# Behaviour Correlates of Neurotransmitter Activity

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**ABSTRACT:** Most disorders of motor activity including disturbances of muscle tone and of locomotor activity observed in patients with neurological disorders have been reproduced experimentally in animals. Most motor disorders of the extrapyramidal type including those associated with Parkinson's disease and choreiform and athetoid involuntary movements, have been reproduced exclusively in primates. This is most likely related to the highly complex organization of the extrapyramidal and related nervous mechanisms subserving the corresponding peculiar type of motor control in the primate brain. Other types of motor disturbances including cervical and trunkal dystonias, ataxia, hypotonicity, spasticity and intention tremor, however, have been successfully induced in various mammalian species. The latter types of motor disorders are related to disturbances of central nervous mechanisms which show similar patterns in the brains of different animal species. Histopathological and neurochemical changes associated with extrapyramidal disorders have been discovered and more precisely determined as a consequence of the development of new technical approaches. Therefore numerous morphological, physiological and neurochemical data concerning the extrapyramidal system are now available but a better knowledge of their precise and subtle interrelationship is greatly needed in order to develop more efficient therapeutic procedures.

**RÉSUMÉ:** Une majorité des troubles moteurs, y compris les perturbations du tonus musculaire et de l'activité locomotrice rapportés en pathologie humaine, ont été reproduits de façon expérimentale. La plupart des troubles moteurs de type extrapyramidal y compris ceux associés à la maladie de Parkinson ainsi que les mouvements involontaires choréiformes et athétosiques n'ont été reproduits que chez les primates. Selon toute évidence, ceci est relié à l'organisation complexe des structures nerveuses extrapyramidales et des mécanismes nerveux associés et propres aux primates. D'autres anomalies motrices telles les dystonies cervicales et tronculaires, les ataxies, l'hypotonicité, la spasticité et le tremblement intentionnel peuvent être reproduits de façon expérimentale chez diverses espèces de mammifères. Ces variétés de troubles moteurs sont associés à des troubles de mécanismes nerveux centraux qui partagent une organisation similaire d'une espèce à l'autre. Les modifications histopathologiques et neurochimiques en cause dans les troubles extrapyramidaux sont maintenant beaucoup mieux identifiés suite à la mise au point de nouvelles techniques applicables au système nerveux central. Aussi de nombreuses données morphologiques, physiologiques et neurochimiques relatives au système extrapyramidal sont maintenant disponibles. Cependant, il nous faudra, dans l'avenir, en préciser les subtiles interrelations, dans l'espoir de développer des thérapeutiques plus efficaces au regard des troubles extrapyramidaux.

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A great amount of information dealing with the morphology and physiology of the nervous mechanisms which underly motor control, has been obtained especially over the last two decades. Concurrently numerous neurochemical and neuropharmacological data related to the neural control of motor activity and its disturbances have also been reported. Therefore our knowledge concerning the physiopathology and the neuropharmacology of extrapyramidal disorders has made rapid progress over this period. Although we are better informed than previously concerning the identification of the nervous structures involved in various types of motor disorders or the related neurochemical changes, it is still hazardous to attempt to pinpoint the precise nervous mechanisms and the related electrophysiological and neurochemical correlates underlying such disturbances.

Most disorders of motor control, including disturbances of muscle tone and of locomotor activity as well as involuntary movements associated with various neurological diseases or syndromes have been either reproduced in experimental animals or even clinically induced. As a matter of fact disturbances of muscle tone including hypo or hyper-tonicity and dystonias and various types of dyskinesias including choreiform, athetoid or ballistic movements have been experimentally reproduced in animals by lesions or drugs or a combination of both procedures. Similar disturbances have also been observed in man following either pharmacological or neurosurgical procedures applied to improve or counteract other nervous disorders. Certain disturbances of motor control or activity and, more especially those associated with Parkinson's disease have also been successfully induced in monkeys by lesions or drugs.

Postural or parkinsonian tremor, rigidity associated with the cogwheel phenomenon and akinesia or bradykinesia as observed in parkinsonian patients as well as lesion-induced choreiform, athetoid and ballistic movements, also encountered in human pathology, have been successfully reproduced exclusively in primates. This finding is most likely related to the fact that the nervous mechanisms which underly the corresponding types of motor activities have a highly complex organization which is peculiar to primates. In fact certain nervous structures such as

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the parvocellular division of the red nucleus, certain areas of the neo-olive and neocerebellum as well as corresponding relay nuclei and nervous interconnections relating these structures to the motor cortex and the cranial and spinal motor nuclei are highly developed exclusively in the primate brain. Correspondingly certain other nervous structures, also more directly related to these types of extrapyramidal disorders such as the putamen, the substantia nigra, the pallidum as well as the thalamic intralaminar and ventral anterior and ventrolateral nuclei are much better developed in primates than in other mammals (Poirier et al., 1969a, 1972, 1975). Consequently we must take account of these peculiarities in assessing the relationship that may exist between the production of certain motor disorders such as those described above, and morphological, physiological and neurochemical disturbances at the level of the corresponding nervous structures. Other motor disturbances including trunkal dystonia, torticollis, ataxia, dysmetria, hypotonicity, intention or volitional tremor, spasticity as well as turning or circling behaviour have been successfully induced by lesions or drugs in several mammalian species including primates, cats, dogs, rats etc. It is interesting to mention here the fact that the disturbances associated with the latter group of motor disorders involve related nervous mechanisms in various mammalian species. As a matter of fact, the various parts of the cerebral and cerebellar cortices and corresponding nervous pathways as well as the corresponding relay nuclei (large-celled red nucleus, olivary and cerebellar nuclei, brain stem nuclei, neostriatum, substantia nigra) involved in these latter types of motor disorders share similar patterns of neuronal organization in different mammalian species.

Therefore the above summarized data must be taken into account in order to gain precise and definite information that may prove pertinent in correlating findings derived from the experimental material and those underlying motor disorders in patients. In view of the fact that postural or parkinsonian tremor has been more adequately reproduced as an isolated phenomenon than other "extrapyramidal" motor disturbances in the monkey it appears appropriate to focus on this type of extrapyramidal disorder. In addition, numerous data derived from several approaches may be closely related to the nervous mechanisms whose impairment is responsible for the appearance of postural tremor. Moreover the information obtained from this experimental model may prove useful in the understanding of other types of extrapyramidal disorders since the involved nervous mechanisms underlying them are partially common.

**Histopathological changes**

Postural tremor characterized by alternate contractions of antagonistic muscular groups associated with rhythmic oscillations and bursts (as recorded on the electromyogram) of about 4-7 per sec has been experimentally induced by differently placed brain lesions in monkeys. Although it has been observed as an incidental finding following the involvement of the cerebellar apparatus in monkeys (Carpenter, 1958, Ferraro and Barrera, 1936; Mettler, 1946; Walker and Botterel, 1937) and in patients (Cooper, 1965) lesion-induced postural tremor has been more consistently displayed by monkeys with lesions located in the ventral and medial part of the brain stem between the levels of the upper pons and of the caudal hypothalamus and subthalamus (Carpenter, 1956; Mettler and Whittier, 1947; Peterson et al., 1949; Ward et al., 1948). Postural tremor of a more sustained type has been repeatedly reproduced by lesions of the ventromedial tegmental area of the upper pons and midbrain (Goldstein et al., 1969b; Poirier, 1960; Poirier et al., 1966, 1969a). Upper brain stem ventromedial tegmental lesions resulting in postural tremor have been shown to be associated with a marked cell loss in the ipsilateral substantia nigra (Poirier, 1960). This led to the hypothesis that this type of tremor may involve the combined interruption of nigral ascending efferents and the corresponding rubral complex. Such a morphological change in the substantia nigra is closely related to the well-established neuropathological changes observed in the substantia nigra of patients with parkinsonism (Hassler, 1938; Trétiakoff, 1919). More recent studies involving the cytology and the distribution of the different types of neurons of the substantia nigra in various species (Giguère et al., 1983; Marchand et al., 1979; Poirier et al., 1983) show that the latter structure is not homogeneous. As a matter of fact, several types (at least four) of neurons each having unique cytological features, may be identified in the substantia nigra (SN). Taking account of the fact that the SN is an important pathological target in several types of motor disturbances, those morphological peculiarities may prove to be important in assessing and identifying the precise nervous mechanisms and neurochemical correlates involved in a specific type of motor disturbance.

**Associated neurological changes**

The disclosure by Austrian research workers (Bernheimer et al., 1961; Ehringer and Hornykiewicz, 1960; Hornykiewicz, 1966) of decreased concentrations of serotonin (5-HT), norepinephrine (NE), and, especially, dopamine (DA) in several extrapyramidal structures of the brains from patients who had suffered from Parkinson's disease, prompted several studies aiming at the possible role of these brain monoamines in the control of motor activity. Investigation in this area was further stimulated by the development of the histofluorescence technique by Scandinavian investigators (Carlsson et al., 1962). This technique led to the identification of various groups of serotoninergic and catecholaminergic neurons within the brain stem, including the dopaminergic neurons of the substantia nigra and nucleus parabrachialis pigmentosus (pars dorsalis of the substantia nigra) and corresponding numerous endings in the neostriatum (Andén et al., 1965; Dahlstrom and Fuxe, 1964). The combined use of biochemical and histopathological approaches contributed to more firmly establish the existence of a close relationship between the retrograde degeneration of the nigral neurons (especially those of the compacta type) and the associated DA decreased concentrations in the corresponding caudate nucleus and putamen following midbrain ventromedial tegmental lesions in the monkey (Poirier and Sourkes, 1965; Poirier et al., 1966; Sourkes and Poirier, 1966), the cat (Poirier et al., 1967) and the rat (Andén et al., 1966b; Faull and Laverty, 1969). Ventromedial tegmental lesions producing sustained postural tremor of the contralateral limbs were found to be associated with decreased concentrations of both DA and 5-HT in the neostriatum of the lesioned side (Poirier et al., 1966; Sourkes and Poirier, 1966). The decreased DA and 5-HT striatal concentrations resulting from the interruption of fibers at the level of the ventromedial tegmental area are also associated with significant decreases of the main catabolites of these monoamines, homovanillic acid (HVA) and 5-hydroxy-indolacetic acid (5-HIAA), respectively, at the level of the same

structures (Langelier et al., 1973; Sharman et al., 1967) as also disclosed in the brains of parkinsonian patients (Bernheimer et al., 1973; Hornykiewicz, 1972; Lloyd and Hornykiewicz, 1970). These neurochemical changes more likely result from the lack of important enzymes involved in the metabolism of DA and 5-HT as suggested by the fact that ventromedial tegmental lesions also cause significantly decreased activities of the enzymes tyrosine hydroxylase (Poirier et al., 1969b) and DOPA (5-HTP) decarboxylase (Andén et al., 1966a; Goldstein et al., 1969a; Lancaster et al., 1970) in the striata of monkeys and cats, a feature which is also conspicuous in the brains from parkinsonian patients (Lloyd and Hornykiewicz, 1970). In fact all these studies underline the importance of the neurochemical correlates of extrapyramidal disturbances and, more especially those related to the control of motor activity. They have revealed to us the nature and the topographic distribution of the neurochemical neuromodulators such as those underlying cholinergic, gabaergic and catecholaminergic mechanisms. Further knowledge concerning the subtle interrelationships that exist between these mechanisms is now greatly needed in order to gain a more efficient knowledge of extrapyramidal disorders.

**Neurological and neuropharmacological data**

Harmaline and harmine, short-acting monoamine oxidase inhibitors (Udenfriend et al., 1958), greatly exaggerate lesion-induced tremor and may also induce tremor in lesioned monkeys that do not spontaneously display tremor following certain lesions (Poirier et al., 1966; Sourkes and Poirier, 1966). These effects appear rapidly (usually within 10 min) following the i.m. injection of the drug. Harmaline administered in several doses over a 24-hr period, however, causes a two-fold increase of brain 5-HT (as after 1 hr) and a marked decrease of DA associated with a greater decrease of its main metabolite, homovanillic acid (HVA), in the neostriatum (Singh et al., 1967). In the light of these data, it seems that the rapid effect of harmaline in inducing postural tremor in lesioned monkeys might involve not only its peculiar effect on monoamine metabolism, but, in addition, it might depend on another unknown chemical influence such as interfering with the dopamine receptors, or else, releasing or activating certain cholinergic mechanisms. The latter possibilities are further supported by the disclosure that harmaline may greatly increase lesion-induced postural tremor. In this respect, it must be recalled that the neostriatum and its striopallidal and strionigral fibers display high cholinesterase (Olivier et al., 1970) and gabaergic activities (Kim et al., 1971), respectively. Acetylcholine and its synthetizing enzyme, choline acetylase, however, appear to be concentrated in the intrinsic neurons of the neostriatum (Butcher and Butcher, 1974; Lynch et al., 1972; McGeer et al., 1971).

Harmaline has also been shown to induce tremor in the ipsilateral limbs of monkeys with lesions that destroyed the olivo-cerebellar fibers after their decussation, or the lateral (dentate) cerebellar nucleus or the fibers of the superior cerebellar peduncle before their crossing. The latter findings constitute the basis to infer that this loop which encompasses the parvocellular division of the red nucleus, its descending rubro-olivary fibers, the corresponding part of the inferior olive and its efferent fibers, the cerebellar cortex, and the lateral cerebellar nucleus and its efferent fibers coursing in the superior cerebellar peduncle, represents an important mechanism in the control of motor activity (Larochelle et al., 1970). On the other hand, alpha-methyl-p-tyrosine (AMT) has also been investigated in monkeys with lesions of the rubro-olivo-cerebello-rubral loop which, however, spared the brain stem ascending monoaminergic pathways (Bédard et al., 1970). AMT is a known inhibitor of tyrosine hydroxylase in vitro (Udenfriend et al., 1965) and in vivo (Spector et al., 1965). It does not modify the concentration of serotonin, but prevents the conversion of tyrosine to levodopa and thus leads to a lack of synthesis of dopamine and norepinephrine. This inhibitor, however, does not prevent the formation of dopamine and norepinephrine from exogenously administered levodopa. The injection of alpha-methyl-p-tyrosine causes postural tremor in the ipsilateral limbs of monkeys with lesions of the lateral cerebellar nucleus. This effect takes place approximately 5 hr after the parenteral injection of about 150mg per kg of AMT and in time this corresponds to an important decrease of brain dopamine and norepinephrine (Corrodi and Hanson, 1966). Under these circumstances, the injection of levodopa (approx. 30 mg/kg) to animals whose dopaminergic nigrostrial pathways are intact, abolishes the AMT-induced tremor within 10 to 15 min for a period of approximately 45 min after which tremor reappears (Bédard et al., 1970; Larochelle et al., 1971). The latter finding more specifically points to the importance of the inactivation of the neostriatal DA mechanism in the production of postural tremor. The latter suggestion is further substantiated by the fact that reserpine which depletes brain monoamines stores, and thioproperazine, which together with other phenothiazine derivatives apparently blocks the dopaminergic receptors, also induce unilateral tremor in monkeys with lesions of the rubro-olivo-cerebello-rubral loop on one side (Larochelle et al., 1971). As a matter of fact the latter drugs have been shown to interfere with the metabolism of brain monoamines (Andén et al., 1970; Carlsson et al., 1957; Holzbauer and Vogt, 1956; Laverty and Sharman, 1965; Pletscher et al., 1955) and, therefore, they may, in some way or another, duplicate the effect of the lesions encountered in parkinsonism.

On the one hand, anticholinergic drugs, in spite of serious side-effects, have been shown to counteract parkinsonian signs. On the other hand, postural tremor induced in lesioned monkeys by the administration of alpha-methyl-tyrosine (AMT), reserpine and thioproperazine is abolished by benztropine (Larochelle et al., 1971). In view of the fact that the neostriatum (caudate nucleus and putamen) is rich in acetylcholine and the corresponding metabolic enzymes (see above) it is conceivable that the striatal cholinergic mechanisms, locally deprived of an important incoming influence as a consequence of the disruption of the dopaminergic endings, play an important role in the genesis of the abnormal rhythmic bursts associated with postural tremor.

As mentioned above, postural tremor induced by certain drugs (alpha-methyltyrosine, reserpine) may be readily and transiently suppressed by levodopa provided the nigrostriatal pathway is intact. These results must be compared with those reported in parkinsonian patients chronically administered levodopa (Barbeau et al., 1971; Cotzias et al., 1967; Yahr et al., 1969) and in monkeys displaying postural tremor following lesions. The disturbances associated with these lesions parallel the histopathological and biochemical changes described in human Parkinson's disease. Levodopa, generally speaking, does not reduce tremor rapidly in parkinsonian patients or in monkeys with extensive lesions of the nigrostriatal pathways.

This suggests that the disruption of the dopaminergic endings in the neostriatum (associated with degeneration of the nigrostriatal fibers) cannot be easily overcome. Therefore beneficial effects associated with levodopa given chronically and in large amount more likely involve profound and sustained metabolic disturbances of monoamine metabolism in different areas of the brain (Langelier et al., 1973).

**Data derived from other approaches and conclusion**

As mentioned above, postural or parkinson-like tremor apparently involves the combined impairment of the nigro-striatal mechanism and of the rubro-olivo-cerebello-rubral loop (or nervous connections directly related to this loop). This in turn leads to the release of rhythmic bursts by the α-motoneurons as a consequence of an imbalance of nervous activity within different brain stem centers acting on these neurons.

In the light of the data summarized above, it appears that the most important disturbance within the striopallidal system contributing to the production of postural tremor involves the dopaminergic mechanism, which essentially corresponds to the nigrostriatal pathway. The latter nervous pathway encompasses neurons of the compacta types located in the pars compacta and dorsalis of the SN and their endings in the ipsilateral caudate nucleus and putamen. The latter structures, in turn, give rise to strionigral fibers which are particularly rich in acetylcholinesterasic and most likely, gabaergic fibers as well as substance P (Gale et al., 1977; Kanazawa et al., 1977; Kim et al., 1971; McGeer et al., 1971; Olivier et al., 1970). Therefore the latter group of fibers may belong to a feedback mechanism by which the neostriatum controls its own needs in dopamine (DA).

More data involving combined morphological, electrophysiological and neurochemical approaches are needed in order to more accurately establish the functional interrelationship between the nigral neurons and the various areas of the neostriatum. At any rate an impairment of the dopaminergic mechanism of the neostriatum apparently leads to a disturbance of spontaneous activity within the corresponding neostriatum in response to the peripheral administration of levodopa (Ohyé et al., 1970). On the other hand, Filion et al. (1974) and Filion (1979) have studied unit activity in the internal division of the globus pallidus on either side in a monkey with lesion-induced postural tremor and rigidity (associated with the cogwheel phenomenon) of the four limbs and akinesia (Péchadre et al., 1976). Their electrophysiological data suggest that, under such conditions, the pallidum may play an important role in the production of the positive parkinsonian signs. As a matter of fact, using a technique for recording extracellular unit activity in unanesthetized animals, Filion and collaborators (1974, 1979) demonstrated that all neurons showed a high rate of discharge, a more or less continual rhythmic activity around 13 Hz (that had never been recorded in normal monkeys) and, from time to time, bursts of discharge at the frequency of tremor. Apomorphine, a dopamine agonist, injected while recording from these neurons resulted in less rhythmic activity and decreasing rates of discharges up to a complete arrest followed by a gradual return to preinjection rates and patterns of discharge. These changes were coincident with the decrease and recovery of the tremor, rigidity and akinesia. Among the neurons investigated in the external division of the pallidum in the same monkey a few displayed rhythmic activity and, under apomorphine, they did not show any change in the rate of discharge that correlated with the modification of the clinical signs. These data, obtained in a monkey with a bilateral interruption of the nigrostriatal dopaminergic pathways (Péchadre et al., 1976), bring evidence of an associated defect in the outflow of the strio-pallidal system which, however, may be corrected when a dopamine agonist is used to counteract the signs of parkinsonism.

The above summarized data dealing mainly with the experimental model of postural tremor, to a certain extent, give some insight as to the possible nervous mechanisms involved in other but related extrapyramidal disorders. As a matter of fact only slight differences most likely exist between the nervous disturbances underlying various types of motor disorders. As mentioned above more precise information concerning the subtle neuropathological and neurochemical changes associated with different but related extrapyramidal disorders is therefore much needed in order to develop more efficient therapeutic procedures than those presently prevailing.

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