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MEMORY DISORDERS AND VASOPRESSIN.

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INTRODUCTION

Neuropeptides related to the pituitary hormones vasopressin and oxytocin 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, 1969). With respect to the involvement of vasopressin, a number of important observations has been done (for recent reviews, see van Ree et al., 1978; Rigter en Crabbe, 1979; de Wied, 1980): 1. Rats which lack endogenous vasopressin have memory disturbances. 2. These behavioral deficits can be corrected for by treatment with exogenous peptide. 3. Experimental memory disturbances of other origin (eg. CO_2-treatment or ECT) were also effectively treated with the neuropeptide. 4. Intact rats show enhanced learning performance after treatment with the peptide. 5. Vasopressinergic nerve fibres 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 congeners 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 testprocedures 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 heterogenous 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 I. Aminoacid sequence of some relevant neuropeptides.

Arginine^8-vasopressine (AVP)	H-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2
Lysine^8-vasopressine (LVP)	H-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2
Desglycinamide^9-arginine^8-vasopressine (DGAVP)	H-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-OH
Desglycinamide^9-lysine^8-vasopressine (DGLVP)	H-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-OH
1-Desamino-D-arginine^8-vasopressine (DDAVP)	(desamino) Cys-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH_2
Oxytocine (OXT)	H-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2
ACTH (4-10)	H-Met-Glu-His-Phe-Arg-Trp-Gly-OH

CLINICAL STUDIES ON THE ANTIAMNESTIC EFFECTS OF VASOPRESSIN: A REVIEW.

The first clinical trial concerning the possible antiamnesic effect of vasopressin was performed with patients that suffered from a posttraumatic amnesia (three patients) and chronic alcoholism (one patient) (Oliveros et al. 1978). The active substance (Lysine^8-Vasopressin, LVP; for aminoacidsequence 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 9 days (table II). Another study in which an alcoholic with an amnesic syndrome was treated with LVP also mentioned an improvement: this patient was reported to remember more, and to have better concentration, attention and time orientation (Le Boeuff et al. 1979). Other investigators however, did not find any effectof LVP or DDAVP in alcoholics which were older and had more serious memory defects (Blake et al. 1978; Tinklenberg 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 DDAVP or LVP (see table I; DDAVP shares the effect of LVP on kidney urine excretion but has no vascular effects; DGAVP has virtually no effects but has only behavioral effects which are mediated by the brain), no effect could be found. Higher doses of DDAVP or DGAVP were also ineffective (Jenkins 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 memorydisturbed patients had decreased levels of neurophysine-I, the vasopressin-transportprotein. The levels of circulating neurophysine-I increased to normal levels in four out of five improved patients after treatment with LVP.

A study with memorydisturbed traumapatients has also been performed by our group (Verhoeven et al., unpublished results). This preliminary study investigated DGAVP effects in some patients suffering from an amnesic syndrome

that was a result of brain trauma (N=6), cerebral hypoxia (N=2), cerebral vascular insufficiency (N=1), and brain surgery (N=1). 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 visuel 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 peptidetreatment. However, six out of ten patients reported a subjective improvement from the fourth day of treatment on. These results were interpreted to indicate that it may be essential to have better tests to evaluate possible treatment effects.

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.

Diagnose	Authors	N	peptide*	design	improved memory
Brain Trauma	a	3	LVP	A	3
	b,c	6	LVP, DDAVP, DGAVP	A	-
	d	8	LVP	B	-
	e	7	LVP	A/B	5
Chronic Alcoholism	a	1	LVP	A	1
	f	1	LVP	A	1
	g	2	LVP	A	-
	h	4	DDAVP	B	-
(Pre)senile dementia	i	10	LVP	C	9
	j	6	DDAVP	B	4
	h	3	DDAVP	B	-
Depression	j	4	DDAVP	B	3
	k	2	DDAVP	B	2
Diabetes insipidus	l	5	DDAVP	A	5
	m	5	DDAVP	A	-
	n	16	LVP, DDAVP	D	16
Healthy volunteers (young)	o	3	DDAVP	B	3
	p	6	DDAVP	B	6
	n	10	LVP, DDAVP	D	10
Healthy volunteers (aged)	q	12	LVP	B	12
		114			80

Authors: a. Oliveros et al.; b. Jenkins et al.; c Jenkins et al.; d. Koch et al.; e. Timsit Berthier et al.; f. Le Boeuff et al.; g. Blake et al.; h. Tinklenberg et al.; i. Delwaide et al.; j. Gold et al.; k. Weingartner et al.; l. Gilot et al.; m. Waggoner et al.; n. Laczi et al.; o. Anderson et al.; p. Gold et al.; q. Legros et al.

Design: A. Open pilot study; B. Double blind, placebo controlled study; C. Singleblind 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 correlate with levels of neurophysins-1 in the blood. Effects were also found in senile demented patients (average age 80 years; Delwaide et al. 1980):one administration of LVP improved the performance of 9 out of 10 patients. Interestingly, the peptide effect was still present after 48 hours. Another group of investigators reported that some of their patients, suffering from Alzheimer dementia, did improve after treatment with DDAVP (Weingartner 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 benefical effects in a disease which is characterised by a kind of disordered passive avoidance behavior (automu tilation behavior of children suffering from Lesch Nyhan disease; Anderson et al. 1979). Memory defects in other patients were also effectively treated with LVP, namely in patients which suffered from hereditary diabetes insipidus (Gilot et al. 1980; Laczi, et al. 1981; Waggoner et al. 1978). Interestingly, the hormone oxytocin which in animals has an opposite effect on memory consolidation (Bohus et al. 1978; Wimersma et al. 1980) had a similar effect in humans, in that this peptide accelerated 'forgetting' in normal subjects (females, Ferrier et al., 1980).

Taken together, these vasopressin studies published until now claim that 80 out of 114 subjects benefit from the peptidetreatment (Table II). The question remains how to interprete the differences between studies that do or do not find treatmenteffects. One interpretation of the data is, that some patients may not respond to treatment, due to the fact that there is 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 treatmenteffects arise from the fact that vasopressinstudies differ in a number of important variables:

1) The type of patient (posttraumatic, 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 'a judgement from responsible clinician', relevant or irrelevant tests of 'memory', 'attention' and the like, and complete testbatteries. 5) These tests were usually not in parallel version to enable repeeted testing 6)The design differed between open studies, single- or doubleblind studies, placebo-controlled or cross-over studies (Table II). 7) The vasopressinfragment used, i.e. LVP or DDAVP or DGAVP. This distinction is of importance due to possible antidiuretic sideeffects (DDAVP and LVP) and vascular side effects (LVP). 8) Peptide treatment, dose, frequency, duration, and route of administration (intranasally, intravenously, intramuscularly, etc.).

These differences between the vasopressinstudies may explain some of the inconclusive data obtained until now. In addition, as reported above, our own vasopressinstudy has been inconclusive, in that some patients reported subjective effects after treatment which could not be shown with the psychological tests used. Therefore, research in our institute has been directed at developing a new research methodology to enable a better differentiation between kinds of patients and types of memory disorder. It was a first aim to develop better tests, that would be able to discern between aspects of memory; tests that could be administered in parallel versions, to enable the evaluation of treatment effects. Our second aim was the investigation wether types of patients, types of memory disorder, and severity of symptoms could be objectified by the use of the new testmethodology. The hypothesis was, that we should be able to find whether or not the 'problempoints', 1-6 are of importance in the study of vasopressineffects in memory disorders.

ON MEMORY COMPLAINTS AND MEMORY DISORDERS.

As summarised above, conclusions as to treatmenteffects of vasopressin or its fragments are difficult due to the differences between the studies reported in the literature until now. This may apply especially to the nature of the patient populations to be treated. There are a number of different disorders which can underly memory complaints. (For a review on the neuropsychology of memory, see Newcombe, 1980. See also Dimond, 1981 and Luria 1976). For instance, memory complaints can be the result of an overall decrease in the rate of information processing in the brain (eg. decreased rate of perception, or motor output). Such a patient may complain about his memory, but his true problem may have to do with the fact that people talk to fast, and that other things in everyday life happen too quickly. Another type of memory complaint may be related to a certain type of behavior disorder: Patients having a disorder in the planning of their behavior manifest difficulties in the performance of complex behavioral acts: such a patient complains that he forgot what to do, and how to do it. Other types of memory disturbances have to do with attention (when you cannot focus your attention to the things you have to learn, this attention deficit may show itself as a memory deficit). Still other types of memorydisorders are related to the fact that the patient has a language disorder; that is, he cannot find the words that are necessary to describe what he has in memory.

Table III. Suggested relation between aspects of memory and brain structure.

ASPECT OF MEMORY	IMPORTANT BRAIN STRUCTURE
Consolidation	Thalamus
Retrieval	Frontal cortex
Spatial/temporal memory	Hippocampus
Memory for words	Temporal cortex, left
Memory for faces	Temporal cortex, right
Rate of thinking and working	Brain stem, ascending fibres

That memory complaints can be a manifestation of some very different disorders is further demonstrated by neuropsychological data concerning different brain structures involved in different aspects of memory. Table III summarises some of the known, or suggested relations between 'Aspects of Memory' and 'Brain Structure'. This ofcourse suggests that lesions or dysfunctions in different brain structures may give rise to different kinds of memory defect (Newcombe, Dimond, Luria). The fact that there are several different types of memory disorder is of importance, in the light of a possible specific effect of vasopressin. The animal experiments show that DGAVP may primarily affect the consolidation and retrieval of information (or a process, common to both) (Bohus et al., 1978). It is therefore to be expected that vasopressin has a beneficial effect on certain types of memory disorder and not on others. As has been shown in the preceding paragraph, treatment effects have been investigated in a large number of different pa-

tientgroups; these groups may be homogenous with respect to etiological factors, but heterogenous 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 informationprocessing in the brain, a planningdefect, an attentiondeficit, a languagedisorder, etcetera. 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 summarises a first attempt at differentiating patient groups, and aimed at providing more homogenous groups.

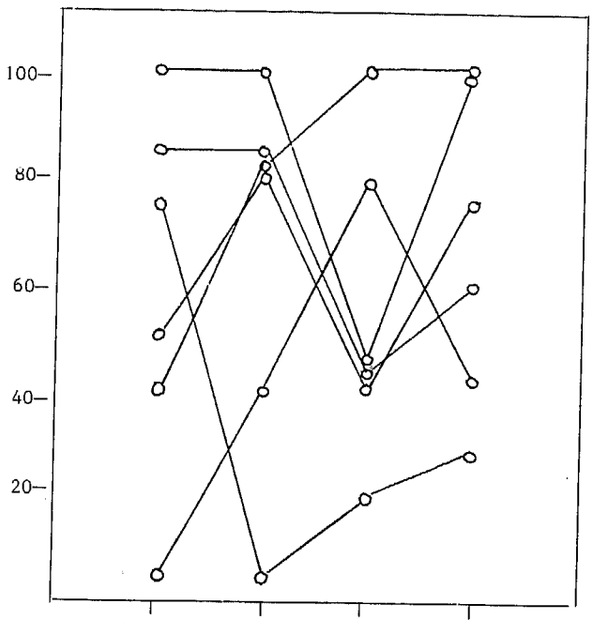
MEMORY DISORDERS IN POSTTRAUMATICS, AND SENILE DEMENTED PATIENTS.

The question whether it is indeed the case that seemingly homogenous patient populations are heterogenous 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 testprocedures 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). (Jolles et al., in preparation). The testbattery was devised so as to gain insight into all relevant cognitive functions which might have to do with (aspects of) memory (that is: auditory memory versus visual memory; consolidation of word memory versus retrievel from word memory; the effect of interference ('distraction'); the rate of perception and working; the planning/organisation of memory; motorfunctions and languagefunctions). 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 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 on gross neurological investigation showed no major signs of aphasia or other cognitive deficits. Patients with stable memory complaints, that is, the memory complaints had not changed for a period of at least six months, were taken; and the period between the accident and the moment of psychological testing varied between 10 months and 4 years. The second group consisted of patients suspected of (pre) seniele dementia. The ages ranged from 55 to 72 years. Gross neurological examination revealed that these patients differed with respect to the degree of deterioration (ranging from early beginning dementia to severe dementia).

All subjects were tested with the neuropsychological testbattery described above. It appeared that the 20 posttraumatic patients tested differed widely in their testprofile. Some relevant data obtained with 7 subjects are summarized in fig. 1. (The data will be published in detail elsewhere). As the figure shows, there are patients which are selectively affecte' in one of the aspects of memory. For instance, some patients show either an inferior auditive memory, or an inferior visual memory or a decreased rate of information processing. Other patients show a more complex pattern of deficits; but the specific combination of deficits differs from patient to patient. The seven subjects depicted are more or less representative for the twenty 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. TESTPROFILE OF TRAUMA CAPITIS PATIENTS.
Performance (% of normal individuals).

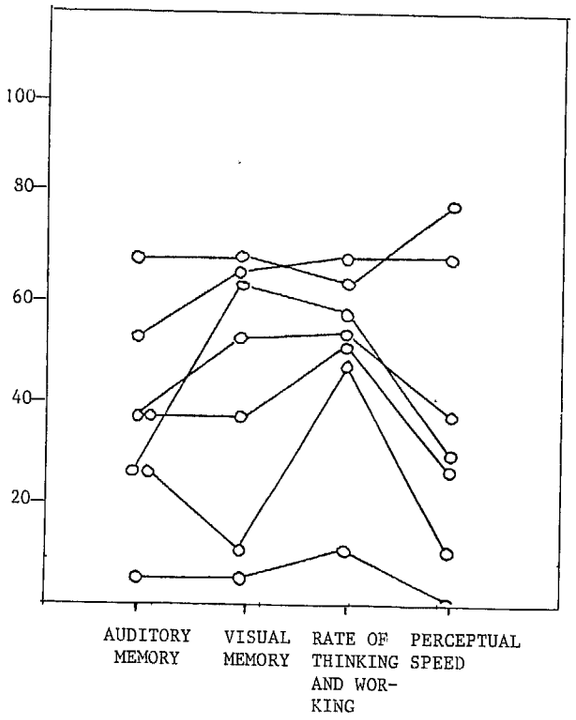


Twenty posttraumatic patients were tested with a testbattery which combines some existing neuropsychological tests with test procedures originally devised in the psychological laboratory and now adapted for use in the clinic. These testseries consist of Luria-Christensen neuropsychological assessment procedure; the Bentontest for recognition and recall of visually presented stimuli; the Oxford test for face recognition; the Symbol Digits Substitution test; the Stroop interference test; Recall of words triplets according to Brown Peterson; Fifteen word learning test in direct and delayed recall and delayed recognition; Memory comparison test (digits/letters and letters/letters) based upon the additive factor method of Sternberg; Lexical decisiontask, 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 wordlearningtest; 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 temporo-parieto-occipital region in the

right hemisphere. Another patient, primarily affected in auditory (word) memory has had a surgery involving the left temporal lobe. The third patient, primarily characterised by a decreased rate of perception and working, evidenced neurological signs of a brainstem contusion. In conclusion, the data indicate that the group of 'posttraumatic amnesics' is very heterogenous 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).



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 porcedure).

The other 7 patients as a rule were slower then normal. There were differences between these patients in the neuropsychological testprofile, as indicated for 4 tests 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. As 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 amnesics' or senile demented patients can be heterogenous 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 antiamnesic 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. 'posttraumatics' or 'Alzheimers'), 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 vasopressineffects. Some data from animal research support this notion, as some researchers found that vasopressin loses its effect when certain relevant brainstructures are leasioned (Van Wimersma Greidanus 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 testing 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 the rat may relate to the consolidation and retrieval of information, or a process common to both (van Ree et al., 1978; Rigter and Crabbe, 1979; de Wied, 1980). Therefore, patientgroups with a similar disorder could preferably be used in the clinical trials. In addition, the relative longtermeffects 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 DGAVP in which these notions are tested.

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