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Time-Related Memory Effects of Vasopressin Analogues in Rats

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GAFFORI, O. J. W. AND D. DE WIED. *Time-related memory effects of vasopressin analogues in rats.* PHARMACOL BIOCHEM BEHAV **25**(6) 1125–1129, 1986.—The present study was designed to investigate critical time periods for the memory modulating effect of vasopressin and several analogues in rats using a passive avoidance test as the behavioral paradigm. AVP, AVP-(4–8) and AVP-(5–8) were more effective when given immediately after the learning trial (consolidation), while AVP-(1–8) (DGAVP) and AVP-(5–9) were more active when administered one hour prior to the retention test (retrieval). DDAVP and AVP-(4–9) were highly active both when given immediately after the learning trial or 1 hour before the retention test. The period between 12 and 18 hr after the learning trial appeared to be another sensitive period. Administration, in particular of DGAVP, and AVP-(5–9) at 12, 15, and 18 hr after the learning trial induced marked retention of the avoidance response at the 24 hr retention test. Injection at 6 and 21 hr after the learning trial was the least effective in facilitating passive avoidance latencies. The more stable analogue DDAVP facilitated avoidance latencies irrespective of the time of administration. Vasopressin and related peptides exert a long term effect on avoidance behavior. However, DGAVP and AVP-(5–9) facilitated passive avoidance behavior at the 24, 48, and 72 hr retention test if administered immediately after the learning trial. If injection was postponed till 15 hr after the learning trial, passive avoidance behavior was facilitated at the 24 hr retention test only. Thus, whereas post-trial injection affects consolidation processes, the treatment between 12 and 18 hour after the learning trial may involve other mechanisms concerned with circadian metabolism, distribution, brain sensitivity to neuropeptides and behavioral performance.

Vasopressin neuropeptides Passive avoidance behavior Consolidation Retrieval Sensitive periods

THE neurohypophyseal hormone vasopressin and related peptides increase resistance to extinction of active avoidance behavior, facilitate retention of passive avoidance behavior and reverse or prevent experimentally induced retrograde amnesia [11]. These effects are of a long term nature and have been interpreted as an effect on memory processes.

Studies involving vasopressin have utilized a number of different vasopressin analogues as [Lys^8]vasopressin (LVP), [Arg^8]vasopressin (AVP), their desglycinamide analogs (DGAVP and DGLVP) and smaller fragments of the neurohypophyseal hormones [22]. Another AVP analog, [desamino-D-Arg^8]vasopressin (DDAVP), which is a potent antidiuretic with minimal vascular action [20] has become clinically popular because of its route of administration (intranasally) and its longer half-life which prolongs its antidiuretic effects. DDAVP has been found to be as effective as other vasopressin analogs in reversing the effects of puromycin-induced amnesia in mice [32] but less active than AVP in the maintenance of a conditioned avoidance response [33]. Burbach *et al.* [5,6] have shown that vasopressin can be converted to fragments by rat brain synaptic membranes which are behaviorally markedly more active that the parent molecule but inactive on blood pressure and diuresis. The peptides [pGlu^4,Cyt^6]AVP-(4–9) and [pGlu^4, Cyt^6]AVP-(4–8) were found to enhance passive avoidance latency in much lower doses as compared with the parent molecule AVP [5,12].

There exists a critical time period for the behavioral effect of vasopressin to occur. Administration immediately after the behavioral session produces the maximal behavioral effect. If injection is given at 3 hr before or after the session the effectiveness of the treatment is markedly decreased while administration at a time interval of 6 hr before or after the session is ineffective [2, 3, 10]. The present study was designed to investigate the memory modulating effects of some of these vasopressin analogues and to analyse the critical time period of their effect using a passive avoidance test as the behavioral paradigm.

METHOD

Animals

Male Wistar rats of an inbred strain (CPB-TNO, Zeist, The Netherlands) weighing 160–180 g, were used. The animals were housed 5 per cage at room temperature (20–21°C). All animals had access to commercial food and tap water ad lib and were kept on a controlled illumination schedule (light on between 6 a.m. and 8 p.m.). They were handled on two consecutive days prior to the start of the experiment. Rats were transported from the animal house to the experimental room 1 hr before the experiment.

Passive Avoidance Behavior

Animals were trained in a step-through type one trial

TABLE 1

EFFECT OF VASOPRESSIN AND RELATED PEPTIDES ON RETENTION OF A ONE TRIAL PASSIVE AVOIDANCE RESPONSE

Treatment[2]	Latency (median sec) of the Retention Test (24 hr)													
	0 hr[1]		6 hr		12 hr		15 hr		18 hr		21 hr		23 hr	
placebo	79	(57–101)[3]	42	(39–62)	77	(69–101)	70	(43–83)	74	(52–83)	75	(52–89)	80	(62–81)
AVP[4]	300‡	(241–300)	163*	(101–189)	211†	(182–241)	251†	(182–300)	162*	(118–173)	189†	(121–210)	238†	(182–261)
DGAVP	231†	(161–300)	62	(41–79)	251†	(182–300)	300‡	(183–300)	282†	(183–300)	163*	(119–183)	300‡	(246–300)
DDAVP	300‡	(261–300)	210†	(138–300)	300‡	(264–300)	300‡	(212–300)	243†	(137–300)	182†	(126–243)	300‡	(219–300)
placebo	79	(49–99)	53	(34–67)	82	(62–101)	75	(72–87)	70	(61–82)	72	(62–89)	80	(54–101)
[pGlu[4],Cyt[6]]-AVP-(4–9)[5]	300‡	(213–300)	154*	(105–182)	179†	(124–260)	164*	(108–182)	146*	(107–183)	151*	(106–182)	300‡	(241–300)
[pGlu[4],Cyt[6]]-AVP-(4–8)	300‡	(212–300)	121	(92–137)	162*	(110–183)	158*	(103–172)	162*	(102–200)	116	(69–131)	182†	(141–213)
[Cyt[6]]-AVP-(5–9)	180†	(141–300)	136*	(94–163)	300‡	(234–300)	300‡	(182–300)	273†	(182–300)	172*	(136–268)	300‡	(236–300)
[Cyt[6]]-AVP-(5–8)	300‡	(236–300)	123	(94–168)	168*	(112–182)	152*	(108–183)	168*	(107–300)	122	(90–138)	171†	(142–216)

Treatment was given subcutaneously at different times after the learning trial.
[1]Hr after the learning trial.
[2]Number of animals per group=6.
[3]Values are given as median (in parentheses the 25th and 75th percentile).
[4]Dose per rat 3 μg SC.
[5]Dose per rat 0.3 μg SC.
Different from rats simultaneous treated with placebo (*$p<0.05$, †$p<0.02$, ‡$p<0.002$) Kruskal-Wallis test and subsequent Mann-Whitney U-test.

TABLE 2

EFFECT OF DGAVP AND AVP-(5–9) GIVEN IMMEDIATELY OR AT 15 HR AFTER THE LEARNING TRIAL ON THE RETENTION OF PASSIVE AVOIDANCE BEHAVIOR AT 24, 48, AND 72 HR RETENTION TEST

	24 hr				48 hr				72 hr			
	A		B		A		B		A		B	
saline[1]	83	(60–90)[2]	65	(61–99)	57	(33–64)	42	(27–63)	42	(24–60)	33	(21–61)
DGAVP[3]	242†	(183–300)	300‡	(261–300)	210†	(180–246)	47	(39–72)	163*	(103–182)	34	(12–60)
AVP-(5–9)[4]	193†	(162–243)	300‡	(300–300)	163*	(103–184)	58	(42–81)	111*	(83–143)	40	(18–70)

A—treatment immediately after the learning trial.
B—treatment at 15 hr after the learning trial.
[1]Number of animals per group.
[2]Values are given as median (in parentheses 25th and 75th percentile).
[3]Dose per rat 3 μg SC.
[4]Dose per rat 0.3 μg SC.
Different from placebo treatment (*$p<0.05$, †$p<0.02$, ‡$p<0.002$) Kruskal-Wallis test and subsequent Mann-Whitney U-test.

learning passive avoidance test. The experimental apparatus consisted of an illuminated platform (40 W bulb, placed 30 cm above) attached to a large, dark compartment equipped with a grid floor. After habituation to the dark compartment (2 min), rats were placed on the platform and allowed to enter the dark compartment; since rats prefer dark to light, they normally enter within 15 sec. After every trial, the door separating the platform and the dark box was closed and the animals were allowed to remain in the dark box for 10 sec. On the next day after three more trials, an unavoidable scrambled footshock (0.25 mA, 2 sec) was delivered through the grid floor of the dark compartment (learning trial). The median entrance latencies at the learning trial for the different groups in the various experiments ranged from 3 to 10 sec, and the differences between groups were not significant. Rats were removed from the shock box 10 sec after the termination of the shock. Great care was taken to ensure that animals actually received the shock: (1) the current level was frequently verified by direct measurement; (2) the shock delivery was regularly monitored by the experimenter (fingers on the grid); (3) behavior of every animal was observed; when they received the shock; animals displayed obvious signs of mild distress (running, jumping, squeaking); (4) metal grids and walls were scrupulously cleaned with dry towels between experiments and between the learning trial; the rats were placed on the platform and the latency to enter

the dark compartment was measured up to a maximum of 300 sec. The subjects were tested in a predetermined order to diminish bias in the results. Injections were performed at different times after the learning trial: 0 hr, 6 hr, 12 hr, 15 hr, 18 hr, 21 hr, and 23 hr. The learning and the retention test were always performed at the same time of the day-night cycle between 2 p.m. and 5 p.m.

Peptides

[Arg^8]vasopressin (AVP-(1–9); AVP), [desglycinamide-(Arg^8)]vasopressin (AVP-(1–8); DGAVP); [des-amino-[D-Arg^8]vasopressin (DDAVP); [$pGlu^4$,Cyt^6]AVP-(4–9) (AVP-4–9)), [$pGlu^4$,Cyt^6]AVP-(4–8)] (AVP-(4–8)), [Cyt^6]-AVP-(5–9) (AVP-(5–9)) and [Cyt^6]AVP-(5–8) (AVP-(5–8)) were used. Immediately prior to the experiments peptides were dissolved in one drop of 10^{-5} NHCl, then diluted with saline (0.9% NaCl, pH 6.5–6.7) and injected subcutaneously in a volume of 0.5 ml per rat. Control animals received the same volume of saline. Based on previous studies [12], a dose of 3 μg/rat for AVP, DGAVP and DDAVP, and 0.3 μg/rat for AVP-(4–9), AVP-(4–8), AVP-(5–9) and AVP-(5–8) was chosen. Peptides were generously donated by Organon Research Laboratories, Oss, The Netherlands.

Statistical Analysis

Passive avoidance latencies were analysed with Kruskal-Wallis and subsequently with Mann-Whitney U non-parametric test.

RESULTS

Vasopressin neuropeptides significantly facilitated passive avoidance behavior at the 24 hr retention test when given 0 or 23 hr after the learning trial (Table 1). AVP, AVP-(4–8) and AVP-(5–8) were significantly the most active when given immediately after the learning trial (maximum latency of 300 sec), $U(6,6)=1$, $p<0.002$, for every peptide, DGAVP and AVP-(5–9) when given 23 hr after the learning trial (maximum latency of 300 sec), $U(6,6)=0$, $p<0.002$, for each peptide. DDAVP and AVP-(4–9) were significantly highly active both when given at 0 or 23 hr after the learning trial (maximum latency of 300 sec), $U(6,6)=1$, and 0, $p<0.002$, respectively. Treatment at 6 hr after the learning trial was without effect when DGAVP, AVP-(4–8) and AVP-(5–8) were used (latency of 62, 121 and 123 sec), $U(6,6)=11$, 8, and 13, respectively, $p>0.05$, while treatment with AVP (latency: 163 sec, $U(6,6)=6$, $p<0.05$); DDAVP (latency: 210 sec, $U(6,6)=3$, $p<0.02$); AVP-(4–9) (latency: 154 sec, $U(6,6)=6$, $p<0.05$); and AVP-(5–9) (latency: 136 sec, $U(6,6)=7$, $p<0.05$) exerted a small but significant increase in avoidance latencies. The effect of AVP and AVP-(4–9) was however significantly lower than when given immediately after the learning trial (AVP: $U(6,6)=4$, $p<0.02$; AVP-(4–9), $U(6,6)=5$, $p<0.02$). Effects of vasopressin neuropeptides were in general also rather low when given 21 hr after the learning trial: treatment with AVP-(4–8) (latency: 116 sec, $U(6,6)=10$, $p>0.05$); and AVP-(5–8) (latency: 122 sec, $U(6,6)=9$, $p>0.05$) was without significant effect; treatment with AVP (latency: 189 sec, $U(6,6)=3$, $p<0.02$); DGAVP (latency: 163 sec, $U(6,6)=7$, $p<0.05$); DDAVP (latency: 182 sec, $U(6,6)=4$, $p<0.02$); AVP-(4–9) (latency: 151 sec, $U(6,6)=6$, $p<0.05$); and AVP-(5–9) (latency: 172 sec, $U(6,6)=6$, $p<0.05$) induced a small but significant increase in avoidance latencies.

Administration of the vasopressin neuropeptides at 12, 15, and 18 hr after the learning trial facilitated passive avoidance behavior significantly. This was most clearly seen following DGAVP, DDAVP and AVP-(5–9). Administration of these peptides at 12, 15, and 18 hr after the learning trial induced similar avoidance latencies than when the injection was performed at 0 or 23 hr after the learning trial, i.e., nearly maximum avoidance latencies at the 24 hr retention test: (DGAVP: latency at 12 hr, 251 sec, $U(6,6)=4$, $p<0.02$; at 15 hr, 300 sec, $U(6,6)=0$, $p<0.002$; at 18 hr, 282 sec, $U(6,6)=2$, $p<0.02$); (DDAVP: latency at 12 and 15 hr, 300 sec, $U(6,6)=0$, $p<0.002$ for each time; at 18 hr, 282 sec, $U(6,6)=2$, $p<0.02$); and (AVP-(5–9): latency at 12 and 15 hr, 300 sec, $U(6,6)=0$, $p<0.002$; at 18 hr, 273 sec, $U(6,6)=2$, $p<0.02$). The effect of DDAVP was marked irrespectively of the time of treatment. Avoidance latencies of saline-treated rats did not vary much although latencies were slightly lower when the injection was given at 6 hr after the learning trial.

In the next series of experiments, DGAVP and AVP-(5–9) were injected at 15 hr after the learning trial and tested either at 24, 48, or 72 hr after the learning trial. The effect of this treatment was compared with administration immediately after the learning trial. As can be seen from Table 2, post-learning injection of DGAVP and AVP-(5–9) significantly facilitated passive avoidance behavior at the 24, 48, and 72 hr retention test: (DGAVP: latency at 24 hr, 242 sec, $U(6,6)=3$, $p<0.02$; at 48 hr, 210 sec, $U(6,6)=4$, $p<0.02$; at 72 hr, 163 sec, $U(6,6)=7$, $p<0.05$); (AVP-(5–9): latency at 24 hr, 193 sec, $U(6,6)=4$, $p<0.02$; at 48 hr, 163 sec, $U(6,6)=5$, $p<0.05$; at 72 hr, 111 sec, $U(6,6)=7$, $p<0.05$). However, injection at 15 hr after the learning trial, facilitated passive avoidance behavior at the 24 hr retention test only (DGAVP and AVP-(5–9), latency: 300 sec, $U(6,6)=1$ and 0 respectively, $p<0.002$). At the 48 and 72 hr retention test, the latencies of thus treated rats were not different from those of saline treated animals.

DISCUSSION

The present study confirms previous observations that vasopressin and vasopressin analogues facilitate consolidation and retrieval of memory processes as tested in a passive avoidance test [3, 5, 12, 24]. DDAVP appeared to be as active as AVP and DGAVP, independent of whether the peptide was given immediately after the learning trial or before the retention test. This is in contrast with studies on active avoidance behavior in which it was found that DDAVP had a much lower effect than AVP [33]. This may be due to the fact that another behavioral paradigm was used and that the origin of the peptide differed [36] from that of the present study. Other studies also indicated behavioral effects of DDAVP. DDAVP facilitated learning of a brightness discrimination task [8] and improved spatial working memory in a 24-arm radial maze [7]. Administration of DDAVP in humans was shown to have a beneficial effect on learning and memory in a number of patients [23,35] and in healthy subjects [1]. Interestingly, in the present study DDAVP affected consolidation as well as retrieval processes, this probably is due to its long term effect.

The shorter fragments of vasopressin are markedly more active than the parent molecule, when given immediately after the learning trial AVP-(4–9), AVP-(4–8), and AVP-(5–8) or 1 hr prior to the retention test AVP-(4–9) and AVP-(5–9). This agrees with previous studies [5, 12, 15]. The critical period for the behavioral effect of vasopressin to occur

amounts to several hours before or after acquisition of an active avoidance response [2,10]. Using a one trial passive avoidance test, Bohus *et al.* [3] found that vasopressin treatment given immediately after the learning trial or 1 hr prior to the retention test were the most effective. If the administration was postponed for 6 or 18 hr the effect of the peptide had disappeared. The present results again show critical periods for vasopressin and related peptides. In order to be fully active, peptides had to be administered immediately after the learning trial or 1 hr prior to the retention test. In general, the lowest effects of the peptides were seen at 6 and at 21 hr after the learning trial. Surprisingly, there appeared to be more than the two known sensitive periods. These were best observed after treatment with DGAVP and AVP-(5–9). Apart from the first one at 0 and the second one at 23 hr, injection between 12 and 18 hr after the learning trial caused maximal retention. The first and second period have been interpreted as effects on respectively consolidation and retrieval processes [3]. The 12 to 18 hr period must be the result of another process since administration of the peptides did not result in a long term effect. In contrast to the post-learning treatment which facilitated passive avoidance behavior at the 24, 48, and 72 hr retention test, administration of DGAVP and AVP-(5–9) at 15 hr after the learning trial facilitated passive avoidance behavior at the 24 hr retention test only. Thus, treatment at 15 hr after the learning involves other mechanisms possibly concerned with circadian variation in metabolism and distribution, brain permeability processes, and behavioral performance.

This 12 to 18 hr period might be understood in terms of resistance against enzymatic degradation. However, although the various vasopressin neuropeptides have half-lifes of different duration (J. Verhoef, personal communication), all were active at the 24 hr retention test, when given between 12 and 18 hr but not 6 hr after the learning trial. Thus, the sensitive period cannot easily be explained in these terms.

Circadian organization may play a critical role in memory processes [18, 19, 31, 34]. Disruption of circadian organization in the rat results in a temporary memory disturbance [9,30], in particular memory retrieval processes [13]. This memory disturbance can be improved by treatment with peptides related to ACTH and vasopressin [14]. The performance in retention tests in a variety of appetitive and aversive tasks fluctuates rhythmically, with optimal retention occurring 24 hr after training [18, 19, 34]. In studies dealing with retention of avoidance responding, Kamin [21] found that over shorter intervals aversively motivated behavior shows a peculiar U-shaped retention function with a decline of performance at 1 and 6 hr after the training. Kamin [21] suggested that subjects after an aversive experience are temporarily in a different state, presumably as a consequence of the stress. In fact, adrenal steroids were found to play an important role in this respect [4]. The failure of retrieval at intermediate retention intervals was confirmed by various studies [18,31]. Holloway and Wansley [18] found that retention of passive avoidance behavior is enhanced at both 12 and 24 hr after training. In contrast, retention measured at 6 and 18 hr after the learning trial was significantly impaired. The effects of vasopressin and related peptides in the present study were lowest when injected at 6 and at 21 hr after the learning trial. It may be therefore that this reflects U-shaped function of the sensitivity of the brain to peptides in general and of the memory modulating effect of vasopressin and related peptides in particular caused by the stress of the learning trial.

The better performance after treatment with AVP between 12 and 15 hr after the learning could have to do with the fact that this period corresponds to the time between 3.00 a.m. and 6.00 a.m. and effects of drugs in rats are maximal during the night phase which corresponds to the peak of their activity cycle [27]. Sandman *et al.* [28] found that α-MSH produced a greater inhibition in passive avoidance behavior in the dark period. However, this does not seem to be the case in the present experiments. The effects of the peptides on passive avoidance behavior appeared to be similar when learning and testing were performed in the morning or in the evening (data not shown). Circadian variations in mechanisms associated with learning and memory appeared to be correlated with the levels of AVP in the CNS. Sandman *et al.* [28] and Davies *et al.* [9] found that rats display a daily variation in performance of a passive avoidance task, with optimal retention during the light phase of the day/night cycle. At this period AVP levels are highest in the paraventricular, supraoptic, suprachiasmatic nuclei [26], in the cerebrospinal fluid [25,29] and in the plasma of rats [17]. Interestingly in man, the circadian rhythm of vasopressin is the reverse of that of the rat and AVP levels in human plasma are higher during the night than during the day [16].

The present results may have relevance for the clinical use of vasopressin and vasopressin analogues. In some memory tests DDAVP is as good as AVP or DGAVP. It has however, the disadvantage that it is a strong antidiuretic agent and, if used chronically, may induce water retention. In addition, our data show that there is little relation between half-life of vasopressin and related peptides and their CNS effects. Time of administration is at least as important as metabolic degradation. Time-related studies also in the human may therefore reveal more effective treatments than have been administered so far.

REFERENCES

1. Beckwith, B. E., T. Petros, S. Kanaan-Beckwith, D. I. Couk, R. J. Haug and C. Ryan. Vasopressin analog (DDAVP) facilitates concept learning in human males. *Peptides* **3:** 627–630, 1982.
2. Bohus, B., R. Ader and D. de Wied. Effects of vasopressin on active and passive avoidance behavior. *Horm Behav* **3:** 191–197, 1972.
3. Bohus, B., G. L. Kovács and D. de Wied. Oxytocin, vasopressin and memory: opposite effects on consolidation and retrieval processes. *Brain Res* **157:** 414–417, 1978.
4. Brush, F. R., J. S. Myer and M. E. Palmer. Effects of kind of prior training and intersession interval upon subsequent avoidance learning. *J Comp Physiol Psychol* **56:** 539–545, 1963.
5. Burbach, J. P. H., G. L. Kovács, D. de Wied, J. W. van Nispen and H. M. Greven. A major metabolite of arginine vasopressin in the brain is a highly potent neuropeptide. *Science* **221:** 1310–1312, 1983.
6. Burbach, J. P. H., X. C. Wang, J. A. ten Haaf and D. de Wied. Substances resembling C-terminal vasopressin fragments are present in the brain but not in the pituitary gland. *Brain Res* **306:** 384–387, 1984.
7. Burešová, O. and J. Škopková. Vasopressin analogues and spatial working memory in the 24-arm radial maze. *Peptides* **3:** 725–727, 1982.

8. Couk, D. H. and B. E. Beckwith. Effects of desmopressin acetate (DDAVP) on the learning of a brightness discrimination. *Peptides* **3:** 521–526, 1982.
9. Davies, A., V. Navaratman and P. H. Redfern. A 24 hour rhythm in passive avoidance behavior in rats. *Psychopharmacologia* **32:** 211–214, 1973.
10. De Wied, D. Long term effect of vasopressin on the maintenance of a conditioned avoidance response in rats. *Nature* **232:** 58–60, 1971.
11. De Wied, D. Behavioural actions of neurohypophysial peptides. *Proc R Soc Lond [Biol]* **210:** 183–195, 1980.
12. De Wied, D., O. Gaffori, J. M. van Ree and W. de Jong. Central target for the behavioural effects of vasopressin neuropeptides. *Nature* **308:** 276–278, 1984.
13. Fekete, M., J. M. van Ree, R. J. M. Niesink and D. de Wied. Disrupting circadian rhythms in rats induces retrograde amnesia. *Physiol Behav* **34:** 883–887, 1985.
14. Fekete, M., J. M. van Ree and D. de Wied. The ACTH-(4–9) analog Org 2766 and desglycinamide^{9}-(Arg^{8})-vasopressin reverse the retrograde amnesia induced by disrupting circadian rhythms in rats. *Peptides* **7:** 563–568, 1986.
15. Gaffori, O., G. L. Kovács, J. M. van Ree and D. de Wied. Structure activity relationship studies with C-terminal fragments of vasopressin and oxytocin on avoidance behavior in rats. *Neurosci Lett [Suppl]* **22:** S506, 1985.
16. George, C. P. L., F. H. Messerli, J. Gynest, W. Nowaczynski, R. Boucher, O. Kuchel and M. Rojo-Ortaga. Diurnal variation of plasma vasopressin in man. *J Clin Endocrinol Metab* **41:** 332–338, 1975.
17. Greeley, G. H., M. Morris, J. C. Eldridge and J. S. Kizer. A diurnal plasma vasopressin rhythm in rats. *Life Sci* **31:** 2843–2846, 1982.
18. Holloway, F. A. and R. Wansley. Multiphasic retention deficits at periodic intervals after passive avoidance learning. *Science* **180:** 208–210, 1973.
19. Holloway, F. A. and R. A. Wansley. Multiple retention deficits after active and passive avoidance learning. *Behav Biol* **9:** 1–14, 1973.
20. Huguenin, R. L. and R. A. Boissonat. Synthese de la desamino^{1}-Arg^{8}-vasopressine de la desamino^{1}-Phe^{2}-Arg^{8}-vasopressine, deux analogues possedant une activité antidiuretique plus élévée que celle des vasopressines naturelles. *Helv Chim Acta* **49:** 695–699, 1966.
21. Kamin, L. J. The retention of an incompletely learned avoidance response. *J Comp Physiol Psychol* **50:** 457–460, 1957.
22. Kovács, G. L., B. Bohus, D. H. G. Versteeg, G. Telegdy and D. de Wied. Neurohypophyseal hormones and memory. In: *Advances in Pharmacology and Therapeutics, II, Vol 1, CNS Pharmacology, Neuropeptides*, edited by H. Yoshida, Y. Hagihara and S. Ebashi. Oxford: Pergamon Press, 1982, pp. 175–187.
23. Laczi, F., Zs. Valkusz, F. A. Lászlo, A. Wagner, T. Jardanhazy, A. Szasz, J. Szilard and G. Telegdy. Effects of lysine-vasopressin and 1-deamino-8-D-arginine-vasopressin on memory in healthy individuals and diabetes insipidus patients. *Psychoneuroendocrinology* **7:** 185–192, 1982.
24. Lebrun, C. J., H. Rigter, J. L. Martinez, Jr., G. F. Koob, M. Le Moal and F. E. Bloom. Antagonism of effects of vasopressin (AVP) on inhibitory avoidance by a vasopressin antagonist peptide (dPtyr-(Me)AVP). *Life Sci* **35:** 1505–1512, 1984.
25. Mens, W. B. J., E. A. D. Andringa-Bakker and Tj. B. van Wimersma Greidanus. Changes in cerebrospinal fluid levels of vasopressin and oxytocin of the rat during various light-dark regimes. *Neurosci Lett* **34:** 51–56, 1982.
26. Noto, T., H. Hashimoto, Y. Doi, T. Nakajima and N. Kato. Biorhythm of arginine-vasopressin in the paraventricular, supraoptic and suprachiasmatic nuclei of rats. *Peptides* **4:** 875–878, 1983.
27. Rusak, B. and I. Zucker. Neural regulation and circadian rhythms. *Physiol Rev* **59:** 449–520, 1979.
28. Sandman, C. A., A. J. Kastin and A. V. Schally. Behavioral inhibition as modified by melanocyte-stimulating hormone (MSH) and light-dark conditions. *Physiol Behav* **6:** 45–48, 1971.
29. Schwartz, W. J., R. J. Coleman and S. M. Reppert. A daily vasopressin rhythm in rat cerebrospinal fluid. *Brain Res* **263:** 105–112, 1983.
30. Stephan, F. K. and N. S. Kovacevic. Multiple retention deficit in passive avoidance in rats is eliminated by suprachiasmatic lesions. *Behav Biol* **22:** 456–462, 1978.
31. Tapp, W. N. and F. A. Holloway. Phase-shifting circadian rhythms produces retrograde amnesia. *Science* **211:** 1056–1058, 1981.
32. Walter, R., P. L. Hoffman, J. B. Flexner and L. B. Flexner. Neurohypophyseal hormones, analogs and fragments: Their effect on puromycin-induced amnesia. *Proc Natl Acad Sci USA* **72:** 4180–4184, 1975.
33. Walter, R., J. M. van Ree and D. de Wied. Modification of a conditioned behavior of rats by neurohypophyseal hormones and analogues. *Proc Natl Acad Sci USA* **75:** 2493–2496, 1978.
34. Wansley, R. A. and F. A. Holloway. Multiple retention deficits following one-trial appetitive training. *Behav Biol* **14:** 135–149, 1975.
35. Weingartner, H., P. Gold, J. C. Ballenger, S. A. Smallberg, R. Summers, D. R. Rubinow, R. M. Post and F. K. Goodwin. Effects of vasopressin on human memory functions. *Science* **211:** 601–603, 1981.
36. Zaoral, M., J. Kolc and F. Sorm. Synthesis of 1-deamino d-D-gamma aminobutyrine-vasopressin, 1-deamino 8-D-lysine-vasopressin and 1-deamino-8-D-arginine-vasopressin. *Collecta Clln Czech Chem Commun* **32:** 1250–1257, 1966.