Effects of des-glycinamide⁹-[arginine⁸] vasopressin upon spatial memory in the hole-board search task

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The hole-board search task (HBST), a spatial learning test, was used to measure errors, working memory, reference memory, sequence, and response bias. Various dosages of desglycinamide⁹-[arginine⁸] vasopressin (DGAVP; 0.17, 0.5, 1, 3, and 10 μg) were administered in double blind experiments 1 h prior to six training sessions in the HBST. Body weight loss was a covariant in a repeated measures multivariate analysis of variance. Reliable changes in all dependent variables were observed. DGAVP dosages of 0.17 and 0.5 $\mu\text{g} \times$ sessions were both significant for the error measure, relative to saline controls. Both dosages showed increased errors (i.e., less learning), relative to saline controls. Pretreatment with DGAVP 0.5 $\mu\text{g} \times$ sessions produced a significant decrease in working memory performance, relative to saline controls. Pretreatment with DGAVP 1 $\mu\text{g} \times$ sessions was significant and revealed improved performance on errors, working memory, reference memory, and sequence variables, relative to saline controls. DGAVP 10 μg decreased the sequence of visits to food holes significantly. DGAVP 0.17 μg significantly decreased first hole food visits, relative to controls. The results offer further evidence that DGAVP effects performance errors (learning), working memory (short-term memory), reference memory (long-term memory), and sequence of visits to food holes (spatial memory). The dosage of DGAVP is critical in facilitating performance in the HBST.

The effect of vasopressin (AVP) on memory processes was originally proposed by de Wied (1964, 1965). Also, data from more recent investigations lend support to this notion (Beckwith, Till, Reno, & Poland, 1990; Bruins, Kumar, & Schneider-Helmert, 1990; Popik & van Ree, 1992; for other studies, see de Wied et al., 1988, and Jolles, 1988).

Other explanations of the effect of AVP involve arousal or response bias properties of AVP (Sahgal, 1984; Sahgal, Keith, & Lloyd, 1990), aversive properties of AVP (Ebenezer, 1988), and motivational effects of AVP (Alliot & Alexinsky, 1991). Individual differences in memory formation and accessibility of memory in rats may mask some of the effects of AVP on memory processes (Strupp, 1989; Strupp, Bunsey, Bertsche, Levitsky, & Kesler, 1990). In the radial maze spatial learning task, both pretrial and posttrial injections of AVP₄₋₉, a

fragment of AVP, alleviated forgetting, but mainly in nonproficient rats (Strupp, 1989).

Reference memory and working memory showed different responses to dosages of AVP in a two-lever auto-shaping task (Sahgal et al., 1990). The results indicate that general responsiveness was not a factor and working memory might have been impaired by AVP, while reference memory in the autoshaping procedure was increased.

The motivation and motor activity effects of AVP may account for its information retention properties (Alexinsky & Alliot, 1987). AVP interacted with food deprivation and hole-board exploration. Food-deprived rats showed increased exploratory activity, relative to non-food-deprived rats. AVP treatment decreased exploratory activity in the hole board in a dose-dependent fashion for food-restricted and non-food-restricted rats (Alliot & Alexinsky, 1991).

The dosage of AVP may account for differences in memory improvement. Skopkova, Croiset, and de Wied (1991) have shown memory facilitation and interference with two dosages of des-glycinamide-arginine-vasopressin (DGAVP), using an active shuttlebox shock avoidance task.

Another explanation for the effect of AVP on memory processes involves the aversiveness of AVP given in conditioned shock avoidance or conditioned taste aversion

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experiments. AVP can replace the unconditioned stimulus of shock- or lithium-induced malaise (Ebenezer, 1988; Ettenberg, van der Kooy, Le Moal, Koob, & Bloom, 1983; Le Moal et al., 1984). However, other results do not support the aversiveness explanation of AVP on memory effects. Des-glycinamide-lysine-vasopressin (DGLVP) did not induce a conditioned taste aversion for saccharin-flavored water (Vawter, 1978), but it did increase resistance to extinction of the taste aversion (Vawter & Green, 1980).

The CNS effects of AVP on mediating behavior has received neurochemical support. DGAVP (des-glycinamide⁹-[Arg⁸]vasopressin) is an endogenous peptide in rat plasma (Laczi, Burbach, van der Kleij, de Wied, & Wiegant, 1991). EEG average evoked potentials to auditory tones in humans were affected by administration of AVP (Fehm-Wolfsdorf, Bachholz, Born, Voigt, & Fehm, 1988). AVP and related neuropeptides are behaviorally active when administered intracerebrally (de Wied, Gaffori, van Ree, & de Jong, 1984), and the activity is blocked by AVP receptor antagonists (for a review of central effects of AVP, see de Wied et al., 1988).

The present study reports the results of three double-blind experiments, utilizing varying doses of DGAVP pretreatment in the hole-board search task (HBST). The effects of DGAVP on errors, working memory, reference memory, sequence, and response bias were measured. The HBST, as modified (Vawter & van Ree, 1989), provides measures of these variables. The HBST was chosen as a nonaversive spatial learning task. DGAVP was tested because it has virtually none of the peripheral effects of AVP (de Wied et al., 1988; Lande, Witter, & de Wied, 1971).

METHOD

Animals

All rats were male Wistar (TNO, Zeist), with initial weights of 160–225 g. They were housed in groups of 4 to 6 and were handled by the same experimenter. Experiments were performed between 1000 and 1900 h in a sound-attenuated room outside of the animal colony room. The rats were maintained with the lights on from 0700 to 1900 h daily in a temperature-controlled environment. Three separate experiments were conducted since only a small number of rats could be tested daily by the same experimenter. Experiment 1 utilized DGAVP 0.17 μ g ($n = 7$), DGAVP 0.5 μ g ($n = 7$), and saline controls ($n = 7$). Experiment 2 used DGAVP 1 μ g ($n = 7$), DGAVP 3 μ g ($n = 7$), and saline controls ($n = 7$). Experiment 3 used DGAVP 10 μ g ($n = 9$) and saline controls ($n = 9$).

Apparatus

The HBST apparatus as described by Vawter and van Ree (1989) is a Plexiglas square box with an open top for observation. A start box is attached along one wall and separated from the main arena by a sliding door. The floor of the main arena consisted of a raised Plexiglas floor, with 16 holes (each 3.5 cm in diameter). The surface the rat walked on to the bottom of the food well was 3.8 cm. The hole board was dimly illuminated by a 40-W incandescent bulb, 2 m above the center of the hole board.

Procedure

The basic habituation and acquisition procedure of Oades (1981), as modified by Vawter and van Ree (1989), was followed. The experimental protocol consisted of 5 days of habituation and 6 days of acquisition. The rats' initial weights were obtained, then the rats were food deprived for 24 h, with water available ad lib. The rats were then maintained on standard rat chow given daily in the amount of 6.5 g. Two habituation trials were given with no food in any holes. Three further habituation trials were 15-min sessions for each rat in the HBST apparatus, with one Noyes food pellet, 45 mg, available in all 16 holes. Six acquisition days were given consecutively, and each rat was tested in the same order, so as not to confound deprivation level or testing time (File & Day, 1972). One food pellet was placed in the same four holes, and 10 daily trials were given. After each daily testing session, the rats were returned to food cages and fed.

Peptide treatment. All experiments were performed double blind. Synthetic des-glycinamide⁹-[arginine⁸]vasopressin (DGAVP) was dissolved in 0.9% NaCl. The concentration of DGAVP was diluted with 0.9% NaCl to final dosages of 0.17, 0.5, 1, 3, or 10 μ g per 0.5 ml. Each rat was given a subcutaneous injection of 0.5 ml of DGAVP or saline solution 1 h prior to each acquisition session.

Data collection and analysis. The experimenter observed the rat's visit to each hole until four food pellets were consumed, concluding a trial. The hole visits were defined as a head dip into the hole, where the rat's nose penetrated to the eye level of the rat. Data was collected on an HP80 microcomputer, and a BASIC program calculated the following variables for each rat: food-hole visits, food-hole revisits, non-food-hole visits, and non-food-hole revisits. The following dependent performance variables were then used for data analyses: *Errors* were the total number of holes visited and revisited until four food pellets were consumed for 10 consecutive trials, minus 40 for the total food-hole visits (minimum score = 0). *Working memory* was the total number of revisits to food holes or non-food holes occurring during 10 trials. *Reference memory* was the ratio of the daily total number of visits and revisits to food holes divided by the total number of visits and revisits to non-food holes. *Sequence* was the number of identical order of visits to four food holes that occurred during the acquisition session (maximum score = 10). *First hole visit* was the number of identical first hole visits on each trial after emerging from the start box summed across 10 trials (maximum score = 10). *First hole food visits* were summed for only 10 trials. A maximum score of 10 indicated only food holes were first visited during the acquisition session.

The above measures were statistically analyzed by the SPSSPC+ 4.01 multivariate analysis of variance (MANOVA) program (Norusis, 1990). The MANOVA program employed a repeated measures design on the sessions factor. The between-subjects factor was pretreatment with DGAVP dosages or saline. Simple contrasts were utilized between peptide and saline controls, and comparisons are reported when the significance level of $p \leq .05$ was met for Pillai's trace (V) or univariate F tests (Norusis, 1990). Analyses of doubly multivariate repeated measures design for the dependent variables of errors, working memory, reference memory, and sequence were carried out using daily body weight as a covariant.

RESULTS

Saline Control Pool

Initial body weights for the saline controls appeared less for Experiments 1 and 2 than for Experiment 3 (initial body weights [$\pm$ SEM] for Experiments 1, 2, and 3

were 194.6 g [± 1.3], 164.0 g [± 1.3], and 214.1 g [± 0.9], respectively, from ad-lib feeding schedule prior to food restriction). The percentage of body weight loss for saline controls appeared to be higher for Experiments 1 and 2 than for Experiment 3, as shown in Table 1. The deprivation level ranged from 7.1% to 20.6% of initial baseline weights during training for Experiment 3 versus a range of 17.7%–24.0% for Experiments 1 and 2. All rats were fed the same amount of food in each experiment. The percentage of weight loss calculated from predeprivation weight was elevated for lighter rats in Experiments 1 and 2 relative to that for heavier rats in Experiment 3.

To determine if saline controls could be pooled, the dependent variables in the HBST were analyzed between experiments. A doubly multivariate MANOVA was computed for the dependent variables, with experiment as a between-subjects factor, sessions as a within-subjects factor, and daily percentage of body weight loss as a covariant. The main experiment effect was not significant. The interaction of experiment $\times$ sessions effect was significant [$V(40,396) = 0.585, p < .006$]. Multivariate comparison of the interaction experiment $\times$ sessions between Experiments 1 and 3 saline controls indicated significant differences [$V(4,96) = 0.227, p < .003$], with similar results for comparison of the interaction of experiment $\times$ sessions between Experiments 2 and 3 [$V(4,96) = .154, p < .003$]. Thus, pooling of all three experiments was abandoned.

To determine if the data from Experiments 1 and 2 could be pooled, since deprivation levels appeared equivalent, the MANOVA procedure above was repeated with Experiments 1 and 2. As expected, the experiment factor again was not significant. The interaction of experiment $\times$ sessions was also not significant, indicating that Experiments 1 and 2 were similar in the rate of improvement in all variables measured. Therefore, Experiments 1 and 2 were pooled, and DGAVP dosages of 0.17, 0.5, 1.0, and 3.0 μg were further analyzed by one MANOVA. A second MANOVA separately analyzed the 10- μg DGAVP dosage and saline control group. The pooled experiments differed significantly from that of

Experiment 3 in terms of deprivation levels, which influenced all variables measured. A direct comparison of the results between the 10- μg dosage and other groups is not reported.

DGAVP Dosages

Figures 1A–1D display the four DGAVP dosages and saline control group means on each acquisition day for errors, working memory, reference memory, and sequence variables, respectively. A MANOVA was computed for Experiments 1 and 2 pooled, since the experimental controls were equivalent. The design used a treatment factor (five groups of 0, 0.17, 0.5, 1.0, and 3.0- μg DGAVP), sessions factor (six acquisition sessions), and repeated measures on errors, working memory, reference memory, and sequence variables. The percent of body weight loss was entered as a covariant for each rat daily. Contrasts between saline controls and each level of DGAVP treatment were computed.

The main effect of peptide treatment was not significant for any treatment group, relative to saline. The regression of body weight loss on between-group multivariate measures was not significant. The sessions multivariate factor was highly significant [$V(20,716) = 1.209, p < .0005$], which indicated that performance on all dependent measures significantly changed between sessions.

0.17- and 0.5- μg DGAVP. The univariate interactions for errors were significant for DGAVP 0.17 $\mu\text{g} \times$ sessions and DGAVP 0.5 $\mu\text{g} \times$ sessions [$F(5,179) = 2.38, p < .05$, and $F(5,179) = 2.276, p < .05$, respectively]. The interactions were explored using t tests, and they are reported in Table 2. Error rates increased for DGAVP 0.17 and 0.5 μg groups, relative to saline controls groups. On Acquisition 4, the DGAVP 0.5 μg group errors (95.1 ± 12.7) were significantly higher than saline controls' errors [$69.9 \pm 6.4; t(19) = 2.24, p < .05$].

The univariate interaction of DGAVP 0.5 $\mu\text{g} \times$ sessions for the measure of working memory was also significant relative to that for saline controls [$F(5,179) = 2.300, p < .05$]. Table 2 reports the results of t tests for this interaction. On Acquisition 4, the DGAVP 0.5 μg group scored higher on working memory (39.2 ± 4.7) than did saline controls [$19.8 \pm 3.3; t(19) = 2.51, p < .005$].

1- μg DGAVP. The multivariate interaction of DGAVP treatment $\times$ sessions was significant for the dosage comparison of DGAVP 1.0 μg with saline controls [$V(20,716) = 0.187, p < .021$]. Figures 1–4 show the four dependent measures relative to DGAVP 1.0 μg and the saline control group. The interaction was further explored by t tests for each dependent variable. The DGAVP 1 μg group was compared with the saline group for each acquisition session and reported for Acquisitions 2, 3, 4, and 5 in Table 2. Table 2 highlights the significant differences between dosages of DGAVP, relative to saline. Data in Table 2 have omitted Acquisitions 1 and 6, since in no case were comparisons significantly dif-

Table 1
Percentage of Body Weight Loss for Saline Controls in Acquisition Sessions 1–6 of Experiments 1–3

Acquisition Session	Experiment					
	1		2		3	
	%	SEM	%	SEM	%	SEM
1	19.0	0.8	17.7	0.1	7.1	0.2
2	19.2	0.8	18.0	0.1	9.3	0.2
3	19.4	0.1	20.5	0.1	9.9	0.1
4	20.0	0.5	18.9	0.1	10.3	0.1
5	20.8	0.6	18.8	0.1	12.4	0.2
6	24.0	0.7	21.3	0.1	20.6	0.3

Note—Body weight was determined prior to each daily acquisition session and divided by initial weight to form a percentage of body weight loss.

Figure 1. (A) Error group mean scores, (B) working memory group mean scores, (C) reference memory group mean scores, and (D) sequence group mean scores, with DGAVP dosages shown for six daily acquisition sessions. Saline controls are shown with open circles ○---○. DGAVP-treated rats are 0.17 µg ●---●, 0.5 µg ■---■, 1 µg ▲---▲, and 3 µg ◆---◆.

ferent between DGAVP and saline groups by *t* tests. Dosages and dependent variables are reported in Table 2 when the MANOVA result was statistically significant.

On Acquisitions 2 and 5, errors were significantly decreased for the 1-µg group relative to those for the saline controls. Working memory scores decreased signifi-

cantly (i.e., improved) on Acquisition 5 for the 1-µg group relative to saline group. Reference memory was significantly higher on Acquisitions 2 and 5 for the 1-µg group relative to that for the saline group. The sequence of visits increased on Acquisition 5 for the 1-µg group relative to that for saline controls [7.66 ± 0.33 SEM and

Table 2
Comparison of DGAVP and Saline Group Mean Scores for Errors,
Working Memory, Reference Memory, Error, and Sequence

DGAVP (μ g)	Acquisition Sessions							
	2		3		4		5	
	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>
Error Scores								
Saline	118.7	6.0	87.8	6.6	69.9	6.4	58.5	4.7
0.17	112.2	15.9	107.4†	6.1	95.1†	12.7	60.1	9.3
0.5	141.4†	11.0	96.8	6.9	93.7*	7.7	64.5	6.0
1.0	92.1*	11.0	71.3	5.8	55.0	6.8	38.5†	4.9
Working Memory Scores								
Saline	40.8	3.6	25.4	3.9	19.8	3.3	15.4	2.1
0.5	54.4†	9.7	25.4	4.3	39.2†	4.7	14.7	2.6
1.0	29.3	8.4	18.6	1.9	15.8	3.9	7.8*	2.1
Reference Memory Scores								
Saline	0.51	0.02	0.68	0.04	0.89	0.07	0.99	0.07
0.5	0.42*	0.01	0.56	0.03	0.63*	0.05	0.87	0.06
1.0	0.62*	0.05	0.75	0.06	1.07	0.19	1.36*	0.18
Sequence Scores								
Saline	3.85	0.34	4.35	0.26	4.6	0.40	5.64	0.45
1.0	4.16	0.54	5.00	0.68	5.33	0.49	7.66†	0.33
Saline§	4.22	0.40	5.11	0.51	4.77	0.59	6.55	0.68
10§	3.62	0.40	3.63†	0.32	4.62	0.26	5.00	0.94

* $p \leq .05$, two-tail probability Student t test comparing saline and DGAVP group means. † $p \leq .005$, two-tail probability. ‡ $p \leq .07$. §10- μ g comparison used a separate control group.

5.64 ± 0.74 SEM, respectively; $t(11) = -3.23$, $p \leq .005$].

10- μ g DGAVP. The MANOVA for saline and 10- μ g DGAVP treatment groups indicated the main treatment factor was not significant. The multivariate interaction of treatment $\times$ sessions was not significant. The univariate measure of sequence was significant [$F(1,14) = 5.43$, $p < .05$]. Table 2 shows the sequence group means for the DGAVP 10 μ g and saline controls for Acquisitions 2, 3, 4, and 5 for comparison with the other doses of DGAVP. DGAVP-10- μ g-treated rats showed a decreased sequence score (3.63 ± 0.32), relative to saline controls [$5.11 \pm .51$; $t(16) = -2.47$, $p < .05$] on Acquisition 3.

Response Bias

One measure of response bias is a count of the identical first hole (food or non-food) visits for each trial. The first two holes located adjacent to the start box were non-food holes, and, without exception, all rats on the first 10 trials visited non-food holes first. The main effect of treatment was not significant in contributing to differences of first hole visit scores ($F \leq 1$). The sessions factor was highly significant [$F(10,300) = 6.00$, $p < .0005$]. The interaction of DGAVP $\times$ acquisition was also non-significant ($F \leq 1$) for first hole visits.

The measure of the total number of first hole food visits indicate the rat unlearns the initial non-food-hole visit response. The first hole food visits did not surpass six visits in the HBST. A MANOVA for dosage of DGAVP (0, 0.17, 0.5, 1.0, and 3.0 μ g) was computed

with first hole food visits as the dependent measure. Each session was compared with the mean for the previous sessions within each dosage. The main treatment was not significant, although DGAVP 0.17, 0.5, and 1.0 μ g barely failed significance ($ps < .1$). The interaction of sessions $\times$ DGAVP .17 μ g was significant [$F(5,36) = 2.34$, $p < .05$]. First hole food visits were significantly lower for the DGAVP-0.17- μ g group ($2.00 \pm .79$) on Acquisition 4 than for the saline control group ($4.29 \pm .55$) mean first food hole visits [$t(19) = -2.39$, $p < .05$].

DISCUSSION

The rate of errors, working memory, reference memory, and sequence improvement in the HBST for saline controls was dependent upon deprivation level as previously reported (Vawter & van Ree, 1989). Saline controls were pooled in the present experiment, where no differences in dependent measures were detected; however, body weight loss was used as a covariant to control for the effect of deprivation level on the dependent measures.

The 1- μ g dosage of DGAVP improved errors, working memory, reference memory, and sequence scores, relative to those for the saline controls. In the HBST, error scores may represent learning, working memory scores may be a measure of short-term memory, reference memory is a measure of long-term memory, and sequence scores represent spatial memory. Performance on all variables improved with DGAVP 1.0 μ g, while

suboptimal dosages of DGAVP impaired short-term memory and learning. A similar interference in first hole food visits was noted with the lowest dose of DGAVP. The highest dosage of DGAVP, 10 μ g, did not influence learning, short-term memory, or long-term memory; however, it did decrease spatial memory in the HBST.

Spatial memory was reliably increased with DGAVP 1 μ g across sessions, whereas in a separate experiment, DGAVP 10 μ g decreased spatial memory. A direct comparison of the results of 1- and 10- μ g DGAVP dosages is limited by the fact that the groups differed in the percentage of deprivation that influences the rate of spatial memory increase (Vawter & van Ree, 1989).

The dosage of DGAVP is critical for improvement or impairment of the same behavioral variables in the HBST. Interestingly, DGAVP did not effect the outcome of any variables measured on the first training day (i.e., the first 10 trials in the HBST). This would argue against a pure arousal interpretation of the present results.

Evidence that DGAVP exerts memory effects via response bias was also not obtained. For example, while DGAVP significantly increased long-term memory, there was no change in the preferences of rats' first hole visits to food or non-food holes. With the lowest dose of DGAVP, learning of the HBST was reduced and first hole food visits were significantly decreased. This learning interference was not related to an increased response bias. DGAVP, in any dosage, did not alter the preferences to non-food holes first visits.

Resistance to extinction of open-field responses may have occurred and may explain the decrease in learning of the HBST and decreased first hole food visits observed with the lowest dose of DGAVP. During habituation in the HBST, the rats were given food pellets in all 16 holes. After 3 days of food reward in the open field, the rats were then rewarded during training with only four food holes baited. Rats given DGAVP would increase resistance to extinction by (re)visiting all 16 former food holes. These findings are consistent with results using conditioned avoidance responses (Skopkova et al., 1991).

Spatial memory and long-term memory in the HBST appear to be linked. When spatial memory decreased significantly, there was no change in long-term memory. However, when spatial memory increased significantly, it was also associated with a significant increase in long-term memory. This study confirms other reported studies that DGAVP modulated the number of acquisition errors, both increasing and decreasing errors over learning trials, depending on dosage. The present results point to a dissociation between the effects of DGAVP on learning, short-term memory, long-term memory, and spatial memory. Whether DGAVP modulates attention or arousal to explain the present results awaits further research.

This study offers further evidence that DGAVP is behaviorally active when administered in a double-blind procedure. A replication of this HBST study, giving

DGAVP and other related AVP neuropeptides and antagonists to specific brain sites, is needed to understand the mechanism of action.

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