Current Views on Parkinson's Disease

Donald B. Calne

SUMMARY: Since the introduction of levodopa therapy, there have been major advances in the understanding and treatment of Parkinson's disease. However, the problems and limitations associated with this form of treatment are now becoming increasingly apparent. This article reviews some of the current knowledge concerning the etiology and pathophysiology of Parkinson's disease and discusses some practical approaches to drug therapy.

RÉSUMÉ: Depuis l'introduction de la thérapie utilsant le levodopa, il y a eut des changements majeurs sur la compréhension et le traitement de la maladie de Parkinson. Cependant les problèmes et les limitations relatifs à cette facon de traitement sont devenus de plus en plus apparents. Cet article démontre quelques faits concernant l'étiologie et pathophysiologie de la maladie de Parkinson et présente une vue partielle de la thérapie pharmacologique.

Can. J. Neurol. Sci. 1983; 10:11-15

The explosive development in the treatment of Parkinson's disease which took place fifteen years ago, has been followed by an increasing awareness of the limitations of levodopa therapy, and frustration generated by the unresolved dilemmas posed by late adverse reactions and declining efficacy. These therapeutic problems have provided a continuing stimulus for further efforts to elucidate the aetiology, pathophysiology, and pharmacology of Parkinson's disease. Advances in these areas have been modest, but there has been progress in the development of innovative approaches to pharmacotherapy and some promising new antiparkinson compounds have been produced.

ETIOLOGY

While the etiology of Parkinson's disease remains unknown, there has been a sustained effort to find evidence that might contribute to the quest. Three hypotheses have been pursued: genetic, the possibility of infective or immunological damage, and toxic pathological processes caused by free radicals.

1. Genetic Factors:

Occasional patients with Parkinson's disease have a clear history of dominant autosomal inheritance in the family. This is more frequently encountered where there is a young age of onset (Barbeau and Pourcher, 1982). Roy et al (1982) have proposed that there are two groups of patients with genetically determined Parkinson's disease: (1) those with predominant tremor and a dominant pattern of inheritance, in whom there is an abnormally high prevelance of blood relatives with essential tremor and (2) those with predominant akinesia and rigidity, in whom there is an autosomal recessive form of inheritance.

Ward et al (1983) have employed the technique of twin analysis to evaluate genetic contributions to Parkinson's disease, and their conclusions are rather different. Sixty seven patients and their twins were examined by the authors, and a remarkably low concordance rate was found. There were 48 monozygotic twins and 20 dizygotic twins (one patient was a quadruplet with both a monozygotic and dizygotic twin). In only two pairs was typical Parkinson's disease found in both twins. Ward et al concluded that genetic factors were unlikely to play an important role in the origin of Parkinson's disease in the majority of patients. They also inferred that since twins generally grow up in the same environment, risk factors should be sought after adolescence. Early and mid adult life seems to be the relevant period for seeking causal agents, because striatal dopamine falls slowly with age, and the tissue concentration appears to decline by some 80% before symptoms appear (Riederer and Wuketich, 1976).

More studies are required to resolve the controversy over whether genetic factors are important in the etiology of the majority of cases of Parkinson's disease. The present conflicting reports should provoke further observations to confirm or refute the genetic hypothesis, which remains only one of several possibilities at present.

2. Infective and immunological theories:

It is known that infective disease of the nervous system, in particular viral encephalopathy, can produce the clinical features of the parkinsonian syndrome. With this background, it is appropriate to consider the possibility of an infective or allergic etiology for idiopathic parkinsonism. The search for evidence has been conducted in several directions. Attempts have been made to find morphological clues of inflammatory or spongiform changes in the brain, to grow viruses from tissue or body fluids, and to detect changes in antibody titres or abnormal patterns of immunoglobulins. In addition, portions of brain from patients have been injected into the brains of primates to detect unconventional (slow) viruses. The common denominator of all these studies has been the failure to detect any statistically significant, reproducible positive results (Duvoisin, 1981). The findings leave open the possibility that Parkinson's disease may be caused by a hitherto unobserved type of infective particle, or that multiple episodes of individually trival

From the Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, B.C.

Address reprint requests to Dr. D.B. Calne, Division of Neurology, Health Sciences Center Hospital, 2211 Wesbrook Mall, Vancouver, B.C., Canada V6N 1W5.

infections, influenza for example, might result in cumulative damage to the brain without leaving any trace of the infective process.

3. Toxic Processes: Free Radicals:

Exposure to certain toxic agents, such as manganese, can produce clinical features resembling Parkinson's disease, and the specific neurotoxin, 6-hydroxydopamine, is employed to prepare an animal model of striatal dopamine deficiency. It is therefore reasonable to examine the possibility that a toxic process might contribute to the etiology of Parkinson's disease. Examination of the brain and body fluids of parkinsonians has failed to reveal abnormal concentrations of any putative toxin. However, an intriguing proposal has been made that toxic damage to the nigrostriatal pathway occurs as the result of "autotoxicity", deterioration in the capacity to trap and destroy the highly reactive free radicals that are normally formed by oxidative metabolic processes. Manganese and 6-hydroxydopamine may elicit neuronal damage by interfering with the removal of free radicals (Heikkila and Cohen 1972; Donaldson et al 1982). A number of threads of evidence can be woven together in support of this hypothesis. (1) Catecholamine metabolism, in dopaminergic neurons, provides a particularly rich supply of free radicals such as superoxide. (2) It has been reported that certain enzymes which destroy free radicals, such as peroxidase, are normally present in unusually high concentrations in dopaminergic neurons; these enzymes are depleted in the dopaminergic areas of the brain in patients with Parkinson's disease (Ambani et al, 1975). (3) Epidemiological reports have established an inverse relation between the habit of smoking cigarettes and the prevelance of Parkinson's disease (Baumann et al, 1980). One possible explanation for this finding is the speculation that smoking results in a slight but sustained elevation of reducing agents, such as carbon monoxide, in the tissues, and this in turn provides some protection from oxidative cell damage.

While there is no firm evidence either for or against the speculation of nigrostriatal vulnerability to free radicals, this hypothesis has the attraction of therapeutic implications. Free radical trapping agents, such as vitamin E, could be given to patients with early disease to determine whether such treatment might modify the progress of their deficits. Since some of the free radical trapping agents are devoid of adverse effects, it might also be possible to study the incidence of Parkinson's disease developing prospectively, in a large group of elderly normal subjects who receive either vitamin E or placebo for a protracted period of time.

Before leaving the topic of toxic agents as possible etiological factors, it is appropriate to mention two curious cases of Parkinsonism precipitated suddenly and irreversibly following the administration of "home made" meperidine. Both patients were seen by the author; one subsequently committed suicide and was found to have histological changes in the substantia nigra similar to Parkinson's disease (Davis et al 1979). Since meperidine itself has not been reported to induce Parkinson's disease, it is possible that a contaminant may have been responsible.

PATHOPHYSIOLOGY

The quest to understand the role of the basal ganglia and how their function is disturbed in Parkinson's disease is one of the Gordian knots of motor physiology. Attempts to formulate a single coherent hypothesis to explain the physiological basis of tremor, rigidity and bradykinesia have been universally unsuccessful. This is not surprising when so little can be said about how the basal ganglia contribute to what is generally acknowledged to be their major function, the control of movement. Recent studies have led to proposals that the basal ganglia are responsible for planning the integrated patterns of neuronal activity required for the execution of movements (Marsden, 1982). While such a concept, if correct, would explain bradykinesia in patients with lesions of the basal ganglia, the relationship of tremor and rigidity to motor planning is less direct. There has been considerable interest in the finding of enhanced long latency (M2) reflexes in the limbs of patients with rigidity (Tatton and Lee, 1975), but while some workers have suggested that this reflex traverses cerebral pathways (Tatton et al, 1978), others have claimed that these reflexes are generated in the spinal cord (Tracey et al, 1980), and yet others have even proposed that the long latency responses derive from vibration produced in the periphery (Hagbarth et al, 1981). Most physiologists agree that parkinsonian tremor results from oscillations, in the basal ganglia, of neuronal activity that is accessible to modification by peripheral input; but there are even controversies here, on such simple questions as whether perturbation of the limb can reset the tremor cycle (Teräväinen et al 1979, Lee and Stein 1981).

In summary, the physiology of the basal ganglia, and its disturbance in Parkinson's disease, remains one of the most difficult areas in which to make firm progress.

PHARMACOLOGY

Pharmacology has been a more fertile field for advances in elucidating the biology of Parkinson's disease. Since the discovery of dopamine as a neurotransmitter in the striatum and substantia nigra, these regions have proved to be a veritable cornucopia for the demonstration of other active agents, such as GABA, glycine, acetylcholine, substance P, somatostatin, and cholecystokinin. The regional profiles of concentrations of these various substances, their synthetic enzymes, their metabolites, and their receptors are currently undergoing characterization in healthy brains and in Parkinson's disease (Javoy-Agid et al, 1983). Some extremely interesting points are beginning to appear, such as depletion of choline acetyltransferase in the cerebral cortex. This enzyme is concerned with the synthesis of acetylcholine, and the decrease correlates with the extent of dementia in parkinsonian patients (Agid et al, 1983), an observation in accord with the findings in Alzheimer's disease.

It is also becoming recognized that the various active humoral agents in the basal ganglia probably have very different ways of communicating information between neurons; some conventional neurotransmitters seem to be released for fast, transient and highly localized effects at synapses, while other substances, often termed neuromodulators, have slower actions over more diffuse areas. Furthermore, it seems that in many cases one neuron contains more than one active agent, such as dopamine and cholecystokinin (Hokfelt et al, 1980), and that a monoamine and a peptide may even coexist in the same in-

tracellular vesicle (Pelletier et al, 1981). In this context, it is of interest that while cholecystokinin is localized in several regions of the human brain, this peptide is selectively depleted in the substantia nigra in Parkinson's disease (Studler et al, 1982).

These complexities at the presynaptic level are being matched by the characterization of multiple categories of receptor for dopamine. At least two subtypes of dopamine receptor (D1 and D2) have been proposed (Kebabian and Calne, 1979) and there may be more (Seeman, 1980). The most important receptor for eliciting the therapeutic response in Parkinson's disease seems to be the D2 receptor. There is evidence for an antagonistic interaction between D1 and D2 receptors in the striatum (Stoof and Kebabian, 1981), and indirect observations suggest that both receptor types may be located on the same striatal neuron (Stoof and Kebabian, 1982).

These new concepts may have an impact on therapy. If more selective agonists and antagonists can be developed for the various physiological active substances that are abnormal in Parkinson's disease, and particularly if agents can be found that are specific stimulants or blockers for the subtypes of dopamine receptor, it may be possible to improve the therapeutic index of treatment by tailoring drug combinations for particular needs. A start in this direction has already been achieved with the ergot derived dopamine agonists, which induce less dyskinesia than levodopa. By developing agents with more prolonged kinetic profiles, it may prove possible to prevent or ameliorate fluctuations in response (wearing off reactions) more effectively than has hitherto been possible.

A final interesting point which has arisen from these pharmacological advances is the recognition that since some active agents are released diffusely, rather than requiring precise neuron to neuron contact, function can be restored in animal models of Parkinson's disease by transplanting neurons into the brain and allowing them to survive in the immunologically privileged situation afforded by the blood-brain barrier (Perlow et al, 1979). Experiments in animals have shown repeatedly that these goals are attainable, and recently there has been a preliminary report of a human study in which cells from the adrenal medulla were transplanted into the brain of a single patient with severe Parkinson's disease (Kolata 1982). These cells, which are capable of producing catecholamines, including dopamine, were obtained from the patient's own adrenal. The patient survived the procedure but so far no change in his neurological status has been observed. With due attention to the ethical sensitivities, this type of operation is likely to be repeated until we have a more definite impression of its potential.

PHARMACOTHERAPY

Increasing experience with levodopa has led to more widespread recognition of the late management problems, notably severe dyskinesia, fluctuations in response, psychiatric symptoms and declining efficacy. Although not proven, there is a high level of suspicion that some of these difficulties might be related to a high cummulative intake of levodopa, so most neurologists tend to use lower doses than previously, and often start levodopa therapy later in the course of the disease, (Fahn and Calne, 1978).

Levodopa is now almost always employed with a decarboxylase inhibitor (carbidopa or benserazide). The optimal dose of decarboxylase inhibitor is 100-200 mg daily, so when patients are starting treatment, or being maintained on a low dose of levodopa in the region of 400-500 mg daily, it is best to prescribe the levodopa:decarboxylase inhibitor ratio of 4:1. If they need doses in the region of 1000 mg levodopa daily, it is more appropriate to use the 10:1 preparation. It is often helpful to mix tablets between these ranges, for example alternating between Sinemet 100/25 and 100/10, so that the intake of decarboxylase inhibitor is in the desirable area of 100-200 mg daily, whatever the level of levodopa dosage.

Since dopaminergic ergot derivatives induce less dyskinesia than levodopa, and generally have a more prolonged action, they have been tried as initial therapy. However, they are not usually capable, by themselves, of achieving a sufficient level of efficacy, so levodopa has to be added (Stern et al, 1979).

A logical approach to the problem would be starting patients on a combination of low doses of levodopa together with low doses of a dopaminomimetic ergot preparation, instead of either drug alone. It will be of interest to see if the late problems of levodopa therapy can be reduced in this way.

Another strategy for dealing with late management difficulties is temporary withdrawal or substantial reduction of levodopa therapy - the "drug holiday". The indications for this procedure, the dose schedule, and the results reported vary widely. While it is entirely rational and safe to stop levodopa in patients who are clearly toxic from the drug (with profound dyskinesia or psychosis), the procedure should be carried out in hospital where close monitoring will permit the levodopa to be restarted rapidly when the patient's neurological status is appropriate.

It has been suggested that after prolonged treatment with levodopa the dopamine receptors develop a fluctuating or sustained reduction of sensitivity which can be helped by temporary withdrawal of therapy. This is the theoretical basis for a "drug holiday". However, in patients with a declining or fluctuating response to levodopa, the risks of stopping treatment are substantial. There are several anecdotal reports of death from aspiration consequent upon impaired swallowing in this situation.

Because of persisting doubt over the rationale for the procedure and, more importantly, the catastrophic complications that can occur, there is no general agreement that drug holidays still have a role in management, unless patients are suffering from acute levodopa toxicity. In these circumstances cessation of therapy is standard practice in most fields of neurology, so the term "drug holiday" is perhaps misleading.

CONCLUSIONS

Since the discovery that Parkinson's disease is a "dopamine depletion syndrome" there have been continuing efforts to understand more about the normal functions of the basal ganglia, the cause and nature of their pathological

derangements, and the various ways in which pharmacotherapy might be improved. Progress has been made in some areas, but much work remains to be done. Parkinson's disease continues to be a major challenge for the neuroscientist and the neurologist. In this review two practical management suggestions are put forward. First, it is argued that relatively low doses of levodopa (Sinemet or Prolopa) be combined with similarly low doses of a dopaminergic ergot (bromocriptine) in the early treatment of Parkinson's disease, in an effort to minimize the deleterious consequences of a high cumulative dose of levodopa. Second, the dangers of a "drug holiday" are stressed, with a proposal that temporary withdrawal of levodopa be confined to patients who are frankly toxic, with psychosis or severe dyskinesia.

REFERENCES

Agid, Y., Ruberg, M., Dubois, G. and Javoy-Agid, F. (1983). Biochemical substrates of mental disturbances in parkinson disease. Proceedings of the VII International Symposium on Parkinson Disease, Frankfurt. Advances in Neurology, Raven Press, New York. (In press).

Ambani, L.M., Van Woert, M.H. and Murphy, S. (1975). Brain peroxidase and catalase in Parkinson disease. Archives of Neurology 32: 114-118.

Barbeau, A. and Pourcher, E. (1982). New Data on the Genetics of Parkinson's Disease. Canadian Journal of Neurological Sciences 9: 53-60.

Baumann, R.J., Jameson, H.D., McKean, H.E., Haack, D.G., Weisberg, L.M. (1980). Cigarette smoking and Parkinson disease: 1. A comparison of cases with matched neighbours. Neurology 30: 839-843.

Donaldson, J., McGregor, D. and LaBella, F. (1982). Manganese neurotoxicity: a model for free radical mediated neurodegeneration? Canadian Journal of Physiology and Pharmacology 60: 1389-1405.

Davis, G.C., Williams, A.C., Markey, S.P., Ebert, M.H., Caine, E.D., Reichert, C.M., Kopin, I.J. (1979). Chronic Parkinsonism secondary to intravenous injection of meperidine. Ann. Psychiat. Res. 1: 249-254.

Duvoisin, R.C. (1981). The cause of Parkinson's disease. In: Movement Disorders. Edited by Marsden, C.D. and Fahn, S., London: Butterworth Scientific, pp. 8-24.

Fahn, S. and Calne, D.B. (1978). Considerations in the management of parkinsonism. Neurology 28: 5-7.

Hagbarth, K.E., Hagglund, J.V., Wallin, E.U. and Young, R.R. (1981). Grouped spindle and electromyographic responses to abrupt wrist extension movements in man. Journal of Physiology 312: 81-96.

Heikkila, R.E. and Cohen, G. (1972). In vivo generation of hydrogen peroxide from 6-hydroxydopamine. Experientia 28: 1197.

Hokfelt, T., Johansson, O., Ljungdahl, A., Lundbert, J.M. and Schultzberg, M. (1980). Peptidergic neurones. Nature 284: 515-521.

Javoy-Agid, F., Ruberg, M., Taquet, H., Bokobza, B., Ajid, Y., Gaspar, P., Berger, B., N'Guyen-Legros, J., Alvarez, C., Gray, F., Eccourolle, R., Scatton, B. and Rouquier, L. (1983). Biochemical neuropathology of Parkinson disease. Proceedings of the VIIth International Symposium of Parkinson's Disease, Frankfurt. Advances in Neurology, Raven Press, New York. (In press).

Kebabian, J.W. and Calne, D.B. (1979). Multiple receptors for dopamine. Nature (London) 277: 93-96.

Kolata, G. (1982). Grafts correct brain damage. Science 217: 342-344.

Lee, R.G. and Stein, R.B. (1981). Resetting of tremor by mechanical perturbations: A comparison of essential tremor and parkinsonian tremor. Annals of Neurology 10: 523-531.

Marsden, C.D. (1982). The mysterious motor function of the basal ganglia: The Robert Wartenberg Lecture. Neurology 32: 514-539.

Pelletier, G., Steinbusch, H.W.M. and Verhofstad, A.A.J. (1981). Immunoreactive substance P and serotonin present in the same dense-core vesicles. Nature 293: 71-72.

Perlow, M.J., Freed, W.J., Hoffer, B.J., Seiger, A., Olson, L., and Wyatt, R.J. (1979). Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 204: 643-647.

Riederer, P. and Wuketich, St. (1976). Time course of nigrostriatal degeneration in Parkinson's Disease. Journal of Neural Transmission 38: 277-301.

Roy, M., Boyer, L., Barbeau, A. (1982). A prospective study of 50 cases of familial Parkinson's disease. Paper presented at the VIIth International Symposium on Parkinson's Disease. Frankfurt, Germany. (In press).

Seeman, P. (1980). Brain dopamine receptors. Pharmacological Reviews, 32(3): 230-287.

Stern, G., Lees, A. and Shaw, K. (1979). Ergot derivatives without levodopa in parkinsonism. In: Dopaminergic Ergot Derivatives and Motor Function, Edited by Fuxe, K., and Calne, D.B., Oxford: Pergamon Press, pp. 337-341.

Stoof, J.C. and Kebabian, J.W. (1981). Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. Nature 294: 366-368.

Stoof, J.C. and Kebabian, J.W. (1982). Independent in vitro regulation by the D-2 dopamine receptor of dopamine-stimulated efflux of cyclic AMP and K+ stimulated release of acetylcholine from rat neostriatum. Brain Research 250: 263-270.

Studler, J.M., Javoy-Agid, F., Cesselin, F., Legrand, J.C. and Agid, Y. (1982). CCK-8-Immunoreactivity distribution in human brain: selective decrease in the substantia nigra from parkinsonian patients. Brain Research 243: 176-179.

Tatton, W.G., Bawa, P., Bruce, I.C. and Lee, R.G. (1978). Long loop reflexes in monkeys: an interpretative base for human reflexes. In: Cerebral Motor Control in Man: Long Loop Mechanisms. Edited by John E. Desmedt., Basel, New York: Karger. Progress in clinical neurophysiology, Vol. 4, pp. 229-245.

Tatton, W.G. and Lee, R.G. (1975). Evidence for abnormal long-loop reflexes in rigid parkinsonian patients. Brain Research 100: 671-676.

Teräväinen, H., Evarts, E. and Calne, D. (1979). Effects of kinesthetic inputs on parkinsonian tremor. In: Advances in Neurology. Edited by Poirier, L.J., Sourkes, T.L. and Bedard, P.J., New York: Raven Press, 24: 161-173.

Tracey, D.J., Walmsley, B. and Brinkman, J. (1980). "Long-loop" reflexes can be obtained in spinal monkeys. Neuroscience Letters 18: 59-65.

Ward, C.D., Duvoisin, R.C., Ince, S.E., Nutt, J.D., Eldridge, R. and Calne, D.B. (1983). Parkinson's Disease in twins and in a set of quadruplets. Neurology, (In press).

https://doi.org/10.1017/S0317167100044498 Published online by Cambridge University Press