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Neuropeptides: Animal Behaviour and Human Psychopathology

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Summary. Animal studies have demonstrated that neuropeptides modulate nervous system functions. It has been postulated that disturbances in neuropeptide systems may be aetiological factors in psychiatric and neurological disorders. Neuropeptides related to ACTH/MSH, including ORG 2766, increase motivation and attention and facilitate recovery processes after nerve damage. These peptides may be effective during the early stage of dementia. Vasopressin and related peptides improve memory processes in animals and humans. In addition, these peptides influence social behaviour, mood and addictive behaviour. The non-opioid γ-type endorphins have neuroleptic-like activities in animals and antipsychotic effects in a category of schizophrenic patients. Peptides related to CCK have also been found to be effective in these patients. Some neuropeptides, e.g. TRH and PLG, have been reported to exert antidepressant effects. Further research may eventually produce neuropeptides with therapeutic action in psychiatric and neurological diseases.

Key words: Neuropeptides – ACTH – Vasopressin – γ-type-Endorphins – TRH – Aging – Memory – Schizophrenia – Affective disorders

Introduction

Neuropeptides are endogeneous substances present in nerve cells and involved in nervous system function. They are formed in large proteins and several may be formed in the same molecule such as ACTH, β-LPH, β-endorphin etc. in pro-opiomelanocortin (POMC). A cascade of processes takes place in peptidergic neurons in response to genetic information, which results in biologically active neuropeptides. These processes determine the quantities of neuropeptides synthesized and their biological activity through size, form and derivatization. Transcription of a gene into precursor RNA is the initial step. Splicing of the precursor RNA results in formation of mature mRNA. Alternative splicing patterns may generate different mRNAs from a single gene, resulting in different sets of neuropeptides. For example, calcitonin and calcitonin gene-related peptide (CGRP) are derived from the same gene but are encoded by different mRNAs, depending on the cell in which they are expressed. In thyroid tissue the mRNA encodes calcitonin, affecting calcium metabolism, and in brain tissue it encodes CGRP with vasodilating effects (Rosenfeld et al. 1983). Different mRNAs from one gene control the production of substance P and the various tachykinins in a similar way (Nawa et al. 1984; Nakanishi 1985). Enzymatic processing of peptide precursors translated from mRNA forms sets of biologically active principles. Whereas differential splicing of precursor RNA can be a cell-specific phenomenon, processing of neuropeptides from the same precursor can also be cell-specific as, for example, with POMC. The anterior pituitary corticotrophs and the intermediate lobe melanotrophs convert POMC into two completely different sets of peptides. β-LPH and ACTH are the main products in the anterior lobe, while part of β-LPH is further processed to γ-LPH and β-endorphin [βE-(1–31)] (Eipper and Mains 1980). In the intermediate lobe ACTH is processed to α-MSH and corticotrophin-like intermediate lobe peptide [CLIP or ACTH-(18–39)]. More γ-LPH and βE-(1–31) relative to β-LPH is produced in this tissue than in the anterior pituitary. Both tissues produce γ-MSH-related peptides from the 16-K N-terminal fragment (Pedersen et al. 1982). α-MSH, ACTH fragments and βE-(1–31) are the predominant peptides produced in brain tissue; how-

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ever, further processing to γ- and α-type endorphins also takes place. POMC peptides undergo several non-proteolytic co- and post-translational modifications such as acetylation, glycosylation and phosphorylation, which may affect their biological activity.

Animal studies on the influence of the various neuropeptides related to ACTH, the endorphins and the neurohypophyseal hormones have revealed that, apart from their function as hormones, these peptides act as neuropeptides which modulate nervous system functioning (De Wied and Jolles 1982; De Wied 1984). These peptides affect motivation, attention, concentration (arousal), aggression, social behaviour, grooming behaviour, developmental processes, nerve cell regeneration, sexual behaviour, pain, addiction, mood, learning and memory processes, food intake, temperature regulation, and maternal behaviour. In addition, peptides related to β-endorphin appear to exert psychostimulant and neuroleptic-like effects and peptides related to ACTH exhibit neurotrophic effects. Congenital or acquired disturbances in neuropeptide systems may well be aetiological factors in psychiatric and neurological disorders. These disturbances might be caused by changes in the gene structure or gene expression or the processing of precursor molecules or their metabolism and their binding sites. These changes, in turn, may cause disturbances in the composition of neuropeptides or their biological effect.

ACTH Neuropeptides and Ageing

In experimental animals, neuropeptides related to ACTH/MSH affect several kinds of behaviour, such as avoidance, approach, discrimination and rewarded behaviour. These and other findings have been interpreted as effects on learning, motivation, attention, concentration and memory retrieval processes (De Wied and Jolles 1982). These peptides also cause behavioural stereotypy characterized by stretching and yawning and excessive grooming behaviour, but only after intracranial administration (Gispen and Isaacson 1986). ACTH neuropeptides facilitate recovery from peripheral nerve damage (Bijlsma et al. 1983). Also, functional recovery after destruction of some parts of the brain is accelerated when animals are treated with ACTH neuropeptides (Nyakas et al. 1985; Van Ree and Wolterink 1987). In addition, these peptides modulate agonistic and social behaviour (Niesink and Van Ree 1984). Several substitutions in the sequence ACTH-(4–9) have led to a highly selective and potent neuropeptide (Org 2766) (Van Nispen and Greven 1986). This peptide is 1000 times more active than ACTH-(4–10) on active avoidance behaviour but has a markedly reduced steroidergic, fat-mobilizing and opiate-like activity. The peptide is effective in facilitating (functional) recovery after peripheral and central nerve damage. These substitutions not only cause potentiation and prolongation of activity but also the incorporation of other activities, e.g. on social behaviour.

ACTH and related peptides, in particular Org 2766, have been studied quite extensively in humans in connection with a wide range of cognitive performance tasks, among others (Gaillard 1981; Pigache and Rigter 1981; Kragh Sørensen and Lolk 1987). All trials were double blind. Studies using acute systemic administration of either peptide have failed to demonstrate a consistent effect of peptide treatment on the performance of subjects on memory tests and other tests of cognitive performance, with the exception of tests requiring sustained vigilance. Also, certain tasks of visual perception and discrimination are enhanced after peptide treatment. These effects have been related to improved task-directed motivation under peptide treatment.

Subchronic oral treatment with Org 2766 appears to improve mood, with reduction in self-rated anxiety and depression, to increase self-rated competence, to enhance observed sociability, to improve ward behaviour, to have a positive effect on feelings of competence and to exert a greater cooperation in institutional life. These effects have been found in a wide range of subjects, including retarded adult patients, healthy aged subjects with mild cognitive impairment but nevertheless active in the community, and rather more impaired geriatric in-patients. Positive effects have been found even with the lowest dose of 10 mg/day and the shortest treatment period of 1 week. The effect of peptide treatment increases when the peptide is given for 1 month at a dose of 40 mg/day. Doses up to 80 mg/day for 1 month or 10 mg/day for 6 months are well tolerated and cause no side-effects. In a recent study including 156 mildly and moderately demented patients using 5–80 mg/day for 1 month, Org 2766 induced a small but significant therapeutic effect, mainly on the SCAG total score but in particular on cognitive and somatic functioning (Kragh-Sørensen and Lolk 1987). These effects were almost unrelated to the dose administered. Clinically relevant effects were seen in 25% of the patients. Post hoc analysis showed the best effects in mildly demented patients with comparatively good orientation who complained of lack of energy. These results warrant further research in a more homogeneous group of mildly demented patients and using sophisticated test procedures to analyse the cognitive functioning of the patients. Org 2766 may be effective during a

very early stage of dementia in that the peptide may prevent the usual deterioration of the disease. To test this possibility the diagnosis should first be improved towards early detection of dementia.

Vasopressin neuropeptides and memory disturbances

Several studies mainly performed in rats in aversively motivated tasks suggest that vasopressin and related peptides affect learning and memory processes (De Wied 1984). Both consolidation of acquired information and retrieval of consolidated information is facilitated by vasopressin neuropeptides. More recent studies have uncovered a multitude of central effects of the neurohypophyseal hormones, ranging from brain development to maternal behaviour, from temperature to cardiovascular regulation and sexual behaviour (De Wied 1984). In addition, vasopressin neuropeptides decrease acquisition of heroin and cocaine self-administration and attenuate brain stimulation reward, which suggests that these peptides can interfere with addictive behaviour (Van Ree 1987).

Vasopressin and related peptides have been administered to humans in many studies, including volunteers and patients with various disorders, e.g. memory disturbances (Legros and Lancranjan 1984; Van Ree et al. 1985a). Because patients suffering from post-traumatic amnesia, chronic alcoholism and dementia (senile dementia, multi-infarct dementia, dementia in parkinsonian patients) frequently complain about memory problems, these patients have been included in most of the human studies focusing on memory effects of vasopressin. In addition, elderly people have been studied, since a decrease in neurophysin blood levels has been found over the age of 50. When vasopressin has a physiological role in modulating learning and memory processes in humans, untreated patients suffering from diabetes insipidus may have problems with their learning and memory abilities and could benefit from treatment with vasopressin neuropeptides. Indeed, diabetes insipidus patients scored lower on certain tasks aimed at measuring attention and short- and long-term memory, but this was observed only in patients with the congenital variant of this disease and not in patients with acquired diabetes insipidus (Laczi et al. 1987). Some studies have been carried out in children with learning disorders. Vasopressin neuropeptides have also been applied in psychiatric patients, including patients suffering from schizophrenic psychosis and depression, and heroin addicts.

The various aspects related to the treatment markedly have differed among the studies. The design of the studies has been open or blind, cross-over or placebo-parallel. The peptides have been administered intranasally (most frequently used route), orally or intramuscularly once or three times a day for 1–14 days. For a more general medical use of these peptides, the probable oral effectiveness of the peptides is of particular interest. However, only DGAVP has been administered via the oral route in two studies in brain trauma patients and in one study in children; in addition, the peptide has been administered sublingually to heroin addicts (Fraenkel et al. 1983). In addition to pitressin, which was administered in earlier studies in psychotic patients, four other different vasopressin congeners have been used, namely AVP, LVP, DDAVP and DGAVP. The peptides AVP and LVP induce cardiovascular changes and an antidiuretic action, while DDAVP elicits an antidiuretic effect. These effects hamper the "double-blind" character of studies and may interfere with the expected effects on brain function. The peptide DGAVP seems to be devoid of these peripheral side-effects and may therefore be recommended for human studies. Although beneficial effects have been reported following a single administration, which parallels the effects observed in animal experiments, others have found that the improvement started after 4–5 days. Long-term effects of the peptides have been described.

It seems quite difficult to define a common denominator of the effects of vasopressin treatment, as reported in the various studies. It should first be mentioned that there have been a number of studies showing no treatment effects of vasopressin. This may be related, for example, to the type of patients, the psychological tests applied for treatment evaluation and the treatment variables. It is worth mentioning that treatment effects have been observed in almost all studies with volunteers. These effects have been described as facilitation of learning, memory, attention and concentration. In most of the categories of patients beneficial effects have been reported with regard to memory functions, particularly retrieval processes, although not in all studies. Different underlying mechanisms have been proposed for the vasopressin-induced enhancement of memory processes. In general, two actions can be distinguished: a diffuse non-specific activating action and a specific action on certain aspects of memory and related processes. However, both actions may be present, as suggested by the results of a study by Nebes et al. (1984), which showed that the slope as well as the interception in a memory comparison task are changed by DDAVP treatment, indicating specific memory and "non-specific" effects. These authors conclude that both short-term and long-term memo-

ries (but not semantic memory) are improved by DDAVP to the same degree in young and old volunteers.

A number of studies have shown that attention, concentration and learning of patients and volunteers are improved by vasopressin treatment. The social behaviour of some patients suffering from post-traumatic amnesia, dementia and schizophrenia has improved following vasopressin treatment. Schizophrenic patients improved clinically with respect to negative symptoms and the factor anergia. In addition to an enhancement of cognitive functions, positive effects on mood and energy have also been observed in schizophrenics, in patients with primary affective disorders and in demented and brain trauma patients. A facilitation of the methadone detoxification and a decreased intake of heroin and cocaine have been found in heroin addicts treated with vasopressin.

In general, it has been reported that patients with severe deficits respond less favourably to vasopressin than patients with mild symptomatology. This has been observed in patients suffering from brain trauma, chronic alcoholism, dementia and affective disorders. Thus, patients with more serious head injuries, patients suffering from Korsakoff's syndrome or Alzheimer's disease or severely depressed patients hardly responded to vasopressin treatment. This may be related to the severity of the symptoms or to the degree of brain damage. A lack of effect of vasopressin may be due to lesions in the brain areas on which the peptide can be expected to act.

Although various effects of vasopressin treatment have been described, the target patient population for vasopressin neuropeptide is thus not yet well defined. With respect to cognitive disorders, sophisticated neuropsychological test procedures, including information-processing tasks, may contribute to the definition of such a patient population and to the evaluation of the effects of treatment. Future studies in humans should also take into account other interesting influences of vasopressin, e.g. on social behaviour, mood and addictive behaviour. Desglycinamide (Arg^8)-vasopressin or the recently discovered potent fragments of vasopressin (Burbach 1986) may be recommended for these studies, because these peptides are practically devoid of the peripheral "side"-effects on water homeostasis and blood pressure that accompany treatment with vasopressin or DDAVP.

Neuropeptides and Schizophrenia

β-Endorphin [βE-(1–31)] and related peptides produce a variety of effects which are also induced by morphine and related compounds. Fragmentation of this opioid peptide causes the generation of neuropeptides with different CNS effects. γ-Endorphin [βE-(1–17), γE] and the non-opioid fragments $desTyr^1$-γ-endorphin [βE-(2–17), DTγE] and desenkephalin-γ-endorphin [βE-(6–17), DEγE] possess neuroleptic-like effects in animals (De Wied 1978). Arguments in favour are their influence on avoidance behaviour, their positive effects on grasping responses, the reduction in electrical self-stimulation elicited from the ventral tegmental area and nucleus accumbens, and their antagonistic influence on apomorphine-induced hypolocomotion (Van Ree and De Wied 1982). α-Endorphin [βE-(1–16), αE] and related non-opioid peptides produce effects which resemble those of psychostimulant drugs, such as amphetamine (De Wied 1978; Van Ree et al. 1980). Other fragments of β-endorphins, such as βE-(10–16), may possess serotonine-like effects (Gaffori and Van Ree 1985) or opioid antagonistic effects as reported for βE-(1–27) and βE-(1–26) (Hammonds et al. 1984).

The neuroleptic-like effect of γ-type endorphins led us to postulate the existence of endogenous neuropeptides with neuroleptic-like activities. Since the α-type endorphins have effects which resemble the effects of psychostimulants and since both types of peptides are derived from βE-(1–31), the hypothesis was put forward that a defect in the biosynthesis, metabolism or bioactivity of γ-endorphin or a related peptide may be an aetiological factor in schizophrenia that is thought to be caused by an imbalance between α-, β-, and γ-type endorphins (De Wied 1978). Several clinical trials (Van Ree et al. 1985b, 1986) have indicated that DTγE and DEγE indeed possess antipsychotic effects in a category of schizophrenic patients. The peptides were usually administered intramuscularly at a dose of 1 mg/day (DTγE) or 3 mg/day (DEγE) for 8–10 days. The design of these studies (except one) was double-blind, either placebo-controlled or cross-over. Of the total of 79 patients, 16 did not respond to treatment (maximal response $< 20\%$ as assessed by the Brief Psychiatric Rating Scale) and 25 showed a slight response (20%–50%), while 20 displayed a moderate (50%–80%) and 18 others a marked response ($> 80\%$). This contrasts with the response of patients treated with placebo only. Of the 20 treated patients, 17 did not respond, while 3 showed a slight response. Taking a score of at least 50% maximal response to treatment as indicating a clinically significant improvement, a clinically obvious therapeutic effect was observed in about half of the patients.

When patients responded to treatment the effect started after 3–7 days of active treatment and all symptoms, including positive and negative symp-

toms, decreased. Eleven patients treated with γ-type endorphins for one or two consecutive treatment periods remained free of psychotic symptoms for at least 6 months (Van Ree et al. 1982). Some evidence was found for an improved functioning of these patients in the period after peptide treatment, as compared with that before treatment, i.e. relapse was postponed, less treatment with neuroleptics was required and social functioning was improved. The effect of DTγE and DEγE in schizophrenic patients has also been studied by others. In nine trials including a total of 87 patients, 24 patients responded favourably to treatment (Bourgeois et al. 1980; Casey et al. 1981; Emrich et al. 1981; Fink et al. 1981; Korsgaard et al. 1982; Manchanda and Hirsch 1981; Meltzer et al. 1982a, b; Tamminga et al. 1981; Volavka et al. 1983). In one of the two trials with DEγE performed by others, the peptide induced the same antipsychotic action as haloperidol (Kissling et al. 1984). In the other trial, a significant improvement of psychotic symptomatology was found with 10 mg DEγE, but not with 1 and 3 mg administered daily for 4 weeks, as compared with placebo treatment (Azorin et al. 1986). Thus, γ-type endorphins may have an antipsychotic action in a number of schizophrenic patients. No side-effects of γ-type endorphin treatment have so far been reported. It is of particular interest that extrapyramidal side-effects were not observed in any of the studies.

The response of the patient varied from no response to complete remission of psychotic symptoms. Analysis of the collected data revealed that the presence and intensity of motor symptoms such as retardation and catatonic symptoms negatively influenced the response of the patients to peptide treatment. In addition, reduced responsiveness has been observed in patients with a long duration of the most recent psychotic episode or who had been treated previously with high doses of neuroleptics. The patients responded less when the intensity of negative symptoms was more severe at the start of the experimental treatment. No differences in this respect were found for the positive symptoms. Finally, patients treated with γ-type endorphins have been tested for antigens of the HLA system, the major histocompatibility system. Patients responding to the treatment with γ-type endorphins had a higher incidence of HLA-B_{13}, B_{15} and B_{22} antigens in particular (Claas et al. 1984; Van Ree et al.1986). This suggests that genetic factors are associated with a good response to γ-type endorphins and supports the notion that an inborn error in the generation or metabolism of γ-type endorphins may be an aetiological factor in schizophrenia. Other evidence in favour of the hypothesis is that in vitro processing of βE-(1–31) to DEγE is enhanced in post-mortem putamen tissue of schizophrenic patients (Schoemaker and Davis 1984). This may be caused by neuroleptic treatment of the patients, since DEγE formation is increased in rats chronically treated with haloperidol (Davis et al. 1984). The levels of α- and γE are increased in post-mortem brain tissue of schizophrenic patients. The γE-containing fraction from these brains appears to be biologically inactive, although the amino acid composition of γE isolated from pituitary tissue of schizophrenic patients is identical to that of synthetic material and the nucleotide sequence of γE-cDNA is unchanged (Wiegant et al. 1987; Bovenberg et al. 1986). Thus, the deviant biological activity of γE is not based on a mutation in the γE encoding regions of the POMC gene. The defect might be caused by an abnormal derivatization of γE, which may interfere with its activity. However, the exact structure of the peptide has not been established.

Several clinical trials have been performed to investigate the antipsychotic action of CCK (cholecystokinin)-related peptides in schizophrenic patients (Moroji et al. 1982a, b; Itoh et al. 1982; Nair et al. 1982, 1983, 1986; Bloom et al. 1983; Lotstra et al. 1984; Hommer et al. 1984; Mattes et al. 1985; Van Ree et al. 1984; Verhoeven et al. 1986). Various peptides were used in these trials, e.g. CCK-33, CCK-8 and ceruletide. The design of the studies was open or single-blind, uncontrolled; double-blind, placebo controlled; or double-blind, placebo cross-over. The dose of the peptides varied between approximately 2 and 50 μg and in most studies the peptide was given intramuscularly and only once. In some studies, however, the intravenous route was used and sometimes repeated injections were given. In all but one of the studies neuroleptic therapy was maintained and the patients were at least partly resistant to the therapy. In general, an improvement of symptomatology was reported for most studies. The onset of the therapeutic effect was rather rapid and the effect persisted for several days or weeks, even after a single injection. Although the therapeutic effect was statistically and in some cases clinically significant, the amelioration was in general partial and not always impressive. Moreover, in only two of the five double-blind studies was a significant improvement found. Nevertheless, there were patients that responded well to CCK-related peptides. In the largest study to date (Itoh et al. 1982) improvement was associated with a younger age and shorter hospitalization.

In a trial in which DEγE was compared with ceruletide, no marked differences were observed among these peptides, either in the effectiveness of treatment or in the characteristics of the patients responding to either peptide (Verhoeven et al. 1986).

Neuropeptides and Affective Disorders

Several neuropeptides have been studied as a possible therapeutic agent in depression (Prange et al. 1987). In particular, releasing and release-inhibiting hormones have been used. These hormones also possess CNS activity. In rats, CRH enhances neuronal activity in a variety of brain structures and stimulates sympathetic drive. It affects several types of behaviour, including learned behaviour (Veldhuis and De Wied 1984) and its central administration results in a generalized activation of the sympatho-adrenomedullary system (Brown et al. 1982). A central role for CRH in adaptation and in the neuroendocrine and autonomic response to stress has been suggested. TRH is an endogenous mediator in arousal behaviours, since administation of this neuropeptide in animals results in locomotor and behavioural stimulatory effects (Reichlin 1986). In addition, TRH has analeptic effects and may function to stabilize the level of behavioural arousal (Nemeroff et al. 1984). LH-RH affects the sexual behaviour of animals. In females it facilitates lordosis behaviour and in males reduces latency to intromission and ejaculation (Moss and Foreman 1976). LH-RH also has effects on learned behaviour. The tripeptide PLG, also referred to as MIF-I (melanophore inhibiting factor) is the C-terminal part of oxytocin. PLG mimics certain effects of vasopressin and oxytocin on memory processes, on development of morphine tolerance, and on dependence and acquisition of heroin self-administration (Van Ree and De Wied 1983). In addition, it exerts other effects; for example, it prevents experimentally induced amnesia (Walter et al. 1975).

In depressed patients most studies with neuropeptides have used the tripeptide TRH (Prange et al. 1987). The peptide appears to be ineffective in most double-blind studies using oral administration. However, after intravenous administration, a short-lasting antidepressant effect has been observed in about half of the studies, which include more than 500 patients. An improvement of clinical significance has been found in only a limited number of patients.

Oral administration of the tripeptide PLG has been reported to exert an antidepressant effect in three out of four studies. The antidepressant effect of PLG occurs rather rapidly and is long-lasting. It seems that lower doses of PLG are more effective than higher doses. PLG is reported to be at least as effective as imipramine. The antidepressant effect of the peptide starts earlier and the peptide less often fails compared with imipramine.

Some depressed patients have been treated with the decapeptide LHRH, but in only one open trial were some slight effects found, in particular improved sleep. DDAVP, given intranasally to a limited number of depressed patients, improves cognition, while in some an antidepressant effect has been observed as well. Whether the mood-increasing effect of DDAVP is secondary to the improvement of cognition remains to be elucidated.

It has been postulated that a functional lack of endogenous opioids may be related to the pathogenesis of depressed symptomatology. This postulate has led to five trials, in which β-endorphin was administered to a total of 31 patients. In about half of the patients an antidepressant effect was observed after a single, intravenous injection. The effect started soon after the injection and lasted some hours. In some patients hypomanic or manic symptoms were observed after treatment. A positive effect of β-endorphin has been found in one out of three double-blind studies. The enkephalin analogue FK 33–824 has been studied in two studies including 13 depressed patients. In 8 patients a short-lasting antidepressant effect was found. It is not clear whether the effects of β-endorphin and FK 33–824 are related to an antidepressant action or to the inherent opiate action. There have been some reports that the opioid antagonist naloxone may worsen the conditions of depressed patients. In addition, a beneficial effect of naloxone in manic patients has been reported. The non-opioid fragment of β-endorphin, desTyr^1-γ-endorphin (DTγE), which exerts an antipsychotic action in some schizophrenic patients, has also been given to depressed patients. Chazot et al. (1985) reported that DTγE treatment resulted in an antidepressant effect in 8 of the 10 patients. Others have also found some antidepressant action of DTγE.

In conclusion, several peptides have been studied in affective disorders. However, except for TRH, there have only been a limited number of trials with the various peptides. Nevertheless, some promising leads are available (e.g. the antidepressant effect of PLG) and it will be worthwhile to pursue these further. More detailed research in this field may eventually disclose neuropeptides with therapeutic action in affective disorders.

Concluding Remarks

The results with neuropeptides in the clinic so far have been less dramatic than the developments in the laboratory. One of the problems may be the mode of administration of neuropeptides and the penetration of sufficient amounts through the blood brain barrier. More knowledge on the bioavailability, kinetics, and lipid solubility is needed to improve effective treatment. There is some doubt whether these pep-

tides enter the brain even when administered in pharmacological doses. However, animal experiments suggest that only picogram amounts are needed to achieve effects, and such amounts are difficult to measure in the brain. Neuropeptides may have dual or U-shaped effects and may elicit different responses following acute or chronic administration. These make it difficult to determine dose, frequency and duration of treatment. Many of these problems might be solved if more sensitive methods for measuring the respective neuropeptides in body fluids and brain become available. Knowledge on the structural requirements of neuropeptide-receptor interaction is needed in order to enable the synthesis of analogues and of conventional compounds which are more rigid and which may be more effective than the original endogenous ligands. It can be expected that the present drugs for the treatment of psychopathology will be replaced by neuropeptides, neuropeptide analogues and eventually their more rigid imitations with more specific effects and fewer side-effects than the drugs in use today. This will lead to a more fundamental approach to the treatment of psychiatric and neurological diseases, retardation, ageing and possibly dementia.

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