Vasopressin and human behaviour

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Vasopressin and Human Behavior

JELLEMER JOLLES

1. Introduction

Peptides related to the pituitary hormone vasopressin (VP) have been found to influence aspects of memory processes and learning in laboratory animals (De Wied, 1969; see De Wied, 1983, for review). This finding has led to the suggestion that VP might have a clinical application in the treatment of human memory disorders. Unfortunately, it is not simple to state whether VP has been found effective. This is because clinical studies differ with respect to the nature of the patient population (e.g., brain trauma, alcoholism, depression) and the methods of testing used. In addition, there is wide variation in pharmacological parameters, such as the dose, route, and frequency of peptide administration. Accordingly, some studies report positive effects of VP administration, whereas others are negative (Jolles, 1983*b*).

It is the purpose of this chapter to summarize the studies performed to date and to evaluate the sources of difference. In addition, attention is paid to the nature, type, and context of the cognitive response in order to ascertain whether the peptide might possibly have a specific action on particular cognitive processes and not on others. In this respect, it is important to recognize that there are different aspects of memory and cognition, each of which may have its own underlying neural substrate. Furthermore, disparate memory and cognitive disorders are often characterized by similar complaints. Accordingly, it is not to be expected that VP treatment should be equally effective in each type of impairment.

In order to assist the evaluation of the treatment studies in this respect, an overview is given on the neuropsychology of memory and on methods of testing

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used to assess the effects of VP. Also discussed are animal studies with VP as well as its congeners that are pertinent to this topic.

2. *Vasopressin and Cognitive Disorders*

2.1. *Animal Studies*

VP-like peptides appear to improve the performance of normal rats in a variety of behavioral paradigms that measure the acquisition and retention of aversively motivated behavior (De Wied, 1983). In addition, rats characterized by a decrease or a lack of endogenous VP demonstrate impaired performance on learning and memory tasks. This appeared in three different conditions of VP deficiency: neurohypophysectomy, hereditary defects in the production of VP (the Brattleboro rat), and treatment with VP antiserum (De Wied, 1983; van Wimersma Greidanus *et al.*, 1975). Interestingly, the impaired behavior could be restored by treatment with VP or congeners. Similar effects were found in animals with impaired performance due to treatment with CO_2, electroconvulsive shock, or inhibitors of protein synthesis.

Several arguments suggest that VP has a direct effect on the central nervous system (CNS): It appears that the dosage of the peptide needed to elicit a particular behavioral effect is much lower after central than after peripheral administration. Second, VP fragments devoid of classic-peripheral-endocrine effects ([Lys^8,$dGlyNH_2^9$]VP, dGLVP) still display the behavioral effect. Finally, extensive systems of vasopressinergic fibers have been demonstrated in brain (Buys, 1987), suggesting that central peptidergic mechanisms do exist. However, there is some dispute on the relative importance of peripheral versus central factors in the mechanism of action of the peptide (Gash and Thomas, 1983; De Wied, 1984).

The behavioral effect of VP is longer lasting than that of adrenocorticotropic hormone (ACTH)—days instead of hours. In addition, the peptide improved both the initial acquisition of the information and the retention of the material, whereas no clear-cut effects of ACTH on acquisition have been reported (see De Wied, 1983).

2.2. *Human Studies: General*

The behavioral evidence suggesting that VP enhances memory processes has led to the suggestion that the peptide might have application in the treatment of human memory disorders. Unfortunately, there are many differences between the studies with respect to aspect(s) of memory affected, type of patient, severity of the defects, and methods used for treatment evaluation (see Sections 4 and 5; see also Jolles, 1983*b*, 1986*a*). In addition, the studies differ with respect to the dose, route, frequency, and duration of the peptide administration and experimental design used (e.g., open, blind). Furthermore, different VP congeners have

been used that differ with respect to the peripheral side effects. The porcine pituitary peptide [Lys^8]VP (LVP) has been used in many investigations and has antidiuretic, vasopressor, and behavioral effects; its congener, desamino[D-Arg^8]VP (dDAVP), has antidiuretic and behavioral effects, and [dGlyNH$_2^9$]VP (dGVP) has only the behavioral effects.

2.3. *Head Trauma*

The first clinical trial concerning the antiamnesic effects of VP-like peptides was performed with three patients who suffered from post-traumatic amnesia and with one patient who had chronic alcoholism (Oliveros *et al.*, 1978) (see Table I). LVP was administered by nasal spray. Cognitive functions were not measured systematically, but a clinical impression was that all patients improved after 3 to 9 days. Timist-Berthier *et al.* (1980) treated seven patients with LVP nasal spray and indicated that five patients improved on tests that are supposed to measure attention or short-term visual retention. In addition, clinical improvement was found in activity, motivation, and social adjustment. The peptide effect developed in time and was maximal after weeks/months. Furthermore, all seven memory-disturbed patients had decreased levels of vasopressin-neurophysin (VP-NP), the VP-transport protein. These levels increased to normal in four of five patients who improved after treatment. Drago *et al.* (1981) reported a beneficial effect of treatment with LVP in a brain trauma patient. A study with memory-disturbed trauma patients had been conducted in our Institute (W. M. A. Verhoeven, A. F. M. M. Verdonck, and J. M. van Ree, 1980, unpublished observations), where six brain trauma patients were treated with dGVP nasal spray in a double-blind crossover study. No statistically significant effects were seen on the tests of visual memory and concentration (e.g., Benton visual retention test, Bourdon Wiersma test, and tapping test). However, five of six patients reported a subjective improvement with respect to general activity and general well-being from the fourth day of treatment on. Basal levels of VP and neurophysins in blood and cerebrospinal fluid (CSF) were in the normal range for all patients and did not change as a result of the peptide treatment. Two more recent studies in which dGVP (0.1 or 1.0 mg) was taken orally for 1 month in a placebo-controlled double-blind design have shown that mild but not severe brain trauma patients experienced a positive effect of the treatment. The test parameters affected were especially the rate of memory retrieval and other aspects of the rate of information processing, measured with a Sternberg-type Memory Comparison task (J. Jolles, R. Hijman, A. Elderson, W. M. A. Verhoeven, J. M. van Ree, and D. De Wied, in preparation) (see also Section 5).

Likewise, Legros (personal communication, 1984) reported a clinically significant treatment effect of LVP in four of ten post-traumatic patients (compared with controls). The peptide was mildly effective in three patients and not effective in three others. The four patients whose condition improved had the lowest (i.e., undetectable) levels of VP-NP; interestingly, the treatment with VP appeared to increase these levels.

No treatment effects were seen in patients with more serious head injuries.

TABLE I
Vasopressin Studies in Brain Trauma Patients

Investigators	*N*	Peptide	Dose	Route[a]	Frequency[b]	Duration	Design[c]
Oliveros *et al.* (1978)	3	LVP	11–30 IU	IN	4–5×	1 to several weeks	A
Jenkins *et al.* (1979)	6	dDAVP	4 μg	IM		6 weeks	A
Timsit-Berthier *et al.* (1980)	7	LVP	14 IU	IN	2×	15 days	F
	7	LVP	14 IU	IN	2×	15–30 days	A
W. M. A. Verhoeven, A. F. M. M. Verdonck, J. M. Van Ree, J. Jolles, R. Hyman, A. Elderson, and D. De Wied (unpublished data)	6	dGVP	200 μg	IN	tid	2 weeks	E
Drago *et al.* (1981)	1	LVP	25 IU	IN		2 weeks	E
Jenkins *et al.* (1981)	5	dDAVP	160 μg	IN	4×	1 week	A
Koch-Henriksen *et al.* (1981)	5	LVP	22.5 IU	IN		2 weeks	F
Fewtrell *et al.* (1982)	6	LVP	16 IU	IN		2 weeks	E
Reichert and Blass (1982)	7	LVP	16 IU			6 weeks	F
Jolles *et al.* (in preparation)	8	dGVP	0.1 mg 1.0 mg	PO	1×	4 weeks	E

[a]IM, intramuscular; IN, intranasal; PO, per os (orally).
[b]The frequency of administration per day up to the total amount stated under Dose. If not stated otherwise, frequency is once per day.
[c]A; open study; B; single blind; C; single blind crossover; D; single-blind placebo-controlled within groups/subjects; E, double-blind crossover; F; double-blind placebo-controlled between groups; G; double-blind crossover within groups/subjects.

TABLE II
Vasopressin Studies in Alcoholic Patients[a]

Investigators	*N*	Peptide	Dose	Route	Frequency	Duration	Design
Blake *et al.* (1978)	2	LVP	16 IU	IN	4×	15–21 days	A
LeBoeuf *et al.* (1978)	1	LVP	22.5 IU	IN	3×	14 days	G
Oliveros *et al.* (1978)	1	LVP	11 IU	IN	4×	Several weeks	A
Drago *et al.* (1981)	2	LVP	25 IU	IN		14 days	E
Tinklenberg *et al.* (1981*a*, 1982)	2	dGVP	200 μg	IN	tid	5 days	F
	4	dGVP	10–20 μg	IN	tid	3–8 days	E
Franceschi *et al.* (1982)	6	LVP	15 IU	IN		7 days	E
Jenkins *et al.* (1982)	1	dDAVP	40 μg	IN	4×	1 week	E
Láczi *et al.* (1983*b*)	8	dGVP	80 μg	IN	1×	7 days	F
Peabody *et al.* (1983)	4	dGVP	92 μg	IN	tid	5 days	F
Jennekens *et al.* (1985)	5	dGVP	1 mg	PO	1×	5 days	E

[a]See Table I for details and abbreviations.

TABLE III
Vasopressin Studies in Elderly People and in Senile Dementia

Investigators	*N*	Peptide	Dose	Route	Frequency	Duration	Design
Legros *et al.* (1978)	12	LVP	16 IU	IN	3×	3 days	F
Delwaide *et al.* 91980)	10	LVP	15 IU	IN		Single dose	G
Jensen (1980)	6	LVP	30 IU	IN		1 month	E
Weingartner *et al.* (1981*b*)	7	dDAVP	30–60 μg	IN		Several times	G
Tinklenberg *et al.* (1981*a*, 1982)	1	dGVP	200 μg	IN	tid	5 days	F
	2	dGVP	10–20 μg	IN	tid	3–8 days	E
Durso *et al.* (1982)	14	LVP	16 IU	IN	2×	10 days	F
Franceschi *et al.* (1982)	18	LVP	15 IU	IN		7 days	E
Jenkins *et al.* (1982)	3	dDAVP	40 μg	IN	4×	1 week	E
Ferris *et al.* (1983)	20	LVP	16 IU	IN	2×	7 days	E
Bucht (cited in Legros and Lancranjan, 1984)	11	LVP	15 IU	IN	2×	3 weeks	F
Jennekens *et al.* (1985)	4	dGVP	1 mg	PO		5 days	E
Peabody *et al.* (1985)	5	dGVP	92 μg	IN	tid	5 days	F

[a]See Table I for details and abbreviations.

For instance, no effect was seen after treatment of such patients with low doses of dGVP or LVP (Jenkins *et al.*, 1979); higher doses of dDAVP and dGVP were also ineffective (Jenkins *et al.*, 1981). Several other studies with patients treated with LVP were also negative (Koch-Henriksen *et al.*, 1981; Fewtrell *et al.*, 1982; Reichert and Blass, 1982). Therapeutic efficiency may depend on the extent to which degenerative processes have taken place in the brain: relatively less serious defects seem to benefit more from peptide treatment.

2.4. *Amnesic Syndrome Associated with Chronic Alcoholism*

Oliveros and co-workers (1978) treated an alcoholic patient with LVP and reported a beneficial effect of this peptide. A subsequent investigation by Le Boeuf *et al.*, (1978) reported a similar effect in an alcoholic patient with the amnesic syndrome (see Table II). This patient remembered more and had better concentration, attention, and time orientation after intranasal application of LVP. A more recent study of two alcoholic patients treated according to a double-blind crossover design with LVP also reported a treatment effect (Drago *et al.*, 1981). Peabody *et al.* (1985) gave some preliminary evidence that the peptide might affect the performance on a word-learning task, but Tinklenberg *et al.* (1981*a*, 1982) found no improvement in alcoholic patients treated with dGVP or dDAVP. Apart from the fact that different peptides were used, the duration of treatment was also much shorter in the latter study. Other negative outcomes in severe chronic alcoholics (Korsakoff syndrome) were reported by Blake *et al.* (1978) and Jenkins *et al.* (1982) (see Table III). In addition, Jennekens *et al.* (1985) did not find treatment effects of dGVP administered orally in 1-mg sublingual tablets. The behavioral and cognitive deficits in the five Korsakoff patients treated by these investigators can be regarded as severe. It might be that a serious amnesic syndrome induced by alcohol does not benefit from treatment with VP analogues. This notion is strengthened by recent studies by Láczi *et al.* (1983*b*), who failed to find an effect of dGVP on memory or attentional processes in 14 patients with Korsakoff syndrome. However, positive treatment effects were found on these parameters in a later study with mild alcoholic subjects who had memory deficits but no anamnesic syndrome (Lázci *et al.*, 1983*b*).

2.5. *Aging and Senile Dementia*

Twelve patients (aged 50–64 years) hospitalized with somatic complaints were treated with LVP applied intranasally (Legros *et al.*, 1978). These patients performed better than did control subjects on tests of attention and memory. The same investigators reported later that the scores of one parameter of the Rey memory test correlated with levels of basal neurophysins in the blood (Legros and Gilot, 1979). Effects of LVP were also found in senile demented patients, average age, 80 years (Delwaide *et al.*, 1980); a single administration of LVP improved the performance of 9 of 10 patients on a word-list retention task; these effects were

still present after 48 hr. Others have also reported that single administration of dDAVP can improve the memory for semantic structures (i.e., word memory) in a fluency task in patients suffering from progressive dementia (Weingartner *et al.*, 1981*b*). Ferris (1983) treated 20 patients suffering from mild to moderate dementia with LVP for periods of 7 days in a placebo-controlled crossover study. Consistent, but small, improvements on memory tests were noted. However, in a study specially selecting patients for Alzheimer disease and then treated with LVP, Durso *et al.* (1982) found no effects on test of memory, learning, and visual perception. The only measurable effect concerned an improved performance in a reaction-time test. These investigators concluded that VP might have a nonspecific activating effect (Durso *et al.*, 1982). A similar suggestion was made by Tinkleberg *et al.* (1981*a,b*, 1982), who also investigated the effects of VP analogues on Alzheimer disease. Neither dDAVP nor dGVP had measurable effects on the tests used. An impression was that some patients might experience more energy and less depression, especially those with comparatively mild dysfunctions. These same workers later found some preliminary evidence in favor of a dGVP effect on a word-learning test in senile dementia of Alzheimer type (SDAT) (Peabody *et al.*, 1985).

Interestingly, improved memory was reported in 5 of 11 patients suffering from multi-infarct dementia, treated in a double-blind placebo-controlled design. Social behavior improved in 8 of 11 subjects (Bucht *et al.*, cited in Legros and Lancranjan, 1984). More severely demented multi-infarct and SDAT patients did not benefit from peptide treatment (Franceschi *et al.*, 1982). In addition, dDAVP appeared to be ineffective in another study with three SDAT patients (Jenkins *et al.*, 1982), and Jennekens-Schinkel *et al.* (1985) were unable to obtain treatment effects of 1 mg dGVP administered in sublingual tablets to four patients with mild Alzheimer disease. Intranasal LVP treatment has not been effective on neurological and psychiatric parameters in a double-blind study with parkinsonian patients (Jensen, 1980). Taken together, there is some evidence in favor of the hypothesis that VP treatment may be more effective in patients with senile dementia who have less extensive neural degeneration.

2.6. Depression and Schizophrenia

Several investigators have claimed that the antiamnesic action of VP-like peptides is related to an antidepressant effect. In studies in which patients with endogenous depression and cognitive disorders were treated with dDAVP (Weingartner *et al.*, 1981*a*; Gold *et al.*, 1979) (see Table IV), three of four patients manifested a significant improvement in the level of cognitive functioning. After 4 weeks, they were back at their pretreatment level. In a follow-up study by the same researchers in two depressed patients, dDAVP appeared to counteract the amnesia that is a characteristic side effect of electroconvulsive shock therapy. Others reported that LVP improved memory processes in three depressed patients (Drago *et al.*, 1981). Likewise, Vranckx and co-workers (cited in Legros and Lancranjan, 1984) found a beneficial effect of LVP treatment in moderately

TABLE IV
Vasopressin Studies in Depression and Schizophrenia[a]

Investigators	*N*	Peptide	Dose	Route	Frequency	Duration	Design
Depression							
Gold *et al.*, 1979	4	dDAVP	60–160 μg	IN		3–7 weeks	G
Weingartner *et al.*, 1981*a,b*	2	dDAVP	40–60 μg	IN		3 days	G
						2 weeks	E
Drago *et al.*, 1981	3	LVP	25 IU	IN		Single dose	E
Lerer *et al.*, 1983	9	dDAVP	25 μg	IN			
Psychosis						Several months	A
Forisz, 1952*a,b*	80	Pitressin	10 IU	IM		4 weeks	A
Vranckx *et al.*, 1979	16	LVP	7.5–45 IU	IN	1–6	3 weeks	C
Korsgaard *et al.*, 1981	16	LVP	22.5,67.5 IU	IN	tid		

[a]See Table I for details and abbreviations.

TABLE V
Vasopressin Studies in Other Patients[a]

Investigators	*N*	Peptide	Dose	Route	Frequency	Duration	Design
Diabetes insipidus							
Gilot *et al.* (1980)	5	dDAVP	?	?		3 days	A
Láczi *et al.* (1982)	16	LVP	1.5, 10 IU	IN, IM		Single dose	E
						7 days	
		dDAVP	4,10 μg	IN, IM		7 days	E
Láczi *et al.* (1983*a*)	13	dGVP	3,30 μg	IM		3 days, 3 days	G
		dGVP	80 μg	IN	2×	7 days	G
Waggoner *et al.* (1978)	7	dDAVP		IN	2×	4 months	A
Brain hypoxia							
W. M. A. Verhoeven, A. F. M. M. Verdonck, and J. M. Van Ree (unpublished data)	1	dGVP		IN		2 weeks	E
Fewtrell *et al.* (1982)	1	LVP	16 IU	IN		2 weeks	E
Lesch-Nyhan disease in children							
Anderson *et al.* (1979)	3	dDAVP	40 μg	IN		Single dose	B
Attention and learning disorders in children							
Eisenberg *et al.* (1982)	5	dDAVP	20 μg	IN		3 days	A
	7	dDAVP	20 μg	IN		10 days	E

Cerebrovascular insufficiency W. M. A. Verhoeven, A. F. M. M. Verdonck, and J. M. Van Ree (unpublished data)	1	dGVP	200 μg	IN	tid	2 weeks	E
Brain Surgery W. M. A. Verhoeven, A. F. M. M. Verdonck, and J. M. Van Ree (unpublished data)	1	dGVP	200 μg	IN	tid	2 weeks	E
Encephalitis Koizumi *et al.* (1981)	1	VP	12 USP	IN	3×	2 weeks	G
Hypothalamic disorders Calandra *et al.* (1980)	1	VP	5 IU	IM		2 weeks	A
Severe neurological diseases Jennekens *et al.* (1985)	7	dGVP	1 mg	PO		5 days	E
Detoxification of heroin addicts							
Fraenkel *et al.* (1983)	15	dGVP	1 mg	PO		5–14 days	F
Van Beek-Verbeek *et al.* (1983)	6	dGVP	1 mg	PO		5 days	F
Down syndrome Eisenberg *et al.* (1984)	9	dDAVP	40 μg	IN		10 days	E

[a]See Table I for details and abbreviations.

depressed patients. By contrast, there was no therapeutic action in more severely depressed patients who did not respond to classic pharmacological treatment. Other negative findings are reported by Lerer *et al.* (1983), who tested the effect of single doses of dDAVP on ECT-induced learning deficits in nine patients suffering from major depressive disorder.

Interestingly, VP effects have also been found in schizophrenic patients, especially on those symptoms that are not influenced by neuroleptics, e.g., emotional withdrawal, anergia, and blunted affect.

As early as 1937, Forisz treated chronic schizophrenic patients with intramuscular Pitressin for prolonged periods (Forisz, 1952*a,b*). About 40% of treated patients improved in that after an initial sedative effect lasting 1–2 weeks, positive symptoms of the psychosis reappeared, eventually resulting in a more social and interested attitude. A number of patients could leave the clinic. More recently, in a study of 16 chronic schizophrenic patients (Korsgaard *et al.*, 1981), a decrease in thought disorder was noted, accompanied by an increase in energy and activity (in 6 of the 16 patients). The increase in activity was not of therapeutic value in four patients because they were agitated/aggressive. In a similar study by Vranckx *et al.* (1979), undesirable effects (especially with respect to the BPRS item, excitement) occurred in only a few patients. These investigators reported that LVP in doses of 15 up to 45 IU may have a beneficial effect on emotional withdrawal and blunted affect.

2.7. Other Patients

Memory processes are reported to be improved in diabetes insipidus patients, in open studies with dDAVP (Gilot *et al.*, 1980; Waggoner *et al.*, 1978) (see Table V), and in double-blind studies with LVP, dDAVP, or dGVP applied either intranasally or intramuscularly (Láczi *et al.*, 1982, 1983*a*). The latter group claims that acute intramuscular injection of dGVP improves aspects of short-term memory; that subchronic intranasal administration of dGVP facilitates both short-term and long-term memory. It would thus appear that different aspects of memory can be manipulated by the nature of the peptide and the route of administration.

Several studies have been performed with patients suffering from deep brain lesions of different etiology. Some reports indicate an effect of VP on amnesia caused by herpes simplex encephalitis (Koizumi *et al.*, 1981) and hypothalamic disorders (Calandra *et al.*, 1980). By contrast, no treatment effect was found in cases of brain hypoxia treated with LVP (Fewtrell *et al.*, 1982) or dGVP (W. M. A. Verhoeven, A. F. M. M. Verdonck, and J. M. van Ree, unpublished data), or in a patient suffering from cerebral vascular insufficiency (W.M.A. Verhoeven *et al.*, unpublished data). A subjective improvement after treatment with dGVP was found in one patient suffering from a disorder of semantic and episodic memory after left temporal brain surgery (W.M.A. Verhoeven *et al.*, unpublished data). Negative results were reported by Jennekens-Schinkel *et al.* (1985), who treated seven patients suffering from several severe neurological diseases with 1 mg

dGVP, administered orally in a sublingual tablet. The neurological diagnoses were as follows: post-traumatic encephalopathy, cerebral shotgun lesion, meningitis, paralysis agitans, olivo-ponto-cerebellar syndrome, panhypopituitarism, and aneurysm of the basilar artery with subarachnoid hemorrhage.

A beneficial effect of dGVP has been reported in children suffering from Lesch-Nyhan disease. This disease is characterized by automutilation behavior interpreted as a disorder of passive-avoidance behavior (Anderson *et a.*, 1979). Specific effects of dDAVP on memory retrieval were reported in a study on children suffering from attention and learning disorders (Eisenberg *et al.*, 1984*a*). Negative results were reported by the same investigators (Eisenberg *et al.*, 1984*b*) in a crossover study with dDAVP in nine Down syndrome patients.

Findings suggesting that dGVP might influence the detoxification of heroin addicts were reported by Fraenkel and co-workers. The peptide was administered as a sublingual tablet and reportedly facilitated detoxification by methadone (Fraenkel *et al.*, 1983). Moreover, there was a longer time course of clinic attendance and a higher percentage of successful detoxifications as compared with placebo treatement (van Beek-Verbeek *et al.*, 1983).

2.8. Healthy Volunteers

Volunteers without memory defects have also been found to benefit from treatment with VP analogues (see Table VI). Six healthy young volunteers appeared to have improved word-list rentention after treatment with dDAVP for 2–3 weeks (Weingartner *et al.*, 1981*a*). Similarly, 10 healthy young subjects improved on some tests, which are throught to measure aspects of memory, after LVP or dDAVP (Láczi *et al.*, 1982). Nine patients without a memory deficit also improved in these respects after dGVP (Láczi *et al.*, 1983*a*). In a study in 36 healthy volunteers reported by Posmurova *et al.* (1983), 8 mg dDAVP was administered intramuscularly. These investigators found significant treatment effects with respect to either learning or short-term memory, or both, for tactile stimuli. Medvedev *et al.* (1981) found that a single administration of VP can be effective. This peptide was administered to 20 students, and the data were taken to indicate that VP would specifically improve long-term memory and recall. More recently, Jenkins *et al.* (1982) did not find an effect of dDAVP in healthy subjects treated for 2 weeks. Likewise, negative findings were reported by Fehm-Wolfsdorf *et al.* (1985) in a study of 17 pairs of monozygotic (Mz) twins treated with 10 IU LVP administered intranasally three times before experimental testing (i.e., 48, 24, and 1 hr prior to testing). More recent studies are important in that there was a careful selection of tasks to be used in the treatment evaluation, thereby giving more insight into the nature of the memory processes affected by VP.

Some preliminary evidence has been found in favor of a peptide effect on word-list retention (Fehm-Wolfsdorf *et al.*, 1984). More clear-cut positive results were reported by Beckwith *et al.* (1982), who showed in a series of experiments with information-processing tasks that acute administration of dDAVP enhanced

TABLE VI
Vasopressin Studies in Human Volunteers[a]

Investigators	*N*	Peptide	Dose	Route	Frequency	Duration	Design
Medvedev *et al.* (1981)	20	VP	25–35 μg	IN		Single dose	G
Weingartner *et al.* (1981*a,b*)	6	dDAVP	30–60 μg	IN	tid	2–3 weeks	F
Beckwith *et al.* (1982)	18	dDAVP	60 μg	IN		Single dose	F
Jenkins *et al.* (1982)	7	dDAVP	40 μg	IN	4×	2 weeks	F
Láczi *et al.* (1982)	10	LVP	1, 5, 10 IU	IN, IM		Single dose 7days	E
		dDAVP	4, 10 μg	IN, IM		7 days	E
Beckwith *et al.* (1983)	8	dDAVP	60 μg	IN		Single dose	F
Fehm-Wolfdorf *et al.* (1983)	17	LVP	20 IU	IN		48 hr	F
Láczi *et al.* (1983*a*)	9	dGVP	3, 30 μg	IM		3 days, 3 days	G
		dGVP	80 μg	IN	2×	7 days	G
Posmurová *et al.* (1983)	36	dDAVP	8 μg	IM		Single dose	G
Beckwith *et al.* (1984)	64	dDAVP	60 μg	IN		Single dose	F
Fehm-Wolfdorf *et al.* (1984)	10	LVP	10 IU	IN		Single dose	F
Nebes *et al.* (1984)	48	dDAVP	10–30 μg	IN	tid	8 days	E

[a]See Table I for details and abbreviations.

the learning performance on a concept-shift task. There was no effect on visual memory, anxiety, blood pressure, or heart rate, which excludes a general arousal explanation. These investigators concluded that the peptide influences memory via an action on attentional processes (Beckwith *et al.,* 1982). A similar finding was done with the Sternberg Memory-Scanning task (see Section 5.3; see also Beckwith *et al.,* 1983). In addition, healthy young male adults treated with dDAVP demonstrated better memory for implicational sentences than did control subjects. Interestingly, this treatment had no influence on women given the same memory task, suggesting that dDAVP may have a sexually dimorphic effect on learning and memory (Beckwith *et al.,* 1984). A similar positive effect on the Sternberg Memory-Scanning Task was found by Nebes *et al.* (1984). These investigators studied the effect of dDAVP in 48 healthy volunteers (24 young, 24 elderly) and found peptide effects on memory comparison time and perceptual motor time in short-term memory and retrieval time in long-term memory. Other aspects of memory were unaffected, again pointing toward a specific influence of the peptide.

3. *Cognitive Disorders and Changes in Cerebrospinal Fluid–Vasopressin Levels*

An increasing number of studies report that cerebrospinal fluid (CSF) levels of VP are abnormal in several types of patients suffering from cognitive deficits. Legros (1975) found a decrease in the blood levels of VP–NP beyond the age of 50 years. Moreover, there was a relationship between the circulating basal neurophysins and a psychometric test parameter (item 7 of Rey's PRM). In addition, there was a reduced VP response to the water-deprivation test in old age (Legros and Gilot, 1979; see also Legros and Lancranjan, 1984). More recently, Sundquist *et al.* (1983) found a slight decrease in CSF–VP levels with increasing age in neurological patients. The VP values were significantly higher in patients with cerebrovascular disease, whereas lower CSF–VP values were found in patients with dementia and Parkinson disease. By contrast, VP levels in the spinal fluid of 10 elderly normal subjects, 9 patients with multi-infarct dementia, and 5 patients with SDAT were all in the same range (Legros and Lancranjan, 1984). The absence of decreased VP levels with age was also reported by both Jenkins *et al.* (1981) and Luerssen and Robertson (1980). Augmented peripheral plasma levels of the peptide were found in patients from the age of 70 onward (Frolkis *et al.,* 1982; Kirkland *et al.,* 1984). Similarly, Legros *et al.* (1980) reported a secondary increase in immunoreactive neurophysins in the blood in the same age group. For a critical evaluation of the data on VP levels and aging in relationship to the morphometry of hypothalamic nuclei containing VP cells, see Chapter 17, this volume.

Changes in VP levels have also been found in psychiatric populations characterized by cognitive deficits. Anorexia nervosa patients were characterized by relatively elevated levels of VP in spinal fluid (Gold *et al.,* 1983) whereas oxytocin (OX) levels were depressed in these patients. Vasopressin levels were also elevated in mania, again with OX in the opposite direction (Gold *et al.,* 1983). The

relationship between these changed levels and the cognitive deficits remains to be established, but the findings as such may prove significant.

4. *Evaluation of Clinical Studies*

4.1. *Pharmacological Parameters*

VP studies differ in many respects, including the type of VP used (VP, LVP, dDAVP, dGVP); the dose, route, frequency, and duration of administration; and the type of experimental design used (e.g., open, blind). Some of these parameters are very important, and the results of the different studies must be interpreted accordingly.

4.1.1. *The Nature of the Vasopressin Congener*

LVP has been the most popular type of VP analogue used, followed by the more recently developed dDAVP and dGVP. VP was used in only three studies and Pitressin in one. LVP, VP, and dDAVP have peripheral side effects (antidiuretic/cardiovascular, and antidiuretic, respectively). Several investigators have noted these changes in patients in whom the antiamnesic action of the peptides was found, after both intranasal and intramuscular application of LVP (Forisz, 1952*a,b;* Timsit-Berthier *et al.,* 1980; Láczi *et al.,* 1982) and dDAVP (Tinklenberg *et al.,* 1981*a*). A crucial point concerns the perception by patients of changes taking place in their bodies. How do we exclude the possibility that the reported effects are secondary to a peripheral effect? This applies to studies in patients with diabetes insipidus (DI) in particular (Gilot *et al.,* 1979; Láczi *et al.,* 1982, 1983*a*), as cognitive functioning in such a patient may change as a result of normalized water retention. Furthermore, "double-blind" may not mean very much when the patient is able to discern placebo treatment from active treatment by the perception of bodily symptoms. Therefore, dGVP, which has virtually no peripheral side effects, may be the agent of choice in studies on behavioral actions of VP-like peptides.

Interestingly, no cognitive deficits were found in eight of nine young patients suffering from DI who had been treated with antidiuretic medication from birth on. The patient with objectified deficits had suffered from a birth trauma. These data were obtained with an extensive neuropsychological investigation as described in Section 4.2.3. It may be that the normal cognitive functioning in these DI patients has to do with the normalized water retention (R. Hijman, J. M. Wit, and J. Jolles, 1985, unpublished observations).

4.1.2. *Route of Administration*

Intranasal application of the peptide is the most frequently used route, although some investigators have also used the intramuscular route. The premise is that the peptide reaches its site of action in the CNS more efficiently via the

intranasal route, but unfortunately there is no evidence that this is indeed the case. On the contrary, Ang and Jenkins (1982) showed that there is a blood–brain barrier (BBB) for VP, dDAVP, and dGVP and that intranasal administration provides no increased access to the CNS. This indicates that we are seriously restricted in the therapeutic use of VP and analogues in humans. Animal work suggests that the amount of VP needed to elicit behavioral effects is 20–40 times greater after intracerebroventricular administration than after application in specific brain nuclei, and another 100–1000 times more peptide is needed after peripheral administration (De Wied, 1976). This creates a problem in clinical trials with VP in which a large amount of VP has to be administered peripherally to reach the CNS, yet the administration of larger amounts of LVP or dDAVP is contraindicated due to peripheral side effects.

4.1.3. Duration of Administration

Some reports suggest that a single administration of VP or dDAVP can induce a measurable antiamnesic effect (Medvedev *et al.*, 1981; Láczi *et al.*, 1982; Anderson *et al.*, 1979; Delwaide *et al.*, 1980) and that these effects are still present after 48 hr (Delwaide *et al.*, 1980), hence the parallel with animal experiments in which acute effects of the peptide have been reported (De Wied, 1976). On the other hand, it is our impression that patients treated with dGVP (intranasally) report a subjective improvement 4–5 days after the start of treatment (W. M. A. Verhoeven, A. F. M. M. Verdonck, and J. M. van Ree, unpublished data). Others have similarly reported that effects of VP develop in time (e.g., Timsit-Berthier *et al.*, 1980) and can be manifested after the end of the period of active peptide treatment. This was one of the important findings in the animal research, in that the behavioral effects of LVP or dGVP can be monitored for many days after administration. These findings have several implications. First, a serious question can be raised with respect to the use of crossover studies without a washout period, as peptide effects may still be present during the post-VP placebo period. Second, a treatment evaluation must be performed some time after treatment termination, to assess the effects of longer duration. Third, brief treatment periods (e.g., less than a week) may be too short for a relevant effect to develop. It is likely that the effects seen after a single administration were dependent on the moment of assessment, as has been found in animal experiments (De Wied, 1971).

4.2. Neuropsychological Parameters

Many different types of patient have been used in the study of the treatment effects of VP-like peptides. A better understanding of both the type of the cognitive changes exerted by VP appears to be necessary to determine those patient populations in which the peptide may be therapeutically active. A brief survey of the relevant neuropsychological parameters may serve to illustrate this point: a more thorough elaboration on this matter may be found in Jolles (1985, 1986*b*).

4.2.1. Memory Processes and the Neuropsychology of Memory

Memory complaints accompany many types of disease. As the brain processes underlying these complaints can be very different (reviewed by Luria, 1976; Newcombe, 1980; Russell, 1981). It is necessary to discriminate relatively true memory disorders from those that are secondary to another disorder. For instance, memory complaints can result from general slowness or from a planning disorder. Alternatively, attentional deficits, language deficits, or concentrational deficiencies can be translated as a memory complaint. Finally, motivation processes and the state of the activation or arousal of the organism can also play a role in a deficient memory performance. This has also been found in animal experiments (see De Wied and Jolles, 1983; Jolles, 1983*a*).

Careful neuropsychological investigation has demonstrated a relationship between the types of memory disorders and the underlying cerebral substrate. A relatively true memory deficit, specific for a particular type of material (e.g., auditory–verbal), is taken to be due to dysfunction of posterior neocortical structures. The brain structure that is primarily involved in memory retrieval is the frontal cortex; consolidation deficits seem to relate to dysfunctions in deep brain structures, notably thalamus and hippocampus. The hippocampus seems to be specifically involved in spatio/temporal memory (O'Keefe and Nadel, 1978) and in handling novelty. There is much evidence to suggest that a disconnection between the different structures in the pathways between hippocampal, diencephalic nuclei and neocortical structures can give rise to an amnesic syndrome. However, the specific features of this amnesic syndrome depend on the nature and location of the lesion (Lhermitte and Signoret, 1972; Newcombe, 1980). In addition to these neocortical and limbic structures, structures in the brain stem appear to play a role in memory processes. Brain stem nuclei, the reticular formation, specific thalamic nuclei and ascending fibers to basal forebrain and neocortex seem to be involved in the rate of information processing (Luria, 1976, 1980). According to Squire and Davis (1981), many memory-active drugs act primarily or exclusively on this extrinsic system (see also Jolles, 1983*a*).

It is important to discern the aspects of higher cognitive learning and memory described from motor learning or skill learning. It appears that their cerebral substrate is different (McGeer *et al.*, 1978). The brain areas involved in skill learning are the cerebellum and pathways to and from the basal ganglia and motor areas of the neocortex. This is why the aspects of human learning and memory that are usually studied in human psychopharmacology are different from those studied in nonhuman psychopharmacology. The relative importance of motor learning is much greater in animal studies, because the animal is required to perform an act, such as climbing a pole or stepping through a door. By contrast, studies in human subjects rely much more on higher cognitive processes, such as learning and retention of words or complex visual scenes.

In conclusion, several different memory processes exist; these different aspects of memory depend on a different cerebral substrate. It is therefore important to specify the action of drugs in terms of an action on different aspects of memory and cognition.

4.2.2. *Nature of the Patient Population*

It is not to be expected that one drug will have a beneficial effect in all neurological and psychiatric disorders in which memory processes are affected. Nevertheless, many clinical studies with VP have been performed under this false premise. The remainder of this section is concerned with a brief description of the similarities and differences among four types of subjects that have been used frequently in clinical studies with VP.

Aging. Elderly subjects are characterized by an age-associated decline in all cognitive functions tested (intellectual functioning, memory, language functions, problem solving, and perception). Well-stored skills and knowledge are preserved until old age, but there is increasing inefficiency in the consolidation of new information (mild senescent forgetfulness), which may relate partly to decreased speed of information processing and partly to a planning deficit (see Jolles, 1986*b*).

Senile Dementia. The pattern of cognitive deficits in SDAT appears to be qualitatively similar to that of normal aging (Jolles and Hijman, 1983; Jolles, 1986*b*); the same applies to the similarities between the presenile and the senile form of SDAT (Sulkava and Amberla, 1981). The early stages of SDAT are difficult to discern from depression, although differences with respect to the nature of the memory deficits appear to be present (Jolles, 1985). There is a clearly definable course of progression in SDAT; such symptoms as general lowering of activity and deterioration of short-term memory and awareness appear before apraxic, aphasic, and agnosic deficits. Vascular types of dementia (multi-infarct dementia) are characterized much more by focal deficits relating to the location of the infact(s) (see Jolles, 1985, 1986*b*).

The relative lack of VP effects in the moderate and severe stages of dementia, in contrast to mild dementia (Section 2) may have to do with the extent to which degenerative processes have taken place in the brain. The peptide effects found in aged volunteers (Nebes *et al.*, 1984; Legros *et al.*, 1979) attract attention to the group of aged subjects suffering from mild senescent forgetfulness as a potential treatment group.

Brain Trauma. The brain trauma group is etiologically homogeneous but very heterogeneous with respect to the nature of the memory disorder. The nature of the cognitive and memory defects is dependent on the nature, extent, and localization of the cerebral damage. A general phenomenon appears to be a slowing of general information processing ability and deficits in concentration and attention. Aspects of a planning disorder appear in several patients; memory disorders are often profound, but they can be either a true memory disorder or secondary to slowness or to a planning disorder.

Peptide effects in brain trauma patients can be expected to be dependent on the nature and extent of the neuroanatomical destruction that has taken place. The reported data (Section 2) are suggestive of this notion in that moderately affected patients generally appear to give more clear-cut positive results than do more severely affected trauma patients.

Alcoholism and Korsakoff Syndrome. A general finding in subjects suffering from Korsakoff syndrome is impaired recent memory. Many arguments favor the

conclusion that the underlying mechanism is a deficit in the consolidation of new information (Newcombe, 1980; Russell, 1981). Disorientation regarding time and place is another characteristic attributed to the loss of recent memory. Many of the higher cognitive functions appear to be impaired in addition to memory, whereas lack of insight into the condition is also characteristic of the syndrome. Generally, the nature of the cognitive deficits seen in Korsakoff syndrome relates strongly to the nature and extent of the anatomical lesions; in addition, all alcoholics appear to have impairments similar to those found in Korsakoff syndrome, but to a lesser extent (see Russell, 1981; Butters, 1985).

The alcoholic/Korsakoff patient was formerly regarded as a good subject for peptide treatment in view of the clear-cut amnesic syndrome. The complex pattern of deficits, however, may prevent the buildup of a reliable peptide effect. In addition, the extensive degeneration of the subcortical structures may destroy the site of action of VP.

4.3. Nature of Tests Used for Diagnosis and Treatment Evaluation

Much information has been gathered on the nature of memory and of memory disorders, yet no adequate method exists for use in the clinic (see Russell, 1981; Jolles, 1985, 1986*b*). It is generally recommended that a test battery be used to measure different aspects of memory and cognition. Speed tests appear to be especially important, in view of those studies in which VP effects were found on speed factors (Durso *et al.*, 1982; Tinklenberg, 1981*a*, 1982) and the effects found in studies in which information-processing tasks were used (Beckwith *et al.*, 1982, 1983, 1984; Nebes *et al.*, 1984). In addition, these tasks may give more information on the specific aspects of cognition that are affected by VP.

The most widely used clinical measures are the Wechsler Memory Scale, subtests from the Wechsler Adult Intelligence Scale (WAIS), the Benton test, and word-learning tests. Generally, these standard psychometric tests have the advantage of being standardized and that published norms are generally available. However, they are usually crude and insensitive and do not give any insight into the aspects of information processing that are involved. In addition, these tests generally do not exist in sufficiently parallel versions, thereby prohibiting their use in repeated testing in VP trials.

Procedures based on information processing models may prove more relevant for human psychopharmacology (Nebes *et al.*, 1984; Beckwith *et al.*, 1982, 1983, 1984). This paradigm strives toward examining cognitive processes by analyzing behavior in quantifiable components and qualitative patterns. Reaction time measurements are used to probe into the different stages of information processing (Brand and Jolles, 1985, 1987), and this enables inferences on the cognitive processes underlying the performance that is measured. There are a number of additional advantages of the approach: There are many quantifiable data which lend themselves for evaluation studies; there is usually a good test–retest reliability, which indicates that learning effects are small; and the approach lends itself especially to computerized testing (Branconnier, 1983; Jolles, 1985).

The approach characteristic of behavioral neurology is based on a model of

TABLE VII
Battery of Tests Used for the Assessment of Cognitive Deficits

Test	Parameter tested	Investigators
Luria-Christensen Battery	Motor-, perceptual-, language-, and higher cognitive functions	Luma (1973) Christensen (1975)
Rey Work Learning Test	Learning, consolidation vs. retrieval; rate of retrieval; sensitivity to interference	Luma (1976); Brand and Jolles (1985*a*)
Memory Comparison Task	Rate of perception/motor output; rate of memory comparison	Sternberg (1975); Brand and Jolles (1987)
Stroop Task	Color naming; retrieval of words and color-names; color–word interference	Lezak (1983)
Trail-Making Task (adapted version)	Rate of perception, retrieval of letters, concept shift	Lezak (1983); Vink and Jolles (1985)
Road Map Test	Speed, left–right discrimination, mental rotation	Lezak (1983)
Symbol Digit Modalities Test	Speed of perception and motor output	Lezak (1983)

brain–behavior relationships; it consists of a set of procedures that systematically assess motor, perceptual, language, memory, and higher cognitive functions (Luria, 1980; Christensen, 1975). The approach is systematic and theoretical but nonstructured and not standardized. Its theoretical nature permits an interpretation from the behavioral/cognitive deficits to brain dysfunctioning and vice versa. A disadvantage is its qualitative nature, which prohibits the use of the paradigm in the assessment of treatment efficacy (Jolles, 1985).

A combination of the psychometric, information-processing, behavioral paradigms can be fruitful in assessing cognitive disorders and drug treatment effects. The test series used for the assessment of cognitive deficits in our clinic consists of the tests and tasks described in Table VII (see Jolles, 1985). In addition to this test series, other tests are used to examine any specific deficits more closely. These tests are chosen from standard batteries (e.g., the tapping test from Halstead Reitan Neuropsychological Test Battery or Block design from WAIS) or from experimental tasks, used in an *ad hoc* fashion. This neuropsychological approach toward individual assessment lends itself particularly to a profile analysis that permits a description of the cognitive strengths and weaknesses of the subject (Jolles, 1985). Tests used for the evaluation of drug-treatment effects are chosen from this battery of assessment techniques.

4.4. Nature of the Vasopressin Effect

When evaluating clinical studies with VP and it analogues, one is tempted to conclude that the peptides have many different effects on cognition. However, there are indications that similar mechanisms may underlie the seemingly differ-

ent findings. For example, Weingartner *et al.* (1981*a,b*) suggested that VP may affect human memory through inducing more efficient organization and encoding of memory. Others suggest that VP facilitates attention (Legros *et al.*, 1979; Beckwith, 1982) and concentration (Legros *et al.*, 1979). Still others find that VP especially affects speed. An effect on reaction time (faster) was the only significant VP effect found by Durso *et al.* (1982) in senile demented patients. Similarly, W. M. A. Verhoeven *et al.* (unpublished observations) found intranasal administration of VP to improve the speed of motor performance (tapping test) in patients with brain trauma. The observations in schizophrenic patients support the notion of an effect on the rate of working, thinking, and so forth, in that VP had an activating effect (Forisz, 1952*a,b;* Vranckx *et al.*, 1979; Korsgaard *et al.*, 1981). The peptide effect reported in depressed patients (Gold *et al.*, 1979; Weingartner *et al.*, 1981*a,b*) may be based on the same mode of action of the hormone, because a decrease in the rate of thinking and working is a characteristic of depressed patients. Finally, on the basis of behavioral observations of patients, some workers have suggested that VP might have a general nonspecific activating effect, which may be different terminology for the same effect described by others (Tinklenberg *et al.*, 1981*a,b;* 1982).

Our own studies suggest that there might be an increase in the rate of information processing, which can manifest itself as an increased efficiency in the organization of memory, but also in a subjective feeling of increased energy and better mood. It may be the case that all the different interpretations reflect the same basic mechanism of action of VP, expressed in different terms.

There is some fundamental neurobiological and neuropsychological knowledge that favors such a notion. For instance, both animal and human studies suggest that the effects of VP on cognitive, affective, and electrophysiological parameters resemble those of agents that increase CNS activation, such as catecholamine agonists (Weingartner *et al.*, 1980; Reus *et al.*, 1979; Timsit-Berthier *et al.*, 1982). In addition, there is some evidence that the effects of VP on animal behavior are mediated by ascending catecholaminergic systems, notably norepinephrine (NE) (see Section 6.3). The available evidence thus suggests that VP influences the extrinsic aspects of memory by modulating the synaptic efficacy of the ascending fiber system (possibly on its termination in telencephalic areas, i.e., neocortex and limbic cortical areas). Again, a terminological problem appears, as some authorities traditionally describe the behavioral functions associated with the activity of the ascending fiber system in terms of arousal and (nonspecific?) activation, whereas others view these as memory processes in view of their modulating effect on activity in the anatomical memory circuit (described in Section 5.1). Recent experiments (Nebes *et al.*, 1984) with sophisticated methods based on information-processing techniques do not support the concept of a diffuse nonspecific general action of the peptide (put forward by Durso *et al.*, 1982; Tinklenberg *et al.*, 1982; Gash and Thomas, 1983). Accordingly, there is increasing evidence in favor of a specific action of the peptide (see also De Wied, 1984). Several other investigators have suggested that NE may enhance the impact of significant stimuli, while dampening the effect of less significant inputs. This would result in an improved signal-to-noise ratio (Segal and Bloom, 1976; see also Woodward *et al.*, 1979). Strupp *et al.* (1983) suggested that VP directly, or indi-

rectly, might have a similar effect on information processing. When analyzed on the behavioral level, this would be termed selective attention. Interestingly, there is experimental evidence in favor of this interpretation (Beckwith *et al.*, 1982). *al.*, 1982).

Strupp *et al.* (1983) suggested that a dose–response relationship exists such that at physiological levels, VP may play a role in adaptive processes by focusing attention on the most important aspects of the environment, while at higher levels this narrowing of focus may result in rigidity or perseveration. There are many arguments in favor of such a notion with respect to other hormones, such as ACTH (Strupp *et al.*, 1983; see also De Wied and Jolles, 1983). In addition, there is a trend toward impaired reversal learning in animals treated with VP (Couk and Beckwith, 1982). Interestingly, high doses of LVP in rats give rise to so-called barrel-rotation behavior (Kruse *et al.*, 1977) which might also be interpreted in terms of perseveration of a specific motor response. All these data indicate that a U-shaped curve with respect to the efficacy of VP treatment might exist in humans. If this is true, there is an optimal dose above which there is no beneficial effect of peptide administration. It remains to be determined what range is most effective for any treatment in humans.

5. *Evaluation of Animal Studies Pertinent to the Possible Treatment Effects in Humans*

5.1. *Impact of Neuropathological Lesions*

Animal studies suggest that the nature and extent of neuropathological lesions must be considered when evaluating the effectiveness of VP treatment. For instance, van Wimersma Greidanus *et al.* (1975, 1976) showed that the effect of VP on avoidance behavior is prevented by lesions in the amygdala and in the rostral septal area and is diminished by lesions in the parafascicular nucleus of the thalamus. In addition, destruction of the dorsal norepinephrinergic bundle by injection with 5-hydroxydopamine has a similar effect in that it prevents the VP-induced facilitative consolidation (Kovacs *et al.*, 1977, 1979, 1980). The implication for human studies is that patients with clear anatomical destruction of these deep limbic structures may lack the neural substrate that mediates the vasopressin effect. This applies especially to patients suffering from amnesic syndrome caused by chronic alcoholism or encephalitis; this may also explain the findings with trauma patients, alcoholic patients, and demented patients described earlier (see Section 5) with respect to the influence of more or less profound brain degeneration.

5.2. *The Neural Substrate for the Action of Vasopressin*

There is much evidence to suggest that VP exerts its behavioral effects via an action on the catecholaminergic nerve terminals. For example, VP enhances NE turnover in specific areas in the brain (Tanaka *et al.*, 1977; Versteeg *et al.*, 1979),

and lesions in catecholaminergic systems prevent the VP effect on behavior (Kovacs *et al.,* 1977, 1980). Moreover, there is electrophysiological evidence that the VP administration may lead to electrophysiological arousal in mid-brain structures (Urban and De Wied, 1978). This is also suggestive of an involvement of ascending catecholaminergic fibers arising in the brain stem. These animal findings are of importance for an interpretation of the human data; again, they are an indication for the involvement of extrinsic aspects of memory and, thus, may serve to bridge the gap between the different interpretations of the cognitive effect in humans. The recent findings on the distribution of vasopressinergic fibers in the brain are in line with the notion that there must be a physiological role of VP that is different from its action on the periphery (i.e., its antidiuretic and vasopressor activity). The demonstration that important vasopressinergic nerve fibers terminate in the amygdala, the septum, hippocampus, and hypothalamic and thalamic nuclei, as well as in structures in the lower brain stem (see Chapter 2, this volume) adds support to the notion that the peptide may have something to do with memory processes as these structures are implicated in attention, memory, and learning in both animals and man (see Section 5.1).

5.3. Nature of the Vasopressin Effect

Generally, VP has been shown to affect memory processes, particularly in aversively motivated learned behaviors. Until now, this effect has not been demonstrated convincingly in nonaversively motivated situations. Interestingly, there is increasing evidence that the memory-enhancing effect of VP in avoidance tasks may have to do with its possible aversive properties. For instance, endogenous VP is normally released by some stressors (Schier, 1979), while peripheral administration of pharmacological doses of VP appear to be aversive to rats (see Strupp *et al.,* 1983, and references cited therein). It has been suggested that the administered peptide may enhance memory by amplifying the aversiveness of the situation (Gold and van Buskirk, 1976). It is relevant in that several LVP-treated subjects experience aversive reactions, such as nausea and vomiting (Forisz, 1952*a,b;* Timsit-Berthier *et al.,* 1980; Láczi, 1982). This effect seems to occur only upon long-term treatment and may be characteristic of intramuscular administration. There is also a strong argument against this hypothesis that the VP effect is mediated by its aversive stimulus characteristics, in that VP fragments, which are practically devoid of the classic endocrine activity in normal rats (e.g., dGVP), still show effects on memory processes. Besides, aversive effects on humans have never been found with dGVP. However, the fact that a reliable treatment effect of VP in animals has only been demonstrated in aversively motivated behaviors may suggest that a treatment effect in humans is at least partly dependent on the task and situations, in that some emotional involvement of the subject may be required.

5.4. The Diurnal Cycle

Most animal studies have tested the animals during the light portion of the diurnal cycle, during which time VP levels are highest in CSF (Reppert *et al.,*

1981; Perlow *et al.*, 1982). VP might possibly have a greater effect on learning if administered during the dark cycle, when endogenous VP is low (Strupp *et al.*, 1983). A similar argument may apply to the situation in humans, in that the moment of peptide administration may appear to be more important than is recognized. In our own studies, VP is routinely administered in the morning after breakfast.

6. *Concluding Remarks*

Clinical trials with neuropeptides, including VP and its congeners, are difficult to evaluate, as there are many sources of difference and error. Nevertheless, it seems that VP does have behavioral effects in humans. This conclusion is based on the fact that most studies find something, be it a clinical impression of improvement or subjective test results. Many studies in which the peptide was ineffective were performed on patients with a complex pattern of neuropsychological deficits or other symptoms suggesting profound brain degeneration. This should not be surprising, because degeneration of the relevant brain structures may well destroy the sites of action of the peptide. More positive effects have been found in moderately (as opposed to severely) traumatized patients. The same is true for the alcoholic/Korsakoff patients and for early versus late stages in senile dementia. Interestingly, 9 of 10 studies in volunteers have reported a positive effect of treatment. Taken together, these findings may indicate that future studies should focus on those patients who have mild deficits without pronouced anatomical destruction. In our opinion, the subjects of choice for peptide studies are patients presenting cognitive dysfunctions resulting from mild brain trauma (e.g., concussion), elderly people with mild senescent forgetfulness, those with very early dementia, and patients suffering from depression. This implies that the patient groups should be more defined neuropsychologically, to assess specific influences on types or aspects of memory. We suggest that information-processing tasks that measure the processes underlying both consolidation and retrieval and other aspects of memory may be the most relevant to study. Better and more specific methods of treatment evaluation (including parallel test versions) should therefore be used. Again, information-processing tasks may prove important in this respect.

Another important point concerns the nature and amount of the active principle. The amount of VP that can be used in humans is limited, due to peripheral side effects, while high doses are necessary to enable sufficient VP or analogues to pass the BBB and reach the CNS. VP congeners, which are resistant to metabolic degradation, would therefore be of value. dGVP is favored above dDAVP, and especially LVP, because its peripheral endocrine effects are much less than those of VP, LVP, and dDAVP. Finally, it may be necessary to treat for relatively prolonged periods of time (weeks) to allow a relevant treatment effect to develop.

Conclusions that can be drawn from the clinical studies performed to date are generally in line with those based on animal experiments. Future patient studies may yield more relevant information when they make more use of the extensive knowledge collected for the past decade in animal experiments, in cognitive psychology, and in the neuropsychological studies of brain–behavior relationships in humans.

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