Neuropeptides and the treatment of cognitive deficits in aging and dementia

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Introduction

Neuropeptides have recently been suggested to be potentially useful in the treatment of cognitive deficits in man. This suggestion has been based primarily upon animal experiments in which peptides derived from the pituitary hormones ACTH and vasopressin appeared to improve performance in several experimental paradigms, designed to measure learning and memory. These data have been interpreted in terms of peptide effects on attentional, motivational and memory processes (see De Wied, 1969; De Wied and Jolles, 1983; De Wied, 1983, for references). Clinical researchers have become interested in the laboratory findings in view of the potential use of the neuropeptides to alleviate symptoms which accompany many neuropsychiatric diseases. Unfortunately, the results obtained in clinical trials up till now are difficult to evaluate because of differences in patient populations and treatment parameters. ACTH-like peptides have been used extensively with human volunteers before clinical trials were done with elderly people and demented patients. The reverse is true for vasopressin-like peptides: many different types of patients have been treated with vasopressin before studies with volunteers were carried out. The present paper will review the current knowledge with respect to the clinical studies with ACTH and vasopressin in elderly and (senile) demented subjects. A brief overview will also be given of the peptide studies which have been performed with other patient groups and rodents. A more detailed description of the clinical effectiveness of vasopressin in other patient populations can be found in Jolles (1983, 1987).

Cognitive dysfunctions in aging and dementia

Complaints of memory and other cognitive functions accompany many neuropsychiatric diseases. The disturbance in the brain processes which underlie these complaints can be very different because of the fact that the etiological and pathogenetic factors are quite varied (see Luria, 1976; Newcombe, 1980; and Russell, 1981, for reviews). It is therefore important to specify the action of the drugs in terms of actions on different aspects of memory and cognition (e.g. Squire and Davis, 1981). This may especially be true because patients suffering from different diseases may have similar complaints. This similarity in the nature of the complaints may result in a wrong impression with respect to drug specificity: it is not to be expected that one drug will have a beneficial effect on all kinds of cognitive (e.g. memory-) deficits in all types of diseases. A brief summary of the nature of the complaints and the cognitive dysfunctions in aging and (pre)senile dementia may illustrate this point. A more thorough description may be found elsewhere (Jolles, 1987; Jolles, 1985; Botwinnick, 1981; Jolles and Hijman, 1983).
Cognitive dysfunctions in aging

Elderly subjects are characterized by an age-associated decline in nearly all cognitive functions (intellectual functioning, memory, language functions, problem solving and perception, Botwinick, 1981; Jolles and Hijman, 1983; Jolles, 1985). Those behavioral functions seem to be preserved in which the person can rely on well-trained skills and knowledge. Thus, well-learned motor skills are preserved as well as expressive language. In addition, passive recognition of old and newly learnt information does not deteriorate significantly, but active encoding in and retrieval from memory does. An increasing inefficiency in the use of new information is observed. Kral (1962) introduced the term 'senescent forgetfulness' distinguishing benign (BSF) and malignant (MSF) forms. BSF is a deficit in the recollection of relatively minor details of an episode while the episode as such can be recalled. This retrieval deficit is not permanent and is situation-dependent. MSF on the other hand is characterized by the loss of the episode itself. The nature of the memory deficit in BSF may be partly related to a decreased speed of information processing in the elderly subject. It may also be a secondary consequence of a decreased effectiveness of behavioral organization, evidenced by a tendency towards inflexibility, cautiousness and conservatism (Botwinick, 1981). 'Stimulus persistence' and the fact that more effort is needed to change opinions and beliefs are taken to be an indication of a deficient behavioral planning and organization. There is some evidence suggesting that frontal neocortical structures are involved (Jolles and Hijman, 1983; Jolles, 1985).

Cognitive dysfunctions in (pre)senile dementia

The pattern of cognitive deficits in dementia of Alzheimer type (AD) appears to be qualitatively similar to normal aging (see Jolles and Hijman, 1983; Jolles, 1985). There are also similarities between the presenile and the senile forms of AD (Sulkava and Amberla, 1981). The early stages of AD are difficult to discriminate from 'normal aging' and depression, although a clear-cut consolidation deficit (in AD) seems to differentiate different types of patients (Braconnier and De-Vitt, 1984; Jolles, 1985). There seems to be a clearly definable progression in Alzheimer's disease; different functions of the brain are affected in a certain order (Strub and Black, 1981; Reisberg et al., 1982; Jolles, 1985). Symptoms such as a general decrease in activity and deterioration of short-term memory and awareness appear first, followed by behavioral dysfunctions such as disorientation and paranoid delusions. Still later, apraxic, aphasie and agnostic deficits appear. In addition, deterioration of logical reasoning and loss of control over complex and simplex behavioral functions appear. In the final stages of the disease, only some basic autonomic functions are still preserved.

AD clearly differs from other types of dementia. For instance, the (pre)senile dementia of Pick's type especially is characterized by behavioral disturbances and deficits in the planning and organization of behavior which are characteristic for dysfunctions of the frontal lobe. Likewise, those dementias which depend primarily upon vascular disorders ('multiinfarct dementia') are defined by a different profile of cognitive dysfunctions due to its focal deficits (e.g. complex visual deficits and disorientation without a memory deficit for verbal material is characteristic for involvement of right-hemispheric structures; Jolles and Hijman, 1983; Jolles, 1985).

ACTH and cognitive disorders

The notion that neuropeptides like ACTH and vasopressin might affect cognitive disorders in patients and elderly persons has been derived primarily from animal studies by De Wied and coworkers (De Wied, 1969, 1976, 1977; De Wied and Jolles, 1983). A brief description of the major preclinical findings serves to illustrate the similarities and differences which can be expected in the effects of the peptides between rodents and man.
Animal studies

Neuropeptides related to the pituitary hormones ACTH and vasopressin affect animal behavior in a number of different test situations. Twenty years of research have indicated that peptides related to ACTH play a central role in the cerebral organization of adaptive behavior (De Wied, 1969; De Wied and Jolles, 1983; Jolles et al., 1982). It has been shown that hypophysectomized rats perform badly in tests which measure conditioned avoidance behavior. That is, in test situations in which the rat has to learn to avoid a mild electric foot shock by climbing into a pole or by jumping over a small fence mounted in the test cage. This behavioral deficit could be normalized by treatment with adrenocorticotropic hormone (ACTH). It turned out later that a similar treatment effect could be observed in intact rats. Fragments of the hormone without corticotropic activity appeared to have a similar effect, suggesting that the peptide might act directly on the brain. Support for this notion came from experiments in which the dosage of the peptide needed to produce a particular behavioral effect was much lower after central than after peripheral administration (De Wied, 1976). In addition, several peptides have been synthesized which have a potentiated behavioral action, but lack the peripheral side effects of the parent compounds. For instance, the synthetic peptide Org 2766 is an ACTH4–9 analog. It has no steroidogenic action but its behavioral action is one thousand times stronger than that of ACTH4–10. It is also reasonably resistant towards enzymatic degradation and thus can be administered orally (Pigache, 1982). The duration of the ACTH effect is relatively short compared to the effect of vasopressin (days). Some consensus exists with respect to the hypotheses concerning the mechanisms of action of the peptide: ACTH-like peptides affect processes that are sometimes described as ‘arousal’, ‘attention’ and/or ‘motivation’ (De Wied and Jolles, 1983; Pigache, 1982). Squire and Davis (1981) summarize these effects in terms of an action on ‘extrinsic aspects of memory’. De Wied has suggested that the peptide temporarily increases the motivational value of environmental stimuli, by selectively inducing a state of arousal in certain limbic structures in the midbrain. This hypothesis is based upon both electrophysiological and neurochemical findings (De Wied and Jolles, 1983).

Human studies, acute or short-term administration

The finding that ACTH-like peptides have an influence on behaviors interpreted in terms of attention and motivation has stimulated similar studies in man. Consistent effects of ACTH4–10 and Org 2766 on memory task performance have not been found: according to Pigache (1982; Pigache and Rigter, 1981) those positive findings which have been published are mostly probably due to methodological shortcomings (e.g. statistical methods which have not been used correctly, and the use of wrong tests). These authors evaluated the properly performed studies and concluded that ACTH4–10 and Org 2766 do not have clear effects on memory processes (Pigache and Rigter, 1981). This absence of significant effects on memory processes has been observed in healthy young subjects, in patients treated with electroconvulsant therapy, children with minimal brain dysfunction, alcoholics and others with signs of cognitive deficits (Tinklenberg and Thornton, 1983).

Initial trials with both healthy subjects and patients have used either a single dose of the peptide (‘acute’ treatment) or a relatively short period of administration (several days). Generally, consistent effects have not been found with respect to cognitive functions and memory measured in information processing tasks (for review, see Gaillard, 1981; Pigache and Rigter, 1981). Single doses of ACTH4–10 or Org 2766 appear to enhance human performance on behavioral tasks under certain conditions. For instance, Org 2766 has been found to enhance performance in visual perception and discrimination tasks (e.g. Beckwith and Sandman, 1982). Likewise, significant peptide effects have been found during tasks which
required sustained attention or vigilance during long and monotonous sessions. Gaillard (1981) has, thus, suggested that ACTH does not influence ‘selective attention’, but ‘task-directed motivation’. This specific motivation cannot be explained as a change in general motivation or activation, because the peptide did not affect the basal heart frequency. Studies with elderly subjects did not produce the clear-cut effects which had been found in younger subjects (Pigache, 1982).

The human vigilance studies are not of immediate clinical importance because the degree of improvement in the individual subjects was too small. However, the studies do provide relevant theoretical information. For instance, consensus has been reached on the hypothesis that the ACTH effects are not on intrinsic, information-containing memory functions per se, but instead on extrinsic memory modulating processes or other factors that affect task performance, especially during prolonged testing sessions (Gaillard, 1981; Tinklenberg and Thornton, 1983; Squire and Davis, 1981).

**Human studies: subchronic administration**

Recent findings with subchronically administered Org 2766 (i.e. for more than 1 week) appear to have positive effects in elderly patients. Ferris and coworkers (1980) treated 50 elderly subjects who suffered mild cognitive impairment but lived in the community. These subjects were not depressed or anxious. Ferris et al. observed a significant decrease in ‘depression’ and an increase in self-rated ‘competence’ on the ‘mood-scales-elderly’ (M-SE). Anxiety was also significantly decreased. In another study, with 35 more severely impaired geriatric inpatients, an observer rating scale was used to evaluate the Org 2766 effect on different behaviors: significant treatment effects were found with respect to ‘ward behavior’ and ‘social behavior’ (Braverman et al., 1980). Other double-blind studies in which 5, 10 or 20 mg Org 2766 per day was administered reported significant effects with respect to ‘anxiety’ and ‘social behavior’ (Pigache and Rigter, 1981). In yet another study in which the peptide effect was evaluated by a self-rating scale (Profile of Mood-Scales, POMS), significant peptide effects were not found (Branconnier and Cole, 1977). In addition, Org 2766 did not affect hyperkinetic children (cf. Pigache and Rigter, 1981).

In contrast to these effects obtained with subchronic administration, there has never been any effect of this peptide given only once (Pigache, 1982).

These findings suggest that ACTH peptides, especially if given repeatedly for a longer period of time, can affect human behavior under certain conditions. With respect to their mechanism of action, an action on extrinsic memory processes is most probable. It remains to be seen whether the positive effects on mood and social behavior can be explained by the fact that there is an anatomical correlation with respect to the cerebral substrate involved: ascending fibers (noradrenergic and serotonergic fibers) which are known to be involved in the behavioral effects of the ACTH peptides in animals (De Wied and Jolles, 1983) are also involved in mood and depression in man (Van Praag, 1982) and in AD (Rossor, 1982). Clinical trials in depressed subjects or in very early dementia could be more promising than studies with more deteriorated subjects in whom more extensive neuroanatomical degeneration has taken place.

**Vasopressin and cognitive disorders**

**Animal studies**

Vasopressin-like peptides appear to improve the performance of normal rats in a variety of behavioral paradigms which measure the acquisition and retention of aversively motivated behavior (De Wied, 1983; Van Wimersma Greidanus et al., 1985). In addition, rats characterized by a decrease or lack of endogenous vasopressin have an impaired performance of particular learning and memory tasks. This phenomenon was observed under three different conditions of vasopressin-deficiency (De Wied, 1983; Van Wimersma Greidanus et al., 1975), namely neurohypophysec-
tomy, hereditary deficits in the production of vasopressin (the Brattleboro rat), and vasopressin antiserum treatment. Interestingly, under these conditions, the impaired behavior could be restored by treatment with vasopressin or its congeners. Similar treatment effects were found in animals with impaired performance due to treatment with CO₂, electroconvulsive shock, or inhibitors of protein synthesis.

There are several arguments which suggest that there is a direct effect of the peptide on the central nervous system (CNS); it appears that the dosage of the peptide which is needed to elicit a particular behavioral effect is much less after central than after peripheral administration (see De Wied, 1983). Secondly, vasopressin fragments exist which have been reported to be practically devoid of classical peripheral-endocrine effects (e.g. desglycinamide-lysine⁵-vasopressin, DGLVP; De Wied, 1983). Incidentally it appears that desglycinamide-arginine⁸-vasopressin (DGAVP) binds to vasopressin receptors in the kidney in in vitro experiments (Ravid et al., 1985). This suggests that the desglycinamide peptides may also have some peripheral effects in vivo; however, effects of DGAVP and DGLVP on blood pressure and/or water retention have until now not been found in normal rats, whereas the behavioral effects seem to be similar to those of the parent compound. Finally, extensive systems of vasopressinergic fibers have been demonstrated in the brain (Bays, 1978), 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, 1984; see De Wied, 1984).

The behavioral effect of vasopressin is longer-lasting than that of 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 processes have been reported (see De Wied, 1983). Generally, the data with respect to the nature of the vasopressin effect are more in line with a hypothesis in terms of memory processes than those on ACTH.

Research which has interpreted the behavioral action of vasopressin in terms of 'memory processes' has led to the application of the peptide in the treatment of human memory disorders. Unfortunately, there are many differences between the studies with respect to the aspect(s) of memory affected, the type of patient, the severity of the defects and the methods used for treatment evaluation (see Jolles, 1983 and 1986, for an extensive elaboration on these parameters). In addition, the studies differ with respect to the dose, route, frequency and duration of peptide administration and the experimental design used (open, blind, etc.). Furthermore, vasopressin congeners have been used which differ with respect to the peripheral side effects: the mother hormone lysine⁵-vasopressin (LVP) has antidiuretic, vasopressor and behavioral effects; its congeners desamino-arginine⁸-vasopressin (DDAVP) has antidiuretic and behavioral effects and DGAVP has been claimed to have only the behavioral effects (Jolles, 1983, 1987, but also see above).

**Aging and senile dementia**

Twelve patients (aged 50–64 years) who were hospitalized with somatic complaints were treated with LVP applied intranasally (Legros et al., 1978). The peptide-treated patients performed better than control subjects on certain tests of attention and memory. The same investigators reported subsequently that the scores on one of these memory tests correlated with the levels of neurophysin-I in the blood (Legros and Gilot, 1979). Effects of LVP were also found in patients with senile dementia (average age 80 years, Delwaide et al., 1980): a single administration of LVP improved the performance of nine out of ten patients on a word list retention task, and these effects were still present after 48 h. Others have also found that a single administration of DDAVP can improve memory for semantic structures (i.e. word memory) in patients suffering from progressive dementia.
(Weingartner et al., 1981b). This was also found in a later study in which seven patients suffering from primary degenerative dementia were treated with gradually increasing doses of DDAVP for 10 days. The demented patients were better able to generate appropriate words to verbal stimuli than controls. The authors suggested that the peptide helps facilitate access to semantic memory (Kaye et al., 1982). In addition, they noted that these patients showed enhanced arousal with increased motor and speech activity.

Ferris (1983; Ferris et al., 1986) treated 20 patients suffering from mild to moderate dementia with LVP for periods of 7 days in a placebo-controlled cross-over study. Consistent but small improvements on memory tests were noted. However, in another study in which carefully diagnosed Alzheimer patients were treated with LVP, effects on tests of memory, learning and visual perception were not observed. The only detectable effect concerned an improved performance in a reaction-time test. These authors concluded that vasopressin might have a 'non-specific activating effect' (Durso et al., 1982). A similar suggestion was made by Tinklenberg et al. (1981, 1982, 1986), who treated patients suffering from a primary degenerative disorder (Alzheimer type). Neither DDAVP nor DGAVP had measurable effects on the tests used. These authors suggested that some patients had more energy and less depression after administration of the compound. This was especially the case in patients with comparatively mild dysfunctions. These same authors later observed some changes on a word-learning test indicating improvement (Peahody et al., 1985). Preliminary data from another study are suggestive of a 'significant improvement in cerebral function' in five out of 20 parkinsonian patients with incipient dementia. These patients had been treated with LVP in an open design (Legros and Lancerjan, 1984).

Improved memory has been reported in five out of 11 patients suffering from multiinfarct dementia, treated in a double-blind placebo-controlled design (Bucht et al., 1986). Social behavior improved in eight out of 11 subjects. Several studies have been published with negative results. Jenkins and coworkers (1982) treated three patients suffering from 'early dementia of the Alzheimer type' (aged 58–65 years) with DDAVP. They observed that none of their patients showed significant improvement with the peptide on any of the test procedures used. Similarly, Franceschi et al. (1982) did not find statistically significant changes in a mixed population of patients suffering from Alzheimer's disease (n = 10) and multiinfarct dementia (n = 8). These patients had been treated with intranasal LVP for 7 days. Intranasal LVP treatment has been equally ineffective in a double-blind study with parkinsonian patients (Jensen, 1980) in which peptide effects were studied on neurological and psychiatric variables. Evidence is thus available in favor of the hypothesis that vasopressin treatment may be more effective in patients with less extensive degeneration in the brain than in patients with very extensive damage.

**Depression**

Disturbances in mood, 'energy' and initiative are frequently encountered in elderly subjects and in (pre)senile dementia (e.g. Strub and Black, 1981; Botwinick, 1981). Several authors have noted that the peptide effects which they observed in dementing persons seemed to be restricted to these 'general' psychological functions. It was thus hypothesized that the — possible — antraminic effect of vasopressin-like peptides might be a manifestation of an antidepressant action.

In a study in which patients with endogenous depression and cognitive disorders were treated with DDAVP (Weingartner et al., 1981a; Gold et al., 1979), three out of four patients showed a significant improvement in cognitive functioning. However, upon discontinuation they were back at their pretreatment level after 4 weeks. In a follow-up study in two depressed patients, DDAVP appeared to counteract the amnesia which is a characteristic side effect of electroconvulsive shock therapy. Others have reported that LVP improved memory processes in three depressive patients.
(Drago et al., 1981). Likewise, Legros and Lan-ccranj (1984) cite a preliminary study by Vranckx and coworkers, who reported a beneficial effect of LVP treatment in moderately depressed patients. According to these authors, there was no therapeutical action in more severely depressed patients who did not respond to classical treatment.

Clinical studies in other patients and in healthy volunteers

The observation that vasopressin affects the performance of laboratory animals in tests that are presumed to imply aspects of learning and memory processes, has stimulated clinical trials with the peptide in many different types of patients. The common denominator in all of these patients was the presence of memory complaints and/or deficits. Clinical trials have thus been performed with patients suffering from brain trauma, chronic alcoholism, schizophrenia, diabetes insipidus and attentional deficits (see Jolles, 1983, 1987, for a review). Several of these findings with patients and healthy volunteers deserve attention. For instance, studies in both brain trauma patients and chronic alcoholic/Korsakoff subjects suggest that the treatment only has a measurable effect in patients with relatively mild cognitive deficits and minimal brain damage (Jolles, 1983, 1986, for references). In schizophrenic subjects, vasopressin appeared to induce the reappearance of positive psychotic symptoms such as delusions and hallucinations (first) and a more social and interested attitude (later). A decrease in thinking disorder, blunted affect and emotional withdrawal was noted, accompanied by an increase in energy and activity. These studies point — again — to a peptide effect on those psychological functions which are associated with energy, activity and interest.

Studies in human volunteers especially are important for our understanding of the nature of the peptide effects. In a series of studies with information processing tasks, Beckwith and coworkers showed DDAVP effects on learning a concept shifting-task. There were no effects on visual memory, anxiety, blood pressure and heart rate, which excluded a 'general arousal' explanation (Beckwith et al., 1982, 1983, 1984). Similar findings were obtained by others: Nebes and coworkers (1984) reported peptide effects on memory comparison time and perceptual-motor time in short-term memory and retrieval time in long-term memory. As other aspects were unaffected, these data seem to show that the peptide has a more or less specific influence.

Cognitive disorders and changes in CSF vasopressin levels

There is an increasing number of studies which report that cerebrospinal fluid (CSF) levels of vasopressin (VP) are abnormal in several types of patients suffering from cognitive deficits. Legros (1975) found a decrease in the CSF levels of neurophysin (the vasopressin transport protein) in patients of 50 and older. Moreover, there was a relationship between the circulating neurophysin and some psychometric memory tests. In addition, a reduced vasopressin response to the water deprivation test in old age has been observed (Legros and Gilot, 1979; see also Legros and Lancerjan, 1984). More recently, Sundquist and coworkers (1983) found a slight decrease of the CSF-VP levels with increasing age in neurological patients. The VP values were significantly higher in patients with cerebrovascular disease, whereas lower CSF values were found in patients with dementia and Parkinson's disease. On the other hand, vasopressin levels in the CSF of 10 elderly normal subjects, nine patients with multiinfarct dementia and five patients with AD were all in the same range (Legros and Lancerjan, 1984). A decrease of vasopressin levels with age was not observed either by Jenkins et al. (1981) and Luerssen and Robertson (1980). Swaab et al. (1986) provide a critical evaluation of the data on VP levels and aging.

Changes in AVP levels have been found in several psychiatric populations characterized by cognitive deficits: elevated levels of AVP in spinal
fluid were found in anorexia nervosa patients (Strupp et al., 1983), whereas oxytocin levels were depressed in these patients. AVP levels were also elevated in mania, again with oxytocin being decreased (Strupp et al., 1983). The relation between these changed levels and the cognitive deficits remains to be established, but the findings as such may prove to be of importance.

Conclusions and suggestions for future research

The clinical studies with peptides related to ACTH and vasopressin are different with respect to many treatment parameters and other variables. It is therefore not possible to draw definite conclusions as to whether these peptides are clinically effective or not. However, results which have been obtained up till now do allow a set-up of research strategies which are potentially more promising than others. For instance, when vasopressin-like peptides appear to have more clear-cut effects in particular patient populations under certain treatment conditions, clinical trials can be planned in which these variables are systematically controlled. The following variables are potentially relevant in this respect:

The nature of the drug. Both animal studies and human studies with ACTH4–10 and the ACTH4–9 analog (Org 2766) have shown that the analog is behaviorally more potent (de Wied and Jolles, 1983; Pygate, 1982). This increased behavioral activity can possibly be explained by an increased resistance towards metabolic degradation (Witter et al., 1975) which effectively prolongs the bio-availability of the peptide. This point is of particular relevance because the route of administration does not favor the penetration of the drug into the CNS, where it is supposed to act: Org 2766 is administered orally, and the vasopressin-like peptides are usually administered via nasal spray. Unfortunately, there is as yet no indication that administration via the nasal route provides better access to the CNS. In addition there is as yet no indication of the mechanism(s) by which peptides might pass the blood–brain barrier (Ang and Jenkins, 1982). Intramuscular administration which will — theoretically — increase the effective amount of peptide in the body will — for obvious reasons — never become a routine method of administration.

A research strategy which may be particularly important is concerned with development and use of peptide congeners that are chemically modified
so as to resist enzymatic breakdown. In addition, use of peptide fragments with increased behavioral potency deserves attention. This is especially the case for vasopressin-4–9 which has recently been shown to be behaviorally potentiated compared to the parent compound and its desglycinamide fragment (Burbach et al., 1983).

Finally, in addition to ACTH and vasopressin, other (neuro)peptides, such as somatostatin deserve attention as there appears to be a fairly selective decrease in the brain content of this substance in aged and demented subjects. Combination therapy of neuropeptides with drugs related to the classical neurotransmitters deserves attention because of findings in animal experiments that the peptides may modulate ongoing activity in classical — e.g. monoaminergic — synapses (e.g. De Wied and Jolles, 1983).

Other treatment parameters. Longer treatment periods with both ACTH and vasopressin seem to produce more clear-cut results. This is the case for subchronic administration of Org 2766 in elderly and dementing subjects but also for vasopressin. The studies with human volunteers are an exception in that acute administration did produce significant effects: it may be the case that these latter studies produced such effects because more homogenous groups were employed and because potentially interfering variables were more rigidly controlled. Clinical studies may thus need at least 2–4 weeks of peptide administration before a treatment effect develops which is strong enough to be observed. A related point concerns the amount of active peptide which may be administered. The amount of LVP or DDAVP which can be used in humans is limited due to peripheral effects on blood pressure and water retention. DGAVP, which lacks (at least most of) the peripheral effects, is therefore favored over the other congeners. DGAVP can be employed in a higher dose, and this may increase the amount of active principle that eventually reaches its site of action in the CNS. This is especially important in view of the blood–brain barrier which is difficult to pass for peptides. However, it must be kept in mind that biphasic dosage effects have been reported for ACTH- and vasopressin-like peptides in animal studies (e.g. Jolles et al., 1972). This suggests that some optimal dose level may exist for vasopressin (Jolles, 1987) as has already been shown for other psychoactive drugs.

Some methodological issues. It is beyond discussion that future studies must be controlled (e.g. double-blind placebo-controlled or cross-over with a sufficient number of cases per group). However, it must be acknowledged that studies which are methodologically sound from a scientific point of view may not be clinically relevant. It is, of course, important that group means for peptide-treated groups and placebo groups are statistically different. Such an observation, however, does not teach us very much about the potential clinical effectiveness of the peptide. It is, therefore, important to know more about the number of subjects per group that have responded favorably. Given the recently growing interest in single case methodology, use of multiple single case designs must be initiated.

Combination with non-biological treatment. On the basis of observation in electrophysiological and neurochemical experiments De Wied (1977) proposed that neuropeptides like ACTH can increase the motivational value of environmental stimuli by creating a temporary state of arousal in certain limbic midbrain structures.

It has been suggested for many years that the action of pituitary hormones on peripheral organs causes the organism to be optimally prepared for the effect of a changing environment. These hormones may thus play a role in adaptive behavior. It seems quite probable that the neuropeptides act upon the central nervous system in ways similar to peripherally acting mother hormones (e.g. 'stress hormones'). One common denominator of all the studies with ACTH and vasopressin in animals and humans is that the peptides change the effectiveness with which the
organism processes environmental (sensory) stimuli and organizes its behavior in accordance with these stimuli; the peptides may thus improve the manner in which the organism copes with environmental demands. If this is the case, it may be that environmental stimulation is important for the expression of the peptide effects. This suggestion implies that a combination of drug therapy (e.g., neuropeptides) and environmental stimulation (e.g., training the deficient cognitive deficits) deserves consideration in the treatment of maladaptive behavior. A thorough evaluation of the impact of all variables which appear to influence the treatment effects of neuropeptides is not only relevant with respect to the neuropeptides. These studies, if properly performed, may also help us to define the optimal way to test the possible effects of other biological or non-biological methods of intervention. In addition, when the nature of the treatment effects is carefully considered, they may add to our insight into the cognitive deficits in aging, depression, or early beginning dementia as well as into the relevant etiological and pathogenetic factors.

References


Discussion

J. H. CHRISTINA: (1) What kind of psychometric or clinical tests do you perform to assess the degree of dementia?

(2) Why do you ask for a better patient differentiation (for clinical trials) taking into consideration that the population you are going to treat is a very heterogeneous one?

ANSWERS: (1) The methods that were used by all authors that I have reviewed in the present paper were psychiatric in nature (for details see Jolles, 1986). Especially the earlier papers are usually based upon DSM-III criteria and/or clinical impression. The differentiation between mild, moderate and severe is always based upon clinical criteria and not upon psychometric tests.

(2) Your second question must be based upon a small misunderstanding. In my opinion, nearly all studies performed up till now used heterogeneous patient groups. Strong arguments favor the foundation of groups that are more homogeneous with respect to etiology and cognitive deficits; to decrease intra group variability and characterize those patients who benefit most from the peptide or potential other treatments.

E. FLIBERS: In view of the fact that effects of VP and ACTH (analogues) have been found in so many different conditions, could you speculate on their mode of action in the brain? Is there indeed evidence for your hypothesis that these peptides act via the midbrain?

ANSWER: An answer to this question requires more space than is present in this discussion. The hypothesis of De Wied, that ACTH-like peptides increase a state of arousal in limbic midbrain structures, has been based upon electrophysiological experiments in which changes in hippocampal theta rhythms...
have been found. In addition, neurochemical experiments investigating the influence of the peptides on ascending catecholaminergic fibers point into the same direction.

D. M. GASH: Given the propensity for only clinical studies reporting positive results to be published, careful consideration must be given to those studies which have found no beneficial effects of vasopressin treatment. Is it accurate to conclude that the clinical effects of vasopressin on cognition are rather modest and only affect a subpopulation of the cognitively impaired patient population? Is it also possible to explain the effects of vasopressin in terms of altered mood or a general effect on the level of arousal?

ANSWER: The treatment effects reported in the clinical studies up till now are indeed rather modest. It must be taken into consideration however, that the studies which have been performed correctly, were based upon a group-comparison design in which group means were statistically evaluated. Given the fairly strong arguments which favor the notion that particular population(s) of patients may respond better than others (e.g. patients with only mild deficits without gross lesions), this may mean that patients who are a ‘responder’ in the clinical sense are not characterized as such due to the design used. Future studies must, in my opinion, use a multiple single-case design to allow statements of treatment effects in individual subjects.

With respect to the possibility that the vasopressin effects might be described in terms of altered mood and a general arousing effect, it seems to me that the discussion in the literature on this topic is confounded by semantic problems. The notion of what constitutes ‘memory’, ‘arousal’, ‘attention’, etc., seems to me to depend upon the discipline and/or the paradigm used. I tend to agree with you that vasopressin does not affect memory per se. However, an effect on more general mechanisms which are necessary for memory processes seems reasonably well established in animal experiments. The methodology in human studies, in my opinion, does not yet allow any conclusions as to the possible mechanisms and aspect(s) of cognition involved.

References