Vasopressin and related peptides

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VASOPRESSIN AND RELATED PEPTIDES: ANIMAL AND HUMAN STUDIES

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Abstract

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In animals, vasopressin and related peptides are present in specific neuronal pathways in the brain and modulate brain processes. It has been suggested that in particular memory processes, including consolidation and retrieval, short and long term memories are facilitated by vasopressin. Evidence has been presented that endogenous vasopressin is involved in these processes. But also other effects of these peptides e.g. an attenuation of acquisition of heroin self-administration have been reported. Vasopressin and related peptides have been administered to humans in a number of studies including volunteers and various patient populations with and without complaints about memory. Beneficial effects on several aspects of memory, learning, attention and concentration have been found, but not in all studies. Patients with severe deficits seem to benefit less from the peptide treatment. This may be related to the amount of brain damage. Beneficial effects of vasopressin treatment have been reported in schizophrenics and heroin addicts. In addition effects on social behavior, energy and mood of certain patients have been noted. The target patient population for vasopressin neuropeptide is thus not yet well defined. With respect to cognitive disorders, sophisticated neuropsychological test procedures, including information-processing tasks, may contribute to define such a patient population. These tasks may also be applied for treatment evaluation. It should however be kept in mind that other interesting influences of vasopressin e.g. on social behavior, mood and addictive behavior, may also appear of clinical significance. Future studies in humans may yield more detailed information in this respect. Desglycinamide (Arg^8)-vasopressin or the recently discovered potent fragments of vasopressin may be recommended for these studies, because these peptides are practically devoid of the peripheral "side" effects on water homeostasis and blood pressure accompanying treatment with vasopressin or desamino-(D-Arg^8)vasopressin (DDAVP).

Keywords: vasopressin, animals, humans, cognition, memory.

Introduction

The hormone vasopressin is synthesized in nerve cell bodies in hypothalamic nuclei (nucleus paraventricularis and nucleus supraopticus) and transported via the axons of these nerves to the posterior pituitary, where the hormone is stored. Specific stimuli evoked by regulatory mechanisms in the body, including the brain, can lead to increased activity along the axons, resulting in secretion of vasopressin into the blood stream. Through this transport medium, vasopressin reaches its peripheral and possibly its central target sites, where it exerts specific effects (e.g. antidiuretic, blood pressure increasing and behavioral effects).

Vasopressin is also present in distinct neuronal pathways in the brain (Buijs et al., 1983). The cell bodies of these neurons in the rat are located in the nucleus suprachiasmaticus, the nucleus paraventricularis, the bed nucleus of the stria terminalis and others. These neurons terminate widespread in the brain; terminals are present e.g. in areas of the limbic system, hypothalamus, brain stem and spinal cord. Vasopressin can be released from these terminals, and acts as neurotransmitter or neurohormone. The anatomical data support the initial effects of vasopressin, which were originally evidenced from behavioral effects of this hormone (De Wied, 1965).

A lot of evidence is available to date, originating e.g. from behavioral, biochemical, and electrophysiological experiments in various animal species (for references see Van Ree et al., 1978; Van Wimersma Greidanus et al., 1983, Versteeg, 1983), indicating that vasopressin and related neuropeptides affect and modulate brain processes. Although it is impossible to place all these effects into one conception concerning the mode of vasopressin action, the attempt to label some of the behavioral effects as an action on learning and memory processes has stimulated both animal and human investigations. However, it should be kept in mind that the concepts of learning and memory originating from animal and human studies are not identical and exchangeable and neither are the various other concepts from different disciplines in this respect. This hampers the discussion about this matter. Nevertheless, this survey endeavours to summarize the effects of vasopressin and related peptides in animals and humans, focussing on learning and memory processes in particular.

Synopsis of animal studies

Arguments in favor of an influence of vasopressin neuropeptides on memory processes in rats stem from observations on aversively motivated behavior in particular (for references see Van Ree et al., 1978; Van Wimersma Greidanus et al., 1983; De Wied, 1984). These peptides induce a long lasting resistance to extinction of one and two way active avoidance behavior, that persists beyond the actual presence of the peptide in the body. The time of administration of vasopressin is critically related to task, in that the peptide is especially active when administered in the period of some hours before to some hours after the behavioral procedure (Bohus et al., 1972). Memory processes involve consolidation and retrieval of acquired information. These aspects of memory have been experimentally defined using the passive avoidance behavioral test procedure, a simple "step through" apparatus, which consists of a dark box to which an illuminated platform is attached. The dark environment is preferred by the rat over the platform. The learning trial consists of an unpleasant experience in the dark box (electric footshocks of short duration). Rats are tested for retention e.g. 24 h after the learning trial. Consolidation of the information takes place within a few hours after the learning trial, while retrieval of information is needed during the retention test. Vasopressin neuropeptides facilitate retrieval when administered both after the learning and before the retention trial, suggesting that consolidation as well as retrieval processes are stimulated by these peptides. Although not all investigators found similar effects, recent experiments indicate that this may be due to the conditions of the experimental procedure. Acquisition of avoidance behavior is improved by vasopressin neuropeptides, but only when the rate of acquisition is low, suggesting that under certain conditions learning is affected by these peptides.

Prevention and reversal of retrograde amnesia by vasopressin neuropeptides also favors the memory hypothesis. The passive avoidance behavioral test has been employed and amnesia was induced by CO_2-inhalation, electro-convulsive shock or pentylenetetrazol, but also puromycin-induced retrograde amnesia for a maze-learning task in mice has been studied to explore the effects of vasopressin neuropeptides. Besides, retrograde amnesia can be induced by disrupting circadian organization of rats by changing the day-night cycle, resulting in an attenuated retrieval of recently acquired information (Fekete et al., 1985). This behavioral deficit can be restored by vasopressin neuropeptides. The amnesia studies generally point to an effect of these peptides on retrieval processes.

The influence of vasopressin neuropeptides is not restricted to aversively motivated behavior. Peptide effects have been reported on food and sexually motivated behavior. How-

ever, interpretation of these observations within the scope of the memory hypothesis has been questioned. Recently, we have studied the vasopressin action using the hole board food search task as developed by Oades, in which hungry rats can search for 4 food pellets consistently placed in 4 out of 16 holes (Oades and Isaacson, 1978). The data allow to distinguish between learning, working and reference memories and the strategy of the rat to obtain the food pellets. A vasopressin neuropeptide (DGAVP) facilitated learning, working (comparable to short term) and reference (comparable to long term) memories, but did not affect the strategy of the rats (Gaffori et al., in preparation). Vasopressin may have in addition a special effect on certain rewarded behaviors. Vasopressin neuropeptides reduce acquisition of heroin self-administration in rats and the electrical selfstimulation elicited from the lateral hypothalamus or the ventral tegmental area. Moreover, vasopressin treated rats were slower in reaching the learning criteria using a continuously reinforced schedule. However, although the reviewed animal data certainly are consistent with the memory hypothesis, other explanations for the action of vasopressin are possible as well and have indeed been suggested, like an effect on arousal mediated processes (Messing and Sparber, 1984; Sahgal, 1984).

Vasopressin in the body has been implicated in the mechanisms underlying memory processes as tested with the mentioned behavioral procedures. Removal of the posterior pituitary results in facilitated extinction of active avoidance behavior, which behavioral deficit can be corrected by treatment with vasopressin. In addition a homozygous variant of the Brattleboro strain, lacking the ability to synthesize vasopressin, shows deficits in the active and passive avoidance behaviors, which are restored by treatment with vasopressin neuropeptides. Similar findings have recently been observed in the hole board food search task (Gaffori et al., unpublished data). Temporary bio-inactivation of vasopressin by injecting vasopressin antiserum into the brain ventricle attenuates both consolidation and retrieval as assessed with the passive avoidance behavioral test. Intravenous administration of the antiserum is not effective in this respect, suggesting that vasopressin in the brain rather than in the periphery is important for these effects. This notion is supported by the findings showing that the dosage of the peptides needed to elicit the behavioral effects is much lower after central than after peripheral administration and that central administration of vasopressin antagonists, which does not interfere with the peripheral effects of vasopressin, effectively antagonized the behavioral effects of vasopressin neuropeptides injected either centrally or peripherally (De Wied et al., 1984).

Concerning the site of vasopressin action in the brain with respect to memory processes, lesion studies point to the importance of certain limbic areas including the septal region and the hippocampus. Microinjection of picogram amounts of vasopressin into these structures and the dorsal raphe nucleus mimics the effect of peripherally administered vasopressin on consolidation, while local injection of vasopressin-antiserum induces an opposite effect. Destruction of the ceruleo-telencephalic noradrenaline system with 6-hydroxydopamine prevents the facilitatory effect of vasopressin on consolidation, but not on retrieval processes. In addition biochemical studies have shown that vasopressin modulates monoaminergic neuotransmission. Thus, vasopressin may exert its memory effects via an interaction with catecholamine transmission and the lesion studies indicate that the vasopressin memory effects are absent when certain brain structures are damaged.

Besides behavioral effects, vasopressin (AVP) has antidiuretic and blood pressure increasing effects. Peptides have been synthesized in order to dissociate these effects from each other. DDAVP (desamino-(D-Arg^{8})-vasopressin) induces antidiuretic activity, hardly changes the blood pressure, and facilitates memory processes, albeit with a somewhat lower potency than vasopressin. DGAVP (desglycinamide-(Arg^{8})-vasopressin) is practically devoid of the antidiuretic and blood pressure increasing effect of vasopressin, but is nearly as potent as vasopressin in facilitating memory processes. This dissociation is even more pronounced in the recently discovered peptides, probably generated by brain enzymes in vivo from vasopressin e.a. [pGlu^{4},Cyt^{6}]AVP-(4-9), [pGlu^{4},Cyt^{6}]AVP-(4-8), [Cyt^{6}]AVP-(5-9), [Cyt^{6}] AVP-(4-8) (Burbach et al., 1983). These peptides potently mimic the effects of vasopressin on memory consolidation and retrieval and on experimentally induced amnesia. Some evidence is available that these various peptides may selectively facilitate consolidation and retrieval processes (Gaffori et al., submitted).

Human studies

Vasopressin and related peptides have been applied to humans in many studies, involving volunteers and patients with various disorders including memory disturbances. A summary of these studies is presented in Table 1 (for references and details see Jolles, 1983, 1985; Legros and Lancranjan, 1984). The studies are quite different in a number of aspects, which will briefly be discussed.

Table 1

Human studies with vasopressin-related peptides

	NUMBER OF STUDIES	POSITIVE TREATMENT EFFECT	NUMBER OF SUBJECTS TREATED WITH VASOPRESSIN
PATIENTS			
Brain trauma	14	8	103
Alcoholics	11	4	48
Elderly/dementia	13	7	135
Diabetes insipidus	6	6	58
Children with learning/attention disorders	6	4	62
Depression	6	5	22
Psychosis	3	3	112
Addiction	3	3	24
Others	4	2	6
Total	66	42	570
VOLUNTEERS	15	13	319

References: Eisenberg et al., 1984; Fehm- Wolfsdorf et al., 1983; Fraenkel et al., 1983; Jensen, 1980; Legros et al., 1983; Lerer et al., 1983; Posmurova et al., 1983; Reichert and Blass, 1982; personal communications of Beckwitz, Eisenberg, Hijman, Jolles, Laczi, Fehm-Wolfsdorf and Wit; for other references see Jolles, 1983; 1985; Legros and Lancranjan, 1984;

Type of patients

Because patients suffering from a post-traumatic amnesia, chronic alcoholism and dementia (senile dementia, multi-infarct dementia, dementia in Parkinsonism patients) frequently complain about memory problems, these patients have been included in most of the human studies focussing on memory effects of vasopressin. In addition, elderly people have been studied, since a decrease of neurophysin blood levels beyond the age of 50 has been found. When vasopressin has a physiological role in modulating learning and memory processes in humans, untreated patients suffering from diabetes insipidus may have problems with their

learning and memory abilities and could benefit from treatment with vasopressin neuropeptides. Indeed, diabetes insipidus patients scored lower on certain tasks aimed to measure attention and short and long term memory, but this was observed only in patients with the congenital variant of this disease and not in patients with acquired diabetes insipidus (Laczi et al., in preparation). Some studies with children with learning disorders have been carried out. Vasopressin neuropeptides have also been applied to psychiatric patients, included patients suffering from schizophrenic psychosis and depression, and heroin addicts.

It is hardly conceivable that in all these categories of patients the memory disturbances, if present, are similar. Indeed, psychological testing of patients suffering from e.g. posttraumatic amnesia and senile dementia have revealed that marked differences are present between these groups of patients, but also within one category (Jolles, 1983, 1985). Moreover, memory complaints not only accompany different types of diseases, but the brain processes underlying these complaints may be quite different. A memory disorder may be due to disturbances in memory processes or secondary to other disorders, like a decrease of the rate of information processing, decreased attention, or a disorder in the behavioral organization or planning. This complicates the studies of vasopressin in humans, since the variation between subjects may mask the treatment effects. Thus, it may be advised to select for future studies patients with a certain homogenity with respect to the disorders underlying their memory complaints as revealed from sophisticated psychological testing, rather than applying the diagnostic classification used sofar. In addition, the severity of the symptoms and the degree of brain damage may be important aspects, as will be discussed later.

Psychological tests

Various psychometric tests have been used to gather information about the memory disturbances of the patients and to evaluate treatment effects. Since the tests are generally applied several times to the same person, the availability of parallel versions seems a condition sine qua non, in particular when another than a placebo-parallel design is followed. This requirement has not been met in all studies. The use of quite different tests hampers the comparison of the outcome of the various studies. Most of the applied tests measure performance rather than the disturbed aspect of cognitive dysfunctions. Recently, test procedures based on information processing models (e.g. the Sternberg Memory Comparison task) have been applied (Nebes et al., 1984; among others). This test allows to discriminate between effects on the speed of perceptual and motor processes and those on memory comparison. A combination of the psychometric, the information processing, and the behavioral neurology approach may be fruitful in assessment of cognitive disorders and to evaluate treatment effects (Jolles, 1985).

Another problem arises from the human studies with vasopressin neuropeptides; the subjective versus the objective effects of treatment. Patients sometimes judged that vasopressin treatment led to beneficial effects with respect to memory complaints, but the outcome of the psychological test procedures did not support these subjective feelings. This may be related to the fact that some patients incorrectly label their complaints as memory disturbances. It may also be that the applied test procedures are not dealing with the complaints of the patients or that the effects of vasopressin are not strong enough to produce significant changes in the psychological tests.

Treatment variables

The various aspects related to the treatment markedly differ among the studies. The design of the studies was open or blind, cross-over or placebo-parallel. The peptides were administered intranasally (most frequently used route), orally or intramuscularly once or three times a day for 1 to 14 days. For a more general medical use of these peptides, of particular interest is the probably oral effectiveness of the peptides. However, only DGAVP has been administered via the oral route in two studies with brain trauma patients and in one with children (Jolles et al., Wit et al., unpublished data); in addition the peptide was sublingually administered to heroin addicts (Fraenkel et al., 1983). That these peptides may be effective via the oral route is supported by animal data showing that this

administration leads to similar effects as subcutaneous treatment (Van Ree, 1982). Besides pitressin in the earliers studies with psychotic patients, 4 different vasopressin congeners have been used i.c. AVP, LVP, DDAVP and DGAVP. The peptides AVP and LVP induce cardiovascular changes and an antidiuretic action, while DDAVP elicits an antidiuretic effect. These effects hamper the "double-blind" character of studies and may interfere with the expected effects on brain function. The peptides DGAVP seems to be devoid of these peripheral side effects (Laczi et al., 1983) and may therefore be recommended for human studies. Although beneficial effects have been reported following a single administration, which parallels the effects observed in animal experiments, others have found that the improvement started after 4 - 5 days. Long term effects of the peptides have been described. This questions the use of a cross-over design without wash-out period.

Vasopressin effects in humans

It seems quite difficult to define a common denomination of the effects of vasopressin treatment as reported in the various studies. Beforehand, it should be mentioned that there are a number of studies showing no treatment effects of vasopressin. This may be related to the variables discussed in the preceding section e.c. the type of patients, the applied psychopharmacological tests and the treatment variables. It is worthwhile to mention that treatment effects have been observed in 13 out of the 15 studies with volunteers. These effects have been described as facilitation of learning, memory, attention and concentration (Table 2). In most of the categories of patients beneficial effects on memory functions, particularly retrieval processes, have been reported, although not in all studies. In the schizophrenic patients and addicts, memory functions were not evaluated. Concerning the vasopressin-induced enhancement of memory processes, different underlying mechanisms have been proposed. In general, two actions can be distinguished: a diffuse non-specific activating action and a specific action on certain aspects of memory and related processes. However, both actions may be present as is suggested by the results of a recent study by Nebes et al. (1984), showing that the slope as well as the interception in a memory comparison task are changed by DDAVP treatment, indicating specific memory and "non-specific" effects. These authors conclude that both short term and long term memories, but not semantic memory is improved by DDAVP to the same degree in young and old volunteers. That short term and long term memory may be affected is supported by the data of a series of studies by Laczi and coworkers (1983 and unpublished data). A number of investigators have suggested that vasopressin neuropeptides shorten the reaction time of the patients, due to a non-specific action on the rate of information processing resulting in an increased efficiency in the organization of memory. Others have proposed that the facilitation of memory is due to an enhanced attention and concentration of the patients. More extensive and detailed studies are needed before definite conclusions can be made regarding the underlying mechanism of vasopressin action in particular with respect to memory functions.

A number of studies have shown that attention and concentration of patients and volunteers are improved by vasopressin treatment. Improvement of learning has been observed in various patients and volunteers. Social behavior of some patients suffering from post-traumatic amnesia, dementia and schizophrenia increased by vasopressin treatment. Schizophrenic patients improved clinically with respect to negative symptoms and the factor anergia (emotional withdrawal, motor retardation, blunted or inappropriate affect) These negative symptoms are, generally, rather resistant to neuroleptic treatment. An increase in energy, activity and mood has been reported in schizophrenics. Positive effects on mood and energy have also been reported in patients with primary affective disorders and in demented and brain trauma patients, in addition to an enhancement of cognitive functions. A facilitation of the methadone detoxification and a decreased intake of heroin and cocaine have been reported in heroin addicts treated with vasopressin (Fraenkel et al., 1983). Summarizing, vasopressin may stimulate processes related to learning, memory, attention and concentration in patients and volunteers; the peptide may beneficially affect post-traumatic amnesia, negative symptoms of schizophrenia and addictive behavior of heroin dependent subjects, elevate mood and energy in various patients and increase social behavior in certain patients. However, it should be stressed that these effects have not consistently been observed in all studies and that the clinical significance of the improvements have been questioned. Moreover, not all beneficial effects are based on appropriate and objective testing.

Table 2

Reported beneficial effects of vasopressin neuropeptides

PATIENTS	LEARNING	MEMORY	ATTENTION CONCENTRATION	SOCIAL BEHAVIOR	MOOD ENERGY	REMARKS
Brain trauma		+	+	+	+	light > severe especial rate of retrieval/information processing
Alcoholics	+	+	+			mild > severe
Elderly/dementia	+	+	+	+	+	mild > severe
Diabetes insipidus		+			+	
Depression	+	+			+	moderate > severe
Schizophrenia				+	+	improvement of anergia and negative symptoms
Children with learning/ attention disorders	+	+				
Addiction						decreased intake heroin and cocaine
Others		+				
VOLUNTEERS	+	+	+			

In general it has been reported that patients with severe deficits respond less favourable to vasopressin than patients with mild symptomatology. This has been observed in patients suffering from brain trauma, chronic alcoholism, dementia and affective disorders (Table 2). Thus, patients with more serious head injuries, patients suffering from Korsakoff's syndrome or Alzheimer's disease or severely depressed patients hardly responded to vasopressin treatment. This may be related to the severity of the symptoms or to the degree of brain damage. This latter seems reasonable when taken into consideration that in animals vasopressin effects on memory processes can hardly been evoked after specific brain lesions. Thus, a lack of effect of vasopressin may be due to lesions in the brain areas on which the peptide can be expected to act. Possibly, vasopressin may be particularly effective in patients with low levels of endogenous peptide. In that case treatment with vasopressin can be regarded as a substitution therapy. Decreased levels of neurophysin (the vasopressin transport protein) have been found in the blood of men beyond the age of 50. Vasopressin levels in cerebrospinal fluid (CSF) were not changed with age and in patients with multi-infarct amnesia or with Alzheimer's disease (see Legros and Lancranjan, 1984). A decreased CSF level of vasopressin has been reported in depressed patients as compared to control subjects and manic patients, while high levels were found in amnesic patients as compared to non-amnesic patients. Although a slight decrease of vasopressin levels in certain brain areas has been found in patients with Alzheimer's disease, the levels did not significantly differ from those of controls matched for age. The size of vasopressin cell profiles in the nucleus supraopticus and the nucleus paraventricularis of post-mortem brain showed little change with age, and was not altered in patients with Alzheimer's disease; the highest value was found in the age group of 80 - 100 years (Swaab et al., 1985). Interestingly, in the suprachiasmatic nucleus a marked decrease in the number of vasopressin cells was observed in 80 - 100 years old patients, and this decrease was even more pronounced in patients with Alzheimer's disease. This suggests that distur-

bances in vasopressin systems in senescence and in Alzheimer's disease are not general but restricted to certain specific pathways. The data yet available about vasopressin levels in CSF and brain are however not sufficient to draw conclusions with respect to the relation between these levels and the effectiveness of vasopressin.

An important aspect is the clinical significance of the vasopressin effects in humans. Most studies in volunteers have revealed effects of peptide treatment on processes such as learning, memory, attention and concentration, but the studies in patients have shown less consistent results. This may be related to the type of patients and the degree of brain damage, as discussed before. Since patients with mild deficits responded particularly to peptide treatment, vasopressin neuropeptides may be recommended for patients with light brain trauma (e.g. concussion), elderly people with mild senescent forgetfulness, patients with very early dementia and depressed patients with mild to moderate symptomatology. In addition, beneficial effects of vasopressin have been reported in schizophrenia, especially on the neuroleptic-resistant negative symptomatology, in heroin addicts and in children with learning and attention disorders. These findings need further exploration, before these patients can be regarded as a target population for vasopressin neuropeptides. Also the reported beneficial influence on social behavior, mood and energy is worthwhile to study in more detail.

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