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Effects of desglycinamide-arginine-vasopressin (DG-AVP) on memory processes in diabetes insipidus patients and non-diabetic subjects

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Abstract. The effects of desglycinamide[9]-arginine[8]-vasopressin (DG-AVP) on memory processes have been studied in patients with central diabetes insipidus (DI) and in non-diabetic control patients. Acute im injection of DG-AVP improved some aspects of short-term memory. Subchronic intranasal administration of DG-AVP facilitated short-term memory more consistently and in addition improved long-term memory. DG-AVP increased the attention, but only in the non-diabetic subjects. The effects of DG-AVP on memory processes persisted after discontinuation of treatment. DG-AVP did not affect the parameters for water and electrolyte metabolism, blood pressure and pulse rate neither in DI nor in the control patients. Thus, the memory effects of DG-AVP are probably mediated by a direct action on the central nervous system.

Animal studies have suggested that endogenous vasopressin might have a physiological role in memory formation (de Wied et al. 1975; van Wimersma Greidanus et al. 1975; van Ree et al. 1978). This has been confirmed in human studies (Laczi et al., in press), indicating that patients with central diabetes insipidus (DI) are inferior to healthy volunteers in several tests designed to measure the short-term and long-term memories. Lysine[8]-vasopressin (LVP) or 1-desamino-8-D-arginine-vasopressin (DD-AVP) treatment restored the memory deficit of DI patients (Laczi et al., in press).

Evidence that the behavioural effects of vasopressin are independent of its classical endocrine actions comes from studies with analogues of the hormone. Desglycinamide[9]-lysine[8]-vasopressin (DG-LVP) and desglycinamide[9]-arginine[8]-vasopressin (DG-AVP), which have virtually no pressor or antidiuretic activity (de Wied et al. 1972), are nearly as effective as LVP and arginine[8]-vasopressin (AVP) in normalizing memory deficits and mimic the effects of LVP and AVP on memory processes in animal experiments (de Wied 1976).

The aim of the present study was to measure the influence of DG-AVP on the short-term and long-term memories as well as on the attention in DI patients and in control subjects.

Methods

Subjects

The investigations were carried out on 13 DI patients of both sexes, of whom 10 have been investigated in a previous study (Laczi et al., in press). The clinical data on these patients are listed in Table 1. None of them suffered from any other endocrine disease. Nine patients of both sexes (7 females and 2 males) were investigated as a non-diabetic control group. The mean age of the controls was 27 years (range 16–37 years). They had been admitted for various diseases (e.g. hirsutism, neurosis, inactive duodenal ulcer).

Both patients groups were hospitalized and all medications were withdrawn at least 10–14 days before testing of the baseline psychological and laboratory parameters. Both groups were of approximately the same scholastic and educational level. None of the patients had graduated from college or university.

Memory and attention tests

1. Bourdon test (Lipmans 1922): the subjects, whose mother tongue was Hungarian, had to underline the letters 'e' in a standard French text. The time required to perform the task is determined. This test is used to measure attention.

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

3. Acoustic memory test for names and numbers (Böszörményi & Moussong-Kovács 1967): 5 names and 5 numerical data present in a simple story must be written down immediately after acoustic presentation of the story. A maximum of 10 points is awarded for correct recall of the data. On repeated examination the names and numbers are changed. This serves as a test of the short-term memory.

4. Optical memory test for names and numbers (Benton & Spreen 1961): there are 3 names and 4 numbers inside and on the perimeter of a geometric figure (a pentagon). After observation for 30 s, the figure must be drawn from memory. Evaluation: correctly recalled names and numbers are awarded 2 points each if situated in the correct place, otherwise 1 point each. Correct drawing of the geometric figure attains 2 points. The maximum performance is 16 points. On repeated examination, the figure, the names and the numbers are changed. This is a test for short-term memory.

5. Ranschburg-Ziehen's word-pair memory test (Lipmans 1922): 10 word-pairs each 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 subject must recall its pair. The recall test is repeated 24 h later. The number of correctly recalled words is given as a 'performance value'. Results attained by each individual are expressed as percentages of the maximum score. On subsequent repetitions of this test, the word-pairs are changed, but the same degree of difficulty is retained. This is a test for both short-term and long-term memories.

Table 1.
Main clinical data on patients with central diabetes insipidus.

Initials	Age (years)	Sex	Duration of illness (years)	Diuresis before treatment (l/24 h)	Urine osmolality (mosm/l)	Aetiology	Medication
1. T.S.	29	male	5	20	104	skull injury	Adiuretin
2. N.I.	24	male	4	8	164	virus infection	untreated
3. S.M.	36	female	20	16	121	virus infection	Adiuretin
4. D.T.	24	male	5	18	112	Hand-Schüller-Christian disease	Prednisolone
5. T.J.	31	female	5	14	130	skull injury	Adiuretin
6. P.L.	23	male	4	5	260	unknown	Adiuretin
7. V.L.	48	female	12	12	153	unknown	Adiuretin
8. A.A.	24	male	5	15	129	unknown	Adiuretin
9. G.P.	46	male	27	18	120	unknown	Piton snuff powder
10. K.J.	21	female	8	8	182	virus infection	Adiuretin
11. M.A.	17	male	1	5	270	unknown	untreated
12. T.G.	26	female	14	6	243	unknown	Adiuretin
13. P.J.	27	male	12	20	94	unknown	Adiuretin
Mean ± SEM	29 ± 2.5	–	9 ± 2.1	12.7 ± 1.5	160 ± 16	–	–

Adiuretin SD (Spofa, Prague): 1-deamino-8-D-arginine vasopressin. Piton (Organon, Oss): posterior pituitary extract.

Table 2.
Influence of DG-AVP treatment on different laboratory parameters in diabetes insipidus patients.

Treatment	Diuresis 1/24 h	Urine osmolality (mosm/l)	Se Na^+ (mmol/l)	Se K^+ (mmol/l)	Blood pressure (mmHg)		Pulse rate (min)
					Systolic	Diastolic	
Untreated	12.7 ± 1.5*	160 ± 16	141.8 ± 6.3	4.2 ± 0.4	123.0 ± 3.1	76.1 ± 1.4	77.4 ± 1.6
Placebo (im)	11.3 ± 3.4	150 ± 10	138.2 ± 8.4	3.8 ± 1.2	125.0 ± 3.5	76.5 ± 1.7	76.5 ± 1.6
DG-AVP 3 µg im	12.1 ± 2.3	148 ± 10	141.2 ± 3.4	4.6 ± 1.4	119.6 ± 2.4	76.5 ± 1.5	78.3 ± 1.7
DG-AVP 30 µg im	12.9 ± 3.8	151 ± 10	146.2 ± 4.8	4.2 ± 0.8	123.8 ± 2.4	81.5 ± 1.9	76.6 ± 1.5
Placebo nasal spray	13.4 ± 2.3	168 ± 13	145.3 ± 4.3	4.4 ± 0.3	124.2 ± 2.3	76.9 ± 1.3	79.8 ± 1.2
DG-AVP 80 µg nasal spray for 7 days	12.0 ± 4.0	168 ± 7	140.0 ± 6.2	4.3 ± 0.4	123.8 ± 2.4	79.2 ± 1.8	76.8 ± 1.3

* Mean ± SEM.
None of the parameters were significantly affected by placebo or DG-AVP treatment but the parameters were responsive to DD-AVP or LVP treatment (see Laczi et al, in press).

Treatment and testing schedule

Desglycinamide^9-arginine^8-vasopressin (DG-AVP) was synthetized by Organon (The Netherlands).

The placebo contained the solvent only. Placebo and peptide solutions or ampoules could not be distinguished from each other by inspection. Treatment was given in two studies as follows:

Before the start of study I the memory and attention testings were performed (baseline values). The treatment and testing schedule of study I (the intramuscular study) was as follows:

1) Three days after baseline assessment: im placebo injection and testing.
2) Three days later: 3 µg DG-AVP im and testing.
3. Three days later: 30 µg DG-AVP im and testing.
4) Four days later: testing.

The treatment and testing schedule of study II (the nasal-spray study) was as follows:

1) Intranasal placebo treatment for 7 days and testing on day 7 of treatment.
2) Three days later: intranasal administration of 80 µg DG-AVP daily divided into 2 portions for 7 days and testing on day 7 of treatment.
3) Two weeks after the last treatment: testing.

The interval between study I and II was approximately 1 week.

Testing was started 1 h after im treatment and in study II 1 h after the first intranasal treatment on day 7.

The studies were performed double-blind: none of the psychologists, physicians, and nursing staff were informed about the period of placebo or active treatment.

Statistical analysis of the data

The effect of treatment was analysed by the Friedman two-way analysis of variance and subsequently by means of Wilcoxon's non-parametric ranking test. A probability level of less than 0.05 was accepted as a significance difference. The results of placebo treatment were compared to the baseline values for the same patients, while the DG-AVP results were compared to those of the placebo treatment. The baseline values for the two groups were compared with Mann-Whitney's non-parametric ranking test.

Biochemical measurements

Analyses were performed on the third or seventh day after each treatment (study I or study II, respectively). Plasma samples were assayed for sodium and potassium content by flame photometry. Urine osmolalities were determined by Knauer's osmometer. Data are shown as mean ± SEM. A difference between the values was evaluated by Student's *t*-test.

Results

The main clinical data on the DI patients are given in Table 1. The mean daily diuresis was 12.7 ± 1.5 l, and the urine osmolality was 160 ± 16 mosm/l. The effects of DG-AVP treatment on the water and electrolyte metabolisms, blood pressure and pulse rate are shown in Table 2. Neither placebo treatment, nor im or intranasal administration of DG-AVP induced significant changes in the urine volume, urine osmolality, serum Na^+, serum K^+, blood pressure or pulse rate in the DI patients. The same laboratory parameters were also measured in the control patients, in whom the DG-AVP treatment

Table 3.
Baseline levels of memory tests in untreated diabetes insipidus patients compared to those of untreated control patients.

Tests	Control patients	Diabetes insipidus
Bourdon-test (s) (attention)	88.3 ± 9.3[1] (9)[2]	69.3 ± 6.4 (13)
Maze-learning(s) (spatial orientation)	36.4 ± 2.3 (9)	28.8 ± 4.1 (13)
Acoustic memory (scores) (short-term)	4.2 ± 0.5 (9)	4.5 ± 0.6 (13)
Optical memory (scores) (short-term)	8.4 ± 1.2 (9)	9.1 ± 0.6 (12)
Word-pair memory		
a) short-term (%)	68.9 ± 2.0 (9)	76.4 ± 3.8 (13)
b) long-term (%)	46.3 ± 7.1 (9)	60.7 ± 5.6 (13)

[1] mean ± SEM. [2] Number of observations.

similarly had no effect on these parameters. (Data are not given).

The baseline values for the different psychological tests designed to measure the attention and the short-term and long-term memories are listed in Table 3. The DI patients were not significantly different from the control patients as regards any of these data. No correlation between baseline values of the tests and the daily diuresis or urine osmolality was observed in DI patients. The performance of the 2 patients with congenital DI (Nos. 12 and 13) were lower as compaed to that of the 11 patients with acquired DI in the Bourdon test ($P < 0.05$) and the long-term word-pair test ($P < 0.05$) but not in the other tests.

The influence of placebo and DG-AVP treatment of the control subjects and DI patients as assessed with the different psychological tests, is presented in Tables 4 and 5. The values obtained following placebo treatments were compared to the baseline values for the same patients using Fried-

Table 4.
Influence of acute intramuscular DG-AVP treatment on the performance of diabetes insipidus and control patients as assessed with different psychological tests.

Treatment	Test					
	Bourdon[1] (s)	Maze-learning[1] (s)	Acoustic[2] (scores)	Optical[2] (scores)	Word-pair[1] short-term (%)	Word-pair[1] long-term (%)
Control patients (n = 9)						
Placebo	82.56 ± 7.70"	35.00 ± 3.87	4.44 ± 0.44	8.11 ± 1.30	71.49 ± 4.65	48.86 ± 5.88
DG-AVP 3 µg	74.33 ± 6.05	23.44 ± 1.41**	4.22 ± 0.91	10.22 ± 1.14	67.90 ± 3.47	52.57 ± 5.43
DG-AVP 30 µg	66.56 ± 4.45*	22.78 ± 3.30*	6.11 ± 0.61*	11.44 ± 1.09*	71.48 ± 3.25	48.84 ± 3.29
4 days later	67.00 ± 5.97*	19.11 ± 1.80**	6.89 ± 0.68**	9.11 ± 0.73	68.51 ± 2.49	43.26 ± 4.26
ANOVA testing	$P < 0.05$	$P < 0.01$	$P < 0.01$	$P < 0.05$	n. s.	n. s.
Diabetes insipidus patients (n = 13)						
Placebo	66.62 ± 4.42	31.15 ± 7.00	4.62 ± 0.42	6.69 ± 0.64	71.82 ± 4.30	53.05 ± 5.01
DG-AVP 3 µg	63.92 ± 2.05	23.46 ± 4.82**	4.62 ± 0.66	8.64 ± 1.00	75.38 ± 4.04	59.33 ± 5.27
DG-AVP 30 µg	62.92 ± 1.85	22.38 ± 4.51**	6.31 ± 0.38**	9.15 ± 1.01	80.51 ± 4.10	63.07 ± 5.36
4 days later	68.38 ± 5.84	23.77 ± 4.77**	6.15 ± 0.46**	9.85 ± 0.92	80.25 ± 3.80	63.31 ± 6.56
ANOVA testing	n. s.	$P < 0.001$	$P < 0.01$	n. s.	n. s.	n. s.

" Mean ± SEM. * Different from placebo treatment (* $P \leq 0.05$, ** $P \leq 0.01$).
[1] Decrease, [2] increase, indicates an improvement.

Table 5.
Influence of intranasal DG-AVP treatment for 7 days on the performance of diabetes insipidus and control patients as assessed with different psychological tests.

Treatment	Test					
	Bourdon[1] (s)	Maze-learning[1] (s)	Acoustic[2] (scores)	Optical[2] (scores)	Word-pair[1] short-term (%)	Word-pair[1] long-term (%)
Control patients						
Placebo spray (n = 8)	77.75 ± 5.19"	26.25 ± 2.66	5.13 ± 0.40	11.63 ± 1.10	71.66 ± 6.27	58.73 ± 6.17
DG-AVP spray (n = 9)	64.33 ± 4.67*	16.67 ± 1.19**	7.67 ± 1.50	12.33 ± 0.73	88.07 ± 3.00*	82.19 ± 3.97**
14 days later	58.29 ± 4.24* (7)	14.67 ± 1.05 (6)"'	7.71 ± 0.94 (7)	12.43 ± 1.56 (7)	89.45 ± 2.01 (6)"'	92.75 ± 2.18 (6)"'
ANOVA testing	$P < 0.01$	$P < 0.02$	n. s.	n. s.	$P < 0.05$	$P < 0.02$
Diabetes insipidus patients (n = 13)						
Placebo spray	64.77 ± 2.92	26.77 ± 5.62	5.31 ± 0.44	8.15 ± 0.90	72.84 ± 4.71	57.41 ± 4.85
DG-AVP spray	63.62 ± 1.55	21.92 ± 4.00	7.46 ± 0.62**	11.69 ± 0.84**	83.60 ± 3.30*	78.18 ± 4.35**
14 days later	61.92 ± 1.38	20.77 ± 3.88	6.38 ± 0.47	12.69 ± 0.94**	90.00 ± 2.30**	84.35 ± 3.61**
ANOVA testing	n. s.	n. s.	$P < 0.05$	$P < 0.001$	$P < 0.01$	$P < 0.01$

" Mean ± SEM. "' Only in 5 cases baseline values were available: in all these cases the obtained values were lower or higher than the baseline values.
* Different from placebo treatment (* $P \leq 0.05$, ** $P \leq 0.01$). [1] Decrease, [2] increase, indicates an improvement.

man's testing. Neither acute im treatment with placebo, nor subchronic intranasal placebo treatment caused significant changes in the DI patients. However, in the control patients the baseline values and those obtained after placebo treatments appeared to be different for the Bourdon ($P < 0.05$), the maze-learning ($P < 0.02$) and the optical ($P < 0.05$) tests, but not for the other tests. Further analyses revealed that the performance in the Bourdon test was improved following the first placebo treatment (im) ($P < 0.05$) and a further improvement was noted following the second placebo treatment (intranasal) ($P < 0.05$). Concerning the maze-learning and the optical tests, an improvement of performance was found following the second placebo treatment (first vs second placebo treatment: $P < 0.01$ and $P < 0.05$, respectively), but there were no differences between the values after placebo treatment and the baseline values.

Im treatment with the high dose of DG-AVP improved the attention of the control patients, as measured by the Bourdon test. This effect persisted at least 4 days after injection (Table 4). In these patients an improved performance was observed in the maze-learning test, which was present already after the low dose of DG-AVP and persisted at least 4 days after the high dose. A significant improvement was found in the acoustic and optical tests after the high dose of DG-AVP, which in the case of the acoustic test was also present 4 days after treatment. Neither the short-term nor the long-term memory as assessed with the word-pair test was affected by im treatment with DG-AVP. A quite similar pattern of responding to that observed in the control patients, was found in the DI patients, except that no significant effects were noted for the Bourdon and optical tests.

Intranasal administration of DG-AVP for 7 days enhanced the performance of the control patients in the Bourdon and in the maze-learning test, as was also noted following acute im treatment, and additionally improves short-term and particularly long-term memory function (Table 5). The effects in the acoustic and optical tests, however, were not significant due to a large variation in the data

respectively increased values following placebo treatment (see above). Similar effects on short-term and long-term memory were observed in DI patients following intranasal treatment with DG-AVP. In these patients no significant influences in the Bourdon and maze-learning tests were found. The effects of peptide treatment persisted at least 2 weeks after discontinuation of treatment in both the control and the DI patients.

Summarizing the data, acute im treatment with DG-AVP improved attention (but only in the control patients), and especially the performance in the maze-learning test, had some, but not a consistent effect on short-term memory function, and did not affect long-term memory function. However, intranasal application of DG-AVP for 7 days improved short-term and particularly long-term memory functions, In general, the effects of DG-AVP persisted for 4 days after im treatment and for 14 days after intranasal treatment.

Discussion

The main findings of the present study are that intranasal treatment with DG-AVP for 7 days significantly improved short-term and long-term memories in both DI patients and non-diabetic hospitalized patients with no essential endocrine disorders and that these effects persisted after discontinuation of treatment. Although we in the present studies used a fixed order of application of placebo and DG-AVP and in some but not all psychological tests an improvement was found over time, as can be inferred from the baseline values, it is rather unlikely that the observed effects are induced by learning effects due to repeated testing. Effects over time in baseline values were only observed in control patients and were present only between the first and the second placebo treatment, except for the Bourdon test. Thus, these differences can also be due to a carry over effect of the first DG-AVP treatment. Accordingly, in 2 out of 3 tests in which changes in baseline values were observed, im DG-AVP treatment was effective in the control patients but not in the DI patients and in the third test (maze-learning) the DI patients performed already better than the control patients in the first baseline testing.

The present findings agree well with the observations in rats showing that DG-AVP or DG-LVP treatment improve memory functions in both normal and hereditary DI rats (de Wied et al. 1972, 1975; van Ree et al. 1978) and that the influence of vasopressin related peptides in this respect is of a long-term nature (de Wied 1971). That vasopressin and related peptides improve memory functions has been reported previously in healthy subjects (Laczi et al., in press; Legros et al. 1978; Legros & Gilot 1979), in DI patients (Laczi et al., in press; Gilot et al. 1980), in depressed patients (Weingartner et al. 1981) and in patients suffering from some but not all amnesic syndromes (Blake et al. 1978; Drago et al. 1981; Jenkins et al. 1979; LeBoeuf et al. 1978; Oliveros et al. 1978; Koch-Hendriksen & Nielsen 1981; Timsit-Berthier et al. 1979). In addition, peptide treatment was found to lead to an improvement of attention and concentration in healthy subjects aged from 50–65 (Legros et al. 1978; Legros & Gilot 1979) and in depressed patients (Weingartner et al. 1981). In nearly all of these studies LVP or DD-AVP were used. These peptides have marked effects on the water and electrolyte metabolism and/or blood pressure. In the study reported here, we have used the peptide DG-AVP, which has little effect on water homeostasis and blood pressure. Accordingly, treatment with DG-AVP of DI and control patients did not affect the parameters for water and electrolyte metabolisms, blood pressure and pulse rate, but did improve cognitive functions. Thus, in man too, brain effects and peripheral endocrine effects of vasopressin are apparently dissociated. It may be that as in animal experiments the peptide directly influences the central nervous system mechanisms involved in memory formation, encoding, storage and recall.

The effects of DG-AVP appeared to be quite similar to those of LVP and DD-AVP. First, DG-AVP improved attention in the control patients as was reported by others for LVP and DD-AVP (Legros et al. 1978; Legros & Gilot 1979; Weingartner et al. 1981). In our previous study we did not find such an effect of LVP and DD-AVP which may be due to the difference in baseline performance of the two control groups (Laczi et al., in press). Second, a consistent improvement in the maze-learning test was found for DG-AVP (present study) and for LVP and DD-AVP (Laczi et al., in press), which may be related to the effects of these peptides on processes of attention, concentration and learning. A similar beneficial effect of DG-AVP on maze-learning has been observed in rats

(Bohus 1981). Third, DG-AVP, like LVP and DD-AVP, improved short-term and long-term memory functions. This particular action of DG-AVP was present after subchronic intranasal treatment, rather than after acute im application. Whether the duration of treatment or the mode of administration is the important variable in this respect, is not known.

Baseline values of the different psychological tests designed to measure attention, spatial orientation and short-term and long-term memories were not different in untreated DI patients as compared to those of the non-diabetic patient group. This finding is apparently in contradiction with the previous observation (Laczi et al., in press) that DI patients were inferior to healthy volunteers in these tests. The reason for this discrepancy is a lower performance of the control patients in the present study as compared to that of the control subjects in the previous study. The performance during baseline testing of the DI patients was similar in this and in the previous study. The difference in baseline values in the two control groups might be due to the fact that the healthy volunteers in the previous study had a more homogenous age distribution (range 22–24 years) and another education level than the non-diabetic control patients in the present investigation (range 16–37 years). However, a more important factor might be that while the healthy volunteers of the previous report were free of all diseases, the present non-diabetic group had been hospitalized for various problems not related to vasopressin secretion. Some of these diseases (e.g. neurosis) and/or the hospitalization might have an impact on mental functions. Consequently, other factors than the presumed vasopressin deficiency in DI subjects, may have contributed to the previously reported differences between DI patients had healthy volunteers with respect to memory functions. The finding that the 2 patients with congenital DI have a lower level of attention and of long-term memory as compared to the other DI patients, is interesting, particularly in view of the memory disturbances of hereditary DI rats (de Wied et al. 1975). However, more information in this respect is needed before definite conclusions can be drawn about possible cognitive disturbances due to congenital DI.

The present data favour the hypothesis that vasopressin facilitates long-term and short-term memories in DI patients, as well as in non-diabetic subjects. DG-AVP or other endocrinologically inactive fragments of vasopressin might be recommended for the treatment of patients with memory disturbances instead of LVP or DD-AVP, which in addition exert peripheral effects on circulation and/or water and electrolyte metabolisms.

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