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Neuropeptides in dopamine-containing regions of the brain

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This paper reviews evidence of direct interactions occurring in the central nervous system between peptide- and dopamine-containing neural networks. While it seems fairly clear that neuropeptides are involved in the process of interneuronal communication, their specific role appears to be different from that of classic transmitters (which include dopamine). Neuropeptides coexist with dopamine in specific dopamine-containing neurons; in addition they interact abundantly with the dopaminergic neurons, by acting either on the perikarya or on the dopaminergic nerve terminals. Such interactions are reciprocal and account for some behavioral correlates of neuropeptide and dopamine alterations in the brain. They also shed new light on the pathophysiology of neurological and psychiatric diseases associated with depletion or abundance of brain peptides.

Key-Words: Neuropeptides — opioid peptides — dopamine — substantia nigra — ventral tegmental area — basal ganglia — hypothalamus — Parkinson disease — Huntington disease — schizophrenia

During the last two decades, following the introduction into neurobiological research of several new methods for morphological and pharmacochemical analysis, much effort has been devoted to the study of dopamine systems in brain. Dopamine pathways are non-diffuse, topographically organized circuits, whose hodological organization differs markedly from that of other monoamine-containing systems [104, 105). Dopamine systems functionally interact with a series of other chemically identified neuronal networks, such as those containing acetylcholine, amino acids, and monoamines [16, 54]. In addition, very recent experimental evidence suggests that the relationships between dopamine and some neuropeptides are highly relevant to an understanding of the central nervous system dopaminergic function. This assumption is based on two main considerations. In fact, not only brain peptides have been detected in regions where dopamine neurons and terminals occur [66] but also some recent data suggest that neuropeptides may be involved in the pathogenesis of brain diseases primarily affecting dopaminergic transmission [19,65]. This article reviews the functional relationships occurring between dopamine and brain peptides in normal and pathological central nervous system activity.

Anatomofunctional considerations

As shown by radiochemical and immunohistochemical studies, neuropeptides are distributed in discrete brain regions, where they can be detected in neural somata, processes and terminals [144, 152]. Uneven distribution of brain peptides supports the view that they are involved in the process of interneuronal communication. In agreement with this general consid-

eration, biochemical and pharmacological data also suggest that the role of neuropeptides probably differs from that of *classic* transmitters (e.g., acetylcholine, monoamine, and amino acid) because: first, peptides are rather large molecules, their average molecular weight being more than ten times that of monoamines; second, their concentration in neural tissue is approximately 1000 times lower than that of monoamines [64]; third, peptides originate via the post-translational processing of macromolecular precursors synthesized in the neural cell bodies and transported from there to terminals. Thus, synaptic availability of neuropeptides does not depend (as is the case with most transmitter molecules) upon local synthesis in nerve endings or on reuptake from the synaptic cleft, it depends almost exclusively on synthesis by ribosomes and subsequent axonal transport. This consideration supports the hypothesis that neuropeptides are responsible for long-term synaptic events or for modulating the action of neurotransmitters [5, 17]. In fact, since it can be assumed that the cellular mechanisms involved in the biosynthesis, release and disposal of neuropeptides are, in several ways, more complex than those which operate for *classic transmitters,* they offer correspondingly greater opportunity for control and modulation. Most, if not all, neuropeptides are inactivated by extracellular membrane-bound peptidases, although a contribution from soluble peptidases released from neural or glial cells cannot be ruled out [38].
Morphological data obtained by immunohistochemistry have shown that neuropeptides may coexist with monoamines or with other peptides in some central nervous system pathways [64, 99]. This point, while not ruling out the possibility that some or all neuropeptides may act as primary transmitters to mediate phasic synaptic events [42], further supports the view that neuropeptides act as co-transmitters or modulators.
Therefore, when considering the functional role of neuropeptides in dopamine-containing regions of the central nervous system, several possibilities must be envisaged. First, neuropeptides may coexist with dopamine in the same neuron; alternatively, neuropeptides may be present in nondopaminergic neurons which are organized in a way parallel to the dopamine-containing neurons. In either case, peptides and dopamine would be part of the same pathway. Another possibility is that dopamine- and peptide-containing neurons are connected serially, so that dopamine neurons receive peptidergic afferents (i.e. they possess receptors for neuropeptides), or vice versa. As described below, all these possibilities are represented in the mammalian brain, and this explains why behavioral and pharmacological data are often difficult to interpret in terms of simple models.
Neuropeptides, which are dealt with in the present paper, are listed in table I together with some key references related to their chemical and biological properties. The subdivision of dopamine pathways into different anatomofunctional systems is a commonly accepted criterion [21, 104, 105]. Table II gives the classification of dopamine pathways as used in the present text, which is a modified version of that originally proposed by Moore and Bloom [105]. For the sake of brevity, however, the guidelines of this classification will not be analyzed here [4].

Midbrain efferent system

Immunocytochemical studies have shown that cholecystokinin octapeptide coexists with dopamine in a subpopulation of midbrain dopamine neurons located in the anteromedial region of substantia nigra and in the ventral tegmental area [66, 67, 163]. Cell bodies containing both

TABLE I. *Principal neuropeptides which are mentioned in the text, listed according to the number of their amino acidic residues.*

Name	Number of amino acids	References
Thyrotropin releasing hormone	3	113,128
Enkephalins (Met, Leu)	5	53,68,103
Cholecystokinin	4,8,12,33(*)	35,127
Substance P	11	72
Neurotensin	13	14
Somatostatin	14	52
α-Endorphin	15	53,106
γ-Endorphin	16	53,106
Vasoactive intestinal polypeptide	28	48,49
β-Endorphin	31	53,88,106
Neuropeptide Y	36	157

(*) Cholecystokinin is present in nervous tissue only in the tetra- and octapeptide forms; the latter being amply more represented

TABLE II. *Classification of main dopamine pathways in the central nervous system*

Pathway	Origin	Termination
Midbrain efferent	Substantia nigra (A8, A9)	Neostriatum, globus pallidus, frontal cortex, nucleus accumbens
	Ventral tegmental area (A10)	Cerebral cortex (frontal, suprarhinal, entorhinal, pyriform), olfactory bulb and tubercle, amygdala, lateral septum, neostriatum, nucleus accumbens, habenular nuclei, hippocampus
Retinal	Amacrine-like neurons	Inner and outer plexiform layers
Tuberohypophysial	Arcuate and periventricular nuclei (A12, A14)	Intermediate and posterior lobes of pituitary, median eminence
Periventricular	Medullary group A2, periventricular and periaqueductal groups A11 and A14	Periaqueductal and periventricular gray, tegmentum, tectum, thalamus, hypothalamus

cholecystokinin and dopamine represent approximately from one half to one third of the total population of midbrain dopamine neurons; they project chiefly to the nucleus accumbens, the tuberculum olfactorium, the caudate nucleus, the bed of the stria terminalis, and the central amygdaloid nucleus [102]. In addition, positive immunohistochemistry for cholecystokinin has also been found in nondopaminergic cell bodies projecting to the same forebrain area [67, 98]. Biochemical studies [62, 136] have also shown that receptor sites specific to cholecystokinin are present in regions where dopamine receptors occur, namely in the cerebral cortex, olfactory bulb, caudate nucleus, hippocampus, hypothalamus and midbrain. The topographical interrelationships between cholecystokinin and dopamine receptor sites are not presently known; however, biochemical and behavioral experiments indicate that cholecystokinin can reduce dopamine metabolism and dopamine-mediated stereotyped behaviour, probably by acting on presynaptic dopamine receptor sites [86]. The same hypothesis may also explain why cholecystokinin, when administered iontophoretically or systemically, produces activation of midbrain dopaminergic neurons, while dopamine agonists are inhibitory [142].

A wealth of pharmacological and behavioural data proves that there are functional relationships between enkephalin- and dopamine-containing neuronal systems. The local injection of opiates and of opioid peptides into the ventral midbrain tegmentum induces hyperactivity mediated by activation of midbrain dopamine systems [13, 63, 73, 84, 150]. In addition, the presence of opiate receptors on midbrain dopamine neurons has been documented [93, 173, 174], as has the occurrence of enkephalin-containing terminals, which surround dopamine neurons located in the substantia nigra and ventral tegmental area [56, 76]. A likely hypothesis is that enkephalinergic inputs to midbrain dopamine neurons derive — at least in part — from the striatum, where perikarya containing either enkephalin or GABA, or both, have been detected [24, 25, 28, 32]. Enkephalinergic inputs are thought to be excitatory, since microiontophoretic application of opiates is capable of activating midbrain dopamine cell bodies [111]. It has also been shown that opiate receptors are present in several forebrain nuclei, where they are located presynaptically on terminals of midbrain dopamine neurons [31, 121, 122, 174]. It is therefore possible that excitatory enkephalinergic interneurons may exert presynaptic control on dopamine nerve terminals in selected forebrain territories [31].

Although the coexistence of somatostatin and dopamine in the same nerve cells is unlikely, the existence of close relationships between dopaminergic and putatively somatostatinergic neurons has been demonstrated in several vertebrate species [52, 71, 141, 154]. All these studies show that somatostatin-containing neurons, which are located in many forebrain territories (namely the neocortex, cingulate cortex, olfactory tubercle, neostriatum, nucleus accumbens, amygdaloid complex, hippocampus and lateral septum) receive direct innervation from the midbrain dopamine cell bodies. A direct effect of somatostatin on dopamine terminals located in the striatum is also proven [18], this indicating the possibility of reciprocal influence of dopamine- and somatostatin-containing terminals. The hodological organization of somatostatin-

containing perikarya is not known in detail but they give rise both to regional circuits (e.g., in the striatum [33]) and to long pathways coursing through major anatomical tracts (e.g., the medial forebrain bundle [52]). In addition, somatostatin-containing nerve fibers have been found in the ventral midbrain tegmentum [52]. The neostriatum, in particular, is believed to be rich in both somatostatin-containing cell bodies, probably interneurons [119, 145], and somatostatin-containing afferent projections, which are probably in direct relationship with the mesencephalostriatal terminals [6]. Therefore, direct relationships between somatostatin- and dopamine-containing neurons are likely to occur, and they can explain some behavioral phenomena elicited by somatostatin administration, such as incoordination of motor activity and a peculiar rotatory behavior known as "barrel rotation" [20, 55, 130].

The existence of substance P-containing striatonigral neurons, which are part of the nigrostriato-nigral loop, is now well documented. Substance P-containing cell bodies are located in the neostriatum [91]; their axon terminals reach the substantia nigra and ventral tegmental area, where they form axodentritic synapses with dopamine midbrain neurons [10, 34, 80, 91, 92, 110, 146]. As shown by iontophoretic studies, substance P neurons are excitatory to midbrain dopamine cell bodies [27, 170], from which they also receive feedback influence [60]. Substance P terminals located in the midbrain are functionally connected with the GABAergic striatonigral neurons [75]. The ventral tegmental area also contains terminals of the substance P-containing habenulotegmental neurons [44]; though it is not known whether these neurons are in direct contact with dopamine cell bodies. On the other hand, direct dopamine-substance P interactions are likely to occur in the medial habenular nucleus, where dopaminergic mesencephalohabenular nerve endings may influence the activity of substance P habenulointerpeduncular and habenulotegmental neurons [26, 91, 120]. Immunohistochemical studies [92] have shown that a significant overlap exists between the distribution of dopamine- and substance P-containing nerve terminals in several forebrain territories. This is the case in the frontal cortex, amygdala, neostriatum, nucleus accumbens, lateral septum and lateral habenular nucleus: all these regions receive dopaminergic innervation from the ventral tegmental area [4], while the site(s) of origin of their substance P afferent inputs has not yet been established [91]. The existence of functional interactions between substance P and dopamine nerve terminals in forebrain is also supported by behavioral studies, which point to a different function for substance P in the ventral midbrain tegmentum from its role in the forebrain regions [82, 83, 149].

Many pharmacological and behavioral data suggest that neurotensin shares several properties with neuroleptic drugs, and that it can interfere with dopaminergic transmission [9, 108, 126, 143]. Neurotensin is active when injected into the ventral tegmental area or into the nucleus accumbens, which is consistent with the view that neurotensin systems interact mainly with the mesencephaloaccumbens and mesencephalolimbic pathways (see review by Nemeroff and co-authors [109]). In fact, immunohistochemical studies [57, 74, 161] have demonstrated that neurotensin-containing perikarya are located in the ventral tegmental area, just dorsal to the interpeduncular nucleus, and in the amygdala; neurotensin-containing terminals can be detected in the neostriatum, central amygdaloid nucleus, nucleus accumbens and ventral tegmental area. It has also been shown that the ventral tegmental area is rich in receptors for neurotensin [124, 175]; possibly located on midbrain dopamine perikarya, since neurotensin microinjections into the ventral tegmental area produce behavioral activation, which is mediated through dopamine mesencephalolimbic neurons [79]. These data allow us to conclude that neurotensin neurons are not only organized in a way parallel to the midbrain dopamine efferent system but also that they influence directly both dopamine somata located in the midbrain and forebrain dopamine terminals [29]. An organization of this kind is consistent with the view that midbrain neurotensin neurons possess recurrent axon collaterals impinging upon dopamine somata and also suggests that the relationships occurring between dopamine- and neurotensin-containing neuronal networks are rather complex.

The above data suggest that there are at least four components of the midbrain efferent system, relevant to transmitter molecules (Fig. 1): (1) dopamine-containing neurons; (2) dopamine- and cholecystokinin-containing neurons; (3) cholecystokinin-containing neurons; (4) neurotensin-containing neurons. The efferent projections of these four groups of midbrain neural somata partially overlap, as all of them are directed to forebrain target sites. Cholecystokinin- and neurotensin-containing cell bodies probably correspond to nondopaminergic midbrain neurons, which have been shown to be located both in the substantia nigra and in the ventral tegmental area [1, 2, 3, 164]. In addition to these peptide-containing pathways set "in parallel" to midbrain dopamine neurons, the above data also point to "serial" connections between neuropeptide- and dopamine-contain-

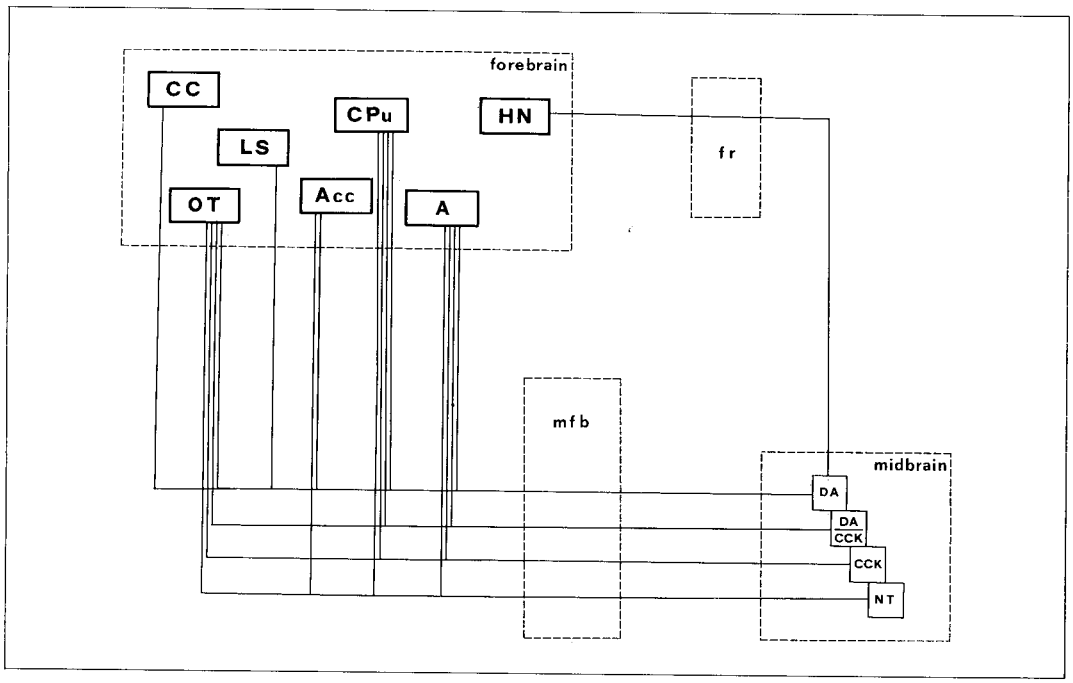

Fig. 1. *Wiring diagram of the organizazion of the midbrain efferent system. Cell bodies which are located in the midbrain contain dopamine (DA), cholecystokinin (CCK), or neurotensin (NT): they project rostrally to several forebrain regions via the medial forebrain bundle (mfb) and the fasciculus retroflexus (fr.) Forebrain target sites are abbreviated as follows: Acc, nucleus accumbens; CC, cerebral cortex; CPu, caudate-putamen; HN, habenular nuclei; LS, lateral septum; OT, olfactory tubercle.*

ing neurons. Thus, peptide-containing systems impinge upon midbrain dopamine cell bodies; they originate from: (1) substance P- and enkephalin-rich somata located in the neostriatum, and (2) somatostatin-containing neurons located in several cortical and subcortical areas of the forebrain. Finally, the above data indicate that dopamine terminals exert a direct action upon peptide-containing neurons, such as in the case of: (1) dopamine innervation of somatostatin-rich cell bodies located in the forebrain, and (2) dopamine innervation of substance P-containing somata located in the habenular nuclei. Further studies will certainly elucidate the still obscure relationships between other neuropeptide-containing systems and the dopaminergic midbrain efferent pathways [147].

Retinal system

In addition to monoamines, the vertebrate retina contains a large number of neuropeptides, namely enkephalins, substance P; glucagon, thyrotropin releasing hormone, cholecystokinin, neurotensin, vasoactive intestinal polypeptide, somatostatin [11, 12, 47, 81, 138, 140, 148]. Immunohistochemical studies have also shown that retinal peptides are almost confined to amacrine cells [11, 81, 100, 160]. Since some of the amacrine cells are known to contain dopamine, what are the relationships between dopamine- and peptide-containing cells in the retina? This question has not been completely answered although preliminary morphological data seem to indicate that the coexistence of peptides and monoamines (particularly dopamine) is fairly common, while the coexistence of different peptides is rare [81].

Tuberohypophysial system

It is well established that several neuropeptides are present in the hypothalamus and pituitary of vertebrates [52]. However, peptides exclusively involved in endocrine functions as hypophysiotropic factors or neurohormones will not be dealt with here (for a review, see ref. 128). The present section will consider only those hypothalamic peptides which have a role in interneuronal communication and are related to dopa-

minergic tuberohypophysial neurons. Firstly, it must be remembered that most studies on the tuberohypophysial system are based on the inhibitory action of dopamine on prolactin secretion from the pituitary [128, 137]. Dopamine is the most important prolactin inhibiting factor, but many data point to other prolactin inhibiting as well as releasing factors [128]. Since not all the prolactin inhibiting activity of hypothalamic extracts can be mimicked by dopamine, it is clear that other molecules (including some peptides) exert inhibitory or stimulant activity on prolactin release.

The presence of peptides that act like morphine in the bovine pituitary was first reported by Teschemacher and Cox [159] and has since been confirmed by several biochemical and immunohistochemical reports (see review in ref. 152). Immunohistochemical studies have provided clear accounts of the topographical organization of endorphin and enkephalin pathways [50, 167], while pharmacological studies have shown that opiates and opioid peptides may affect the release of both adeno- and neurohypophysial hormones [59, 128, 165]. In the case of prolactin release, opiates and opioid peptides increase prolactin secretion through inhibition of dopamine release in the tuberohypophysial neurons [70, 129, 167].

Immunohistochemical studies have demonstrated that endorphin-containing perikarya, which are located in the arcuate nucleus of the hypothalamus, are separate from dopamine-containing tuberohypophysial neurons [70]; further, the presence of a rich arborization of endorphin-containing nerve endings in the median eminence [50] suggests that endorphin and dopamine pathways originating from the arcuate nucleus may be organized in parallel. In the light of this, it has also been proposed that the presence of direct axo-axonal contacts between endorphin- and dopamine-containing neurons may account for the pharmacological action of opiates on prolactin secretion [30]. It is not presently clear whether the dopamine- and enkephalin-containing neurons in the arcuate and periventricular nuclei of the hypothalamus are related in any way. Available data seem to indicate that enkephalin neurons of the hypothalamus are mostly concerned with control of neurohypophysial secretion [165, 166]. The same seems to apply to cholecystokinin- and gastrin-containing cell bodies [163]. Finally, studies on the role of dynorphin in the tuberohypophysial system are under way [22, 24, 114].

Neurotensin is very active on the secretion of several pituitary hormones, including prolactin [96, 132, 169]. As shown by immunohistochemical studies, the organization of neurotensin systems in the hypothalamus is very extensive and complex: however, there seems to be considerable overlap in the topography of dopamine- and neurotensin-containing neurons located in the arcuate nucleus and projecting to the median eminence [78]. Very recently, Ibata and coauthors [69] have demonstrated the existence of tuberoinfundibular neurons containing both dopamine and neurotensin. However, analysis of the functional interactions between dopamine and neurotensin systems is still open for future research, especially as conflicting results have been published on the action of neurotensin on prolactin secretion [95], and interactions between neurotensin, substance P, and opiates are likely to occur [132].

Periventricular system

The organization of the periventricular system as defined by Lindvall and coworkers [90] is still controversial but it has been used in the present classification for reasons that have been discussed elsewhere [4]. Even now the relationships between peptide- and dopamine-containing neurons of the periventricular system cannot be defined in detail. For example, it is particularly hard to understand the relationships occurring between dopamine and the neuropeptides contained in neurons located in the anterior and posterior hypothalamus or in other periventricular regions, as in the case of: (1) enkephalin-rich somata and fibers of the anterior hypothalamic nucleus [51]; (2) oxytocin and vasopressin neurons of the periventricular nucleus projecting rostrally and caudally to various brain regions [15]; (3) gastrin- and cholecystokinin-containing cell bodies located in the periventricular nucleus of the anterior hypothalamus [163]; (4) somatostatin neurons, which seem to be located in the nucleus of the solitary tract as well as in the hypothalamus [115].

It has also been shown that some putatively peptidergic systems, coursing in the ventral and dorsal brain stem tegmentum are organized similarly to dopamine and noradrenaline axons of the periventricular system. In fact, β-endorphin-containing cell bodies, which are located in the arcuate nucleus and medial basal hypothalamus, give rise to some ascending and to descending projections running both dorsal and ventral to the sylvian aqueduct and to the ventricles [24]. In addition, neurotensin neurons located in the anterior hypothalamus (including the anterior hypothalamic nucleus [78]) apparently project caudally to the brain stem and spinal cord, via the ventral brain stem tegmentum [74].

Clinical and pathological findings

Neuropeptide alterations have been demonstrated in several neurological and psychiatric disorders by means of vital and *post mortem* studies: the first are mainly based on cerebrospinal fluid determination of peptide molecules; the latter consist essentially of biochemical and immunocytochemical data obtained from autopsy material. Problems and perspectives related to these techniques have recently been discussed by Edwardson and McDermott [38].

Parkinson disease is the most important neurological disorder associated with impairment of dopamine function in the brain, although it is now generally accepted that this condition also affects other neurotransmitter functions [131]. Studler and coauthors [151] reported that cholecystokinin octapeptide immunoreactivity is selectively decreased in the substantia nigra (and not in the adjacent ventral tegmental area) of parkinsonian subjects and infer that degeneration is confined to mesencephalostriatal neurons, the mesencephalolimbic pathway being unaffected. As shown by Taquet and coauthors [155, 156], methionine-enkephalin is deficient in the midbrain of parkinsonian subjects, a feature indicating a possible compromission of enkephalinergic striatonigral cell bodies. Then there is the finding that substance P levels are reduced in the frontal cortex, hippocampus and entorhinal cortex of parkinsonian patients [46] as well as in patients with Shy-Drager's disease [112]; it is therefore likely that the substance P-containing striatonigral neurons are also affected. Dupont and coauthors [37] reported reduced somatostatin levels in the cerebrospinal fluid as a specific and irreversible abnormality occurring in parkinsonian patients, indicating impairment of somatostatinergic transmission. In this regard, some preliminary data indicate that the reduction of somatostatin levels in Parkinson disease correlates directly with the degree of mental deterioration seen in these patients [46]. Further, since a marked reduction of somatostatin occurs in other neurological diseases associated with progressive dementia (e.g. Huntington chorea [23] and Alzheimer disease [135]), it may be conjectured that somatostatin-containing neurons play a part in maintaining higher cortical activity. In addition, as animal studies show (vide ante), a direct role of somatostatin in generating abnormal motor behavior is a possibility to be taken into account.

It is well documented that Huntington disease is an extrapyramidal disorder primarily affecting the basal ganglia. It has also been proposed that this disease is characterized by a specific impairment of GABA transmission in the striatum, leading to a relative prevalence of dopamine activity in the nigrostriatal pathway [118, 162, 172]. Subsequent investigations, however, have shown a decrease of several neuropeptide levels in the brains of choreic patients, since depletion of substance P, methionine-enkephalin, and cholecystokinin octapeptide occurs in the globus pallidus and in the substantia nigra, indicating a loss of peptidergic inputs along the nigro-striato-nigral loop [43, 45, 176]. Further, receptors for cholecystokinin are significantly reduced, not only in the basal ganglia, but also in the frontal cortex [62]. In contrast to the depletion of several putative neurotransmitters (see also data on somatostatin reported above), neurotensin and neuropeptide Y are significantly increased in the caudate nucleus of choreic patients [41, 97], thus indicating that pathways containing these neuropeptides may be unaffected by the degenerative process.

In the case of schizophrenia, a complex psychiatric disease probably associated with an alteration of dopamine activity in the brain [116], the possible involvement of neuropeptide systems must also be considered. Shortly after the discovery of endogenous opioid peptides it was reported that such materials were elevated in the cerebrospinal fluid of unmedicated schizophrenic patients and that these levels returned to normal after medication [58, 89, 158]. This "endorphin excess" theory of schizophrenia has been supported by a number of reports [7, 36, 39, 40, 87, 134, 171]. The picture has become, however, much more complicated by the suggestion that schizophrenia may be associated with an endogenous opioid deficiency rather than with an excess since beneficial effects of β-endorphin, enkephalin analogues and des-tyr-γ-endorphin on schizophrenic patients have been reported [77, 85, 107, 168]. Unfortunately, these reports have not all been based on double-blind controlled studies and not enough patients been studied in a sufficient number of independent laboratories to pinpoint the role of opioid peptides in schizophrenia. Then there is the possible involvement of non-opioid peptides in schizophrenia, suggested by *post mortem* studies demonstrating that cholecystokinin and somatostatin are reduced in the hippocampus and amygdala [133], but not in the entorhinal cortex [117] of brains of schizophrenics. Neurotensin levels, on the other hand, are increased, in most brain regions [8]. Before are drawn conclusions from these findings it must be remembered that schizophrenia is not a homogeneous clinical entity and that the interpretation of experimental data is complicated by the existence of several different variants of the disease. Another point to bear in mind is the administration of neuroleptic drugs, which interfere significantly

with levels of most neuropeptides in brain [94]. Moreover data based on cerebrospinal fluid determinations are often equivocal [123, 153].

In summary, alterations of some neuropeptide systems are likely to be associated with neuropsychiatric disorders affecting dopaminergic transmission in brain. The list of experimental data mentioned here must still be regarded as preliminary, and does not permit any definite conclusions. However, some anatomoclinical correlations may be outlined as follows. First, it is apparent that neuropeptide pathways directly connected with midbrain dopamine systems are involved in Parkinson disease: this seems to be the case not only for peptidergic neurons impinging upon midbrain dopamine perikarya, but also for cholecystokinin-rich somata located in the ventral midbrain tegmentum, while no data are present in the literature dealing with midbrain neurotensin-containing neurons. Second, somatostatin-containing neurons probably play a part in the pathogenesis of mental deterioration associated with degenerative diseases of the brain. In this connexion, it should be noted that the "somatostatin hypothesis" of dementia is not necessarily incompatible with other similar postulations, such as the "acetylcholine" and the "dopamine" hypotheses. Too little is known about the anatomy of somatostatin pathways to allow detailed anatomoclinical interpretation of circuitries involved in the dementing process. Third, data on neuropeptide alterations in Huntington chorea imply a biochemical selectivity of the degenerative process, which is evidenced by a selective survival of neurotensin- and neuropeptide Y-containing systems. Finally, in our opinion the role of neuropeptides in schizophrenia (as well as in other psychiatric illnesses) has yet to be outlined in a meaningful way.

The possibility of using peptides as drugs for the therapy of neuropsychiatric diseases depends not only upon a clear understanding of the role of neuropeptides in physiological and pathological brain activity, but also on pharmacokinetic properties allowing them to reach their sites of action in the brain. Since virtually all ingested peptides are hydrolyzed to amino acids by endoluminal peptidases, it is obvious that these molecules would have to be administered parenterally. Bloodborne peptides must withstand peripheral inactivation and cross the blood-brain barrier. This does not appear to be a problem for, as has been shown firstly for opioid peptides [125], some, if not all, neuropeptides do enter the central nervous system (see review in ref. 101). In conclusion, neuropeptides are not only important synaptic messengers, but they may also be regarded as putative therapeutic tools. Their application is an open avenue for clinical research in the fields of neurology and psychiatry.

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Sommario

Il presente articolo analizza le relazioni esistenti tra i circuiti dopaminergici centrali e quelli contenenti neuropeptidi. Nonostante si possa affermare con sufficiente certezza che i neuropeptidi siano attivi nei processi di comunicazione interneuronale, il loro ruolo specifico sembra essere alquanto differente da quello dei trasmettitori classici (tra i quali vi è la dopamina). In alcuni circuiti centrali è stata dimostrata la coesistenza di neuropeptidi e di dopamina in una stessa cellula nervosa; tuttavia, la maggior parte delle interazioni dirette tra queste sostanze avviene mediante l'azione dei neuropeptidi sul pericario o sui terminali delle cellule dopaminergiche. Si tratta di interazioni reciproche, responsabili in molti casi di importanti correlati comportamentali. Le interazioni tra dopamina e neuropeptidi sono probabilmente anche alla base dei processi patogenetici di alcune sindromi neurologiche e psichiatriche: un aspetto, questo, capace di aprire nuove feconde possibilità di ricerca sia cliniche che terapeutiche.

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