Clinical Importance of D-1 and D-2 Receptors

*Michèle Beaulieu

ABSTRACT: The existence of subtypes of dopamine receptors as defined by Kebabian and Calne is now well accepted. The D1 receptor is typically associated with stimulation of adenylate cyclase, while the D2 receptor is either independent of adenylate cyclase or mediates its inhibition. Considerable interest has been generated by the potential physiological and clinical roles of these receptor subtypes. Availability of agonists and antagonists specifically acting at the D1 or D2 receptor site has stimulated research to characterize the functional effects of each receptor subtype. This might facilitate the development of effective compounds to control the signs and symptoms of Parkinson's disease and perhaps prevent the induction of debilitating side effects. Recent evidence indicates that D1 receptor stimulation is required to obtain full expression of the D2 receptor site, which has typically been associated with the clinical benefits of dopaminergic therapy. Both pre- and postsynaptic location of the receptors must also be taken into consideration as well as involvement of other neuronal systems. It appears that in PD, progressive involvement of the dopaminergic pathways is the principal pathological course, however, noradrenergic and serotonergic pathways are likewise involved. This multineuronal involvement suggests that drugs acting specifically at receptor sites, located on both pre- and postsynaptic neurons, might be required at different times during the course of the disease process to control its symptoms and/or the complications occurring after long-term treatment with a given drug.

RÉSUMÉ: Importance clinique des récepteurs D-1 et D-2. L'existence de sous-types de récepteurs dopaminergiques tels que définis par Kebabian et Calne est maintenant bien établie. Le récepteur D-1 est associé de façon caractéristique à la stimulation de l'adénylate cyclase, alors que le récepteur D-2 est soit indépendant de l'adénylate cyclase ou sert de médiateur pour son inhibition. La possibilité que ces sous-types de récepteurs aient des rôles physiologiques et cliniques a provoqué un intérêt considérable. La disponibilité d'agonistes et d'antagonistes agissant de façon spécifique aux sites des récepteurs D-1 ou D-2 a stimulé la recherche visant à caractériser les effects fonctionnels de chaque sous-type de récepteur. Il est possible que ceci facilite le développement de substances efficaces pour contrôler les signes et les symptômes de la maladie de Parkinson et peut-être prévenir l'installation d'effets secondaires débilitants. Selon des données récentes, la stimulation des récepteurs D-1 est nécessaire à l'obtention de l'expression totale des récepteurs D-2 qui a été associée de façon caractéristique aux bénéfices cliniques de la thérapie dopaminergique. On doit tenir compte de la localisation pré-synaptique et également post-synaptique des récepteurs ainsi que de l'implication des autres systèmes neuronaux. Il semble que dans la maladie de Parkinson, l'atteinte progressive des voies dopaminergiques est le principal mode d'évolution pathologique; cependant, les voies noradrénergiques et sérotoninergiques sont également atteintes. Cette atteinte multineuronale suggère que des médicaments agissant spécifiquement aux sites récepteurs, localisés sur les neurones pré- et post-synaptiques, pourraient être nécessaires à différents moments pendant l'évolution du processus pathologique pour en contrôler les symptômes et/ou les complications survenant au cours du traitement à long terme avec un médicament donné.

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In 1960, Barbeau[1] and Hornykiewicz[2] respectively demonstrated a loss of dopamine (DA) in the striatum of parkinsonian patients. As a result, interest has been focused on the availability and efficacy of dopaminergic agents used to treat Parkinson's disease (PD). L-Dopa combined with a dopa decarboxylase inhibitor (L-Dopa/DDI) has been demonstrated as an extremely effective therapeutic agent to control the symptoms of PD. However, it is now clear that long-term therapy is required to manage parkinsonian patients. Furthermore, since the progressive nature of the disease ultimately affects several neuronal systems, a number of drug related side effects have been reported which have significantly reduced the efficacy of L-Dopa/DDI treatment. As a consequence, several DA agonists are currently being evaluated to determine their potential advantages in the long-term management of parkinsonian patients. The principal features desirable in these agents is optimal control of signs and symptoms of PD and lack of side effects, in particular, abnormal involuntary movements (AIM), fluctuations in response or psychotic behavior, even after long-term therapy.

It should be emphasized that a number of crucial factors are essential to the development of effective therapeutic agents for PD. Amongst these are an improved knowledge of its progressive pathophysiology, classification and localization of DA receptors and availability of specific DA agonists and antagonists.

*Associate, Medical Liaison Service, Sandoz Canada Inc., Montréal, Canada
Reprint requests to: Dr. Michèle Beaulieu, Medical Liaison Service, Sandoz Canada Inc., P.O. Box 385, Dorval, Québec, Canada H9R 4P5

This manuscript will review the significance of several factors pertaining to the DA receptor and its relation to the brain dopaminergic system: namely, the classification, localization and physiological roles of both D1 and D2 receptors. Increased knowledge in these areas might allow optimal therapeutic management of PD.

Classification of the DA receptor

It is now well accepted that the DA receptor exists in two receptor subtypes termed D1 and D2 by Kebabian and Calne.[3] Their classification was an attempt to clarify the reasons ergoline and dopaminergic agonists, in particular could mimic the effects of DA in certain tissues. In the anterior pituitary gland, both ergots and DA block secretion of prolactin (PRL) from the mammotrophs, while in other tissues, e.g., the striatum, ergots block activity of adenylate cyclase while DA stimulates it. In 1983, Kebabian was able to refine this first hypothesis; using tissue from the intermediate lobe of the rat pituitary gland, he demonstrated that D2 receptor activation resulted in inhibition of adenylate cyclase activity.[4] In addition, the discovery of specific D1 and D2 agonist and antagonist drugs has greatly facilitated the characterization of the receptor subtypes in various tissues.[5,6]

However, the two receptor subtype hypothesis was not readily accepted. This was based on the observation that different classes of dopaminergic agents had different affinities for the receptor sites. Hence, as many as four different receptor subtypes were proposed.[7] It is now recognized that both D1 and D2 receptor sites exist in high and low affinity states,[8,9] and that given the appropriate conditions, either can be in "high or low" states as has been elucidated by Seeman.

Localization of the DA receptor

The DA receptor is localized in pre- and postsynaptic nerve terminals, dendrites, axons and cell bodies. The presynaptic DA receptor is also called an autoreceptor. Its proposed twofold function is to regulate DA nerve terminal activity through a negative feedback system controlling the release and synthesis of DA and to control the firing rate of the neuron.[10] The autoreceptor has characteristics similar to those of a D2 receptor.

Postsynaptic receptors are localized on both dopaminergic and non-dopaminergic neurons, e.g. glutamatergic or cholinergic neurons, which receive DA input and can be of either D1 or D2 subtypes. Typically, the D2 receptor has no effect or inhibits the formation of cAMP. Stimulation of the D2 receptor results amongst others, in inhibiting the secretion of PRL from the anterior pituitary gland and the evoked-release of acetylcholine (Ach) from cholinergic neurons[11] and in reversing parkinsonian symptoms in both animals and humans.[12,13] The functional role of the D2 receptor has been associated with behaviors such as stereotypy, locomotion, vomiting, psychotic activity and normalization of motor activities.

The D1 receptor, on the other hand, stimulates the formation of cAMP, but without modifying the formation of Ach in the striatum.[14] The functional role of the D1 receptor has not yet been determined.

Nevertheless, stimulation of the D1 receptor is associated with behavior abnormalities such as dyskinesia and stereotypy.[15-18] This is clearly shown by an increase in perioral movements induced by the D1 agonist SKF 38393 in neuroleptic treated rats[15] as well as by an increased stereotypy in naive animals treated with a combination of D1 and D2 agonists.[16,17] Similarly, the addition of the specific D1 receptor antagonist SCH 23390 blocks the rotations induced by L-Dopa and apomorphine.[18]

Interactions between D1 and D2 receptors

Recently, Goldstein[19] and Robertson[20,21] each have hypothesized potential mechanisms of action to explain the differential activities of L-Dopa and D2 agonists. Goldstein has postulated that binding of DA to the dopaminergic receptor alters the conformation of D2 receptors from a low to a high affinity state. Formation of this ternary complex (high affinity state) mediates the effects of DA agonists and induces a biological response. D2 agonists, like bromocriptine which has a high affinity for D2 receptors, compete with DA for binding to the receptor when in high affinity state. As bromocriptine dissociates more slowly from the receptor than DA, its biological efficacy is prolonged.

Robertson, however, has pursued this hypothesis a step further and has suggested that D1 receptor activation is required in order that D2 receptor expression is complete. He has demonstrated that the D1 agonist SKF 38393 potentiates the rotational behavior induced by the specific D2 agonists LY 171555 and bromocriptine in rats with unilateral substantia nigra lesions.[21] This synergistic effect is blocked by the D1 antagonist SCH 23390. This clearly indicates that activation of the D1 receptor can modulate the behaviors resulting from D2 receptor stimulation.

Results from these investigators suggest that in the presence of endogenous DA, dopaminergic drugs that are specific for high affinity state D2 receptors or those that do not discriminate between high and low affinity states, e.g., bromocriptine, ensure maximal response of dopaminergic cells. Similar data has been reported recently by Carlson et al.[22] They indicated that concurrent D1 and D2 receptor stimulation is required for complete expression of the postsynaptic receptor-mediated effects of DA agonists in the basal ganglia.

D1 and D2 receptors in Parkinson's disease

Much controversy exists over the respective roles of D1 and D2 receptors in relation to clinical manifestation of PD. Pimoule et al have shown no changes in the number of D1 receptor sites in PD striatum[23] in spite of previously reported decreased activity of adenylate cyclase - cAMP system.[24] These findings suggest, at best, an indirect involvement of the D1 receptor in PD and tend to lend credibility to Robertson's and Goldstein's hypothesis of D1 and D2 receptor interactions.

Published data on the status of D2 receptor binding sites analyzed in post-mortem brain tissue samples of parkinsonian patients are rather confusing. Some studies have shown an increase in the number of post-synaptic D2 receptor binding sites in the striatum of untreated PD patients.[25,26] When studies have been performed on tissue samples from L-Dopa-treated PD patients, results have shown a reduction in D2 binding,[25-27] or no change[28] or increased binding.[29] Recently, Guttman and Seeman have confirmed increased postsynaptic D2 receptor density in untreated PD patients and a reduction to normal level following L-Dopa therapy.[30] These data suggest that both in PD and in animals with substantia nigra lesions, a D2 receptor postsynaptic supersensitivity occurs in keeping with the concept of denervation supersensitivity following DA neuronal loss.

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In addition to receptor changes, presynaptic changes in DA neurons also occur. Associated with the cell loss in the zona compacta of the substantia nigra, there is an increased DA turnover in the remaining DA nigrostriatal neurons as evidenced by increased HVA/DA ratio.[31]

These pre- and postsynaptic changes represent compensating mechanisms for the degeneration of the nigrostriatal DA neurons occurring in PD. The presynaptic compensating mechanism of increased DA turnover is activated first,[31] when a 30% loss of DA occurs. More than a 95% degeneration of nigrostriatal DA neurons is required to activate the second compensatory mechanism of postsynaptic receptor supersensitivity.[32] The major effect of this increase in receptor numbers in specific brain areas may be of pharmacologic importance as it optimizes the sensitivity and selectivity of striatal neurons to the presence of DA or DA agonists. Clinical manifestations of PD occur only with more than 80% DA loss, reflecting the compensatory effect of adaptive mechanisms.

During the decompensation phase, therapy with L-Dopa complements the increased presynaptic activity and postsynaptic supersensitivity to control parkinsonian signs. However, within 5 years, complications in therapy often occur and attempts to correlate them with altered D2 receptor status have been rather unsuccessful. Rinne[26] and Seeman[30] both have shown that treatment with L-Dopa rapidly eliminates the D2 postsynaptic receptor supersensitivity. Seeman however has shown normalization of D2 receptor binding sites. He suggests this down-regulation is not progressive with neither the duration of disease nor that of treatment with L-Dopa.[30] Moreover, he could not correlate the occurrence of fluctuations in performance with down-regulation of the D2 receptor.

On the other hand, Rinne[26] has identified 2 subgroups of PD patients exhibiting either an increased or decreased number of D2 receptor binding sites. He was able to correlate the occurrence of fluctuations in performance, dyskinesias and psychotic episodes with an increase in the number of striatal D2 receptor binding sites in both parkinsonian patients and controls after treatment with neuroleptics. In addition, he indicated that a decreased number of D2 receptor sites was related to loss of response to L-Dopa therapy, dementia and increased disability.[33]

These findings indicate that in parkinsonian patients, L-Dopa therapy can possibly result in 3 distinct outcomes. First L-Dopa induces a sustained normalization of D2 receptors and PD signs which explains why some patients are well controlled with L-Dopa therapy. Second, L-Dopa does not modify or increase even further the D2 receptor supersensitivity with resulting abnormal motor control and psychosis. Third, L-Dopa down-regulates, below normal levels, the D2 receptor and a loss of therapeutic efficacy is observed. It must be emphasized that these hypotheses have to be conclusively proven. At this point in time, there is not enough receptor binding data in untreated and long-term L-Dopa treated patients to confirm the existence of several subgroups of PD patients with altered D2 receptor status. Similarly, more data on the effects of long-term treatment with DA agonists on DA receptor status is required to clearly define the mechanism of action of the various DA agonists.

Several studies combining L-Dopa/DDI with specific D2 agonist, e.g. bromocriptine, have shown better control of dyskinesia and fluctuations in performance.[34,35] This suggests that, possibly, early use of a specific D2 agonist, through its direct action at the postsynaptic level should prevent the development or normalize the postsynaptic receptor supersensitivity and possibly also reduce the increased presynaptic activity. The observed complications in treatment might reflect an imbalance in activity of the receptor subtypes: optimal expression of the D1 receptor and submaximal expression of the D2 receptor. Therapy with a direct acting D2 agonist should optimize the response of the D2 receptor and prevent abnormal motor control.

These findings suggest that in the early decompensation phase, addition of a specific D2 receptor agonist when coupled with endogenous presynaptic overactivity, should control the expression of the parkinsonian symptoms. This is exemplified by the fact that early treatment with bromocriptine alone is quite effective in controlling the symptoms of PD.[36] However, its efficacy can diminish later in the course of the disease, possibly when the endogenous DA levels are too low to activate sufficiently the D1 receptor site. With progression of the disease and the further degeneration of nigrostriatal dopaminergic neurons, the addition of L-Dopa or a direct acting D1 receptor agonist would be necessary to ensure maximal activation of the DA receptors and to control the symptoms of PD.

Pathophysiology of Parkinson's Disease

Another factor that must be considered in the choice of a therapeutic agent in PD is the pattern of neurological degeneration occurring in the brain. Post-mortem analysis reveals that in idiopathic parkinsonism, DA cell loss is more important in the putamen than in the caudate.[31] Similarly, both the number of D2 receptor sites and DA metabolism are more increased in the putamen than in the caudate. This suggests an adaptation mechanism appropriate for the degree of neuronal loss.

The presynaptic overactivity is the first mechanism initiated to compensate for DA cell loss throughout the nigrostriatal tract. Receptor supersensitivity is activated only when the disease has progressed sufficiently and increased DA metabolism cannot fully compensate for DA cell loss.

The time difference for the initiation of these mechanisms indicates, as previously postulated, in earlier stage of disease, a selective D2 agonist would be highly effective in complementing presynaptic overactivity. Only later in the course of the disease, addition of a selective D1 agonist or L-Dopa/DDI could allow maximal binding at the D2 site by inducing a conformation change of the receptor to a high affinity state.

The fact that the putamen is affected earlier in the course of the disease and more severely than the caudate is important. This structure receives afferents from the premotor cortex area and projects efferents back to the motor cortex via the globus pallidus. Any degeneration in the putamen will be reflected by alterations in extrapyramidal motor activities. On the other hand, the caudate nucleus receives inputs from the frontal cortex, and this is associated with psychological and motivational behavioral changes which alter the psychological status of parkinsonian patients as observed usually later in the course of the disease.

Development of DA agonists binding specifically to receptors in selective areas of the brain, e.g. the putamen, could allow control of motor symptoms without inducing psychotic side effects.

With progression of the disease, multineuronal degeneration occurs. Cell losses have been reported in the locus coeruleus where the noradrenergic cell bodies are located.[37] Similar degen-

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eration is demonstrated in the raphe nuclei at the origin of the serotonergic system.[38] However, involvement of neurotransmitters associated with these structures is minimal compared to dopaminergic degeneration. Nevertheless, dopaminergic agonists with additional serotonergic and noradrenergic activity might be positive additions to the therapeutic armamentarium. Recent data have also suggested that glutamate and opiate fibers located in the cortex could interact with efferent DA neurons. However, more work is required to clarify the physiological importance of these interactions with dopaminergic cells on the various neuronal tracts.

Summary

D2 receptors, located pre- and postsynaptically, are involved in controlling the activity of dopaminergic neurons. This regulation occurs both presynaptically and postsynaptically to activate other neurons. D1 receptors, located postsynaptically, have not yet an identified functional role, but it has been hypothesized that their mediation is necessary to allow complete expression of the D2 receptor.

The available data suggest that in the early decompensated phase of PD, a selective D2 agonist should be a useful agent to control the symptoms and signs of the disease. With progression of the disease, or when the patient is not well controlled, combination of a specific D2 agonist with either L-Dopa/DDI or a specific D1 agonist should give optimal symptomatic control.

When receptor related side effects occur, modifications to the therapeutic regimen such as a decrease in the amount of L-Dopa/DDI and/or an increase in the dose of D2 agonist should be effective. Alternatively, a drug acting specifically on autoreceptors might also be useful to regulate presynaptic activity.

References

1. Barbeau A. Preliminary observation on abnormal catecholamine metabolism in basal ganglia disease. Neurology 1960; 10: 446-451.
2. Birkmayer W, Hornykiewicz O. Der L-3, 4-dihydroxyphenylalanin (Dopa) - Effekt bei der Parkinson akinese. Wien Klin Wschr 1961; 73: 787-795.
3. Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979; 277: 93-96.
4. Côté TE, Grewe CW, Tsuruta K, et al. D2 dopamine receptor-mediated inhibition of adenylate cyclase activity in the intermediate lobe of the rat pituitary gland requires GTP. Endocrinology 1982; 110: 812-819.
5. Kebabian JW, Beaulieu M, Itoh Y. Pharmacological and biochemical evidence for the existence of two categories of dopamine receptor. Can J Neurol Sci 1984; 11: 114-117.
6. Seeman P, Watanabe M, Grigoriadis D, et al. Dopamine D2 receptor binding sites for agonists, a tetrahedral model. Molec Pharmacol 1985; 28: 391-399.
7. Seeman P. Brain dopamine receptors. Pharmacol Rev 1980; 32: 229-313.
8. Grigoriadis D, Seeman P. The dopamine/neuroleptic receptor. Can J Neurol Sci 1984; 11: 108-113.
9. Leff SE, Creese I. Interactions of dopaminergic agonists and antagonists with dopaminergic D3 binding sites in rat striatum. Evidence that [^{3}H] dopamine can label a high affinity agonist-binding state of the D1 dopamine receptor. Molec Pharmacol 1985; 27: 184-192.
10. Fuxe K, Agnati LF, Kalia M, et al. Dopaminergic systems in the brain and pituitary. *In*: Flückiger E, Müller EE, Thorner MO, eds. Basic and clinical aspects of neuroscience. The dopaminergic system. Berlin: Springer-Verlag, 1985: 11-25.
11. Stoof JC. Dopamine receptors in the striatum: biochemical and physiological studies. *In*: Kaiser C, Kebabian JW, eds. Dopamine receptors, American Chemical Society Symposium Series 224. Washington: American Chemical Society Press, 1983: 117-145.
12. Nomoto M, Jenner P and Marsden CD. The dopamine D2 agonist LY 141865, but not the D1 agonist SKF 38393, reverses parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset. Neurosci Let 1985; 57: 37-41.
13. Bédard PJ, Di Paolo T, Falardeau P, et al. Chronic treatment with L-Dopa, but not bromocriptine induces dyskinesia in MPTP-parkinsonian monkeys. Correlation with [^{3}H] spiperone binding. Brain Res. 1986; 379: 294-299.
14. Stoof JC, Kebabian JW. Opposing roles for D1 and D2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. Nature 1981; 294: 366-368.
15. Rosengarten M, Schweitzer JW, Friedhoff AJ. Induction of oral dyskinesias in naive rats by D1 stimulation. Life Sciences 1983; 33: 2479-2482.
16. Mashurano M, Waddington JL. Stereotyped behaviour in response to the selective D2 dopamine receptor agonist RU 24213 is enhanced by pretreatment with the selective D1 agonist SK&F 38393. Neuropharmacology 1986; 25: 947-949.
17. Molloy AG, Waddington JL. Sniffing, rearing and locomotor responses to the D1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D1 and D2 antagonists SCH 23390 and metoclopramide. Eur J Pharmacol 1985; 108: 305-308.
18. Gropetti A, Flauto C, Parati A, et al. Dopamine receptor changes in response to prolonged treatment with L-Dopa. J Neural Transm 1986; 22: 33-45.
19. Goldstein M, Lieberman A, Meller E. A possible molecular mechanism for the antiparkinsonian action of bromocriptine in combination with levodopa. Trends Pharmacol Sci 1985; 6: 436-437.
20. Robertson HA, Robertson GS. A possible role for both D1 and D2 receptors? The antiparkinson action of bromocriptine in combination with levodopa. Trends Pharmacol Sci 1986; 7: 224-225.
21. Robertson GS, Robertson HA. Synergistic effects of D1 and D2 dopamine agonists on turning behaviour in rats. Brain Res 1986; 384: 387-390.
22. Carlson JH, Bergstrom DA, Walters JR. Stimulation of both D1 and D2 dopamine receptors appears necessary for full expression of postsynaptic effects of dopamine agonists: a neurophysiological study. Brain Res 1987; 400: 205-218.
23. Pimoule C, Shoemaker H, Reynolds GP, et al. [^{3}H]SCH23390 labelled D1 dopamine receptors are unchanged in schizophrenia and Parkinson's disease. Eur J Pharmacol 1985; 114: 235-237.
24. Shibuya M. Dopamine-sensitive adenylate cyclase activity in the striatum in Parkinson's disease. J Neurol Transm 1979; 44: 287-295.
25. Lee T, Seeman P, Rajput A, et al. Receptor basis for dopaminergic supersensitivity in Parkinson's disease. Nature 1978; 273: 59-61.
26. Rinne U, Lonnberg P, Koskinen V. Dopamine receptors in the parkinsonian brain. J Neurol Transm 1981; 51: 97-106.
27. Olsen R, Reisine T, Yamamura H. Neurotransmitter receptors: Biochemistry and alterations in neuropsychiatric disorders. Life Sci 1980; 27: 801-808.
28. Quik M, Spokes E, MacKay A, et al. Alterations in ^{3}H-spiperone binding in human caudate nucleus, substantia nigra and frontal cortex in the Shy-Drager syndrome and Parkinson's disease. J Neurol Sci 1979; 43: 429-437.
29. Bokobza F, Ruberg M, Scatton B, et al. [^{3}H]-spiperone binding, dopamine and HVA concentrations in Parkinson's disease and supranuclear palsy. Eur J Pharmacol 1984; 99: 167-175.
30. Guttman M, Seeman P. Dopamine D2 receptor density in parkinsonian brain is constant for duration of disease, age, and duration of L-Dopa therapy. Advances in neurology 1986; 45: 51-57.
31. Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's Disease. Advances in Neurology 1986; 45: 19-34.
32. Creese I, Snyder SH. Nigrostriatal lesions enhance striatal [^{3}H] apomorphine and [^{3}H] spiroperidol binding. Eur J Pharmacol 1979; 56: 277-281.
33. Rinne UK, Rinne JO, Rinne JK, et al. Brain receptor changes in Parkinson's disease in relation to the disease process and treatment. J Neural Transm 1983; 18: 279-286.

34. Rinne UK. Combined bromocriptine-levodopa therapy early in Parkinson's disease. Neurology 1985; 35: 1196-1198.
35. Larsen AT, Newman R, LeWitt P, et al. Severity of Parkinson's disease and the dosage of bromocriptine. Neurology 1984; 34: 795-797.
36. Riopelle RJ. Bromocriptine and the clinical spectrum of Parkinson's Disease. Submitted to Can J Neurol Sci.
37. Farley IJ, Hornykiewicz O. Noradrenaline in subcortical brain regions of patients with Parkinson's disease and control subjects. *In*: Advances in parkinsonism, Birkmayer W, Hornykiewicz O, eds., Editiones Roche, Basel 1976: 178-185.
38. Scatton B, Javoy-Agid F, Rouquier L, et al. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 1983; 275: 321-328.

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