Differential effect of desglycinamide\(^{9}\)-(Arg\(^{8}\))-vasopressin on cognitive functions of diabetes insipidus and alcoholic patients

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Abstract. Intranasal treatment with desglycinamide\(^{9}\)-(Arg\(^{8}\))-vasopressin (DGAVP) improved certain aspects of cognitive functions of patients with acquired and congenital diabetes insipidus and of alcoholic patients with mild cognitive impairments. Patients with Korsakoff’s syndrome, presenting with severe cognitive impairments, were resistant to DGVP treatment. DGAVP treatment did not affect blood pressure and water metabolism. The action of DGAVP on cognitive functions is probably mediated by centrally located target sites and may be expressed only in patients in whom these target sites are unimpaired.

The neurohypophyseal hormone vasopressin has been implicated in cognitive processes. Originally this postulate emerged from rat studies showing that exogenously administered vasopressin facilitates certain behavioural responses aimed at measuring memory functions (de Wied 1971; van Ree et al. 1978) and that these responses are disrupted in rats with hereditary hypothalamic diabetes insipidus (DI) lacking the ability to synthesize vasopressin (de Wied et al. 1975). The influence of vasopressin on these behavioural responses appeared to be dissociated from its action on blood pressure and water metabolism, as could be inferred from the effect of fragments of vasopressin e.g. desglycinamide\(^{9}\)-(Arg\(^{8}\))-vasopressin (DGAVP), which are practically devoid of the classic endocrine effects of vasopressin (van Ree et al. 1978; de Wied et al. 1972, 1984). Although a beneficial effect of vasopressin and related peptides on memory functions has been observed in humans, the so far collected data are not consistent (Jolles 1983; Legros & Lancranjan 1984; van Ree et al. 1985). In particular, conflicting results have been reported in patients suffering from Korsakoff’s or Alzheimer’s diseases, which may be related to a more or less widespread pathologic process in the brain of these patients, probably resulting in more or less severity of cognitive disturbances. In most of these clinical trials, vasopressin or 1-desamino-8-D-argininevasopressin has been administered. The inherent antidiuretic properties of these peptides could have interfered with their supposed enhancing action on memory functions. In previous studies we have found that DGAVP has effects on memory processes in some, but not all patients (Laczi et al. 1983a,b).

For the present series of clinical trials we raised the following questions: 1) Has DGAVP a beneficial effect on cognitive functions in different categories of patients as examined using a double-blind placebo controlled parallel design. 2) Is this action of DGAVP dissociated from an influence on blood pressure and water metabolism. 3) Is the effectiveness of DGAVP influenced by the severity of the cognitive disturbances.
Material and Methods

Four different clinical trials were performed. Trial 1 included 19 patients with acquired DI. The mean age of the 8 female and 11 male patients was 28 years (range 20–39 years). The mean (±SEM) duration of illness was 9.3 ± 2.0 years. The etiology of the disease was as follows: unknown (N = 8), skull injury (N = 8), virus infection (N = 3), medication history (N = 2). Apart from 2 untreated patients, the patients were treated with Adiuretin SD nasal drops (Spofa, Praque) containing L-desamino-8-D-arginine-vasopressin. The medication was withdrawn at least 10 days before the experimental procedure.

Trial 2 included 7 patients with congenital DI. The mean age of the 3 female and 4 male patients was 34 years (range 19–46 years). Four of the patients had a family history of the disease. Each patient was treated with Adiuretin SD nasal drops, which was withdrawn at least 10 days before the experimental procedure.

For trial 3, 28 alcoholic patients were selected randomly from a pool of patients admitted for cure. They had been drinking for more than 2 years and showed symptoms of alcoholism with variable degree of physical dependence but did not fulfil the criteria of the Korsakoff's syndrome. The mean age of these 4 female and 24 male patients was 36 years (range 26–55 years). Their mean (±SEM) duration of alcoholism was 9.2 ± 1.1 year.

Trial 4 included 14 patients suffering from Korsakoff's syndrome. The mean age of the 3 female and 11 male patients was 56 years (range 48–66 years). The mean duration (±SEM) of their alcoholism was 29.1 ± 1.7 years and that of their Korsakoff's syndrome 3.4 ± 0.6 years.

None of the patients in the 4 trials suffered from any other disease than indicated. All medication, except 1-desamino-8-D-arginine-vasopressin to DI patients (see above), was withdrawn 21 days before baseline assessment of psychological and laboratory parameters. None of the patients had graduated from college or university. The psychological tests were also performed in 28 healthy volunteers matched for age and intellectual capacity assessed with the Raven's progressive matrices (Raven & Lewis 1958) with the patients of trial 3.

Peptide administration

The trials were performed under double-blind conditions. The patient of trials 1, 3 and 4 were treated with either placebo or desglycinamide2-(Arg8)-vasopressin (DGAVP, Organon International BV, Oss, The Netherlands). The allocation of placebo and DGAVP medication was random. In trial 2, placebo and DGAVP were subsequently administered to all 7 patients because of the limited number of patients. Placebo or DGAVP was intranasally administered for 7 days at a dose of 80 µg (trials 1 and 2) or 160 µg (trials 3 and 4) divided into 2 or 4 portions, respectively.

Psychological tests

Psychological testing was performed on the day before and on the last day of treatment with placebo or DGAVP. The following tests were used:

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 and the number of mistakes made were determined, and on the basis of these data the rate of hits (%) in 60 sec was calculated. This test is used to measure certain aspects of attention.

2) Acoustic memory test for names and numbers (Böszörmenyi & Moussong-Kovács 1967): 5 names and 5 items of numerical data present in a simple story had to be written down immediately after acoustic presentation of the story. A maximum of 10 points was awarded for correct recall of the data. The names and numbers were changed when the examination was repeated. This serves to measure certain aspects of short-term memory.

3) Optical memory for names and numbers (Benton & Spreen 1961): There were 3 names and 4 numbers inside and on the perimeter of a geometric figure (a pentagon). After observation for 30 sec the figures had to be drawn from memory. Evaluation: correctly recalled names and numbers were awarded 2 points each if situated in the correct place, otherwise 1 point each. Correct drawing of the geometric figure yielded 2 points. The maximum score was 16 points. The figure, the names, and the numbers were changed when the examination was repeated. This test also measure certain aspects of short-term memory.

4) Ranschburg-Ziehen's word-pair memory test (Lipmans 1922): The following word pairs feature in this test: noun + noun, noun + adjective, and noun + verb, on the basis of logical connections. The word pairs were read out, and 1 min later the first words of each pair were given and the subject had to recall pairs. The recall test was repeated 24 h later. The number of correctly recalled words was given as a performance value. The results attained by each individual were expressed as percentages of the maximum score. The word pairs were changed on subsequent repetitions of this test, but the degree of difficulty was retained. This is a test to measure certain aspects of both short-term and long-term memory.

Laboratory assessments

Diuresis, urine osmolality, blood pressure, and pulse rate were determined on the day before and during each day of the experiment. Analyses for serum sodium and potassium and plasma osmolality were performed on the day before and on the last day of treatment with placebo or DGAVP. Plasma samples were assayed for
sodium and potassium content by flame photometry. Plasma and urine osmolality were measured with an advanced Digi Matic Osmometer (USA). AVP plasma levels were assessed on the day before treatment using a radioimmunoassay, comparable to that described before (Dogterom et al. 1978). The antisemur was produced in sheep and was specific for AVP. The cross-reactivity with oxytocin was 0.01%, with arginine-vasotocin 0.033%, with ACTH-(1–24) 0.035%, and with LVP 22.3%. The final dilution was 1:500 000. Synthetic AVP (antidiuretic activity 403 IU/mg; Organon, Oss, The Netherlands) was used as a standard and for preparing the tracer. The limit of determination was 1 pg AVP/assay tube. The coefficients of variation within and between assays was 13.3% and 16.3%, respectively (for more details see Laczi et al. 1986).

Statistical methods

The data of baseline psychological assessments were analysed by ANOVA followed by Newman Keuls. The difference between placebo and DGAVP treatment was determined by Student’s t-test. The influence of treatment on laboratory parameters was analysed by Student’s t-test (paired samples).

Results

The data of baseline psychological testing (Table 1) revealed that the patients suffering from acquired DI were not different from the healthy volunteers in any of the tests. The patients with congenital DI, however, had lower scores at the Bourdon test and at the word pair test, both with respect to immediate and to 24-h recall. The alcoholic patients of trial 3 were inferior as compared with the healthy volunteers with respect to their performance in the Bourdon test and the immediate and 24-h recall of the word pair test. The Korsakoff patients were markedly disturbed in all tests.

The effect of placebo and DGAVP treatment is shown in Fig. 1. No differences in the baseline psychological measures were present between the patients treated with DGAVP and the patients simultaneously treated with placebo. In none of the trials did placebo treatment significantly affect the psychological measures (compare the data presented in Table 1 and Fig. 1). Administration of DGAVP led to several distinct effects, depending on the treated population of patients. In the patients with DI, DGAVP increased the performance at the acoustic test and as to both aspects of the word pair test. In addition, the performance at the Bourdon test and the optical test were higher after peptide treatment in the patients with congenital DI. In the alcoholic patients (trial 3), DGAVP increased the performance at the Bourdon test and at the word pair test, but only as to the 24-h recall. No peptide effect was found in these patients at the performance during the acoustic and optical tests and the immediate recall of the word pair test, although a two times higher dose was used as compared with the trial with the DI patients. In the Korsakoff patients we were unable to detect any effect of peptide treatment.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients and subjects</th>
<th>No.</th>
<th>Bourdon (%)</th>
<th>Acoustic (scores)</th>
<th>Optical (scores)</th>
<th>Word-pair</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immediate recall (%)</td>
</tr>
<tr>
<td>3</td>
<td>Healthy volunteers</td>
<td>28</td>
<td>91.0 ± 0.91</td>
<td>5.1 ± 0.4</td>
<td>10.7 ± 0.4</td>
<td>86 ± 1</td>
</tr>
<tr>
<td>1</td>
<td>Diabetes insipidus (acquired)</td>
<td>19</td>
<td>90.1 ± 1.2</td>
<td>6.2 ± 0.4</td>
<td>10.8 ± 0.5</td>
<td>80 ± 1</td>
</tr>
<tr>
<td>2</td>
<td>Diabetes insipidus (congenital)</td>
<td>7</td>
<td>69.4 ± 5.8*</td>
<td>4.6 ± 0.9</td>
<td>8.0 ± 1.2</td>
<td>67 ± 5*</td>
</tr>
<tr>
<td>3</td>
<td>Alcoholes</td>
<td>28</td>
<td>81.9 ± 2.8*</td>
<td>5.0 ± 0.4</td>
<td>11.1 ± 0.5</td>
<td>74 ± 3*</td>
</tr>
<tr>
<td>4</td>
<td>Korsakoff</td>
<td>14</td>
<td>23.2 ± 4.3*</td>
<td>1.8 ± 0.3*</td>
<td>2.2 ± 0.3*</td>
<td>26 ± 4*</td>
</tr>
</tbody>
</table>

1 Mean ± SEM. * Different from healthy volunteers (P < 0.05, ANOVA followed by Newman Keuls analysis).
osmolality were found to be in the normal range and not affected by placebo or DGAVP treatment (Table 2). The main daily diuresis and the urine osmolality were increased in the DI patients, but not in the other patients. Neither placebo nor DGAVP treatment influenced these parameters. Blood pressure and pulse rate of all patients were in the normal range and were not changed by placebo or DGAVP treatment. Plasma AVP levels of the alcoholic and Korsakoff patients were not different from those observed in healthy subjects (3.8 ± 0.5 pmol/l, N = 20) and the AVP level of the individual patients in the different studies were not correlated with their performance at the various psychological tests.

**Discussion**

The present data confirm and extend previous findings showing a beneficial effect of DGAVP on cognitive processes (Laczi et al. 1983a,b; van Ree et al. 1985). Treatment with DGAVP enhanced the performance of the patients as assessed with psychological tests designed to measure certain aspects of attention, short-term and long-term memories. These findings agree well with the interpretation of the outcome of animal experiments dealing with vasopressin action on behavioural responses (de Wied 1971; van Ree et al. 1978; Messing & Spaber 1984). The action of DGAVP on cognitive processes was not accompanied by changes in blood pressure, pulse rate, and parameters for water metabolism, either in the alcoholic or in the DI patients. This suggests that the beneficial effect of vasopressin and related peptides on cognitive processes is dissociated from the classic endocrine action of vasopressin, and probably mediated by a direct influence on the central nervous system.

The performance of patients with acquired DI was not substantially different from that of the control subjects. However, patients with congenital DI had a lower level of performance at the Bourdon and the word pair test with respect to both immediate and 24-h recall, as compared with those with acquired DI and the control subjects. Similar kind of disturbances in such patients have been reported by others (Gilot et al. 1980). Individuals with congenital DI are supposed to lack the ability to synthesize vasopressin owing to changes in the DNA sequence (Schmale & Richter 1984). Thus, in these patients both the hypothalamic posterior pituitary pathways and the brain circuits normally containing vasopressin have a deficit in vasopressin. Considering the central target for vasopressin and related peptides with respect to their action on cognitive processes, the disturbances of the congenital DI patients as found in the present study may be related to the deficiency of vasopressin in the brain. Consequently, in patients with acquired DI the secretion

![Fig. 1.](image)

Influence of intranasal treatment with placebo or DGAVP (80 or 160 µg/day). Testing was performed after 7 days of treatment. Data are presented as mean ± SEM (vertical bars). Different from placebo treatment (Student's t-test): *P < 0.05; **P < 0.01; ***P < 0.001. [] Placebo. □ DGAVP.
Table 2.
Influence of placebo and DGAVP treatment for 7 days on different laboratory parameters. Data of the analyses performed before and on the last day of treatment are presented.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetes insipidus (acquired)</th>
<th>Diabetes insipidus (congenital)</th>
<th>Alcohols</th>
<th>Korsakoff</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline N = 19* Placebo N = 9 DGAVP N = 10</td>
<td>Baseline N = 7 Placebo N = 7 DGAVP N = 7</td>
<td>Baseline N = 28 Placebo N = 14 DGAVP N = 14</td>
<td>Baseline N = 14 Placebo N = 7 DGAVP N = 7</td>
</tr>
<tr>
<td>Diuresis (1/24 h)</td>
<td><strong>11.8 ± 2.0</strong> 10.4 ± 1.4 10.4 ± 2.6</td>
<td>9.9 ± 1.0 9.7 ± 0.5 10.1 ± 1.0</td>
<td>1.0 ± 0.1 1.1 ± 0.1 1.0 ± 0.1</td>
<td>1.1 ± 0.1 1.2 ± 0.1 1.0 ± 0.1</td>
</tr>
<tr>
<td>Urine osmolarity (mosm/kg)</td>
<td>148 ± 12 154 ± 15 160 ± 17</td>
<td>151 ± 9 151 ± 7 144 ± 6</td>
<td>824 ± 58 780 ± 70 740 ± 51</td>
<td>817 ± 68 838 ± 35 834 ± 105</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic</td>
<td>122 ± 5 123 ± 4 120 ± 4</td>
<td>123 ± 3 124 ± 2 123 ± 2</td>
<td>124 ± 5 119 ± 3 121 ± 5</td>
<td>145 ± 3 136 ± 2 143 ± 1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 ± 3 81 ± 4 76 ± 3</td>
<td>76 ± 1 77 ± 1 82 ± 2</td>
<td>83 ± 4 77 ± 2 78 ± 3</td>
<td>85 ± 2 79 ± 1 87 ± 3</td>
</tr>
<tr>
<td>Pulse rate (min⁻¹)</td>
<td>80 ± 3 82 ± 3 78 ± 3</td>
<td>77 ± 2 80 ± 1 78 ± 2</td>
<td>83 ± 3 79 ± 2 78 ± 3</td>
<td>74 ± 1 71 ± 2 73 ± 3</td>
</tr>
<tr>
<td>Na⁺ (mmol/l)</td>
<td>140 ± 1 139 ± 2 140 ± 1</td>
<td>143 ± 1 144 ± 1 143 ± 1</td>
<td>140 ± 1 140 ± 2 139 ± 1</td>
<td>140 ± 1 141 ± 1 140 ± 1</td>
</tr>
<tr>
<td>K⁺ (mmol/l)</td>
<td>4.2 ± 0.2 4.1 ± 0.2 4.2 ± 0.1</td>
<td>4.2 ± 0.1 4.2 ± 0.1 4.4 ± 0.1</td>
<td>4.4 ± 0.2 4.4 ± 0.2 4.2 ± 0.1</td>
<td>4.2 ± 0.1 4.2 ± 0.1 4.2 ± 0.1</td>
</tr>
<tr>
<td>Plasma osmolarity (mosm/kg)</td>
<td>294 ± 2 295 ± 1 293 ± 2</td>
<td>292 ± 1 292 ± 1 292 ± 1</td>
<td>288 ± 2 290 ± 2 292 ± 2</td>
<td>289 ± 1 288 ± 1 289 ± 1</td>
</tr>
<tr>
<td>Plasma AVP levels (pmol/l)</td>
<td>&lt; 1.2 – –</td>
<td>&lt; 1.2 – –</td>
<td>3.8 ± 0.5 – –</td>
<td>3.5 ± 0.2 – –</td>
</tr>
</tbody>
</table>

* N = number of patients. ** Mean ± SEM.
of vasopressin from the posterior pituitary is disturbed, whereas that from pathways directly innervating brain tissue may not be different from that of control subjects. That patients with acquired as well as congenital DI benefit from DGAVP treatment indicates that the central target sites for vasopressin action are unimpaired in these patients.

The Korsakoff’s syndrome is an organic brain disease characterized by anterograde and retrograde amnesia (Squire 1982; Victor et al. 1971). To date, no indications exist for a deficiency of vasopressin in these patients, since their levels of vasopressin in plasma and cerebrospinal fluid seem to be within the normal range (van Wimersma Greidanus & Wintzen 1980). The neuropathological basis of the memory disorder of Korsakoff patients is thought to be caused by lesions along the pathways of the dorsal noradrenergic bundle in the diencephalon and brainstem (Bierly 1977; Mair et al. 1979; Brion & Mikol 1978). We found that the Korsakoff patients are markedly disturbed in the psychological tests which measure certain aspects of attention and short-term and long-term memory function and that their impaired performance could not be beneficially influenced by DGAVP treatment. This suggests that the central target sites for vasopressin may not be operative in these patients owing to extensive brain lesions. Consistently, rats with lesions of the dorsal noradrenergic bundle are resistant to the action of vasopressin related peptides on memory consolidation (Kovács et al. 1979).

In the alcoholic patients who did not fulfil the criteria of the Korsakoff’s syndrome, the disturbances demonstrated with the psychological measures used were less severe and DGAVP treatment enhanced the performance, at least in certain tests. This may be related to the less widespread pathologic disorders in these patients as compared with the Korsakoff patients.

In conclusion, DGAVP may beneficially influence certain aspects of attention and memory functions in DI and alcoholic patients. The peptide does not influence blood pressure and water metabolism, suggesting central target sites for vasopressin and related peptides with respect to their action on cognitive functions. The data also suggest that patients with severe cognitive disturbances as assessed with the psychological measures respond less favourable to DGAVP than patients with mild or no disturbances. This may be related to the severity of the symptoms or to the degree of brain damage. The central target sites for vasopressin should be intact for the expression of vasopressin action as is suggested from the inability of DGAVP to improve performance in patients with Korsakoff’s syndrome.

References


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