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EFFECTS OF LYSINE-VASOPRESSIN AND 1-DEAMINO-8-D-ARGININE-VASOPRESSIN ON MEMORY IN HEALTHY INDIVIDUALS AND DIABETES INSIPIDUS PATIENTS

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SUMMARY

Central diabetes insipidus (DI) patients showed impairments in short- and long-term memory functions, but not in attention and concentration, as compared to healthy individuals. A single i.m. injection or sub-chronic intranasal administration of either lysine-vasopressin (LVP) or 1-deamino-8-D-arginine-vasopressin (DDAVP) normalized the disturbed memory functions in DI patients. These peptides also improved memory functions in healthy individuals.

Key Words—LVP; DDAVP; memory; diabetes insipidus.

INTRODUCTION

VASOPRESSIN has been implicated in learning and memory processes of experimental animals (de Wied, 1965; 1969). In particular, vasopressin promotes consolidation of acquired information and plays a role in retrieval processes or in the expression of stored information (de Wied, 1969). Similar effects have been obtained with des-glycinamide^{9}-lysine^{8}-vasopressin (DG-LVP), which is practically devoid of the classical endocrine activities displayed by the whole vasopressin molecule. The physiological significance of vasopressin in this respect has been demonstrated in three experimental models: posterior lobectomized rats, hereditary DI rats, and the temporary central blockade of vasopressin activity by the intracerebroventricular injection of specific vasopressin antiserum (de Wied, 1965; de Wied *et al.*, 1975; van Wimersma Greidanus & de Wied, 1976). The disturbances in learning and memory abilities of posterior lobectomized and DI rats could be restored by treatment with vasopressin or DG-LVP. Reports concerning the influence of vasopressin on memory processes in humans also have been published. Legros *et al.* (1978) showed that intranasal application of lysine-vasopressin (LVP) improved several aspects of attention and memory in humans aged 50 – 60 yr. Case reports have described a beneficial effect of vasopressin in patients suffering from post-traumatic amnesia (Oliveros *et al.*, 1978), amnesia due to alcoholism (Le Boeuf *et al.*, 1978), psychosis (Vranckx *et al.*, 1978) and depression (Gold *et al.*, 1979).

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TABLE I. MAIN CLINICAL DATA OF PATIENTS WITH CENTRAL DIABETES INSIPIDUS

Number	Name	Age (yr)	Sex	Duration of illness (yr)	Blood pressure (mm Hg)	Volume of urine untreated (l./24 hr)	Etiology	Medication
1	F. P.	51	M	22	130/80	20	Virus infection	Adiuretin
2	Sz. S.	26	M	5	120/80	14	Skull injury	Piton snuff powder
3	P. L.	21	M	2	130/70	17	Unknown	Adiuretin
4	S. M.	36	F	20	110/70	16	Virus infection	Adiuretin
5	D. T.	22	M	5	120/80	18	Hand – Schüller – Christian disease	Adiuretin Prednisolon
6	T. S.	26	M	2	140/80	20	Skull injury	Adiuretin
7	T. J.	29	F	3	120/70	14	Skull injury	Adiuretin
8	V. L.	48	F	10	110/70	16	Unknown	Adiuretin
9	T. G.	24	F	14	130/80	18	Unknown	Adiuretin
10	G. P.	46	M	25	130/80	17	Unknown	Piton snuff powder
11	K. J.	48	F	19	120/80	17	Virus infection	Adiuretin
12	I. A.	24	F	1	110/70	16.5	Unknown	Adiuretin
13	A. A.	24	M	3	130/80	17.5	Unknown	Adiuretin
14	P. M.	38	F	17	120/80	19	Skull injury	Piton snuff powder
15	K. J.	19	F	6	120/70	15	Virus infection	Adiuretin
16	T. F.	32	M	5	130/80	8	Unknown	Adiuretin

The present studies were undertaken to investigate the effect of vasopressin on learning and memory in humans. First, the learning and memory abilities of central DI patients were determined and compared to those of healthy individuals. Second, the influence of vasopressin and an analogue of this hormone on these abilities was studied in both DI patients and healthy subjects. Third, the effectiveness of intranasal application of the peptides was compared with that of intramuscular treatment.

SUBJECTS AND METHODS

Examinations were performed on 16 patients (eight males and eight females) with central DI and on 10 healthy volunteers (two males and eight females). The mean age of the patients was 32 yr (range: 19 – 51 yr), and that of the controls was 23 yr (range: 22 – 24 yr). The main clinical features of the patients with central diabetes insipidus are summarized in Table I. The mean diuresis of the patients was 16.4 ± 0.7 (S.E.M.) litre per day. Before and after treatment, the weight, pulse rate, blood pressure, plasma protein concentration, serum Na^+ and K^+ concentrations, and urinary osmolarity of the patients were measured. The subjects examined did not include any with hypopituitarism or other endocrine deficiencies. All medication was discontinued 10 days prior to experimentation.

All the tests to be detailed below were performed both before and after all the treatment procedures, in both the healthy subjects and the DI patients. Testing prior to treatment was regarded as the basal examination. In the assessment of the acute effects of the drugs, testing was made 1 hr after the injection, while for the sub-chronic effects it was performed on the final day of treatment.

In the assessment of the acute effects, the following agents were administered i.m. on one occasion, in the given sequence:

(1) placebo (physiological saline);
(2) LVP (Sandoz) (10 IU);
(3) 1-deamino-8-D-arginine-vasopressin (DDAVP) (4 μg), a gift of the late Dr. J. Mulder, Malmö;
(4) LVP (Sandoz) (1 IU).

Treatment was given to 10 healthy subjects and 10 DI patients, except in the case of DDAVP treatment, which was given to 10 healthy individuals and six DI patients; the LVP (1 IU) treatment was not given to the healthy subjects, but only to six DI patients.

Labyrinth test

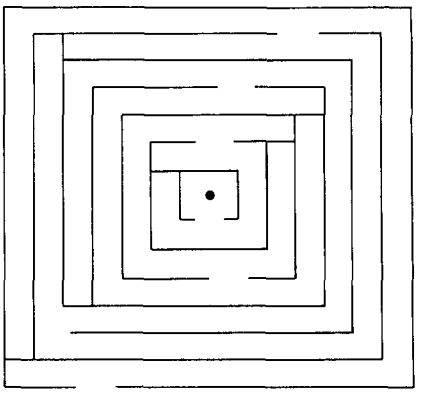

FIG. 1.

For assessment of the sub-chronic effects, the subjects received placebo (physiological saline) for seven days, followed for a further seven days by DDAVP (Adiuretin-SD, Spofa) (10 μg) twice daily in the form of nasal drops. This regimen was carried out on 10 healthy individuals and 10 DI patients. In addition, six DI patients were treated for seven days with LVP (5 IU) nasal drops thrice daily.

A three-day drug-free interval was always inserted between the individual treatment periods. Neither the patients nor the psychologist directing the testing knew the nature of the administered agents.

The following tests were performed to examine attention and short- and long-term memory functions.

1. *Bourdon test* (Lipmans, 1922): the subjects, whose mother tongue was Hungarian, had to underline the letters 'e' in a standard French text. The number of mistakes made and the time required to perform the task were determined, and on the basis of these data points were awarded. This test is used to measure attention.

2. *Labyrinth test* (Chapuis, 1959): starting from the edge of a square labyrinth (Fig. 1), the correct route must be followed to the centre. The time needed for the solution is measured. An improvement is indicated by a decrease in the time spent in finding the correct route. On repeated examination the labyrinth is rotated so as to diminish the possibility of learning. The test provides information on spatial conception, orientation ability, learning ability, and mobility of thinking activity.

3. *Acoustic memory test* for names and numbers (Böszörményi & Moussong-Kovács, 1967): five names and five numerical data present in a simple story must be written down immediately after hearing the story. A maximum of 10 points is awarded for the correct recall of data. Results attained by each individual are expressed as percentages. One of the stories used was the following (words and numbers to be recalled are italicized).

> The *16*-year-old *Péter* and *Sándor* travelled on an excursion to *Budapest*. Before their journey they bought *2* kg of bread and *1* kg of ham at the shop of Mr. *Kovács*. Then, in the shop of Mrs. *Földes* they bought *3* lemons and *10* dkg of sugar.

The italicized names and numbers must be written immediately after a single hearing of the text. On repeated examination, the names and numbers are changed. The test serves as an examination of short-term memory.

4. *Optical memory test* for names and numbers (Benton & Spreen, 1961): there are three names and four numbers inside and on the perimeter of a pentagon (Fig. 2). After observation for 30 sec, the subject must draw the figure from memory. Correctly recalled names and numbers are awarded two points each if situated in the correct place, otherwise one point each. Correct drawing of the geometric figure earns two points. The maximum performance earns 16 points. On repeated examination, the figure, the names and the numbers are changed. This also is a test of short-term memory.

5. *Ranschburg – Ziehen's word-pair memory test* (Lipmans, 1922): 10 word-pairs feature in this test: noun + noun, noun + adjective, and noun + verb, on the basis of logical connections. The word pairs are read out, and 1 min later the first words of each pair are given and the examined subject must recall its pair. The test is repeated 24 hr later. The number of correctly recalled words is given as a 'performance value'. On subsequent

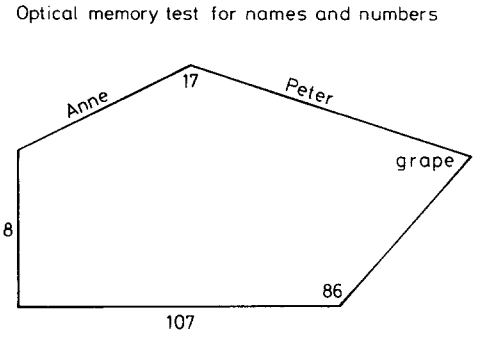

FIG. 2.

TABLE II. COMPARISON OF TESTS ON HEALTHY INDIVIDUALS AND CENTRAL DIABETES INSIPIDUS PATIENTS BEFORE TREATMENT

	Bourdon	Labyrinth	Optical	Acoustic	Ranschburg – Ziehen
Healthy subjects	2.3* (M = 8.0)	18.0 (M = 23.0)	62.5 (M = 87.5)	50.0 (M = 70.0)	87.1 (M = 93.2)
N = 10	15.1†	29.0	100.0	90.0	97.9
Diabetes insipidus	1.2 (M = 4.3)	21.0 (M = 34.5)	38.0 (M = 50.0)	20.0 (M = 35.0)	50.0 (M = 60.0)
N = 16	12.8	75.0	63.0	60.0	90.0
Probability (p)	N. S.	<0.01	<0.02	<0.01	<0.01

*20th percentile.
†80th percentile.
M = median value.
The data were compared by Wilcoxon Rank Sum tests.

repetition of this test, the word pairs are changed, but the same degree of difficulty is retained. This is a test of both short- and long-term memories.

The results were analysed statistically by Wilcoxon tests (Wilcoxon, 1945). For assessment of the effectiveness of treatment, the Wilcoxon Signed Rank test (single-sample variant) was used. Observations were made as to whether the drugs employed induced any changes in the performance tests. With the pretreatment results taken as basis, for each individual treatment the difference was calculated between the post- and pretreatment results. The values were arranged in sequence without attention to the sign (i.e. on the basis of the absolute values) and rank values were ascribed to them. The groups with positive and negative signs then were separated, and the rank values were summed in the two groups. These sums are given in Tables III and IV; they indicate the direction and extent of the change, and serve as a basis for the determination of the significance. The number of cases in which no change resulted after treatment is subtracted from the total number in the group, N; the number obtained is denoted by n, and this is used in the statistical analysis.

The Wilcoxon Rank Sum test (the two-sample variant) was used to compare the pretreatment test values for the healthy individuals and the DI patients. The median values and the 20th and 80th percentiles were determined and are given in Table II.

TABLE III. THE INFLUENCE OF VASOPRESSIN TREATMENT ON MEMORY TESTS IN HEALTHY INDIVIDUALS ($N = 10$)

Treatment	Bourdon*	Labyrinth*	Optical†	Acoustic†	Ranschburg – Ziehen†
Placebo i.m.	$n = 10$ $S - 30$ $S + 25$	$n = 9$ $S - 18$ $S + 27$	$n = 10$ $S - 21$ $S + 34$	$n = 10$ $S - 23$ $S + 32$	$n = 9$ $S - 25$ $S + 20$
1 × 10 IU LVP i. m.	$n = 10$ $S - 22$ $S + 33$	$n = 9$ $S - 44$ ($p < 0.01$‡) $S + 1$	$n = 10$ $S - 33$ $S + 22$	$n = 9$ $S - 30$ $S + 15$	$n = 10$ $S - 52$ ($p < 0.01$) $S + 3$
1 × 4 µg DDAVP i. m.	$n = 10$ $S - 30$ $S + 25$	$n = 9$ $S - 44$ ($p < 0.01$) $S + 1$	$n = 9$ $S - 1$ ($p < 0.01$) $S + 44$	$n = 10$ $S - 3$ ($p < 0.01$) $S + 52$	$n = 9$ $S - 1$ ($p < 0.01$) $S + 44$
Placebo nasal drops for seven days	$n = 10$ $S - 21$ $S + 34$	$n = 9$ $S - 21.5$ $S + 23.5$	$n = 10$ $S - 28$ $S + 27$	$n = 10$ $S - 20$ $S + 35$	$n = 10$ $S - 18$ $S + 37$
20 µg DDAVP nasal drops daily for seven days	$n = 10$ $S - 26.5$ $S + 28.5$	$n = 9$ $S - 44$ ($p < 0.01$) $S + 1$	$n = 10$ $S - 2$ ($p < 0.01$) $S + 53$	$n = 9$ $S - 0$ ($p < 0.01$) $S + 45$	$n = 9$ $S - 0$ ($p < 0.01$) $S + 45$

*Improvement is indicated by a change in the negative direction.
†Improvement is indicated by a change in the positive direction.
‡Probability.
$S-$ and $S+$ = rank sums with indication of direction of change.
The data were compared by Wilcoxon Signed Rank tests.

RESULTS

The data obtained from a comparison of the tests on the healthy subjects and the patients before treatment are given in Table II. No substantial difference was found between the attention and concentration of the patients and those of the healthy individuals (Bourdon test). However, the short-term memory performance of the patients was much lower than that of the control subjects, based on the labyrinth test and the acoustic and optical memory tests. Also, disturbances in long-term memory were observed in the patients (Ranschburg – Ziehen's test).

Placebo treatment did not substantially affect performances of the healthy subjects in the respective test procedures (Table III). Intramuscular administration of LVP or DDAVP hardly influenced the attention and concentration of these subjects (Bourdon test), but it did change their memory performances. Short-term memory was significantly improved after LVP in only one test, and long-term memory (Ranschburg – Ziehen's test) was improved considerably after DDAVP treatment but worsened after LVP injection. Intranasal application of DDAVP for seven days led to findings similar to those observed after a single i.m. injection of this peptide.

The influence of LVP in DI patients (Table IV) was similar to that found in healthy subjects. Placebo treatment did not affect the performance of the DI patients, and their attention and concentration were not markedly changed after LVP treatment, although a

TABLE IV. THE INFLUENCE OF VASOPRESSIN TREATMENT ON MEMORY TESTS IN CENTRAL DIABETES INSIPIDUS PATIENTS

Treatment	Bourdon*	Labyrinth*	Optical†	Acoustic†	Ranschburg – Ziehen†
Placebo i.m.	$n = 8$ $S- 17$ $S+ 19$	$n = 9$ $S- 25$ $S+ 20$	$n = 9$ $S- 23$ $S+ 22$	$n = 10$ $S- 25$ $S+ 30$	$n = 10$ $S- 20$ $S+ 35$
1 × 10 IU LVP i.m.	$n = 10$ $S- 16$ $S+ 39$	$n = 10$ $S- 55$ ($p < 0.01$‡) $S+ 0$	$n = 8$ $S- 6$ $S+ 30$	$n = 8$ $S- 6$ $S+ 30$	$n = 9$ $S- 30$ $S+ 15$
1 × 1 IU LVP i.m.	$n = 6$ $S- 14$ $S+ 7$	$n = 6$ $S- 21$ ($p < 0.05$) $S+ 0$	$n = 6$ $S- 3$ $S+ 18$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$
1 × 4 µg DDAVP i.m.	$n = 6$ $S- 16$ $S+ 5$	$n = 6$ $S- 21$ ($p < 0.05$) $S+ 0$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$
Placebo nasal drops for seven days	$n = 10$ $S- 21$ $S+ 34$	$n = 10$ $S- 18$ $S+ 37$	$n = 10$ $S- 25$ $S+ 30$	$n = 9$ $S- 25$ $S+ 20$	$n = 10$ $S- 22$ $S+ 33$
20 µg DDAVP nasal drops daily for seven days	$n = 10$ $S- 46$ $S+ 9$	$n = 10$ $S- 55$ ($p < 0.01$) $S+ 0$	$n = 9$ $S- 0$ ($p < 0.01$) $S+ 45$	$n = 9$ $S- 0$ ($p < 0.01$) $S+ 45$	$n = 8$ $S- 0$ ($p < 0.01$) $S+ 36$
15 IU LVP nasal spray daily for seven days	$n = 6$ $S- 21$ ($p < 0.05$) $S+ 0$	$n = 6$ $S- 21$ ($p < 0.05$) $S+ 0$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$	$n = 6$ $S- 0$ ($p < 0.05$) $S+ 21$

*Improvement is indicated by a change in the negative direction.
†Improvement is indicated by a change in the positive direction.
‡Probability.
$S-$ and $S+$ = rank sums with indication of direction of change.
The data were compared by Wilcoxon Signed Rank tests.

significant improvement was found after intranasal treatment with LVP for seven days (Bourdon test). In general, short- and long-term memory performance improved markedly after LVP treatment, except after the i.m. injection of the high dose of LVP. The lower dose of this peptide appeared to be more effective than the higher dose. The injection of DDAVP resulted in effects similar to those found after intranasal application of this peptide or LVP. The performances of the DI patients after LVP treatment were not different from those of healthy subjects. Thus, the observed disturbances in memory functions of DI patients can be corrected by LVP treatment.

Intranasal administration of LVP decreased the 24 hr urine production of the DI patients by about 50%, and their urinary osmolarity was increased from 180 ± 20 (S.E.M.) to 480 ± 25 mosm/l. The antidiuretic influence of LVP injected i.m. lasted 3 – 4 hr. The effect of i.m. administration of DDAVP on urinary output lasted about 14 – 17 hr and reduced the diuresis to 3 – 5 litre per day. The intranasal DDAVP treatment completely corrected the disturbance in the urine output and osmolarity of the patients. The water

intake of the healthy subjects was restricted during treatment, and hence no appreciable disturbance occurred in water and salt homeostasis. No side effects were observed following treatment with DDAVP or LVP nasal spray, or i.m. administration of LVP (1 IU). However, the i.m. administration of LVP (10 IU) resulted in abdominal spasms, diarrhoea, excitation and an increase in blood pressure of 20 – 30 mm Hg in most of the treated subjects. In neither group did the peptide treatment cause a change in serum Na, K, total protein, pulse rate or body weight.

DISCUSSION

The present findings show that central DI patients have impairments in short- and long-term memory functions, but not in attention and concentration. These disturbances may be due to the decreased activity of vasopressin in these patients, since treatment with exogenous vasopressin normalized memory functions. However, the DI patients differed from the healthy individuals in their average age and age distribution, and this may have played a role in the observed memory differences. In spite of this, it was found that vasopressin improved the memory of the DI patients, independently of age. In healthy individuals, vasopressin treatment led to an improvement in short- and long-term memory functions. A beneficial effect of LVP on memory functions has been described previously in healthy subjects (Legros *et al.*, 1978) and in patients suffering from post-traumatic amnesia (Oliveros *et al.*, 1978) or amnesia due to alcoholism (Le Boeuf *et al.*, 1978), although others have questioned these latter findings (Blake *et al.*, 1978; Jenkins *et al.*, 1979; Koch-Henriksen & Nielsen, 1981; Jenkins *et al.*, 1981). Gilot *et al.* (1980) described patients with congenital idiopathic DI who showed a decrease of retention on the Benton test being normalised after DDAVP treatment. In depressed patients Gold *et al.* (1979) obtained a considerable improvement in long-term memory functions, and some influence on attention, concentration and short-term memory functions after prolonged intranasal administration of DDAVP. Legros *et al.* (1978) found an improvement of attention and concentration in healthy subjects aged 50 – 65 yr after intranasal application of LVP. We could not replicate these effects on attention and concentration; these functions were neither disturbed in DI patients nor affected by acute or sub-chronic treatment with vasopressin. Only after one week of intranasal administration of LVP to DI patients was an improvement in these functions observed.

Although animal experiments indicate that DDAVP has a much weaker effect on memory compared to the natural hormone, DDAVP also appeared to be effective in improving the memory function in healthy subjects and DI patients. However, more experimentation is needed before definite conclusions can be drawn about the potency of DDAVP compared to that of LVP, particularly since the present data show that a lower dose of LVP was much more effective than the higher dose of this peptide in DI patients. The high dose of LVP even worsened the long-term memory function of healthy subjects. This may be related to the severe side effects observed with this treatment (see Results).

Vasopressin may improve memory function by a direct action on the central nervous system, rather than by an influence on water homeostasis. No relation was found between the actions of LVP and DDAVP on water homeostasis and their actions on memory function. In addition, intranasal administration of the peptides appeared to be as effective

as i.m. injection but did not induce the side-effects observed after i.m. injection in spite of the higher dose level used for intranasal application. Moreover, others have reported that LVP and its analogues also restore the impaired memory function of subjects not suffering from a disturbance in water homeostasis (Legros *et al.*, 1978; Oliveros *et al.*, 1978; Le Boeuf *et al.*, 1978; Vranckx *et al.*, 1978; Gold *et al.*, 1979; Weingartner *et al.*, 1981). In addition, the LVP nasal spray brought about a similar improvement in memory function to that produced by the DDAVP spray, which fully corrected the diuresis, whereas the former reduced the diuresis to only half the starting value. It should be noted, however, that patients with idiopathic or traumatic DI possess the capacity to synthesize and secrete AVP into the CSF. This raises the possibility that the appreciable decrease in their polyuria may play a role in the memory improvement in DI patients following LVP treatment. These peptides, however, also affect memory function in healthy subjects, who have a normal water homeostasis and a normal central AVP function. Furthermore, de Wied *et al.* (1977) observed that treatment with DG-LVP and cyclo-leu-gly increases the AVP level in the blood of rats. They postulated that behavioral effects of these principles may be the result of increased availability of endogenous hormones instead of an intrinsic activity of the injected material. On the basis of these data it is conceivable that treatment with LVP and DDAVP increases AVP secretion from the magnocellular nuclei into the CSF in both healthy subjects and traumatic DI patients.

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