Lack of effect of desglycinamide-arginine-vasopressin (DGAVP) on memory in patients with Korsakoff’s syndrome

F. Laczi1, J. M. Van Ree4, Lujza Balogh3, Anna Szász2,
T. Járdánházy2, A. Wágner2, L. Gáspar1, Zsuzsa Valkusz1, Ilona Dobranovics2,
J Szilárd2, F. A. Lásló1 and D. De Wied4

Endocrine Unit and Research Laboratory1, First Department of Medicine,
Department of Neurology and Neuropsychiatry2, University Medical School, Szeged, Hungary,
Department of Neuropsychiatry3, Municipal Hospital, Szeged, Hungary and
Rudolf Magnus Institute for Pharmacology4, University of Utrecht, Utrecht, The Netherlands

Abstract. The effect of desglycinamide6-[Arg8]-vasopressin (DGAVP) on memory processes was studied in patients with Korsakoff’s syndrome. Intranasal treatment with DGAVP for 7 days affected neither attention nor short- and long-term memories. It is suggested that treatment with DGAVP is not indicated for all types of memory disorders, and that the beneficial effect of this treatment may depend on the integrity of certain brain structures.

Animal studies have revealed that [Arg8]-vasopressin (AVP) plays a physiological role in memory processes (De Wied et al. 1975; van Wimersma Greidanus et al. 1975b; Van Ree et al. 1978; Bohus et al. 1978). Evidence that the memory stimulating effects of AVP are independent of its classical endocrine actions comes from studies with analogues of the hormone. Desglycinamide9-[Lys8]-vasopressin (DGLVP) and desglycinamide9-[Arg8]-vasopressin (DGAVP), which are practically devoid of pressor and antidiuretic activity (De Wied et al. 1972), are practically as effective as vasopressin in facilitating memory processes in experimental animals (De Wied 1976).

Recent observations suggest that AVP may also be involved in human memory processes. AVP and related peptides improve memory functions in healthy subjects (Laczi et al. 1982a; Legros et al. 1978; Legros & Gilot 1979), in diabetes insipidus (DI) patients (Laczi et al. 1982a; Gilot et al. 1980), in depressed patients (Weingartner et al. 1981) and in patients suffering from some but not all amnestic syndromes (Drago et al. 1981; Le Bœuf et al. 1978; Oliveros et al. 1978; Timsit-Berthier et al. 1979; Koch-Henriksen & Nielsen 1981; Jenkins et al. 1979). [Lys8]-vasopressin (LVP) or 1-desamino-[D-Arg8]-vasopressin (DDAVP) were used in nearly all these studies. We observed however that DGAVP improved memory processes in healthy subjects and in DI patients (Laczi et al. 1982b).

Vasopressin is believed to exert its effect on memory via interaction with limbic-midbrain structures; lesions of these areas block the vasopressin effect on memory functions (van Wimersma Greidanus & De Wied 1976; van Wimersma Greidanus et al. 1975a, 1979). The effects of vasopressin in rats are mediated by terminals of noradrenergic-containing nerve fibres present in these limbic midbrain structure (Kovács et al. 1979).

The Korsakoff syndrome is an organic brain disease characterized by anterograde and retrograde amnesia (Squire 1982; Victor et al. 1971). The neuropathological basis of the memory disorder is thought to be caused by lesions along the pathways of the dorsal noradrenergic bundle in the diencephalon and brain-stem (Victor et al. 1971; Malamud & Skillcorn 1956; Bierly 1977; Mair et al. 1979; Brion & Mikol 1978).

We have therefore evaluated the responsiveness of Korsakoff patients to DGAVP treatment. In contrast to the healthy subjects and DI patients in
previous studies, these patients did not respond to DGAVP treatment with an improvement of memory functions.

Materials and Methods

Subjects

The investigations were carried out on 14 patients of both sexes with Korsakoff's syndrome. The clinical data of these patients are listed in Table 1. All patients had a history of chronic alcoholism, and all fulfilled the criteria for Korsakoff's syndrome as described by Squire (1982) and Victor et al. (1971). None of the patients suffered from any other disease. The patients were hospitalized during the trial. All medications were withdrawn at least 10 days before the baseline psychological parameters were tested. The patients were of approximately the same scholastic and educational level. None of the patients had graduated from college or university.

The patients were randomly divided into two groups. Eight patients (1 female and 7 males) with a mean age of 53.5 years (range 48–61 years) were treated with desglycinamide³-[Arg⁸]-vasopressin (DGAVP) and 6 patients (2 females and 4 males) with a mean age of 55.7 years (range 50–65 years) received placebo.

Memory and attention tests

1) Bourdon test (Lipmans 1922): the subjects, whose mother tongue was Hungarian, have to underline the letters 'e' in a standard French text. The time required to perform the task and the mistakes made are determined. The mistakes are included in the value for the time required to perform the test in order to get a parameter characterizing in seconds the performance of the patients. 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 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 thinking activity.

3) Acoustic memory test for names and numbers (Böszörményi & Moussong-Kovács 1967): 5 names and 5 items of 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. The names and numbers are changed when the examination is repeated. This serves as a test of short-term memory.

4) Optical memory 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 figures 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 yields 2 points. The maximum
This page contains a text describing the performance of a memory test and the effects of DGAVP treatment on electrolyte metabolism. The memory test is described as a word-pair memory test, where the participant is given two words per pair and is required to recall them after a delay. The performance is measured as the number of correctly recalled word-pairs per minute.

The effects of DGAVP treatment on electrolyte metabolism are measured by analyzing the serum Na⁺, K⁺, and serum osmolality levels in patients with Korsakoff's syndrome. The table shows the results of the treatment, with baseline and treatment values for both placebo and DGAVP groups. The statistical analysis indicates that the treatment significantly affected the electrolyte levels, with a decrease in serum Na⁺ and an increase in serum K⁺ levels.

Discussion

The main finding of the present study is that intranasal treatment with DGAVP for 7 days did
Table 3.
Influence of intranasal placebo and DGAVP treatment for 7 days on the performance of patients with Korsakoff’s syndrome as assessed with different psychological tests.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Test</th>
<th>Bourdon a,b</th>
<th>Maze-learning a,b</th>
<th>Acoustic b</th>
<th>Optical b</th>
<th>Word-pair b</th>
<th>Word-pair b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(s)</td>
<td>(s)</td>
<td>(scores)</td>
<td>(scores)</td>
<td>short-term (%)</td>
<td>long-term (%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>baseline</td>
<td>282 ± 29*</td>
<td>123 ± 41</td>
<td>1.33 ± 0.49</td>
<td>2.33 ± 0.56</td>
<td>26 ± 6</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>7th day</td>
<td>216 ± 34</td>
<td>89 ± 21</td>
<td>2.17 ± 0.54</td>
<td>2.33 ± 0.33</td>
<td>33 ± 11</td>
<td>17 ± 6</td>
</tr>
<tr>
<td></td>
<td>14 days later</td>
<td>207 ± 37</td>
<td>83 ± 20</td>
<td>2.17 ± 0.54</td>
<td>3.17 ± 0.91</td>
<td>29 ± 6</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>ANOVA2</td>
<td></td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.³</td>
</tr>
<tr>
<td>DGAVP</td>
<td>baseline</td>
<td>235 ± 30</td>
<td>91 ± 15</td>
<td>1.38 ± 0.42</td>
<td>3.00 ± 0.96</td>
<td>28 ± 6</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>7th day</td>
<td>187 ± 18</td>
<td>72 ± 12</td>
<td>2.25 ± 1.67</td>
<td>2.88 ± 0.77</td>
<td>36 ± 8</td>
<td>16 ± 4</td>
</tr>
<tr>
<td></td>
<td>14 days later</td>
<td>183 ± 21</td>
<td>73 ± 14</td>
<td>2.50 ± 0.54</td>
<td>3.00 ± 0.71</td>
<td>38 ± 8</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>ANOVA²</td>
<td></td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.³</td>
</tr>
</tbody>
</table>

* Mean ± SEM. ¹ a decrease (a) or an increase (b) indicates an improvement. ² Kruskall-Wallis test. ³ Wilcoxon’s non-parametric ranking test.

not affect attention, short- or long-term memories in patients with Korsakoff’s syndrome. The baseline values of the different psychological tests designed to measure attention, spatial orientation and short-term and long-term memories were inferior to those observed in healthy subjects in a previous study (Laczi et al. 1982a). This is in agreement with the observation that patients with Korsakoff’s syndrome have a disturbance in consolidation and consequently have difficulties in remembering recent events or acquiring new information (Squire 1982).

The present findings agree well with the observations of Blake et al. (1978), who failed to demonstrate a positive effect of vasopressin in alcohol-induced amnesia. On the other hand, Le Boeuf et al. (1978), Oliveros et al. (1978) and Drago et al. (1981) have demonstrated a beneficial effect of LVP on the memory of patients with Korsakoff’s syndrome. However, all these studies involved LVP which had marked effects on water and electrolyte metabolism and blood pressure. It may also be that the lesion in these patients was less severe than those of the present patient group. Nevertheless, the present study shows that the peptide DGAVP, which is practically devoid of pressor and anti-diurectic activity and which has been previously demonstrated to improve short- and long-term memory in healthy subject and DI patients as assessed with similar psychological tests (Laczi et al. 1982b) was not effective in Korsakoff patients.

Limbic-midbrain structures are believed to mediate the beneficial effect of vasopressin-related peptides on memory processes. Thus, lesions of these areas and of the dorsal noradrenergic bundle block the peptide effect (van Wimersma Greidanus & De Wied 1976; van Wimersma Greidanus et al. 1975a, 1979; Kovács et al. 1979). Microinjection of these peptides into certain limbic-midbrain areas facilitates memory consolidation (Kovács et al. 1979) and retrieval processes (Bohus et al. 1982). Interestingly, clinicopathological studies of the Korsakoff syndrome demonstrated bilateral damage in limbic-midbrain structures along the dorsal noradrenergic bundle (Bierly 1977; Mair et al. 1979; Brion & Mikol 1978; Malamud & Skillicorn 1956; Victor et al. 1971). These lesions may thus be the neuropathological basis of the memory loss in patients with Korsakoff’s syndrome.

The precise mode of action of vasopressin on memory processes has not yet been elucidated. Chemical destruction of the noradrenergic nerve terminals arising from the locus coeruleus prevents the influence of AVP on consolidation of memory but not on retrieval (Kovács et al. 1979). It was therefore proposed that AVP influences memory consolidation through an effect on terminals of the noradrenaline-containing neurons in limbic-midbrain structures (Kovács et al. 1979; Telegdy & Kovács 1979). McEntee & Mair (1978) have observed a decreased level of the primary brain metabolite of noradrenaline in the lumbar spinal
fluid of patients with Korsakoff’s syndrome. They suggested that Korsakoff’s amnesia might result from damage to ascending noradrenergic pathways by limbic-midbrain lesions associated with this disease. If the amnesia in patients with Korsakoff’s syndrome is related to impaired central monoamine systems and if vasopressin modulates the consolidation of memory at the level of the presynaptic terminals of the dorsal noradrenergic bundle, it is not likely that there would be a beneficial effect of vasopressin-related peptides on the memory disorder of Korsakoff’s syndrome. It is consistent with this suggestion that the present study demonstrates that DGAVP is ineffective in improving memory disturbances in patients with Korsakoff’s syndrome.

Thus, DGAVP is not indicated for the treatment of all types of memory disorders. The beneficial effect of treatment with this hormone fragment may depend on the integrity of certain brain structures.

References


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