DRUGS AFFECTING MOVEMENT DISORDERS

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INTRODUCTION

Movement is one of the fundamental properties of life. Without movement, it is almost impossible for humans to communicate with the outside world. To the neurologist, movement disorders can include equally well the restrictions caused by paralysis or atrophy and the addition of abnormal involuntary movements. These changes can be due to biochemical or organic lesions anywhere along the neuraxis, from the cortex to the neuromuscular junction. It would be impossible, within the scope of the present review, to study all these possibilities. We will therefore understand the term "movement disorders" as referring to modifications in motor behavior involving disturbances within the so-called "Extrapyramidal System" (1).

This system, however, is not yet clearly defined and could conceivably include disorders affecting all regions not strictly "pyramidal," such as the cerebellum and parts of the spinal cord. For example, ataxia, myoclonus, and spinal spasticity are truly movement disorders but will not be discussed in the present review. The disorders we will study all involve, in whole or in part, damage to the following centers (the so-called basal ganglia): striatum (caudate, putamen), globus pallidus, thalamus, subthalamic nucleus, substantia nigra. The lesions may be limited to such centers or they may also involve other systems (pyramidal, cerebellar, spinal, cortical) but, at least at some moment in time, symptoms related to damage of the above nuclei are clinically evident.

We could approach the problem of drugs upon movement disorder by listing all "extrapyramidal diseases" and their treatment. Besides the cumbersome enumeration so involved, as exemplified by the list of more than 130 entities in a recent nosography of extrapyramidal disorders (2), no functional analysis would be possible. Thus instead of diseases we have decided to center our discussion around *symptoms*. We will not detail the treatment of Parkinson's disease, a subject well covered recently by many authors (4–13, 34), but will concentrate on the clinical pharmacology of tremor, of rigidity, and of akinesia.

Symptoms of basal ganglia diseases have conveniently been classified by Martin (3) as either negative or positive. The only true negative symptom of basal gangliar disorder is akinesia (or more exactly hypokinesia). Since it is now the one sign best corrected by L-dopa (L-3,4-dihydroxyphenylalanine) and similar drugs, we will study it in detail. The positive symptoms most usually seen are tremor, rigidity, dystonia, chorea, athetosis, and tics. All can to some extent be modified by drugs already on the market, or being tried experimentally. These modifications, and the rationale behind them, will form the basis of the present chapter.

Finally, drugs could affect movement disorders by *causing* them, experimentally (tremorine) or clinically (phenothiazines). The best example of this phenomenon is the production of a parkinsonian syndrome including akinesia, rigidity, and tremor by the chronic use of a number of phenothiazines or butyrophenones, which all act upon central dopamine receptors (14–25). The same drugs can produce abnormal involuntary movements as an acute reaction or a strange chorea-like syndrome when withdrawn after long use: the so-called tardive dyskinesias (17, 26–33). Although this latter subject could be of considerable interest, we will not include its study in the present review limited to drugs that modify *existing non-drug-induced* movement disorders.

THE PHARMACOTHERAPY OF AKINESIA

The problem of akinesia is one of the most fascinating aspects of the physiology of the extrapyramidal system, although its very existence has been recognized clearly only since the introduction of stereotaxic surgery, when separation from rigidity was finally permitted. Early biochemical studies in parkinsonism (35–42) indicated that the phenomenon of bradykinesia was the symptom best correlated with the deficit in dopamine. This was subsequently confirmed by studies that related the presence of akinesia with low dopamine and homovanillic acid (HVA) in the urine (38, 39, 43), the cerebrospinal fluid (39, 44, 45), and the brain (46). The introduction of L-dopa to the therapy of Parkinson's disease (37, 47–49) has confirmed clearly that akinesia is the first symptom responsive to correction (8, 50).

1. Definition of Akinesia

In clinical terms, akinesia as seen in Parkinson's disease is a symptom complex, manifested by a number of phenomena just recently better identified (51, 52). From a study of nearly 100 cases of parkinsonism with almost pure akinesia, we have been able to delineate the following important components of this syndrome (53, 54):

(*a*) A defect in *motor initiative* including slow initiation of movements and a decreased motivation to move, leading to conservation of kinetic energy through the loss of associated movements.

(*b*) A defect in the *kinetic melody,* i.e. the ability to change rapidly from one motor pattern to the next in a smooth flow of movement as dictated by circumstances or willful decisions.

(*c*) A defect in the *strategy of learning.* The patient is unable to perform the Goldstein Sorting Test, in which he is asked to separate a number of common objects

in conceptual groups based for example on size, consistency, color, or other physical or utilitarian characteristics. Unless new possibilities are specifically pointed out to him, the parkinsonian akinetic patient, like the frontal lobe patient (55), is unable to *shift* to a new grouping.

(*d*) A *rapid fatiguability,* first studied by Schwab and collaborators (51) and since confirmed by many others (56).

It is within the scope of this syndrome, as here defined, that the best overall results have been obtained since the introduction of L-dopa. It is extremely important to remember this point because, unfortunately, other symptoms of parkinsonism such as tremor will not respond equally well to the specific replacement therapy. Moreover, misdiagnosis of tremor syndromes as Parkinson's disease has led to the unwarranted prescription of L-dopa, often with alarming complications. The rationale behind the use of L-dopa has been reviewed by many authors (4–11, 37, 39, 41, 42, 57–63, 65, 73, 74) and the actual results compiled and analyzed repeatedly (8, 37, 50, 64–72). We shall limit our discussion to the salient features of the neuropharmacology of akinesia, and emphasize the problems still to be solved.

2. *Rationale for L-dopa Treatment of Akinesia*

For a number of years it had been known that reserpine could produce a parkinsonian syndrome. The reason for this became clearer when Bertler & Rosengren (75) and Sano and collaborators (76) demonstrated that dopamine had a characteristic distribution within the brain different from that of noradrenaline, and that it was depleted by reserpine (80). A specific role for dopamine in the extrapyramidal system was soon postulated by Carlsson (77) and Barbeau (36). In quick succession it was shown that there existed in Parkinson's disease: (*a*) a decrease in dopamine content in the basal ganglia (40, 41), more evident on one side in hemiparkinsonism (78), and correlated with the damage to the substantia nigra (79); (*b*) a decreased dopamine and HVA content in the striatum and substantia nigra (81, 82), the latter being the starting point for a newly identified nigro-striatal dopaminergic pathway (83–86) which, when experimentally destroyed in monkeys or rats, results in significant decreases in the concentrations of dopamine, HVA, tyrosine-hydroxylase and dopa-decarboxylase in the striatum (83, 86–89); (*c*) a decrease in dopa-decarboxylase and glutamic acid decarboxylase in human parkinsonian brain (46, 90, 91); (*d*) a decrease in urinary dopamine excretion (43), and in cerebrospinal fluid (CSF) HVA concentration (for review see 39); (*e*) an increased dopamine turnover rate towards HVA rather than noradrenaline (92–94), indicative of a more generalized defect in dopamine binding or storage, perhaps related to some deficiency in magnesium (38, 39, 95–98, 155).

All of these observations led Hornykiewicz (99, 158) to define a dopamine-deficiency syndrome, which we (53, 54, 58, 59) equate with clinical akinesia as outlined above. The evidence to date (5, 8, 39) indicates that L-dopa is the drug of choice to correct this dopamine deficiency and akinesia, probably through the formation of dopamine by the remaining functional nigro-striatal dopaminergic neurons (41, 42, 73, 79, 99), although some authors still question this conclusion (70, 100). The development of carefully controlled methodology for the study of the

minor pathways of catecholamine metabolism in man (101–111, 156) should soon permit clarification of this problem, especially if plasma levels of dopamine could be measured, perhaps by radioimmunological assays. Thus the rationale for the treatment of akinesia, as opposed to Parkinson's disease *in toto,* involves the design of methods primarily for restoring striatal dopamine function. L-dopa is now clearly established as the leading contender for this role. We will see later that other drugs can be added to decrease the side effects or to substitute for L-dopa, at least in part. However, it is important to remember that akinesia is not the only symptom of Parkinson's disease, and that a dopamine deficiency in the brain is not the only biochemical defect isolated or postulated. Indeed most other symptoms seen in this disease (tremor, rigidity, etc) are probably the result of an imbalance of neurotransmitters within the striatum. The concept of a dopaminergic-cholinergic imbalance was first proposed by McGeer (112) and Barbeau (37, 58) and expanded upon by Duvoisin, Klawans, Steg, and many others (74, 113–115). It now involves complex interrelationships between dopamine, acetylcholine, serotonin, histamine, noradrenaline, and γ-aminobutyric acid (GABA) in various parts of the brain (53, 54, 58, 116) but particularly the extrapyramidal system. We will later draw upon the conclusions of these studies to explain the rationale for the treatment of tremor, rigidity, chorea, and dystonia (see below), such treatment being essentially based on restoration of the disturbed balance (59).

3. Problems With L-dopa Therapy of Akinesia

Slow gradual increments of L-dopa have permitted marked improvement in most of the symptoms of Parkinson's disease, and particularly the reversal of akinesia, in approximately 70% of the patients so treated. The results are almost identical from one center to the next (4–13, 49, 50, 117). However, as has been repeatedly stated, this success was not reached without major and important problems which have been thoroughly discussed by many authors (4, 7, 8, 11, 50, 53, 63, 65, 117–119). A short review of these problems will serve to indicate that, despite evident benefits, L-dopa therapy is not yet a panacea, but that some solutions are already being proposed, based on a wealth of laboratory experiments and clinical observations.

(*a*) *Diagnosis.* The most common cause of therapeutic failures, in our experience, has been the misdiagnosis of Parkinson's disease, particularly with other tremor syndromes. Moreover, encouraged by the initial success of L-dopa, many neurologists have assessed the therapeutic potential of this drug in other disorders, including more than 20 neurological conditions with some akinesia, such as chronic manganese poisoning, progressive supranuclear palsy, the Parkinson-dementia complex of Guam, Wilson's disease (for review see 72, 120). Except in a few rare instances, the results have been uniformly disappointing. The exceptions will be discussed further in this chapter.

(*b*) *Peripheral side effects.* Side effects were encountered to an important degree during the early days of this experimental approach. Better understanding of the necessity of increasing very slowly the daily dosage of L-dopa has permitted some reduction in the incidence of nausea, vomiting, and postural hypotension (8, 50).

The real advance, however, took place when it was realized that because dopamine itself does not cross the blood-brain barrier, the degree of conversion of dopa to dopamine by systemic decarboxylase is of paramount importance in determining the percentage of orally administered dopa available for penetration into the brain and its subsequent action there. The enzymatic barrier for L-dopa has been the subject of detailed experimental studies in animals (121–123). The increase of cerebral dopamine induced by L-dopa is markedly enhanced by inhibitors of dopa-decarboxylase (124–130), and such compounds have been extensively studied in the laboratory and in clinical trials following the initial observation in humans by Birkmayer & Mentasti in 1967 (131). Ro4-4602[1] has been tested in Europe (132–134) and in Canada (135, 136), and its use over the last five years has recently been extensively reviewed (137). MK-485[2] or MK-486 (Methyl-dopa-hydrazine) has been studied mainly in England (138, 139) and the USA (140, 141). α-Methyl-dopa, a drug used for the treatment of hypertension, also possesses some dopa decarboxylase inhibitory capacity and has been partially successful in the same context (142, 143); in fact a recent note (144) claims that it is as powerful as methyl-dopa-hydrazine in potentiating the effects of L-dopa and alleviating undesirable peripheral side effects. All these trials present essentially similar results, indicating that the combination is indeed preferable to L-dopa alone (157). The incidence of nausea and vomiting is considerably reduced or abolished (130, 137). Dopamine is known to possess a number of cardiovascular and renal actions (for review see 145). It could have been expected that L-dopa would also produce some cardiovascular effects. This has indeed been the case with ventricular arrythmias and occasional drops in blood pressure (146). Combined therapy (L-dopa plus a dopa-decarboxylase inhibitor) has considerably reduced or abolished the incidence of arrythmias (136, 137).

Another advantage of combined therapy, besides the marked reduction in L-dopa dosage, has been the possibility of using pyridoxine in patients treated with L-dopa. Since pyridoxine is important in many brain enzymatic processes, such as dopa-decarboxylation, it was feared that large doses of L-dopa would induce a deficiency state, with subsequent complications, and therefore pyridoxine supplements were given to patients to enhance the dopa effect. However, Duvoisin and collaborators (147) reported that such a regimen could negate all beneficial effects in some patients, prompting a number of studies on the mechanism of action behind this phenomenon (148–151). The negative action of pyridoxine in patients with L-dopa can be blocked when peripheral dopa-decarboxylase inhibitors are used, thus slowing down the peripheral degradation of L-dopa (152, 153). The present state of the art concerning dopa-decarboxylase inhibitors has been summarized in a recent Symposium (154).

(*c*) *Psychiatric side effects.* For many years it has been known that a decrease in intellectual ability can be observed in a fair proportion of patients with Parkinson's disease, occasionally leading to actual dementia (159–162). There is also evidence that this mental deterioration in highest integrative functions is more closely asso-

[1] [N'-(DL-seryl)-N²-(2,3,4-Trihydroxybenzyl)-hydrazine] HCl; Hoffmann-LaRoche.

[2] β-(3,4-dihydroxyphenyl)-α-hydrazino-α-methyl-DL-proprionic acid; Merck Sharp & Dohme.

ciated with the symptom akinesia (163, 164). Studies from our laboratory (52, 53, 165) have attempted a quantification of psychomotor components of akinesia and have delineated a significant impairment in the ability to elaborate a motor pattern or plan of action. This impairment was more evident with progressive complexity of the puzzle test utilized. The presence of akinesia is probably the single most important factor in a rapid progression of the illness. Indeed, Hoehn & Yahr (166) demonstrated that 40% of the akineto-rigid patients are invalid within five years, while fewer than 10% of those whose first symptom was tremor reached this stage after the same period. With this background, it was of great interest that along with a more or less specific anti-akinetic effect (8), L-dopa therapy has been observed to produce intellectual awakening or alerting (50, 167–169) and occasionally ameliorated thinking capacity. Some authors have even reported actual improvement in learning ability, auditory perception, and intermediate memory functions (169), as measured by verbal IQ and performance IQ scores (167, 170–173). This improvement appeared to be greatest in tests measuring perceptual organization, such as block designs and object assembly (165, 174), although Klaiber and collaborators (175) noted that even within this test specialization only the simple tasks were modified and the more complex procedures involving a sequence of actions, or making a decision, remained essentially unchanged. Riklan (176), however, still maintains that an increase in behavioral activation or arousal is responsible for the observed increments in test scores of intellectual functions following short- and long-range L-dopa therapy, while Garron and collaborators (177) confirm that late onset of Parkinson's disease and the symptom akinesia tend to be associated with intellectual deterioration.

Short-term results with L-dopa not only showed some evidence of improved intellectual function, but were often accompanied by a vast array of psychiatric disturbances. These have been the subject of a number of reviews (68, 119, 178–181) and even two recent books (182, 183). The reader is referred to these papers, to which there is very little to add. It is evident that the above observations have led many authors to use L-dopa as a research tool in mental disease and to strengthen the arguments in favor of the role of catecholamines, and particularly dopamine, in mental function (184–186).

With more long-term use of L-dopa, many physicians (187–189) are becoming aware of a subtle mental change occurring in some patients on chronic L-dopa therapy, but apparently not correlated to the degree of physical impairment. This motor/psychological dissociation is potentially very important. Patients outwardly intellectually bright, mobile, well oriented, and not depressed, perform at a definitely low level on tasks involving constructive and perceptual organization. In studies using the Kohs block design tests (165) it was shown that, despite the initial improvement within the first few months of L-dopa therapy, there is an inexorable gradual decrease in performance in all groups of parkinsonian patients, with a slow return to pretreatment levels. The slope of this progression is identical to that observed in patients not receiving L-dopa. It was concluded that L-dopa does not stop the underlying progression of the disease, even while correcting the motor

performance for long periods of time. Moreover we could also conclude that L-dopa per se does not appear to be responsible for the progressive loss in intellectual performance, at least as measured with the Kohs block design test. It is thus probable that, as time goes on, we will see more and more of the dementias associated with the advanced state of Parkinson's disease.

(*d*) *Oscillations in performance.* After a certain time on high doses of L-dopa therapy, there appears with progressively increasing frequency in some patients a variation in the level of performance during the day. These diurnal changes were first reported by Cotzias and collaborators (50) and studied in detail by us (8, 53, 137, 190). The patients experienced a bimodal pattern of performance during the day, with good periods usually in the morning and early evening, and bad periods during which akinesia reappeared in the afternoon and late evening. Despite numerous modifications in diet, drug regimen, or dosage, the oscillations became more pronounced. They were made worse by independent patterns of abnormal involuntary movements (AIM) and there appeared, again with increasing frequency, a strange phenomenon marked by a rapid change-over from the "free" to the "rigid" conditions, or inversely. This switch effect has received the name "on and off phenomenon" because of its occasional very rapid unfolding (37). Some clinical characteristics of the patients during the bad periods made them different from the pre-dopa experience and led us and others to use the term "akinesia paradoxica" (137, 191, 193). We have described four types of diurnal oscillations, which are in fact four stages in a continuous process (for complete description see 137, 190). The early (Stage 1) oscillations are the result of a variable deficiency in effective dopamine, as shown through determinations of plasma dopa (156). The more severe oscillations (Stages 2 to 4) are the result of additive phenomena due to L-dopa overdosage, where too much dopamine displaces serotonin and noradrenaline (54, 253). These phenomena involve the simultaneous production of AIM and of a hypotonic akinesia. Clinical experiments designed to accomplish a slow, gradual reduction in L-dopa dosage over a 10 month period (190) conclusively demonstrated a marked reduction in the incidence and severity of these two side effects, without loss of motor performance in almost all subjects. We concluded that in many patients manifesting AIM and hypotonic akinesia we were unnecessarily giving between 1 and 1.5 L-dopa *in excess* of the minimum requirements. This conclusion was supported by the results of plasma dopa determinations in some of these patients (192). From these observations we proposed two L-dopa schedules in the therapy of Parkinson's disease: an *induction* dosage usually fairly high, and a *maintenance* regimen, which required much lower levels of L-dopa.

In the previous paragraphs we have reviewed some of the problems (diagnosis, peripheral, and psychiatric side effects, oscillations in performance) inherent to the long-term pharmacotherapy of akinesia with L-dopa. The other well-known problem, of course, is the development of abnormal involuntary movements. Because this subject is germane to the physiopathology of the "positive" symptoms which will be described later, we will omit a discussion of AIM at this point.

4. L-Dopa Analogs or Substitutes in the Treatment of Akinesia

As seen above, the treatment of akinesia is based essentially upon the replacement of effective brain dopamine. It was thus to be expected that a variety of other approaches would be tried to achieve the same goal. Although, to date, none of the other drugs studied have equalled L-dopa in range of efficacy, it may be worthwhile to summarize these findings:

(*a*) *m-Tyrosine.* Like dopa, *m*-tyrosine penetrates into the brain and is subsequently converted to *m*-tyramine, an amine capable of stimulating dopamine receptors, as demonstrated by its awakening effect in reserpine-treated mice (194) and in preliminary human trials (37, 195). In animal studies, Andén and collaborators (196) and Ungerstedt and collaborators (197) demonstrated that *m*-tyrosine can mimic the behavioral effect of L-dopa treatment after depletion of endogenous monoamine stores. In rats with a unilateral 6-OH-dopamine-induced lesion of the nigro-neostriatal dopamine pathway, the administration of l-*m*-tyrosine in combination with an extracerebral dopa-decarboxylase inhibitor caused marked turning of the rat towards the intact side and mimicked the action of L-dopa in this model (197). Similarly in monkeys with unilateral ventromedial tegmental lesions, the same combination caused a transient relief of the tremor of the ipsilateral extremities (197). Unfortunately recent clinical trials in human parkinsonian patients failed to confirm similar actions in man (198).

(*b*) *γ-Hydroxybutyrate.* γ-Hydroxybutyrate, a natural metabolite of the mammalian brain (199), possesses sedative, hypnotic, and anesthetic properties and has been introduced clinically as an hypnotic agent (200). This compound can produce a selective, dose-dependent increase in brain dopamine in different species, particularly within the basal ganglia (201-204). It appears to stimulate dopamine synthesis without inhibiting either monoamine oxidase or catechol-O-methyl transferase (205). Some preliminary favorable results in man (206) have not been confirmed by others (207).

(*c*) *3-O-Methyl-dopa.* 3-Methyl-4-hydroxyphenylalanine (3-O-methyl-dopa) is an important metabolite of L-dopa in animals and man (208). It has now been demonstrated that this compound, through demethylation, can serve as a precursor to dopamine (209). This property, coupled with a relatively long half-life and its long persistence in the blood was the basis for initial optimistic therapeutic trials (210) which, unfortunately, could not be confirmed, even by the same authors (211–213).

(*d*) *Enzyme inhibitors.* Dopamine is metabolized mainly through three enzymatic systems: dopamine-β-hydroxylase, monoamine oxidase, and catechol-O-methyl transferase (COMT) (for review see 61, 62). Attempts to enhance brain dopamine levels through inhibition of each of these enzymes have been carried out with variable results. In animals disulfiram, a dopamine-β-hydroxylase inhibitor, has been found to be a potent agent in increasing the brain dopamine concentration (214). In man it has not been very useful, mainly because it enhances nausea (215). Another such agent, fusaric acid, had been claimed to be a useful adjuvant by Hidaka (216), but Mena and collaborators (217) could demonstrate no clear-cut effect, except a reduction in L-dopa-induced involuntary movements.

Monoamine-oxidase inhibitors can be useful when used alone in Parkinson's disease (218), but simultaneous use with L-dopa can be dangerous, often producing marked elevations in blood pressure (37, 219). They are not recommended as standard therapy at this stage, except in the presence of idiopathic hypotension (220).

Finally, inhibition of COMT could probably be of some use, especially to help reduce adventitious movements. The best known inhibitor, pyrogallol, is too toxic for human use. Ericsson (221) has initiated preliminary clinical trials with N-butylgallate (GPA-1714) with some potentiation of L-dopa effects and reduction in nausea, vomiting, and involuntary movements. These results have not yet been confirmed by others.

The use of peripheral dopa-decarboxylase inhibitors (Ro4-4602, MK-485, MK-486, α-methyl-dopa) has been discussed above in relation to L-dopa peripheral side effects.

(*e*) *Amantadine.* In 1969, Schwab and collaborators (222) made the fortuitous, but important, discovery that amantadine hydrochloride, used as an antiviral agent on A-2 Asian influenza, also possessed some activity in controlling the symptoms of parkinsonism. This observation created great interest because the structure of the compound was totally unlike that of other known antiparkinson agents (223). These results were soon confirmed by many authors from all parts of the world (224–232). A number of well-controlled double-blind studies (224, 226, 228, 229, 231, 233, 234) leave no doubt that amantadine has a place in the management of Parkinson's disease (235, 236). Recently it has also been used in combination with L-dopa (237–240) with debatable additive results, unless the dosage of L-dopa was not optimal because of side effects. Again the best results were obtained against akinesia, but modifications in rigidity and tremor could be observed in a significant number of cases.

The mechanism of action of amantadine has not yet been clearly delineated. Studies on experimental animals have shown that there exists some interrelationship between amantadine and catecholamines. Amantadine releases catecholamines from neuronal stores in the peripheral nervous system (241–252). It also causes release of dopamine within the brain (242–245). However, amantadine does not clearly modify the CSF concentrations of the metabolites HVA or 5-HIAA (246). High concentration of amantadine inhibits the uptake of dopamine and noradrenaline by rat brain homogenates (245), but this action is weak or inexistent (247–250) at physiological concentrations. The main effect of amantadine appears to be stimulation of dopaminergic structures in the presence of normal neurotransmission in noradrenergic neurons (233, 251). Indeed amantadine antagonized spiroperidol-induced catalepsy and this effect was not abolished by α-methyl-ρ-tyrosine (an inhibitor of catecholamine biosynthesis).

(*f*) *Apomorphine.* Analogs of dopamine have been developed and tried in Parkinson's disease. Surprisingly, their effect has been more important upon the symptom tremor than upon akinesia. They will therefore be discussed in more detail under the appropriate heading.

THE PHARMACOTHERAPY OF TREMOR

1. Classification of Tremor Syndromes and Rationale for Treatment

Tremor is a rhythmic involuntary oscillation of a limb around its position of equilibrium (10). *Physiological tremor* is that form normally present during the initiation of any motor activity and is usually of little apparent clinical significance except when exaggerated. It varies from 5 to 15 cycles per second (254–257). *Postural tremor* is usually present in an extremity during sustained motor activity and is identified most readily in the upper extremity upon resisting gravity. Rarely present at rest, its most common form, benign essential tremor, is usually inherited as a mendelian dominant trait (257–261). It can be limited to the extremities or also involve head, chin, tongue, and speech. *Intention tremor* is seen primarily during movement and usually indicates some involvement of the cerebellum or of the cerebellar outflow system (brachium conjunctivum, red nucleus, and related structures). It can be associated with both resting or postural tremor. It is more an instability of movement than a true tremor. Finally a very common form of tremor is *resting (or static) tremor,* which is present primarily at rest and often disappears upon initiation of movement, to reappear during sustained posture. Its frequency varies from 3–8 cyles per second. This form of tremor is the most frequent in Parkinson's disease, where its mechanism has been thoroughly studied. Parkinsonian tremor is characterized by alternating excitation of flexion and extension muscles. It is not our purpose in this chapter to review these important studies on the mechanism of tremor or on the tremorigenic center, for this has been done by many authors (262–268). Suffice it to recall that normal extrapyramidal function may depend upon a sensitive balance between inhibitory dopaminergic neurons and excitatory cholinergic fibers in the basal ganglia (37, 112). When studying the pathophysiology and treatment of akinesia, we stressed the importance of the nigrostriatal dopaminergic pathways. The other pole of this balance system appears to be involved in the causation of tremor. Indeed neuroleptics, central anticholinesterases, and central muscarinic agents produce tremor in the normal human, while reserpine, tetrabenazine, physostigmine, and acetylcholine all exacerbate parkinsonian tremor by an action that is reversed by central anticholinergic drugs (for review see 4). Finally there is some evidence that serotonin may be involved in the pathophysiology of tremor (87–89).

2. New Antitremor Agents

From the above considerations we see that a number of therapeutic approaches have been used to control tremor in humans, be it of the resting type, as in Parkinson's disease or of the postural type, as in benign essential tremor. We will review only some of the newer compounds, which have recently been experimentally studied.

(*a*) *Anticholinergic and antihistaminic drugs.* These agents have been extensively used for nearly a century, in the form of naturally occurring alkaloids or, since 1940, as synthetic compounds. They are still useful for the partial relief of tremor and rigidity, but not in all patients, if used carefully with a gradual upward titration. Side effects (dryness of mouth, diplopia, confusion, constipation) are frequent. Com-

plete reviews have recently reassessed these substances in the light of present L-dopa therapy (4, 11, 13) and further data will be found in the paragraph on the treatment of rigidity. The only new drug of promise in this class of which we are aware is a dihydromorphanthridine derivative called EX 10-029[3] (269).

(*b*) *Propranolol.* The β-adrenergic blocker propranolol, which is best known in cardiology, has been used against parkinsonian tremor after the stimulation of β-adrenergic receptors was shown to increase tremor (270–272). The first studies, with pronethalol, propranolol, or oxprenolol alone, indicated clear-cut improvement of the action component of parkinsonian tremor, but less so of the resting tremor (273–277). Combined treatment with L-dopa was also evaluated and a significant additive therapeutic action on tremor was seen with this combination (278). There was no further additive improvement on rigidity or akinesia. Propranolol actually proved to be of even more use against essential tremor. The first observation along this line was made by Winkler & Young in 1971 (279) and has since been amply confirmed (280–283). Our own results (283) indicate that 75% of essential tremor patients can benefit from the addition of propanolol.

(*c*) *Apomorphine and pyribedil.* More specific stimulation of dopamine receptors in the brain can be obtained with drugs such as apomorphine (284, 285). Some effect of apomorphine upon parkinsonian symptomatology had been noted as early as 1951 by Schwab and collaborators (286), but it was Cotzias' group that clearly demonstrated this effect, alone or in combination with L-dopa (287–290). This was later confirmed by others (291, 292). With or without L-dopa, apomorphine diminished tremor and rigidity. It decreased bradykinesia mainly in patients receiving L-dopa. Düby and collaborators (290) explained this dual action by the molecule of apomorphine, part resembling dopamine and part resembling phenylethylamine, which can displace neurotransmitters from cellular sites.

In 1971, Corrodi and collaborators (293) described a new type of dopamine receptor stimulating agent which has since been named Trivastal® (ET-155, Pyribedil[4]). Tested upon surgically induced tremor in monkeys, it relieved these tremors while concomitantly evoking involuntary movements (294). Preliminary clinical studies with Trivastal (D. B. Calne, C. Fieschi, T. N. Chase, A. Barbeau, personal communications) indicate that this drug is indeed useful against Parkinson tremor in a certain number of cases. Although its action against dopamine receptors is uncontested, there also appears to be some effect upon the cholinergic system (S. Garrattini, J. Minnich, A. Barbeau, unpublished results). Further studies are needed to elucidate the mode of action of this interesting compound.

(*d*) *Agents modifying brain serotonin.* As indicated above, there is some evidence that serotonin may be involved in Parkinson's disease, particularly in tremor mechanisms (97, 295–297). L-dopa, in some cases, can reduce the resting tremor of parkinsonian patients (8). It also decreases the brain content of serotonin (298), possibly through some displacement or release mechanism. In tremorine-induced

[3]EX 10-029: 11-(3-dimethylaminopropylidene)-5-methyl-5,6-dihydromorphanthridine dicyclohexylsulfamate; Lakeside Laboratories.

[4]Trivastal: 1-(2"-pyrimidyl)-4-piperonylpiperazine; Servier, France.

tremor in mice, 5-hydroxytryptophan and a serotonin-like agent quipazine[5] were found to antagonize the tremor (299). It was thus justified to attempt some modifications of serotonin's metabolism in parkinsonian patients. Van Woert and co-workers (300) first attempted to lower brain serotonin content further with the serotonin depletor D,L-*para*-chlorophenylalanine (*p*-CPA). This depletion was not therapeutically useful in patients with Parkinson's disease and did not consistently produce adverse effects similar to those seen with L-dopa therapy. On the other hand, imipramine and desmethylimipramine, tricyclic antidepressants that inhibit the uptake of serotonin into neural tissue, reportedly ameliorate parkinsonian rigidity and tremor (301, 302). Attempts to increase brain serotonin further with L-5-hydroxytryptophan (5-HTP), or tryptophan with pyridoxine, indicate a rapid exacerbation of both rigidity and tremor (303–305). The mechanism underlying this exacerbation of symptom has not yet been elucidated.

THE PHARMACOTHERAPY OF RIGIDITY

1. Physiopathology and Rationale for Treatment

Rigidity is detected clinically as resistance to passive movement. It differs from spasticity of corticospinal origin in that it affects agonists and antagonists equally, and it is uniform throughout the whole range of passive movement being tested. It is exacerbated by mental concentration or by active movement of another limb.

The central nervous system controls the muscles through two sets of coordinated efferent systems, the α- and γ-motoneurons (306). Two types of experimental rigidity are apparent: α- rigidity is regarded as resulting from direct α-motoneuron drive, while γ- rigidity is attributed to excessive fusimotor activity. It is not yet clear which type of rigidity is predominant in Parkinson's disease. Studies by Steg (307) demonstrate that reserpine treatment of rats with unilateral lesions of the nigro-striatal dopaminergic neurons produce rigidity only on the unoperated side and a marked increase in the α- and decrease in the γ-motoneuron excitability on the contralateral rather than the ipsilateral side. Thus, according to Steg, rigidity is attributed to striatal cholinergic dominance producing α-motoneuronal dominance of efferent muscle control. Similarly γ-deficit is related to akinesia. On the basis of this rationale, it is evident that anticholinergic drugs should be the best approach to the treatment of parkinsonian rigidity. The belladonna alkaloids and synthetic anticholinergic drugs have long been recognized as beneficial in this disease. Their use has been reviewed by many authors (4–13) and will not be further discussed here, except to say that even since the advent of L-dopa, it has still been necessary to resort to combined treatment (308). Recent evidence tends to incriminate chronic anticholinergic drug therapy in the pathophysiology of some adventitious movements in man.

2. Experimental Drugs

In 1969, Coyle & Snyder (309) demonstrated that certain drugs used for the treatment of Parkinson's disease blocked dopamine uptake in striatal synaptosomes from

[5]Quipazine: 2-(1-piperazinyl) quinoline.

rats treated with reserpine, and proposed that this was their main mechanism of action. On the basis of this hypothesis a search for new compounds was undertaken by many laboratories. For example Ohashi, Hitomi & collaborators (310–312) studied Piroheptine,[6] a drug that proved to have some effects in drug-induced tremor (tremorine, oxotremorine, and pilocarpine) and catatonia. It potentiated the L-dopa effect in motor activity and the methamphetamine effect in conditioned avoidance response. However, it should be mentioned that in vivo studies indicate that not all antiparkinson drugs act by blocking dopamine uptake (313, 314). Thus benztropine, ethybenztropine, diphenylpyraline, brompheniramine, chlorpheniramine, and methixene caused a clear-cut but not marked reduction of catecholamine accumulation in the dopamine neurons following intraventricular α-methyl-noradrenaline injections or dopa administration to reserpine-nialamide pretreated rats. Other anticholinergic drugs such as atropine, scopolamine, and benzhexol, and antihistamine compounds such as diphenhydramine and orphenadrine did not cause any certain blockade of catecholamine uptake into the dopamine neurons (314).

Molina-Negro & Illingworth (315) firmly believe that postural rigidity in Parkinson's disease is due to hyperactivity of the γ-system. Based on this hypothesis, the same authors (316) claim good results against the symptom of rigidity with cyclobenzaprine (MK-130). Our own experience with this drug (A. Barbeau, unpublished results) is far from conclusive. We were able to reduce tremor and rigidity only by producing marked somnolence.

In mammals the predominant control over melanocyte-stimulating hormone (MSH) release from the pituitary is exerted by a hypothalamic factor, MSH release-inhibitory hormone or MIF (317). This factor has been isolated from bovine hypothalamic tissue and its structure determined, thereby permitting synthesis of the compound (318). The structure of MIF was shown to be that of a tripeptide: L-prolyl-L-leucyl-glycine amide (Pro-Leu-Gly-NH_2). Melanocyte stimulating hormone will increase skin pigmentation in frogs and parkinsonian symptoms in man, while MIF and dopamine can lighten frogs previously darkened by destruction of the hypothalamus when the substances are applied directly to the pituitary gland (319). This dichotomy was noticed several years ago to offer some justification for the trial of MIF as an antiparkinson agent (320). Recent pharmacological studies have indicated that Pro-Leu-Gly-NH_2 can potentiate the behavioral effects of L-dopa and reduce the tremor induced in mice by administration of oxotremorine. These effects of MIF were shown to be independent of MSH since they occurred in hypophysectomized animals (321, 322). We have now demonstrated that L-prolyl-L-leucyl-glycine amide possesses some antiparkinsonian activity in man and that it can reduce some drug-induced dyskinesias (323). The principal effect of this substance was a clear-cut and significant reduction in rigidity. The mechanism of action of MIF upon catecholamines in the brain is not yet elucidated, but recently Carman (324) has proposed that it may be acting by inhibiting catechol-O-methyl transferase (COMT).

[6]Piroheptine: 3-(10, 11-dihydro-5H-dibenzo-[a, d]-cyclohepten-5-ylidene)-1-ethyl-2-methyl-pyrrolidine.

THE PHARMACOTHERAPY OF OTHER DYSKINESIAS

1. Specific Experimental Approaches

Many other dyskinesias are known to occur in humans. The interest in the biochemistry of Parkinson's disease has revived research into the understanding of such entities as Huntington's chorea, dystonia musculorum deformans, and even congenital athetosis. Many studies are still being carried out on the metabolism of copper, penicillamine, and ceruloplasmin in Wilson's disease (325–328) and L-dopa has even been tried with variable results (329, 330). However, this subject will not be covered in the present review, nor will other uses of L-dopa in a number of other extrapyramidal disorders (for review see 331).

(*a*) *Chorea and tics.* There is a considerable wealth of information from human and animal pharmacological studies indicating that the metabolism of cerebral monoamines must be involved in the pathophysiology of the choreic syndrome. These studies illustrate that the abnormal movements of Huntington's chorea are improved by a variety of agents, such as reserpine, tetrabenazine, α-methyl-paratyrosine, α-methyl-dopa, phenothiazines, and butyrophenones, all of which act by interferring with normal dopamine metabolism either by depleting the amine, by substituting for it, or by blocking the specific receptors on which it acts (116, 333). Conversely L-dopa will make choreic symptoms worse and has even been used as an experimental predictive test (334, 335). This would seem to indicate increased concentration, or at least increased utilization, of dopamine within the extrapyramidal centers of the brain and has led to some therapeutic approaches in order to block this activity (336). This and other aspects of the pathophysiology of Huntington's chorea have been thoroughly reviewed in a recent monograph edited by Barbeau, Chase & Paulson (337). It now appears that more emphasis should be placed on the state of basal ganglia receptor responsiveness than on the absolute concentrations of amines (338). In this context (116) we feel that Huntington's chorea should be considered as a state of dopaminergic dominance, in the same way Parkinson's disease is a state of cholinergic dominance.

An article by the MRC Brain Metabolism Unit of Great Britain (343) has suggested that lithium may stabilize the sensitivity of amine-containing systems in the central nervous system. In view of the reported hypersensitivity of dopamine receptors in Huntington's chorea (341), it is of interest that Dalén (344) has suggested the use of lithium carbonate in this illness, with encouraging results in six patients. This has now been confirmed by others (345, 346) and the approach merits a thorough investigation, especially if lithium proves to be able to reduce receptor hypersensitivity (347).

The important factor for the clinical symptoms may involve the relative degree of stimulation of striatal dopamine and serotonin receptors. It has indeed been shown that 5-hydroxytryptophan, a precursor of serotonin, worsens choreiform movements in patients with Huntington's chorea (339, 340). However, methysergide, a serotonin antagonist, when used chronically did not produce improvement in Huntington's chorea patients (341), thus indicating that serotonin alone has a limited role in the production of chorea. This conclusion is confirmed by recent

studies where D,L-parachlorophenylalanine, a potent inhibitor of serotonin synthesis, was ineffective in modifying motor behavior in Huntington's chorea (342).

Recent developments regarding the role of γ-aminobutyric acid (GABA) as a putative neurotransmitter in the nervous system are of direct import on the understanding and treatment of Huntington's chorea (350). Indeed high levels of GABA and glutamic acid decarboxylase (GAD) have been noted in structures associated with the globus pallidus and substantia nigra (348, 349). Recently some evidence has been obtained to show that the inhibitory influence from the caudate to the substantia nigra is mediated by GABA (351). Thus it is likely that a GABA-ergic pathway exists between the caudate and the substantia nigra on the one hand and the globus pallidus on the other, and that it may be involved in the pathophysiology of the symptoms in Huntington's chorea (350). Such a postulate has now received important experimental evidence through the demonstration of a deficiency in GABA in the brain of Huntington's chorea patients (352) and of a similar deficiency in GAD (353). This important discovery should lead to trials of a number of agents that may increase GABA levels in the brain. Unfortunately this avenue is not easy, for GABA itself does not cross the blood-brain barrier.

A similar rationale could be used for the treatment of tics, particularly those seen in Gilles de la Tourette's disease. To date there is evidence that butyrophenones, and particularly haloperidol, are the best available drugs (354–356).

(*b*) *Dystonia and spasmodic torticollis.* The torsion dystonias have been studied in detail in an excellent review by Eldridge (357) and the rationale for the use of L-dopa in these disorders outlined at the same symposium by Barbeau (358). Some biochemical modifications in CSF were also reviewed by Chase (359). Recently Wooten and collaborators (364) have demonstrated an elevated plasma dopamine-β-hydroxylase activity in patients with autosomal dominant torsion dystonia, but not in the recessive form. Based on these studies Coleman & Barnet (360) first reported some improvement in dystonia musculorum deformans with L-dopa, and in other patients with 5-hydroxytryptophan (361). However Mandell (362) and Barrett and collaborators (363) soon raised doubts, indicating that L-dopa may relieve dystonic posture, but can increase dynamic dystonia. Haloperidol may improve the latter side effects. The literature has remained controversial on the use of L-dopa, apomorphine, haloperidol, or amantadine in the torsion dystonias or spasmodic torticollis (365–368) but there is no doubt that there is a small subgroup of patients who respond dramatically. In our own series of 14 cases, this response has occurred and been maintained 4 times. It is of interest that all 4 such cases were of the autosomal dominant type. Perhaps this is related to the above-mentioned findings of Wooten and collaborators (364).

(*c*) *Athetosis.* A number of extrapyramidal symptoms can result from brain damage in utero or at birth. These have been described in detail in a recent review by Spiegel & Baird (369). Since athetoid cerebral palsy is largely due to damage of the basal ganglia (370), it was almost inevitable that L-dopa would be used in this disorder. Rosenthal and co-workers (332) claimed favorable results, but this has not been the experience of others (8, 365, 369). In our own practice, Diazepam still remains the drug of choice, albeit of very moderate efficacy.

CONCLUSION

The introduction of L-dopa into the therapy of Parkinson's disease has permitted the clinico-biochemical delineation of the principal symptoms, and particularly of the differentiation between akinesia and rigidity. The side effects produced by L-dopa, such as the abnormal involuntary movements, have again focussed the attention of researchers upon the metabolism of cerebral amines in disorders of the basal ganglia. These observations have been the impetus for new experimental therapeutic approaches in Huntington's chorea, torsion dystonia, and other extrapyramidal disorders. The present review can only be considered an introductory chapter into the fascinating pharmacology of these diseases, but it should be sufficient to indicate that these chronic neurological disorders *can* be treated. Accepting this very conclusion is in itself the revolution of the last few years in neurology.

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