


Acknowledgements
We thank Sir Carlsson, Kerstin Fugelström, Ulla Jarl and Gertrude Stridsberg for expert technical assistance. This study was supported by grants from the Swedish Medical Research Council, the American Osteopathic Association, Texas Christian University and the National Science Foundation, International Division.

MEMORY DISORDERS AND VASOPRESSIN.


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INTRODUCTION
Neuropeptides related to the pituitary hormones vasopressin and oxytoxin are involved in memory processes and learning. This notion evolved from the pioneering work of de Wied and coworkers in experiments with rodents (De Wied, 1990). With respect to the involvement of vasopressin, a number of important observations have been done (for recent reviews, see van Ree et al., 1978; Higler and Crabbe, 1979; de Wied, 1980). Rats lack endogenous vasopressin have memory disturbances. 2. These behavioral deficits can be corrected by treatment with exogenous peptide. 3. Experimental memory disturbances of other origin (e.g. CO2-treatment or ECT) were also effectively treated with the neuropeptide. 4. Intracerebral implantation of the peptide. 5. Vasopressinergic nerve fibers can be detected throughout the brain, terminating in brain structures which are known to be crucial for memory: destruction of the structures also destroys the effects of vasopressin.

Findings as described above have suggested that vasopressin and congener might have clinical applications in the treatment of memory disorders in man. A number of clinical studies has been performed. These differ with respect to the nature of the patient population, the methods of evaluation of the amnesia, the vasopressin fragments used, and the dose, frequency and route of administration. As positive as well as negative results were obtained, research in our institute has recently been directed at elucidating the nature of memory disorders with the hope of thereby establishing more rational criteria for the patient population to be treated and the treatment procedures to be used.

In this paper, a review will be given of the clinical trials in which the therapeutic effect of vasopressin has been investigated; the sources of difference between these studies will be critically evaluated, and some information is given concerning the nature of memory disorders. Then the results of a study are described in which new psychological testing methods were developed to enable a differentiation between aspects of memory, attention, and concentration. It appeared that seemingly homogenous populations of patients were very heterogeneous with respect to the nature of the memory disorder. The implications of this finding for studies concerning effects of vasopressin on memory are discussed.
Table 1. Amino acid sequence of some relevant neuropeptides.

<table>
<thead>
<tr>
<th>Neuropeptide</th>
<th>Sequence</th>
</tr>
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<tbody>
<tr>
<td>ACTH (1-19)</td>
<td>V-Ser-Tyr-Phe-Gly-Gln-Asn-Cys-Pro-Arg-Gly-NH₂</td>
</tr>
<tr>
<td>Met-enkephalin</td>
<td>Tyr-Glu-His-Pro-Arg-Tyr-Gly-OMe</td>
</tr>
<tr>
<td>Leu-enkephalin</td>
<td>Tyr-Glu-His-Pro-Arg-Tyr-Gly-OMe</td>
</tr>
<tr>
<td>DGAVP (1-9)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OH</td>
</tr>
<tr>
<td>DGAVP (1-8)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OH</td>
</tr>
<tr>
<td>DGAVP (1-7)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OMe</td>
</tr>
<tr>
<td>DGAVP (1-5)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OMe</td>
</tr>
<tr>
<td>DGAVP (1-4)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OMe</td>
</tr>
<tr>
<td>DGAVP (1-3)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OMe</td>
</tr>
<tr>
<td>DGAVP (1-2)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OMe</td>
</tr>
<tr>
<td>DGAVP (1-1)</td>
<td>Cys-Tyr-Pro-Glu-Ase-Cys-Pro-Arg-OMe</td>
</tr>
</tbody>
</table>

CLINICAL STUDIES ON THE ANTIAMNESTIC EFFECTS OF VASOPRESSIN: A REVIEW

The first clinical trial concerning the possible anti-amnestic effect of vasopressin was performed with patients that suffered from a posttraumatic amnesia (three patients) and chronic alcoholism (one patient) (Olivares et al. 1978). The active substance (lysine⁸-Vasopressin, LVP; for aminoacid sequence of some relevant neuropeptides, see table I), was administered per nasal spray. The cognitive functions were not measured systematically, but a clinical improvement was manifest in all four patients after 3 to 5 days (table II). Another study in which an alcoholic with an amnestic syndrome was treated with LVP also mentioned an improvement; this patient was reported to remember more, and to have better concentration and some orientation (de Bouff et al. 1979). Other investigators however, did not find any effect of LVP or DGAVP in alcoholics which were older and had more severe memory defects (Blake et al. 1978; Tolkowsberg et al. 1981). It may be that the lack of effect of the peptide may relate to the extent that degenerative processes have taken place in the brain.

The hypothesis that a possible therapeutic effect of the peptide may depend on the damage of the brain gains support from studies with patients suffering from memory disorders associated with brain trauma. In a study in which six patients suffering from serious head injury were treated with low doses of DGAVP or LVP (see table I; DGAVP shares the effect of LVP on kidney urine excretion but has no vascular effects; DGAVP has virtually no effects but it has only behavioral effects which are mediated by the brain), no effect could be found. Higher, doses of DGAVP or DGAVP were also ineffective (Johnson et al. 1981). Similarly, negative findings were reported with patients recovering from a serious head trauma, and a long period of coma (Koch-Henriksen and Nielsen 1981). However, LVP did have an effect in patients that had less serious defects (the amnesia was the only rest problem after the head trauma) (Timsit-Berthier et al. 1980). Five out of seven patients improved on tests that are supposed to measure 'attention' or 'short-term visual retention'. In addition, a clinical improvement was found with respect to activity motivation, and social adjustment. This peptide effect developed in time, and was maximal after weeks or months. It has also been found in this study, that the seven memory disturbed patients had decreased levels of noradryphine-1, the vasopressin-transportprotein. The levels of circulating vasopressin-1 increased to normal levels in four of five improved patients after treatment with LVP.

A study with memory disturbed transplants has also been performed by our group (Verhoeven et al., unpublished results). This preliminary study investigated DGAVP effects in some patients suffering from an amnestic syndrome that was a result of brain trauma (N=4), cerebral hypoxia (N=2), cerebral vascular insufficiency (N=3), and brain surgery (N=4). DGAVP was administered per nasal spray and the design was a double blind cross-over study. The tests that were used for the evaluation of treatment effects measured the visual shorttermmemory and reaction time. With respect to the testresults, no treatment effects were seen. The basal levels of vasopressin and neurophysin in blood and in liquor were within normal range in all patients. In addition, these levels did not change as a result of the peptide treatment.

Clinical research with vasopressin has also been performed in elderly people. Twelve patients (aged 50-64 years) that were hospitalised with somatic complaints were treated with LVP (Legros et al. 1978). These patients performed

Table II. Clinical studies involving antiamnestic effects of vasopressin.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Authors</th>
<th>N peptide</th>
<th>design</th>
<th>improved memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain trauma</td>
<td>a</td>
<td>3 LVP</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>b, c</td>
<td>6 LVP,</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DGAVP,</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DGAVP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chronic Alcoholism</td>
<td>d</td>
<td>8 LVP</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>e</td>
<td>7 LVP</td>
<td>A/B</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>f</td>
<td>1 LVP</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>g</td>
<td>1 LVP</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>h</td>
<td>4 DGAVP</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>i</td>
<td>10 LVP</td>
<td>C</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>j</td>
<td>6 DGAVP</td>
<td>B</td>
<td>4</td>
</tr>
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<td>k</td>
<td>3 DRGP</td>
<td>B</td>
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<td></td>
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<td>4 DDAP</td>
<td>B</td>
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<td></td>
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<td>2 DDAP</td>
<td>B</td>
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<tr>
<td></td>
<td>n</td>
<td>5 DDAP</td>
<td>A</td>
<td>5</td>
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<tr>
<td></td>
<td>o</td>
<td>16 LVP,</td>
<td>D</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>3 LVP</td>
<td>B</td>
<td>3</td>
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<tr>
<td></td>
<td>q</td>
<td>6 LVP</td>
<td>B</td>
<td>6</td>
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<tr>
<td></td>
<td>r</td>
<td>10 LVP</td>
<td>D</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>s</td>
<td>12 LVP</td>
<td>B</td>
<td>12</td>
</tr>
</tbody>
</table>


Design: A. Open pilot study; B. Double blind, placebo controlled study; C. Singuliblind study; D. Double blind cross over study.
better than control subject on certain tests of attention and memory. The same group of investigators reported later, that the scores of one of these "memory" tests correlated with levels of vasopressin-1 in the blood. Effects were also found in senile demented patients (average age 80-90 years; Delwaide et al. 1980). Neon administration of LVP improved the performance of 9 out of 10 patients. Interestingly, the peptide still persisted after 48 hours. Another group of investigators reported that some of their patients, suffering from Alzheimer's dementia, did improve after treatment with DDAVP (Weinman et al. 1981). However, in another (preliminary) study with Alzheimer patients treated with DDAVP no significant effects were found on any of the parameters tested (Tinklenberg 1981).

A number of positive findings has been reported concerning the effect of vasopressin in depression. In a study in which four patients with endogenous depression and cognitive disorders were treated with DDAVP (Weingartner et al. 1981; Gold et al. 1979), three out of four patients manifested a significant improvement with respect to the level of cognitive functioning. After four weeks they were back on their pretreatment level. Six young, healthy volunteers appeared to have a significantly improved memory- and learning performance (Weingartner et al. 1981). In a follow-up study by the same group of researchers DDAVP was tested in two patients that were subjected to electroconvulsive therapy (ECT). The peptide appeared to counteract the amnesia which is a characteristic side effect of the ECT.

Furthermore, DDAVP has beneficial effects in a disease which is characterized by a kind of disordered passive avoidance behavior (autism) in children suffering from Leuch-Nyhan disease; Anderson et al. 1979). Memory defects in other patients were also effectively treated with LVP, notably in patients suffering from hereditary diabetes insipidus (Gilbert et al. 1970; Lazzar, et al. 1981; Wagenstrr, et al. 1978). Interestingly, the hormone oxytocin which in animals has an opposite effect on memory consolidation (Bossh et al. 1978; Witter et al. 1980) had a similar effect in humans, in that this peptide accelerated 'forgetting' in normal subjects (Szasz, Ferrier et al. 1980).

Taken together, these vasopressin studies published until now claim that 80 out of 114 subjects benefit from the peptide treatment (Table II). The question remains how to interpret the differences between studies that do or do not find treatment effects. One interpretation of the data is, that some patients may not respond to treatment, due to the fact that there is an extensive degeneration in the brain, or because lesions exist in places which are important for the effect of vasopressin. Apart from this possibility, difficulties in interpreting treatment effects arise from the fact that vasopressin-studies differ in a number of important variables:

1. The type of patient (post traumatic, senile demented, alcoholic, depressed etc.).
2. The type of memory disorder (see next paragraph).
3. The severity of the symptoms.
4. Methods of treatment evaluation differed all the way from repeated testing from repeated clinical examination by neuropsychological data concerning different aspects of memory, 'attention' and the like, and complete psychometric tests.
5. These tests were usually not in parallel version to enable repeated testing.
6. The design differed between open studies, placebo-controlled studies, double cross-over studies (Table I).
7. The vasopressin fragment used, i.e. LVP or DDAVP or DDAVP. This distinction is of importance due to possible antidiuretic side effects (DDAVP and LVP) and vasoactive side effects (LVP).
8. Peptide treatment, dose, frequency, duration, and route of administration.
9. Intranasally, intramuscularly, etc.
10. These differences between the vasopressin studies may explain some of the inconclusive data obtained until now. In addition, as reported above, our own vasopressin studies have been hampered since some patients reported subjective effects after treatment which could not be shown with the psycholog-
client groups; these groups may be homogenous with respect to etiological factors, but heterogeneous with respect to the nature of the memory defect. For instance, memory complaints can be primary, i.e., specific to a memory disorder. Alternatively, these complaints may be secondary to another disorder such as a decrease in the rate of information processing in the brain, a planning deficit, an attention deficit, a language disorder, etc. It is for this reason that patients should be discerned on the basis of their type of memory disorder and not (only) on the basis of etiological factors alone (type of disease, etc.). The next paragraph summarizes a first attempt at differentiating patient groups, and aimed at providing more homogeneous groups.

MEMORY DISORDERS IN POSTTRAUMATIC, AND SENILE DEMENTED PATIENTS.

The question whether it is indeed the case that seemingly homogenous patient populations are heterogeneous with respect to the type of memory disorder, has been investigated in our institute. It was the aim to establish whether new testing procedures can be developed to discern between different types of memory disorder; whether different patients can be discerned, and whether more rational criteria can be developed to establish, which patients should be treated with vasopressin.

A test series was developed, that combines some existing neuropsychological tests, with test procedures originally devised in the psychological laboratory, and now adapted for use in the clinic (see legend to fig. 1). The details of the assessment procedure and its efficacy will be published elsewhere (Jones et al., in preparation). The test battery was devised so as to gain insight into all relevant cognitive functions which might have to do with memory (that is: auditory memory versus visual memory; consolidation of word memory versus retrieval from word memory; the effect of interference ('distraction') on the rate of perception and working; the planning/organisation of memory; motor functions and language functions). The battery was used to test the nature and the degree of memory defects in posttraumatic patients, and in patients suspected of senile dementia. Two groups of subjects were formed. The selection was made from a large sample of patients that applied for vasopressin treatment in our hospital in view of their memory complaints. The first group consisted of posttraumatic patients, which resigned all neuropsychological tests, but which showed no major signs of dementia or other cognitive deficits. Patients with stable memory complaints, that is, their memory complaints had not changed for a period of at least 1 year, and the period between the accident and the assessment of neuropsychological testing varied between 10 months and 4 years. The second group consisted of patients suspected of (pre) senile dementia. The age ranged from 50 to 72 years. Neuropsychological examination revealed that these patients differed with respect to the degree of dementia (ranging from early beginning dementia to severe dementia).

All patients were tested with the neuropsychological test battery described in the figure. Some relevant data obtained with 7 subjects are summarised in fig. 1. The data will be published in detail elsewhere. As the figure shows, there are patients which are selectively defective in one or more aspects of memory. For instance, some patients show either an inferior auditory memory or an inferior visual memory or a decreased rate of information processing. Other patients show a more complex pattern of deficits. The seven subjects depicted are more or less representative for the 20 patients investigated. Interestingly, the data can be understood in terms of the anatomical locus of control nervous system lesions (see also Table III).

Figure 1. Test Profile of Traumatic Patient.

Performance (% of normal individuals).

<table>
<thead>
<tr>
<th>Memory</th>
<th>Memory</th>
<th>Thinking Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Twenty posttraumatic patients were tested with a test battery which combines some existing neuropsychological tests with test procedures originally devised in the psychological laboratory and now adapted for use in the clinic. These test series consist of: Lie-Rosenberg neuropsychological assessment procedure; the Benton task for recognition and recall of visually presented stimuli; the Oxford test for face recognition; the Symbol Digit Substitution test; the Group Inference test; Recall of words and phrases according to Brown Peterson; Fifteen word learning test in direct and delayed recall and delayed recognition; Memory comparison test (digits/letters and letters/numbers) based on the additive factor method of Sternberg; Lexical decision task, combined with several other tasks, used for the assessment of motor and language dysfunctions. The results obtained on four parameters are shown in the figure (total recall: on fifteen word list: immediate recall; total recognition on Oxford test for face recognition; complex reaction time in the Sternberg paradigm; and performance in Symbol Digit Substitution test). The results for seven patients in the figure are representative for the thirteen patients not depicted.

For instance, a patient with a memory defect specific for complex visual material had a large lesion in the temporal-parieto-occipital region in the
right hemisphere. Another patient, primarily affected in auditory (word) memory, had a surgery involving the left temporal lobe. The third patient, primarily characterized by a decreased rate of perception and working, evidenced neurological signs of a brainstem concussion. In conclusion, the data indicate that the group of 'posttraumatic amnesias' is very heterogeneous from a neuropsychological point of view. A similar conclusion can be reached concerning the group of 10 senile demented patients (Fig. 2). It is clear that these patients as a group perform differently from posttraumatics: They generally show an overall decrease, which is manifest in several, or all psychological functions tested. In fact, 3 patients appeared severely demented; they could not be tested with the complete testbattery. Only qualitative tests could be used (Luria 1980), and these tests demonstrated that the patients have an overall decrease in all psychological functions tested (not shown in the figure).

**Figure 2. Testprofile of Senile Demented Patients.**

Performance (%) of normal individuals.

- Auditory
- Visual
- Rate of Perceptual Memory
- Memory
- Thinking Speed
- Working

Ten patients suspected of a senile dementia were tested with the testbattery described in the legend of figure 1. The details are shown for 7 patients as three patients were so severely deteriorated that they could not be tested with the testbattery. The judgement on the disorder of these patients is based upon qualitative test (Luria-Christensen assessment procedure).

The other 7 patients as a rule were slower than normal. There were differences between these patients in the neuropsychological testprofile, as indicated for 2 patients in Fig. 2. Patients in the 'senile dementia' group are clearly different in several respects from the posttraumatics: The patients in the senile group generally show a complex pattern of psychological deficits, whereas these patients deteriorate, the number of cognitive functions affected, increases.

A general conclusion from this study is, that patients which have similar memory complaints may differ with respect to the memory disorder which underlies these complaints. Thus, populations of patients such as 'posttraumatic amnesia' or senile demented patients can be heterogeneous neuropsychologically. For instance, several other cognitive functions were also affected in senile demented patients (such as arithmetic, reading, etc., not shown).

**CONCLUDING REMARKS.**

The finding that patients with similar memory complaints may suffer from a different memory disorder, may have some implications for future research on antememe effects of vasopressin (and other substances). The fact that different kinds of memory defects can be found by the use of proper psychological tests, suggests that the methodology by which the memory defect is diagnosed, is very important. The same applies for the evaluation of treatment effects. Our findings can explain why studies with similar patientpopulations (eg. 'posttraumatic' or 'Alzheimer'), reported different effects of vasopressin. This supports our hypothesis that vasopressin may have selective effects on memory: It is possible that some patients do not benefit from vasopressin treatment, while others do, as the former patients may have more or less extensive degeneration of the brain structures which are important for vasopressin effects. Some data from animal research support this notion, as some researchers found that vasopressin loses its effect when certain relevant brainstructures are lesioned (Van Wimersma Greijsman et al., 1976). Taken together, the studies reported until now and the reviewed data indicate that vasopressin may indeed have effects in memory disorders. It may however be the case that the peptide has selective effects. Future studies should therefore make use of a better testbattery methodology; the patients should be extensively diagnosed neuropsychologically, to enable a judgement on their type of memory disorder. Patient groups should be assembled on the basis of the neuropsychological profile and not only on the basis of etiology. Furthermore, these tests, in parallel versions should be used for the evaluation of treatment effects.

A second point which is relevant for the testing of memory functions in clinical trials with vasopressin, concerns the use of data from animal experiments. It has been found, that the effect of vasopressin in rats may relate to the consolidation and retrieval of information, or a process common to both (van Reus et al., 1978; Rietig and Crabbé, 1979; de Wied, 1980). Therefore, patientgroups with a similar disorder could preferably be used in the clinical trials. In addition, the relative long-term effects of vasopressin used in animal experiments, suggests that the evaluation of treatment efficacy in humans should use both short and long intervals between treatment and psychological testing. We are presently performing a clinical trial with DGVP in which these notions are tested.

**ACKNOWLEDGMENTS.**

The authors want to thank drs. W.M.A. Verhees and A. Eldebrink for their indispensable work in the selection and diagnosis of the patients. The helpful discussions with drs. de Wied, van Praag and van Reus are gratefully acknowledged.
LITERATURE.


