. Psychiat.*, 1993, 150, 656–657.
6. Del Pozo E., Martín-Pérez J., Stadelmann A., Girard J., Brownell J.: Inhibitory action of a met-enkephalin on ACTH release in man. *J. Clin. Invest.*, 1980, 65, 1531–1534.
7. de Wied D.: Neurohypophyseal hormones influences on learning and memory processes. In: *Neurobiology of Learning and Memory*. Eds. Lynch G., McGaugh J., Weinberger N.M., Guildford Press, New York, 1984, 289–312.
8. de Wied D., Elands J., Kovacs G.: Interactive effects of neurohypophyseal neuropeptides with receptor antagonists on passive avoidance behavior: mediation by a cerebral neurohypophyseal hormone receptor? *Proc. Nat. Acad. Sci. USA*, 1991, 88, 1492–1498.
9. de Wied D., van Ree J.M.: Neuropeptides: animal behaviour and human psychopathology. *Eur. Arch. Psychiat. Clin. Neuros.*, 1989, 238, 323–331.
10. Dockray G.J.: Immunological evidence of cholecystokinin-like peptides in brain. *Nature*, 1976, 264, 568–572.
11. Engelmann M., Ebner K., Wotjak C.T., Landgraf R.: Endogenous oxytocin is involved in short-term olfactory memory in female rats. *Behav. Brain Res.*, 1998, 80, 89–94.
12. Engelmann M., Landgraf R.: Microdialysis administration of vasopressin into the septum improves social recognition in Brattleboro rats. *Physiol. Behav.*, 1994, 55, 145–149.
13. Fabre L.F., Puthman H.P.: An ascending single-dose tolerance study of Wy-45,030, a bicyclic antidepressant, in healthy men. *Curr. Ther. Res.*, 1987, 42, 901–909.
14. Gold P.W., Post R.M., Weingartner H., Goodwin F.K.: Central peptide function in affective illness: arginine-vasopressin as a model system. *Adv. Biol. Psychiat.*, 1981, 42, 41–70.
15. Gold P.W., Weingartner H., Ballenger J.C., Goodwin F.K., Post R.M.: Effects of 1-desamino-8-D-arginine vasopressin on behaviour and cognition in primary affective disorder. *Lancet*, 1979, 2, 992–994.
16. Hlinak Z.: Social recognition in ovariectomized and estradiol-treated female rats. *Hormone Behav.*, 1993, 27, 159–166.
17. Kovacs G., Bohus B., Versteeg D.H.: Facilitation of memory consolidation by vasopressin: mediation by terminals of the dorsal noradrenergic bundle? *Brain Res.*, 1979, 172, 73–85.
18. Kovacs G.L., Bohus B., Versteeg D.H., de Kloet E.R., de Wied D.: Effect of oxytocin and vasopressin on memory consolidation: sites of action and catecholaminergic correlates after local microinjection into limbic-midbrain structures. *Brain Res.*, 1979, 175, 303–314.
19. Meisenberg G.: Short-term behavioral effects of posterior pituitary peptides in mice. *Peptides*, 1981, 2, 1–8.
20. Meisenberg G.: Short-term behavioural effects of neurohypophyseal hormones: pharmacological characteristics. *Neuropharmacology*, 1982, 21, 309–316.
21. Montgomery S.A.: Rapid onset of action of venlafaxine. *Int. Clin. Psychopharmacol.*, 1995, 10, 21–27.
22. Morris R.: Developments of a water-maze procedure for studying spatial learning in the rat. *J. Neurosci. Meth.*, 1984, 11, 47–60.
23. Muth E.A., Moyer J.A., Haskins J.T., Andree T.H., Husbands G.E.M.: Biochemical, neuropsychological and behavioural effects of Wy-45-233 and other identified metabolites of the antidepressant venlafaxine. *Drug Develop. Res.*, 1991, 23, 191–199.
24. Nalepa I., Vetulani J.:  $\beta$ -Down-regulation induced by repeated vasopressin treatment. *Eur. J. Pharmacol.*, 1990, 178, 375–376.
25. Nowakowska E., Kus K., Chodera A.: Comparison of behavioural effects of venlafaxine and imipramine in rats. *Arzneim.-Forsch.-Drug Res.*, 2002, in press.
26. Poban V., Alescio-Lautier B., Devigne C., Soumireu-Mourat B.: The behavioral effect of vasopressin in the ventral hippocampus is antagonized by an oxytocin receptor antagonist. *Eur. J. Pharmacol.*, 1998, 361, 165–173.
27. Porsolt R.D., Anton G., Blavet N., Jalfre M.: Behavioural despair in rats: a new model sensitive to antidepressant treatments. *Eur. J. Pharmacol.*, 1978, 47, 379–391.
28. Rogóż Z., Dziedzicka-Wasylewska M., Maj J.: Pharmacological profile of venlafaxine, a new antidepressant, given acutely. *Pol. J. Pharmacol.*, 1998, 50, 107–115.
29. Saletu B., Brünberger J., Anderer P., Linzmayer L., Semlitsch H.V., Magni G.: Pharmacodynamics of venlafaxine evaluated by EGG brain mapping, psychometry and psychophysiology. *Brit. J. Clin. Pharmacol.*, 1992, 33, 589–601.

30. Uvnas-Moberg K., Bjokstrand E., Hillegart V., Ahlenius S.: Oxytocin as a possible mediator of SSRI-induced antidepressant effects. *Psychopharmacology*, 1999, 142, 95–101.
31. van Winersma-Greidanus T.B., Burbach J.P., Veldhuis H.D.: Vasopressin and oxytocin. Their presence in the central nervous system and their functional significance in brain processes related to behaviour and memory. *Acta Endocrinol. Suppl.*, 1986, 276, 85–94.
32. van Winersma-Greidanus T.B., van Ree J.M., Versteeg D.H.G.: Neurohypophyseal peptides and avoidance behaviour: the involvement of vasopressin and oxytocin in memory processes. In: *Neuropeptides and Neural Transmission*. Eds. Marsan C.A., Traczyk W.Z., Raven Press, New York, 1980, 293–300.

*Received: August 5, 2002; in revised form: October 8, 2002.*