Peptides and basal ganglia diseases

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INTRODUCTION

The experimental and clinical research on peptides with regard to their possible function as neurotransmitters or neuromodulators has presented a variety of exciting results in the past years. The growing activity in the investigation of brain peptides suggests to many that whereas the past 25 years in neuroscience have been an era of monoamine research the coming 25 years might be an era of peptides. This may be especially true for the extrapyramidal system and its disorders. While the function of the hypophysiotropic peptides seems largely confined to their endocrinologic action in the hypothalamo-pituitary axis, a number of peptides show a rather wide distribution in the nervous system. Those which currently appear to be true neurotransmitters or neuromodulators are the two pentapeptides methionine-enkephalin and leucine-enkephalin, the undecapeptide substance P and possibly also β-endorphin, thyrotropin-releasing hormone (TRH), neurotensin and angiotensin II.

Although widely distributed in the CNS their concentration varies greatly in different brain regions suggesting a possible association with certain neuronal pathways. Among the brain regions exhibiting especially high concentrations of the putative peptide transmitters, the basal ganglia should be of special interest to both the basic researcher as well as the clinician. Clinical neurological research so far can offer little insight into the possible role that peptide neurotransmitters may play in basal ganglia diseases. On the other hand, the clinician's need for new substances to treat disorders of the extrapyramidal system is very

urgent since many of these disorders are currently without efficient treatment. Even the present treatment of parkinsonism, which certainly constitutes the most efficient one among all basal ganglia diseases, has to cope with severe shortcomings. It is this experimental therapeutic approach that the clinical researcher may choose to face the problem of neuropeptides and their relation to basal ganglia diseases.

MIF (PLG) AND PARKINSON'S DISEASE

The first peptide that was clinically tested for its therapeutic efficacy in an extrapyramidal disorder was the tripeptide PLG (Pro-Leu-GLY-NH_2) which was synthesized by Nair et al. in 1971, and claimed to have MSH-release-inhibitory properties. It is therefore referred to as the melanocyte-inhibiting-factor (MIF). Following a deterioration of parkinsonian symptoms observed after injections of MSH to patients by Cotzias et al. (1967), and after elevated MSH plasma-levels in Parkinson's disease had been measured by Shuster et al. (1973), PLG was soon tested in animal experiments, where an oxotremorine antagonism and L-dopa potentiation could be observed (Plotnikoff et al., 1974; Plotnikoff and Kastin, 1974). Based on these observations Kastin and Barbeau (1972) were the first to use PLG as i.v. infusion in patients with Parkinson's syndrome. In their experiments the substance proved to be effective in reducing tremor and rigidity, and in a lesser degree akinesia. Similar observations were made by Fischer et al. (1974) who also noticed mood brightening under PLG. In a further set of experiments Barbeau (1975) was able to demonstrate potentiation of L-dopa by intravenous PLG in Parkinson patients.

In our own studies with PLG in Parkinson's syndrome we started to use higher doses than Barbeau and Fischer and administered 400 mg daily as a continuous 24-hour i.v. infusion (Gerstenbrand et al., 1976). In a 10-day treatment period with PLG as the sole antiparkinson agent, there was global clinical improvement in 9 of 10 patients. Rigidity and akinesia were influenced more than tremor. There was mood brightening in 5 of 10 patients (Table 1). A depot effect with continuing improvement of up to 4 weeks after cessation of the infusion series was observed in 8 patients. When deterioration finally occurred it was possible to restore the original improvement by a series of 3-5 bolus injections of 400 mg of MIF in 3 of them (Fig. 1). Giving PLG as i.v. bolus injections of 200-400 mg daily in combination with a stable L-dopa therapy we could confirm the L-dopa potentiation seen by Barbeau (Gerstenbrand et al., 1979). Again, tremor was influenced less

Table 1 Evaluation of treatment with MIF (400 mg as 24-hour i.v. infusion) in 10 patients with Parkinson's syndrome

No. of patients	Initials	Age	Sex	Diagnosis	Degree pre- A R T	Degree post- A R T	Global clinical improvement (%)	Psychological state pre	Psychological state post	Depot effect	Remarks
1	F.R.	47	M	P.a.	3 3 0	1 1 0	75	D	N	+	–
2	J.F.	67	M	P.a.	3 3 3	1 2 2	50	D	N	±	–
3	J.K.	61	M	P.a./T	1 1 3	0 0 2	75	D	Hm	±	A 2nd course of treatment produced the same effect
4	E.W.	70	M	P.a.	1 3 2	0 2 1	50	N	N	+	An i.v. injection course produced the same effect
5	J.D.	66	M	P.a.	4 4 1	3 3 1	25	D	N	–	–
6	P.K.	62	F	P.a.	3 3 0	1 2 0	75	N	N	+	–
7	M.S.	67	F	P.a./T	2 2 3	2 2 3	0	D	D	–	Interruption of study. Patient declined further treatment
8	L.H.	64	M	P.a.	1 2 1	0 1 0	75	N	N	+	–
9	Th.Z.	60	M	P.a.	2 2 2	1 1 1	75	D	N	+	–
10	B.S.	68	F	P.a./T	2 1 4	1 1 3	25	D	D	±	Rapid deterioration of tremor after cessation of treatment

Psychological state: D = depressed, N = normal, Hm = hypermanic.
P.a. = paralysis agitans; T = tremor; A = akinesia; R = rigidity; M = male; F = female.

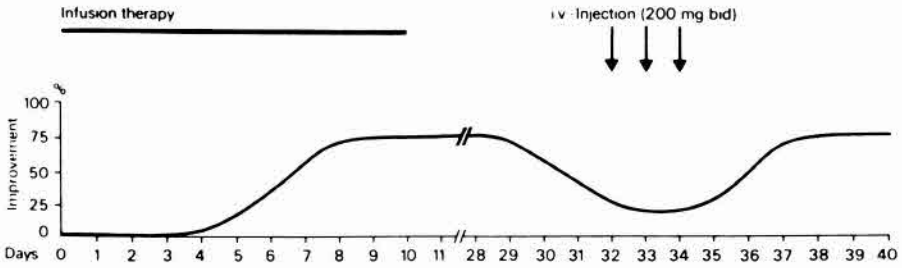

Fig. 1 Course of treatment with MIF-infusions (400 mg/day) in a 47-year-old patient with idiopathic Parkinson's syndrome. (From Gerstenbrand et al., 1976.)

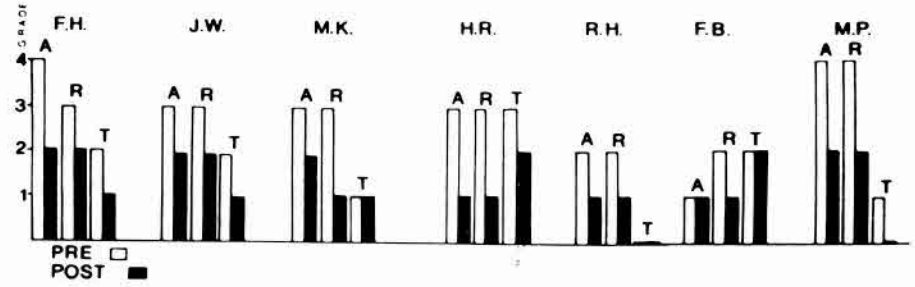

Fig. 2 Effect of treatment with PLG (MIF) 200 mg twice daily in addition to previous levodopa treatment on akinesia, rigidity and tremor in 7 patients with Parkinson's syndrome. (From Gerstenbrand et al., 1979.)

than akinesia and rigidity (Fig. 2). Improvement in motor performance scores averaged between 20 and 40%. The effect of a single PLG-injection became evident within 15 minutes and lasted up to 24 hours (Fig. 3).

The mechanism by which PLG might influence parkinsonism still remains uncertain. No influence on catecholamine or acetylcholine metabolism could be found, nor was there evidence of any influence on release or reuptake of dopamine. An action via the hypothalamo-pituitary axis and peripheral hormones is equally unlikely. A post-synaptic site of action of PLG would most conveniently explain the clinical observations made by several authors; furthermore, the demonstration of specific binding sites for PLG in the rat striatum (Chiu et al., 1980) also points in this direction.

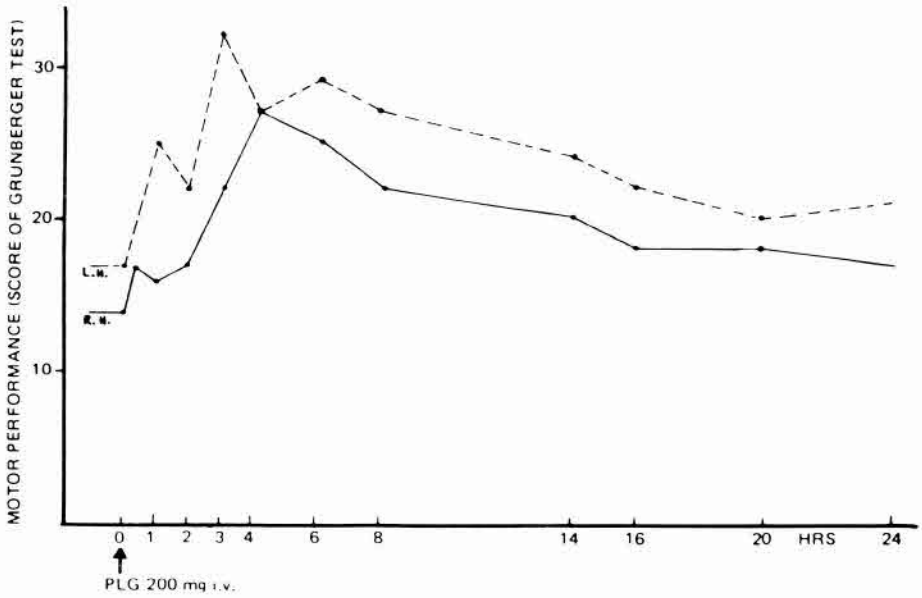

Fig. 3 Motor performance score of Grünberger-test over 24 hours in a 64-year-old Parkinson patient after bolus injection of 200 mg PLG in addition to levodopa therapy. (From Gerstenbrand et al., 1979.)

THE ENKEPHALINS

The discovery of opiate receptors in the brain is one of the most exciting events in contemporary neuroscience. Again it was the basal ganglia where especially high concentrations of opiate binding sites (Kuhar et al., 1973) could be identified. The structural identification of the endogenous ligands of these receptors as two penta-peptides, methionine-enkephalin and leucine-enkephalin, by Hughes et al. (1975) offered vast opportunities to study their pharmacological properties and regional distribution in the nervous system. The highest concentrations of the enkephalins in the rat brain were detected in the globus pallidus (Hong et al., 1977). The immunohistochemical staining of this region corresponds to nerve fibers, the cell bodies of which are located in the caudate nucleus and putamen (Watson et al., 1977). In man, high levels of met-enkephalin are found in the globus pallidus, caudate nucleus, putamen and substantia nigra (Gramsch et al., 1979). A possible pathogenetic role of the enkephalins in Huntington's chorea was suggested by findings of significantly lowered striatal concentrations of enkephalins

after intrastriatal injection of kainic-acid in the rat (Childers et al., 1978) as well as of lowered enkephalin concentration in the globus pallidus and substantia nigra of brains of Huntington patients (Arregui et al., 1979; Emson et al., 1980). Enkephalin deficiency in the caudato-pallidal system and/or striato-nigral system might thus be a factor in the pathogenesis of Huntington's disease.

Clinical investigation of a possible effect of the natural enkephalins in Huntington patients is severely impaired by the very short half-life of these peptides. We were able to perform a clinical trial with a modified met-enkephalin with prolonged half-life (FK 33-824, Sandoz Corporation, Basle, Switzerland) in patients with choreatic syndromes (Gersten-

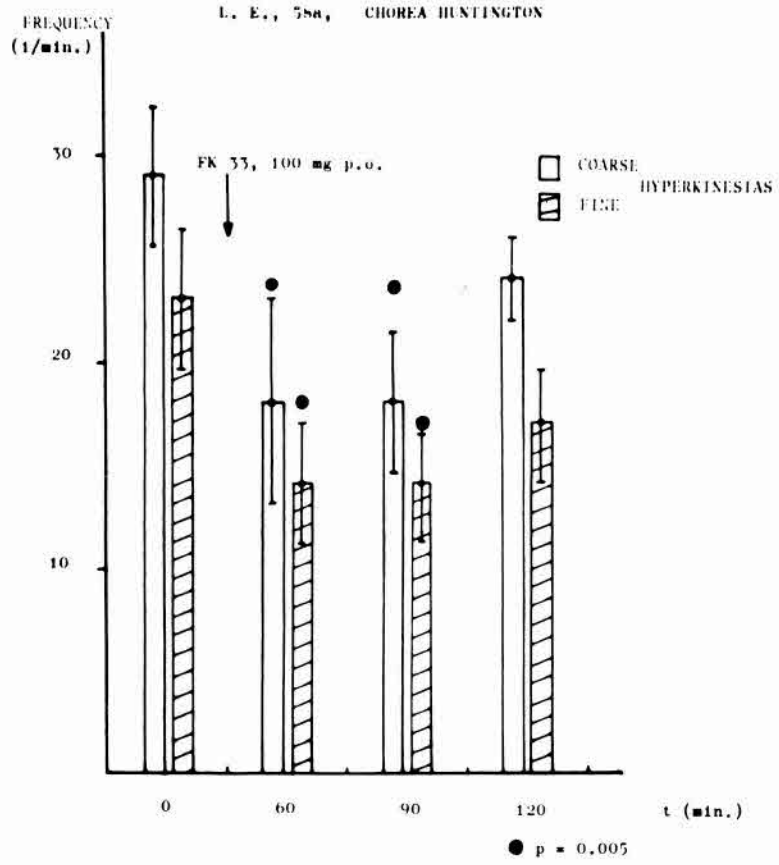

Fig. 4 Significant decrease in frequency of coarse and fine hyperkinesias 60 and 90 minutes following peroral application of 100 mg F.K. 33-824 in a case of Huntington's chorea. (From Gerstenbrand and Poewe, 1980.)

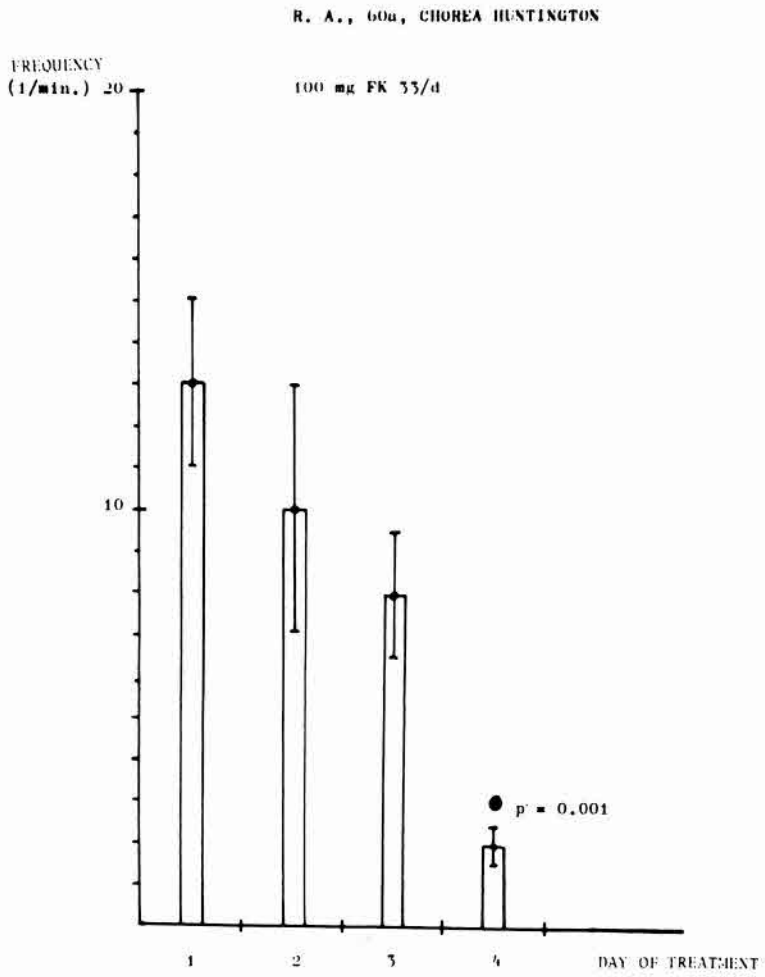

Fig. 5 Significant decrease in basic frequency of coarse hyperkinesias after 4-days treatment with 100 mg F.K. 33-824 daily per os in a case of Huntington's chorea. (From Gerstenbrand and Poewe, 1980.)

brand and Poewe, 1980). 5 patients with Huntington's chorea, 4 with tardive dyskinesia and 1 with a postencephalitic choreatic syndrome were treated orally with the substance in a dosage of 50-100 mg daily. While no influence could be detected in the non-Huntington patients, 3 of the Huntington cases showed a significant reduction in the frequency of hyperkinesias beginning 1 hour after drug ingestion and lasting for about 2 hours (Fig. 4). Another Huntington patient showed a

significant reduction in the basic frequency of his choreatic movements on the fourth day of treatment (Fig. 5). Positive results after i.v. injections of the same substance in Huntington patients have also been reported by Agid and Destee (1981). Side effects included transient flushing and nausea; after i.v. injection of 1 mg in 1 patient, orthostatic reactions as well as restlessness and aggressiveness occurred, and hence the i.v. route of application was discontinued.

Concerning Parkinson's syndrome, current data point to an inhibition of postsynaptic dopamine receptors in the striatum by an enkephalinergic interneuron. Enkephalins would therefore deteriorate the symptoms in L-dopa treated Parkinson patients (Emson et al., 1980). Our experience points in the same direction.

OTHER PEPTIDES

Substance P is another peptide with remarkably high concentrations in the basal ganglia, namely in the substantia nigra. Following lesions to the striatonigral tract, significant drops in the substance P levels of the substantia nigra were noted (Kanazawa et al., 1977a) suggesting the association of substance P with a striato-nigral fiber tract. Decreased nigral levels of substance P were also found in Huntington's chorea (Kanazawa et al., 1977b). However, there are no reports of clinical trials with substance P in Huntington's chorea or other extrapyramidal disorders. Despite a great number of experimental results concerning the possible role of other brain peptides located in the basal ganglia as neurotransmitters – such as neurotensin, angiotensin II and homocarnosine – their possible physiological role in the extrapyramidal system remains obscure. At present it does not seem possible for the clinician to envision their pathogenetic role in basal ganglia diseases.

CONCLUSION

The basal ganglia is one of the most promising regions for neurochemical and neuropharmacological research. Much has been learned about the role of monoamines and acetylcholine as neurotransmitters in the basal ganglia pathways. Insight could be gained into the physiological role of such monoaminergic or cholinergic pathways in the extrapyramidal system. It was even possible to transfer the knowledge gained from such basic research into new and very successful ways of drug

treatment of parkinsonism. At present, neuroscience has opened a new frontier with the discovery of peptide neurotransmitters. Again, especially high concentrations of these substances are found in the basal ganglia. Their possible role in physiology and pathology of the extrapyramidal system is still much more obscure than that of the monoamines. However, experimental findings from animal research and the first clinical observations provide evidence that peptides may play an important future role in the therapy of extrapyramidal diseases.

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