Advances in Neurology, Vol. 45, edited by M. D. Yahr and K. J. Bergmann. Raven Press, New York © 1986.

Dopaminergic–Peptidergic Interactions in Extrapyramidal Disorders: A Review of the Clinical Evidence

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Over the last decade there has been an explosion of neuropeptide research, and we now think that peptides form the largest group of chemical messengers in the nervous system (14,26). The availability of highly sensitive immunoassays and sophisticated immunocytochemical staining techniques has led to the identification of more than 30 peptides occurring in nerve cell bodies and terminals within the mammalian CNS and it is becoming difficult to keep listings like the one in Table 1 updated.

The growing list of recognized neuropeptides contrasts sharply with the relative ignorance as to their possible physiological role in the human brain. Transmitter-like actions in other neurons have been shown for many of them, but—unlike "classical" neurotransmitters—neuropeptides often produce effects of slow onset and prolonged duration, which has led to the use of the term "neuromodulator" to describe their action (8,26). Certain aspects of their possible physiological functions can, furthermore, be inferred from the anatomical distribution of these peptides within the mammalian CNS. The basal ganglia in particular have been shown to contain high concentrations of several of the neuropeptides (see Table 2).

LABORATORY EVIDENCE FOR INTERACTIONS BETWEEN "CLASSICAL" NEUROTRANSMITTERS AND PEPTIDES IN THE EXTRAPYRAMIDAL SYSTEM

It is reasonable to assume that the peptides present in structures of the extrapyramidal system play a part in the regulation of motor behavior. Furthermore, changes in neuropeptide concentrations within the basal ganglia have been detected in the brains of patients suffering from extrapyramidal disorders. Most of the evidence originates from postmortem studies of Parkinson's and Huntington's disease where significant reductions of the enkephalins, substance P, vasoactive intestinal polypeptide (VIP), cholecystokinin (CCK) 8, and angiotensin-converting enzyme have all been reported for various parts of the striatonigral and striatopallidal system (1,2,5,14,15,27). As both diseases are characterized by major alterations of "classical" transmitter activity within the same structures, some form of interaction between the latter and these neuropeptides is likely to play a role in the pathophysiology of these disorders.

Such an interaction between classical transmitters and neuropeptides has been further substantiated by immunohistochemical findings of a coexistence of substances of either category within the same neuron (24,38). Some examples of such coexisting pairs are listed in Table 3. Of particular interest for extrapyramidal pathophysiology is the coexistence of dopamine (DA) and CCK 8 in cells of the dopaminergic mesolimbic pathway, which has been shown to be affected in Parkinson's disease (2). Another dopaminergic–peptidergic interaction in the basal ganglia is suggested by findings which show human mesencephalic DA-neurons to be surrounded by met-enkephalin (Met-Ek)-containing terminals (17).

Further evidence for a close functional association between DA and neuropeptides in the extrapyramidal system has been obtained in animal studies of the neurotoxicity of *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)—a synthetic pethidine derivative causing nigral cell damage and clinical parkinsonism in exposed persons (30). In marmosets exposed to this toxin not only a depletion of striatal DA but also profound changes in the concentrations of substance P, VIP, and neuropeptide Y (NPY) were detected in the region of the substantia nigra (4).

TABLE 1. *Neuropeptides that have been described in neurons not subserving neuroendocrine function*

Peptides of the hypothalamo-pituitary axis
Thyrotropin releasing hormone (TRH)
Somatostatin
Luteinizing hormone releasing hormone (LHRH)
Corticotropin (ACTH)
Growth hormone (GH)
α-Melanocyte-stimulating hormone (α-MSH)
MSH-release inhibiting factor (MIF)
Oxytocin
Vasopressin
Lipotropin
Opioid peptides
Dynorphin
B-Endorphin
Met-enkephalin
Leu-enkephalin
Kyotorphin
Gut peptides
Cholecystokinin (CCK)
Gastrin
Secretin
Motilin
Pancreatic polypeptide (PP)
Avian pancreatic polypeptide
Vasoactive intestinal polypeptide (VIP)
Miscellaneous peptides
Angiotensin
Angiotensin converting enzyme (ACE)
Calcitonin
Glucagon
Substance P
Neurotensin
Neuropeptide Y (NPY)
Bombesin
Bradykinin
Proctolin

CLINICAL EVIDENCE FOR DOPAMINERGIC–PEPTIDERGIC INTERACTIONS IN BASAL GANGLIA DISEASES

While experimental data on interactions between peptides and classical transmitters—particularly the monoamines—in the central and peripheral nervous system are accumulating there are only scarce and often conflicting clinical findings to contribute to this area of neuropharmacology. The clinical data available for the extrapyramidal system are largely restricted to attempts at modifying the changes in dopaminergic activity in the diseases of Parkinson and Huntington by administering peptides or their antagonists.

Enkephalins and DA-System in Basal Ganglia Disease

There are now sufficient data to support the assumption that an interaction between dopaminergic and enkephalinergic neurons in the extrapyramidal system plays a significant role in the pathology of Parkinson's disease (see ref. 2 for review). A 30% to 70% depletion of both Met-Ek and Leu-Ek has been detected in different parts of the striopallidal and strionigral system of parkinsonian brains, but the functional significance of such findings remains obscure. Can anything further be learned from clinical studies of the effects of opiate antagonists on the symptoms of Parkinson's disease? The studies summarized in Table 4 were all based on the conception that the enkephalins might functionally behave as DA-antagonists and that opiate antagonists might therefore exert beneficial effects in Parkinson's disease. That notion rested in part on the observation that the acute administration of opioid peptides induces a hypertonic and akinetic state in rats, which can in turn be reversed by dopaminergic agents (29,43). It has, however, become clear that dopaminergic–peptidergic interactions in Parkinson's disease must be far more complex and that, for example, enkephalins can stimulate striatal DA release (9). It does, therefore, not seem surprising that the results of the clinical studies listed in Table 4 are not consistent. While naltrexone and naloxone produced no effect in two trials, improvement of parkinsonian symptoms as well as a reduction of on-off effects and L-DOPA-induced involuntary movements were observed by others. More than a speculative interpretation of such an improvement of features of Parkinson's disease following naloxone is presently impossible. Such findings do however underline the potential clinical importance of dopaminergic–peptidergic interrelations in this malady.

TABLE 2. *Neuropeptides in the human basal ganglia*

B-Endorphin
Met-Enkephalin
Leu-Enkephalin
Substance P
Neurotensin
Somatostatin
CCK 8
TRH
ACE
VIP
MIF[a]

[a]Based on animal data (7,10,23).
Data from refs. 2,5,12,14,15,22,25,40,41.

TABLE 3. *Example of "coexisting" pairs of a classical neurotransmitter and a neuropeptide within the same neuron*

Classical transmitter	Peptide	Localization
5-HT	Substance P TRH	Medulla oblongata
NE	Somatostatin	Sympathetic ganglia
NE	Enkephalin	Superior cervical ganglion
DA	CCK	Mesencephalon[a]
ACh	VIP	Autonomic ganglia

[a]Also shown in human material.

5-HT, serotonin; NE, norepinephrine; DA, dopamine; ACh, acetylcholine.

Modified from Hokfelt et al., ref. 24.

Nutt and co-authors (32) have also included patients with Huntington's disease in their study of the effects of naltrexone on movement disorders and, as in Parkinson's disease, failed to detect any effect on the clinical symptoms of these patients. The depletion of neuropeptides in the globus pallidus and substantia nigra observed in the brains of patients suffering from Huntington's chorea are even more profound than those described for Parkinson's disease and apart from the enkephalins also include substance P, CCK, angiotensin converting enzyme (ACE), and VIP (see ref. 14 for review).

Looking at the possibility of enkephalinergic interactions with the hyperactive dopaminergic system in Huntington's disease we studied the effects of an orally active synthetic analog of Met-Ek [D-Ala^2-MePhe^4-Met(0)-ol-enkephalin; FK 33-824 Sandoz] on the choreic movements of 5 patients (20,21). The analgesic potency of this enkephalin analog has been shown to be far greater than that of the mother substance (37). In our study it was employed in an open fashion with single doses of 50 to 100 mg given after breakfast on 4 consecutive days to otherwise untreated patients. Evaluation was performed by two independent observers who counted the frequency of involuntary movements for 5 min periods before and at 30 min intervals for 3 hr after drug ingestion using video films of the patients. A significant reduction in the frequency of involuntary movements was evident in 3 patients between 60 and 90 min after drug administration (Fig. 1). No acute effects could be observed in the two other patients although one of them showed a gradual decrease in the frequency of his choreic movements over the 4-day treatment period.

Four patients with tardive dyskinesia were also treated with this compound in a similar fashion but without any change in the features of their disorder. These results were interpreted as being in favor of enkephalinergic inhibition of striatal dopaminergic hyperactivity in Huntington's disease, although the exact site of such inhibition had to remain speculative.

In a double-blind cross-over study using single dose i.v. challenges with 0.5 to 2 mg of the same compound in 12 choreic patients Destee et al. (13) could not find significant changes in the frequency or amplitude of abnormal movements when comparing FK 33-824 to placebo. Similarly Sheehy et al. (39) found no effects of FK 33-824 in two patients with Huntington's disease or in cases of Parkinson's disease, generalized dystonia, torticollis, or tardive dyskinesia.

For a variety of reasons it is premature to draw any conclusion about the role of enkephalinergic–dopaminergic interactions in basal ganglia disease from the clinical studies reviewed above. Not only are the numbers of patients studied very small and the results obtained quite inconsistent; there is also considerable uncertainty about the doses of, for example, Fk 38-824 needed to produce effects in the extrapyramidal system. Equally uncertain is whether opiate antagonists are actually capable of blocking the receptors for enkephalins in the basal ganglia. In view of the experimental and human postmortem evidence outlined earlier in this chapter it does, however, seem very unlikely that the enkephalins should not have a role in the regulation of human motor behavior.

TABLE 4. *Clinical studies of the effect of opiate antagonists on movement disorders*

Reference	Drug	Dose/route	Diagnosis	Results
Nutt et al. (32)	Naltrexone	100 mg/po	PD (N = 6)	NE
			HD (N = 3)	NE
Price et al. (36)	Naloxone	0.8–2 mg/i.v.	PD (N = 5)	NE
Agnoli et al. (3)	Naloxone	2–8 mg/i.v.	PD (N = 15)	Improvement of parkinsonian symptoms
Trabucchi et al. (42)	Naloxone	8 mg/i.v.	PD (N = 6)	Reduction of dyskinesias prolonged "on-time"

PD, Parkinson's disease; HD, Huntington's disease; NE, no effect.

TABLE 5. *Clinical studies of D-Ala²-MePhe⁴-Met(O)-ol-enkephalin (FK33 824, Sandoz) in movement disorders*

Reference	Type of study	Dose/route	Diagnosis	Results
Gerstenbrand and Poewe (20)	Open	50–100 mg/po	HD (N = 5)	Improvement (N = 3)
Gerstenbrand and Poewe (21)			TD (N = 4)	NE
Sheehy et al. (39)	Open	0.25–0.5 mg/i.v.	PD (N = 3)	NE
			HD (N = 2)	NE
			TD (N = 1)	NE
			Dystonia (N = 3)	NE
			Torticollis (N = 3)	NE
Destee et al. (13)	Double blind	0.5–2 mg/i.v.	HD (N = 12)	NE

HD, Huntington's disease; PD, Parkinson's disease; TD, tardive dyskinesia; NE, no effect.

PLG (MIF) in Parkinson's Disease

Ironically the first peptide to be clinically tested in an extrapyramidal movement disorder was the tripeptide PLG (Pro-Leu-NH_2), which itself has so far not been demonstrated in the human brain. Originally identified as a melanocyte-stimulating hormone (MSH)-release inhibiting factor (MIF) in the rat hypothalamus (31) it has now been shown to have a wider distribution in the rat brain, and MIF, the related tetrapeptide Tyr-MIF, and corresponding binding sites are present in the rat striatum (7,10,23).

Soon after its identification PLG (MIF) was shown to possess DOPA-potentiating as well as oxotremorine antagonizing properties in animal experiments (see ref. 35 for review). Based on such data and in view of a report by Cotzias et al. (11) about a deteriorating effect of MSH injections on the symptoms of Parkinson's disease PLG (MIF) was eventually given to Parkinson's disease patients

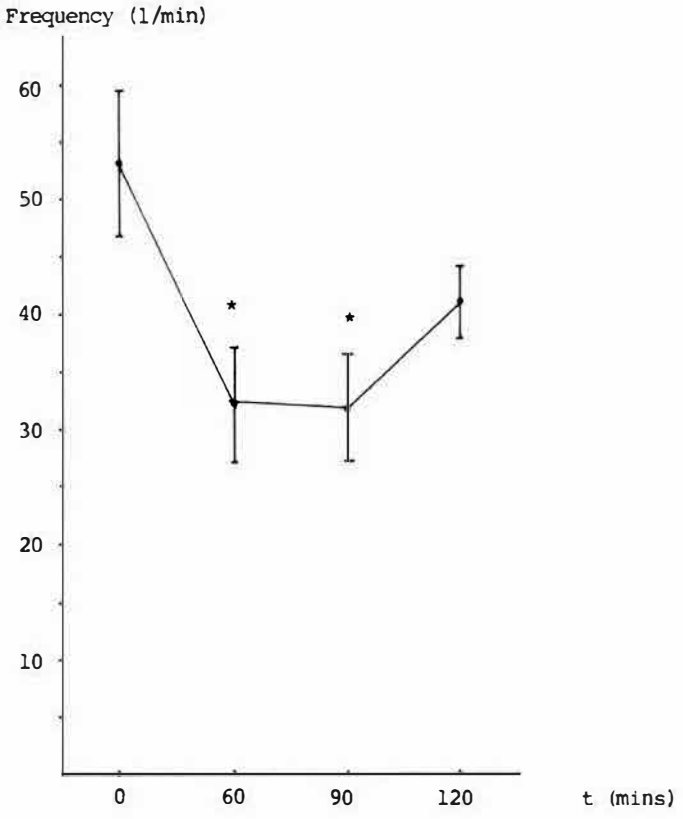

FIG. 1. Significant decrease in this frequency of choreic movements in a patient with HD observed 60 and 90 min after oral application of FK 33-824 $p = 0.005$.* (Modified from Gerstenbrand and Poewe, ref. 20.)

(6,16,28,44). The results of these early trials with PLG in Parkinson's disease were uniformly favorable.

In a first trial by our group PLG (MIF) was given as a continuous 24 hr i.v. infusion in a total daily dose of 400 mg to 10 otherwise untreated parkinsonian patients over a period of 10 days (18). The results were remarkable and showed global clinical improvement of up to 75% in 9 of the 10 patients. The clinical improvement became first apparent on the third infusion day and akineto-rigid symptoms seemed to respond better than tremor. In a second set of clinical trials PLG (MIF) was administered as 200 mg bolus injections twice daily in addition to chronic L-DOPA treatment in 7 patients with Parkinson's disease (19). The improvement in clinical scores observed in this study was taken as evidence for an L-DOPA potentiating effect of PLG (MIF)—similarly to what had been observed by others in animal (35) or human (6) studies. Figure 2 gives an example of an acute effect of a bolus injection of PLG (MIF) on the motor performance of one of the patients of this study. L-DOPA-induced dyskinesias increased in 2 of 3 cases in this group of patients, a finding in line with what was reported by others (44).

Mood brightening effects of PLG (MIF) were noted both in our own trials and in that reported by Fischer et al. (16).

Of all CNS peptides studied in extrapyramidal disorders the results obtained with PLG (MIF) in Parkinson's disease by various groups appear to be the most consistent. They are strongly in favor of a central DA potentiation exerted by this peptide and it is interesting to note that PLG (MIF) has been shown to modify striatal DA-receptor sensitivity in rats chronically exposed to morphine (7). Unfortunately, further pursuit of the possible role of PLG (MIF) in Parkinson's disease has been limited by the lack of orally active analogs. With their availability more insight might be gained into the nature of interaction between PLG (MIF) and DA in Parkinson's disease.

CSF Studies of Neuropeptide Concentrations in Extrapyramidal Diseases

A rather heterogeneous picture emerges from studies of cerebral spinal fluid (CSF) concentrations of various neuropeptides in patients with diseases of the basal ganglia. Met-Enkephalin concentrations in the CSF of Parkinson's disease patients were found both normal or elevated as compared to controls—

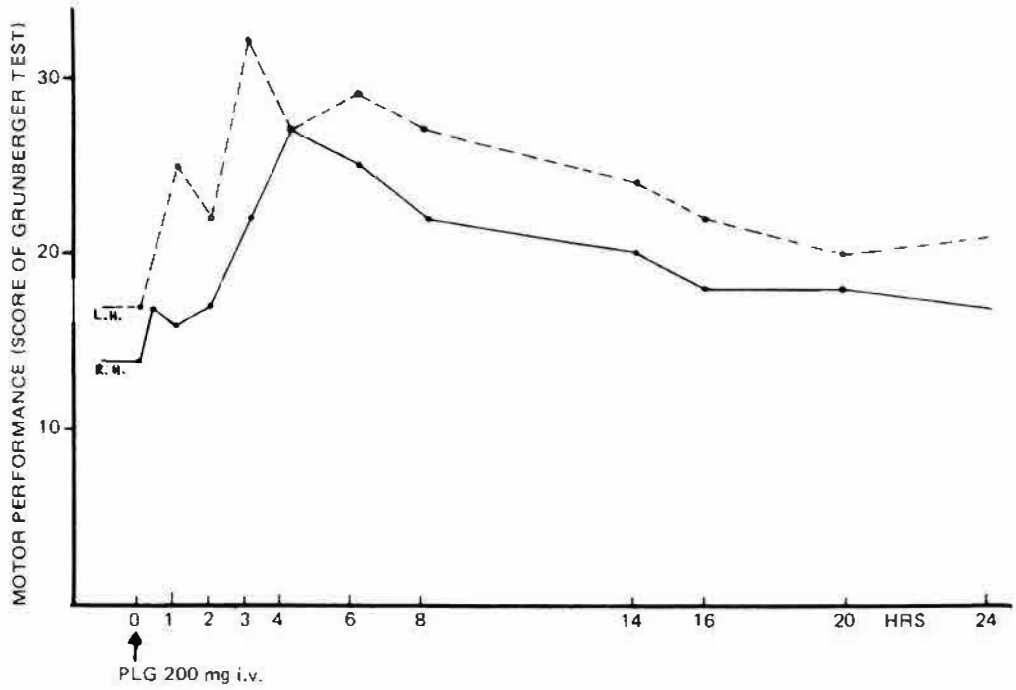

FIG. 2. Motor performance score in a 61 year old patient with PD following bolus injection of 200 mg PLG (MIF). The patient is receiving chronic L-DOPA substitution, baseline values correspond to average of test scores on 5 previous days without PLG administration. LH, left hand; RH, right hand. (From Gerstenbrand et al., ref. 19, with permission.)

depending in part on the duration of the disease (34). CSF concentrations of substance P were found within normal limits in a variety of extrapyramidal disorders, including Parkinson's and Huntington's disease by Nutt et al. (33), whereas Pezzoli et al. (34) reported raised CSF levels of this peptide in Parkinson's disease. The latter finding was thought to reflect compensatory hyperactivity of an excitatory striatonigral substance P pathway in response to the nigral dopaminergic hypoactivity of parkinsonians (34). Clearly the presently available CSF data on neuropeptides in extrapyramidal diseases are too limited to contribute to our understanding of peptidergic–dopaminergic interactions in these disorders. In view of the fact that CSF levels of some of the classical neurotransmitters or their metabolites reflect reasonably well the corresponding intracerebral changes in some extrapyramidal disease there is hope that more can be learned from CSF studies of neuropeptides in the future.

CONCLUSIONS

There is now sufficient experimental evidence to assume an important role of neuropeptides in the regulation of human motor behavior. The structures of the extrapyramidal system are rich in a number of neuropeptides and profound changes of their concentrations have been found to occur in basal ganglia diseases like Parkinson's disease or Huntington's chorea. Current data suggest a close relationship between dopaminergic and peptidergic neurons in the basal ganglia. The clinical information in this area is largely restricted to studies of the actions of opiate antagonists and enkephalin analogs in movement disorders as well as to the effects of the tripeptide PLG (MIF) in Parkinson's disease. On the other hand, various other peptides like thyrotropin releasing hormone (TRH), CCK 8, neurotensin, ACE, and VIP have all been found decreased in the basal ganglia of Huntington's disease or Parkinson's disease patients. The development of orally active analogs of these peptides with sufficient half-lives and blood-brain barrier penetration could mark the beginning of a new era in the clinical neuropharmacology of extrapyramidal diseases.

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