What has been learnt from study of dopamine receptors in Parkinson’s disease?

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Abstract

Since the introduction of dopamine replacement therapy using L-3,4-dihydroxyphenylalanine (L-DOPA) to treat Parkinson’s disease and the recognition of the problems associated with L-DOPA use, numerous studies have investigated dopamine receptor regulation and function in Parkinson’s disease. These studies have provided insight into the pathological process of the disorder and the molecular consequences of chronic dopaminergic treatment, but they have been less successful in identifying new pharmacological targets or treatment regimes that are as effective as L-DOPA at alleviating the symptoms of Parkinson’s disease. This review will present a summary of the reported changes in dopamine receptor regulation and function that occur in Parkinson’s disease and will discuss their contribution to the current pharmacological management of Parkinson’s disease.

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Keywords: Parkinson’s disease; Dopamine receptors; Dopamine agonists; L-DOPA

Contents

1. Introduction ................................................................................................................. 716
  1.1. Pathology of Parkinson’s disease ................................................................. 716
  1.2. Treatment of Parkinson’s disease ................................................................. 716
  1.3. Problems associated with treatments of Parkinson’s disease ............... 716
2. Dopamine receptor expression in normal brain ......................................................... 716
  2.1. Dopamine D₁-like receptors ....................................................................... 717
  2.2. Dopamine D₂-like receptors ....................................................................... 718
3. Dopamine receptor adaptations in Parkinson’s disease ............................................ 719
  3.1. Striatal dopamine receptor expression in Parkinson’s disease ............... 719
  3.2. Extrastriatal dopamine receptor expression in Parkinson’s disease ....... 720
4. Functional alterations in dopamine receptors in Parkinson’s disease ................ ...... 721
  4.1. Dopamine receptor signaling in Parkinson’s disease ................................. 721
  4.2. Transcription factors and immediate early genes ..................................... 722
  4.3. Co-transmitters/neuropeptides ................................................................... 722
  4.4. Receptor trafficking/internalization ............................................................. 722
  4.5. NMDA glutamate receptor interactions ....................................................... 722
5. Treatment strategies .................................................................................................... 723
6. Conclusions .................................................................................................................. 724
Acknowledgment ............................................................................................................ 724
References ....................................................................................................................... 724
1. Introduction

Since the introduction of L-3,4-dihydroxyphenyalanine (L-DOPA) to treat Parkinson’s disease over 40 years ago, numerous studies have examined the status of dopamine receptors in brain in an attempt to understand the mechanisms that underlie the decline in the efficacy of L-DOPA and the increase in the adverse effects of L-DOPA treatment. The impact of the side effects of L-DOPA on the quality of life for patients with Parkinson’s disease often necessitates a reduction in the dose of L-DOPA to a level which does not adequately ameliorate parkinsonian symptoms, which is clearly undesirable for the patient (Péchevis et al., 2005). The purpose of this review is to summarize these findings in order to determine whether they have led to any useful therapeutic advance in the treatment of Parkinson’s disease. They have undoubtedly provided insight into the pathological process of the disorder and the molecular consequences of chronic dopaminergic treatment. But they have been less successful in identifying new pharmacological targets or treatment regimes that are as effective as L-DOPA at alleviating the symptoms of Parkinson’s disease. The focus of this review will be on data obtained from human studies, though data from animal models of the disorder will be followed in the context of the mechanisms of this review will be on data obtained from human studies.

1.3. Problems associated with treatments of Parkinson’s disease

In addition to the systemic side effects (nausea, vomiting and postural hypotension) produced by acute treatment with L-DOPA and dopamine agonists, chronic administration can result in the development of more serious adverse effects. Namely, fluctuations in motor control (end of dose deterioration, on–off phenomenon) and dyskinesias (chorea, dystonia, athetosis). The debilitating motor side effects are compounded by treatment-induced psychiatric disturbances such as, psychosis, mania or delirium (Schrag, 2004). Motor side effects may be caused by alterations in dopamine receptor expression due to progression of the disease process and/or adaptive responses to the drug treatment (Crossman, 1990). Whereas the psychotic effects presumably stem from actions on dopamine receptors in limbic or cortical regions of the brain. In the early stages of Parkinson’s disease treatment with L-DOPA or/dopamine receptor agonists provides effective relief from the motor symptoms. After 4–6 years of treatment, 40% of patients experience motor side effects. The motor side effects increase with time so that following 10 years of L-DOPA and/or dopamine agonist treatment most individuals (95% in some studies) will exhibit some treatment-induced motor complications (Ahlskog & Muenter, 2001). The consequence of these motor complications is that the dose of L-DOPA may have to be reduced to levels which do not provide the desired reversal of parkinsonian symptoms.

2. Dopamine receptor expression in normal brain

There are 5 types of dopamine receptor, which can be subdivided into D1-like (D1, D3) and D2-like (D2, D3, D4), based on their sequence homologies, pharmacology and functional properties (Sokoloff & Schwartz, 1995). Dopamine receptors are widespread throughout brain, but each subtype has a unique distribution. Table 1 summarises the distribution of dopamine receptors in major brain regions. In the following descriptions receptors refers to the receptor protein identified using either a radioligand or an antibody raised against the receptor and mRNA refers to in situ hybridisation or reverse transcription polymerase chain reaction data. The order in which brain regions are listed indicates the relative abundance of the receptor protein or mRNA transcript in human brain. Understandably, in view of the known pathology of Parkinson’s disease and the limited availability of post-
mortem human tissue, most studies have examined striatal regions (caudate, putamen, nucleus accumbens), with extra-striatal areas of the basal ganglia (globus pallidus, substantia nigra) and other extra-striatal brain regions, the thalamus, cortex and cerebellum in particular, receiving less attention. Thus, for some receptor subtypes, expression in a particular brain region may not have been examined in human brain and the receptor is therefore not necessarily absent from that region. Indeed, studies in rodent and non-human primates indicate that dopamine receptor proteins are present in virtually all brain regions examined, albeit at very low levels in some areas. However, there is debate over whether the binding sites, or immunoreactivity represent functional receptors, especially in regions which receive sparse, if any, dopaminergic innervation. These discrepancies illustrate shortcoming in the use of radioligands and, to a lesser extent, antibodies. For example, the dopamine D2 receptor agonist [3H]spiroperidol yield similar yet distinct patterns of labeling, despite each being considered dopamine D2 receptor specific ligands (Camps et al., 1989). This contrasts with studies of dopamine receptor mRNA, where the presence or absence of a transcript is more clear-cut, though mRNA studies can not demonstrate exactly where on the neuron the receptor coded for will ultimately reside, or if the mRNA will be translated into a functioning receptor.

### 2.1. Dopamine D1-like receptors

Dopamine D1 receptors have the most widespread distribution and overall highest density in brain than the other dopamine receptors (Table 1). Dopamine D1 receptor protein has been identified by radioligand binding and receptor autoradiography (Lee et al., 1978, 1981; Bokobza et al., 1984; Pimoule et al., 1985; Raisman et al., 1985; Rinne et al., 1985; Cash et al., 1987; Seeman et al., 1987; De Keyser et al., 1988; Pierot et al., 1988; Cortés et al., 1989a, 1989b; Thibaut et al., 1990; Hall et al., 1993; Augood et al., 2000; Hurley et al., 2001) and by immunohistochemistry (Levey et al., 1993) in post-mortem human brain. The highest densities of dopamine D1 receptor were found in the caudate nucleus, putamen and nucleus accumbens where they were primarily located on GABAergic medium-sized spiny neurons that project to the internal segment of the globus pallidus and the substantia nigra pars reticulata (the direct pathway) and co-localize with substance P and dynorphin (Gerfen et al., 1995; Le Moine & Bloch, 1995b; Aubert et al., 2000). Dopamine D1 receptors were also found on the presynaptic terminals of glutamatergic projections from the cortex and thalamus. Moderate levels of dopamine D1 receptor protein were found in the both segments of the globus pallidus, both parts of the substantia nigra and cerebellum. Low levels were present in most areas of the cortex and other brain regions. The distribution of dopamine D1 receptor mRNA matches that

<table>
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<tr>
<th>Brain region</th>
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Table 1

Distribution of dopamine receptor subtypes in human brain

Relative abundance between brain regions for each receptor subtype and not between receptor subtypes is indicated: +++, high; ++, moderate; +, low; +/-, very low; -, not detected/reported. In general the D1 and D2 receptors are present at 10–100 times the level of the D3, D4 and D5 receptor subtypes.
of the D1 receptor protein in most regions examined (Mengod et al., 1991, 1992; Huntley et al., 1992; Meador-Woodruff et al., 1994, 1996; Augood et al., 2000; Hurd et al., 2001; Hurley et al., 2001, 2003) with the exception of the internal segment of the globus pallidus and subthalamic nucleus, where dopamine D1 receptor mRNA has not been detected.

Few studies have examined the distribution of the dopamine D3 receptor in human brain and those which have used limited brain regions (Table 1). The dopamine D3 receptor has a more restricted distribution than that of the dopamine D1 receptor. Since highly selective dopamine D3 receptor ligands were unavailable, localization studies of the dopamine D3 receptor have been immunohistochemical using selective antibodies or have examined dopamine D3 receptor mRNA. In the dorsal striatum low levels of dopamine D3 receptor immunoreactivity was present on medium-sized spiny GABAergic neurons and large cholinergic neurons, while higher levels of dopamine D3 receptor immunoreactivity were found in the ventral striatum (olfactory tubercle, islands of Calleja) and septal area (Khan et al., 2000). Outside of the striatum, dopamine D3 receptor immunoreactivity was present in the globus pallidus and hippocampal region of human brain (Khan et al., 2000). Studies in rodent and primate brain have demonstrated dopamine D3 receptor immunoreactivity in substantia nigra (in both dopaminergic and non-dopaminergic cell types), thalamus, hypothalamus, hippocampus, cerebellum and throughout the cerebral cortex (Bergson et al., 1995; Ciliax et al., 2000; Khan et al., 2000). Dopamine D5 receptor mRNA has been detected in hippocampus and motor and temporal cortex of human brain (Huntley et al., 1992; Meador-Woodruff et al., 1994, 1996).

2.2. Dopamine D2-like receptors

The distribution of dopamine D2 receptors in brain is very similar to that of the dopamine D1 receptor (Table 1). The major differences being (1) a lower level throughout the cerebral cortex and (2) the presence of presynaptic receptors on the terminals of dopamine neurons in the striatum. Dopamine D2 receptor protein has been identified by radioligand binding and receptor autoradiography techniques (Quik et al., 1979; Camus et al., 1986; De Keyser et al., 1988; Palacios et al., 1988; Camps et al., 1989; Cortés et al., 1989b; Murray et al., 1994; Hall et al., 1996; Goldsmith et al., 1997; Gurevich & Joyce, 1999) and immunohistochemistry (Levey et al., 1993; Gurevich & Joyce, 1999) in post-mortem human brain. The highest densities were found in the caudate nucleus, putamen and nucleus accumbens and were located on dendrites of GABAergic striatopallidal neurons. Moderate amounts were detected in the olfactory tubercle and islands of Calleja. Lower levels were present in the substantia nigra (compascata-recticulata). Low levels of dopamine D2 receptor protein were detectable in the lateral segment of the globus pallidus and hippocampus, with very low amounts in the internal segment of the globus pallidus, all cortical regions and the cerebellum. The distribution of dopamine D2 receptor mRNA was similar to that of the protein and dopamine D2 receptor mRNA has consistently been detected in caudate nucleus, putamen and nucleus accumbens (Huntley et al., 1992; Mengod et al., 1992; Meador-Woodruff et al., 1996; Gurevich & Joyce, 1999; Hurd et al., 2001). However, the degree of overlap is not exact and dopamine D2 receptor mRNA has not been detected in cortex or hippocampus in 1 study (Mengod et al., 1992), or was found, but only at very low (near background) levels by another (Hurd et al., 2001), indicating that dopamine D2 receptors may not be present on the terminals of corticostriatal projections. This supported an earlier study which showed that decortication does not affect striatal dopamine D2 receptor protein levels (Trugman et al., 1986). However, a more recent study found that dopamine D2 receptors were present on the terminals of corticostriatal neurons originating in the prefrontal cortex (Wang & Pickel, 2002). Another area of dissimilarity between receptor protein expression and mRNA levels is the thalamus, where dopamine D2 receptor mRNA was present, but where little, if any, dopamine D2 receptor protein was detectable (Hurd et al., 2001).

The dopamine D3 receptor has a much more restricted distribution than the dopamine D2 receptor (Table 1) and other than the islands of Calleja where the expression level approaches that of the dopamine D2 receptor, the dopamine D3 receptor was expressed at much lower levels (10–100 times) than the dopamine D2 receptor (Lévesque et al., 1992). The highest levels of dopamine D3 receptor protein were in the islands of Calleja, nucleus accumbens and olfactory tubercle, with very low levels in the caudate nucleus and putamen (Landwehrmeyer et al., 1993; Murray et al., 1994; Hurley et al., 1996; Gurevich & Joyce, 1999). In extrastriatal regions of human brain moderate to low levels of dopamine D3 receptor protein were present in both segments of the globus pallidus, the thalamus, hypothalamus, amygdala, both parts of the substantia nigra and the ventral segmental area (Gurevich & Joyce, 1999). In rat brain, in addition to the areas mentioned above, moderate levels of dopamine D3 receptors have been labeled in lobules 9 and 10 of the cerebellum and low densities of binding sites found in prefrontal cortex and hippocampus (Lévesque et al., 1992). A similar distribution of dopamine D3 receptors was found in rat brain using an antibody raised against dopamine D3 receptor specific peptides (Ariano & Sibley, 1994). The expression of dopamine D3 receptor mRNA parallels that of the receptor protein in most brain regions (Landwehrmeyer et al., 1993; Meador-Woodruff et al., 1994, 1996; Suzuki et al., 1998; Gurevich & Joyce, 1999; Hurley et al., 2003).

The distribution of the dopamine D4 receptor is unlike the other dopamine D2-like receptors and resembles a dopamine D1-like receptor distribution in that the highest levels of expression are found in cortical and other extrastriatal brain regions, with very low levels of expression in striatal regions. The distribution of dopamine D4 receptor protein has been determined in brain using [3H]NGD 94-1 (Primus et al., 1997). The highest densities of binding sites were found in the lateral septal nucleus and dorsomedial thalamus, lower levels were detected in the entorhinal and frontal cortex, hypothalamus and hippocampus. No binding was evident in the caudate nucleus, putamen, nucleus accumbens or cerebellum, which agrees with determinations of striatal dopamine D4 receptor density...
obtained using indirect ligand-binding methods, which suggest the presence of very low levels of dopamine D4 receptor protein in striatum (Seeman et al., 1993; Murray et al., 1995). This contrasts with the dopamine D2 and D3 receptors which have high levels of protein in these regions. A study by Mrzljak et al. (1996) in macaque brain using a specific antibody raised against the dopamine D4 receptor found a similar distribution and additionally demonstrated D4-like immunoreactivity on GABAergic neurons of the prefrontal cortex, substantia nigra pars reticulata and both segments of the globus pallidus. Again, virtually no dopamine D4 receptor protein was found in striatal regions. Dopamine D4 receptor mRNA has been detected in areas where the protein is found, namely prefrontal, temporal and occipital cortex and hippocampus, but not in the striatum (Meador-Woodruff et al., 1996). The absence of dopamine D4 receptor mRNA in the striatum indicates that striatal dopamine D4 receptors are present on the terminals of corticostriatal glutamatergic projections (Murray et al., 1995).

3. Dopamine receptor adaptations in Parkinson’s disease

Dopamine receptor expression in Parkinson’s disease has been investigated in vitro using post-mortem tissue and in vivo by functional imaging techniques such as positron emission tomography and single photon emission tomography. Such studies have generated reports of increased, decreased or unchanged levels of expression for the dopamine D1, D2 and D3 receptor subtypes (see below). The conflicting data stem from the varied experimental methods (protocols, ligands, probe type) used to determine the status of the receptors expression, together with the precise brain region examined (e.g. anterior vs. caudal striatal sections). In addition, intrinsic variations in the tissue analysed, such as the patients’ exposure to different drugs, genetic background and agonal state can affect results. There are often 2 components to such studies, namely, a determination of the status of dopamine receptors in the untreated and treated states. The former would provide clues about the neuronal response to denervation, while the latter would give insight into the adaptive response that occurs following treatment.

The functional organization of the striatum has been defined based on the input and output connections and neurochemical characteristics of striatal neurons. One level of organization is the division of the striatum into patch (striosomes) and matrix compartments, which correspond to differential input from the laminar organization of the cortex, while another division is defined by the direct and indirect output pathways (Gerfen, 1992). In the striatum, dopamine D1 and D2 receptors are mainly present on dendrites of GABAergic striatopallidal neurons which receive input from afferent dopamine neurons. Dopamine D1 receptors are also found on the terminals of glutamatergic projections from the cortex and thalamus. Expression of each receptor subtype is enriched on subpopulations of striatopallidal neurons. Dopamine D1 receptors are more highly expressed on GABAergic neurons which innervate the internal segment of the globus pallidus and substantia nigra pars reticulata (the direct pathway) and co-localize with substance P and dynorphin, while dopamine D2 receptors have higher levels of expression on GABAergic neurons which innervate the external segment of the globus pallidus (the indirect pathway) and co-localize with enkephalin (Gerfen et al., 1995; Le Moine & Bloch, 1995a; Aubert et al., 2000). However, there is a degree of overlap, with co-expression of each receptor subtype on most striatal GABAergic neurons, such that the division of striatal neurons should be based on the relative levels of dopamine D1 or D2 receptors, rather than the presence or absence of a particular receptor subtype (Surmeier et al., 1993; Aizman et al., 2000). Dopamine D2 receptors are also present on the terminals of dopamine neurons and therefore also function as autoreceptors. Cholinergic interneurons express dopamine D2 receptor mRNA, indicating that a proportion of dopamine D2 receptors found in the striatum is present on these neurons. Dopamine D3 receptors have a similar distribution to dopamine D2 receptors, except that their density is very low in the caudate nucleus and putamen, with higher levels only found in the islands of Calleja and ventral areas of the striatum. Dopamine D1 receptors co-localize with either dopamine D1 or D2 receptors in up to a quarter of ventral striatal neurons (Le Moine & Bloch, 1995b). Dopamine D3 receptors, like the dopamine D1 receptor, are found at highest densities in the ventral striatum, but unlike the dopamine D1 and D2 receptors, they are not located on dopaminergic neuron terminals, but are found on cholinergic interneurons (Bergson et al., 1995). Dopamine D1 receptors have a very low level of expression in the striatum. The significance of dopamine D4 and D3 receptors in the symptoms or treatment of Parkinson’s disease is unknown.

3.1. Striatal dopamine receptor expression in Parkinson’s disease

In Parkinson’s disease the dopaminergic innervation of the striatum degenerates and consequently presynaptic dopamine D1 receptors are lost. In spite of this, the literature generally supports an increase of dopamine D2 receptor density in the striatum (particularly the putamen) of people with untreated Parkinson’s disease and no change in dopamine D1 receptor expression whether examined in vivo using functional imaging techniques (Hagglund et al., 1987; Rinne et al., 1990a,b; Brooks et al., 1992; Laulumaa et al., 1993; Rinne et al., 1993; Sawle et al., 1993; Shinotoh et al., 1993; Tedroff et al., 1996; Antonini et al., 1997; Turjanski et al., 1997; Dentresangle et al., 1999; Linazasoro et al., 1999; Kaasinen et al., 2000; Ghaemi et al., 2002; Kim et al., 2002; Thobois et al., 2004) or in vitro using post-mortem brain tissue (Rinne et al., 1983; Bokobza et al., 1984; Cash et al., 1987; Cortés et al., 1989b; Joyce, 1993; Piggott et al., 1999; Rinne et al., 1991; Ryoo et al., 1998). Since a proportion of presynaptic dopamine D2 receptors are lost due to the degeneration of dopaminergic neurons, the increase in dopamine D2 receptors could result from increased numbers of dopamine D2 receptors on the remaining dopaminergic neuron terminals, or increased synthesis within striatopallidal neurons or cholinergic interneurons, or all of these locations. Falardeau
et al. (1988) demonstrated in MPTP-treated monkeys that the dopamine D2 receptor response to denervation was dependent upon the extent of the lesion (which is often not known in studies using post-mortem human tissue). That is, incomplete lesions can result in loss of presynaptic receptors without an increased density of postsynaptic dopamine D2 receptors. Since studies have reported increased and no change in dopamine D2 receptor mRNA levels in striatum of MPTP-treated monkeys, it is not clear at what anatomical site the alteration in dopamine D2 receptor expression occurs (Herrero et al., 1996; Morissette, 1996; Goulet et al., 1997, 2000). Following antiparkinsonian drug treatment there is a down-regulation of the elevated dopamine D2 receptors to normal levels in the putamen and often decreased levels in the caudate nucleus, while dopamine D1 receptors remain unaltered or show a modest increase (Rinne et al., 1985; Hagglund et al., 1987; Ahlskog et al., 1991; Rinne et al., 1991; Brooks et al., 1992; Griffiths et al., 1994; Pizzolato et al., 1995; Tedroff et al., 1996; Antonini et al., 1997; Dentresangle et al., 1999; Linazasoro et al., 1999; Ouchi et al., 1999; Hurley et al., 2001). However, despite the level of dopamine D2 receptors being similar to that of controls, the neuronal distribution of striatal dopamine D2 receptors is different in treated Parkinson’s disease (i.e. postsynaptic > presynaptic).

Studies of dopamine D3 receptor expression in post-mortem brain tissue from patients dying with Parkinson’s disease have yielded disparate results. A significant reduction of dopamine D1 receptors in the caudal caudate nucleus (Piggott et al., 1999) and nucleus accumbens, caudate nucleus and putamen (Ryoo et al., 1998) has been reported, while another study (Hurley et al., 1996) found no alteration in dopamine D3 receptor density or mRNA in ventral or dorsal regions of the striatum. The status of striatal dopamine D4 and D2 receptor expression in Parkinson’s disease is unknown.

3.2. Extrastriatal dopamine receptor expression in Parkinson’s disease

Dopamine receptors present on dopamine neuron perikarya and dopaminergic projections to areas other than the striatum are also affected by the neurodegeneration which occurs in Parkinson’s disease. Also, chronic stimulation of extrastriatal dopamine receptors by L-DOPA-derived dopamine or dopaminergic drugs alters extrastriatal dopamine receptor expression. However, as with investigations into striatal dopamine receptors, the results of studies of extrastriatal dopamine receptor expression in Parkinson’s disease frequently yield conflicting data. This, together with the relative dearth of studies which have examined extrastriatal dopamine receptor expression in Parkinson’s disease mean generalizations regarding the expression of extrastriatal dopamine receptors in Parkinson’s disease can not be made.

Using radioligand binding assays a decrease in dopamine D1 receptors was measured in substantia nigra pars compacta and reticulata (Rinne et al., 1985) and pars compacta (Cash et al., 1987) in tissue from Parkinson’s disease cases. However, Cortés et al. (1989b) using autoradiography, found no difference in dopamine D1 receptor levels in either part of this brain region. Nor was any alteration in dopamine D1 receptor expression found in the both segments of the globus pallidus, the cerebellum, hippocampus, entorhinal cortex, occipital cortex, frontal cortex or motor cortex. Indeed, the only brain region where Cortés et al. (1989b) did find a significant reduction of dopamine D1 receptors was the red nucleus, an area involved in motor coordination that receives afferent fibres from the cerebellum, motor cortex and striatum, sends efferent fibres to the thalamus and is reciprocally linked to the substantia nigra (England & Wakely, 1991). Other studies found dopamine D1 receptors to be unchanged in the internal segment and decreased in the external segment of the globus pallidus (Hurley et al., 2001), or unchanged in globus pallidus as a whole (Rinne et al., 1985). With regard to dopamine D1 receptor mRNA, a decrease in the substantia nigra pars reticulata and cerebellar uvula (lobule 9) and no difference in the external segment of the globus pallidus was found in parkinsonian brain (Hurley et al., 2001, 2003).

Dopamine D2 receptors were unchanged in the both parts of the substantia nigra and globus pallidus, red nucleus, cerebellum and frontal cortex of Parkinson’s disease (Bokobza et al., 1984; Cortés et al., 1989b; Ryoo et al., 1998), but were increased in the CA3 region of the hippocampus and deep layers of the occipital cortex (Cortés et al., 1989b).

Dopamine D3 receptor protein was unchanged in both segments of the globus pallidus of parkinsonian brain (Ryoo et al., 1998) and dopamine D3 receptor mRNA was reduced in the uvula (lobule 9) of the cerebellum (Hurley et al., 2003).

Positron emission tomography studies have found reduced dopamine D1 receptor levels in orbitofrontal cortex (Ouchi et al., 1999) and reduced dopamine D2-like receptor densities in dorsolateral prefrontal, anterior cingulate and temporal cortex and medial thalamic nuclei (Kaasinen et al., 2000, 2003).

The above in vitro studies were conducted in brain tissue from patients who were receiving dopaminergic medication at the time of death. Consequently, the treatment is likely to have influenced a significant part of the alterations in receptor expression. This may be particularly so for the extrastriatal brain regions, since these areas receive sparse dopaminergic innervation (Cossette et al., 1999) and the degree to which this is reduced by the neurodegeneration that occurs in Parkinson’s disease is unknown. What is apparent is that in general l-DOPA or dopamine agonist treatment causes dopamine receptor levels to normalise in the areas where pathology is most evident and where the receptor levels were altered before treatment. Whereas l-DOPA or dopamine agonist treatment causes alterations in expression levels in areas where there is little or no obvious pathology and where receptors were usually present at normal levels before treatment.

The significance of the changes in dopamine receptor expression described above to the symptoms of Parkinson’s disease and side effects of treatment are largely unknown. The extrastriatal changes in dopamine receptor expression may reflect compensatory changes. Whone et al. (2002) demonstrated elevated [18F]-DOPA uptake in nigropallidal neurons projecting towards the internal segment of the globus pallidus in...
early Parkinson’s disease. While Bezard et al. (2001) found altered metabolic activity (assessed by 2-deoxyglucose uptake) in the supplementary motor area of presymptomatic and fully parkinsonian MPTP-treated monkeys. Such changes might occur to redress the imbalance of pallidal output pathways that results from loss of dopaminergic input to the striatum. Data from animal models of the disorder indicate that alterations in dopamine receptor expression levels as such are not solely responsible for dyskinesia, or indeed the other motor side effects of treatment (see below). However, the extrastriatal changes (cortical and hippocampal in particular) may play a role in the cognitive and psychiatric symptoms of Parkinson’s disease and side effects of treatment. This is supported by functional imaging studies which show abnormalities in hippocampus and prefrontal cortex of Parkinson’s disease patients (Camicioli et al., 2003; Brück et al., 2004).

4. Functional alterations in dopamine receptors in Parkinson’s disease

The function of dopamine receptors in Parkinson’s disease is altered not only by the disease but also as a consequence of drug treatment. Alterations in the abundance of receptor density may contribute to the complications of treatment. But, for the dopamine D2 receptor in particular, there is no temporal correlation between the alterations in expression levels and the occurrence of motor complications of treatment. It is increasingly recognised however that dopamine receptor signaling cascades are altered both as a consequence of the denervation occurring in Parkinson’s disease and as a result of the dopaminergic drug treatment used to treat the disorder. The functional response of dopamine receptors can therefore change despite no alteration in their expression level by virtue of changes in their coupling to second messengers.

Before the cloning and definitive demonstration of 5 dopamine receptor subtypes, dopamine D1 receptors were defined as being positively linked to adenylate cyclase, while dopamine D2 receptors had negative coupling to the enzyme (Kebabian & Calne, 1979). The number of signaling cascades that dopamine receptors are known to interact with has grown considerably since then and has been extensively reviewed by Neve et al. (2004). The majority of data was derived from studies using transfected cells or animal models since the experimental techniques can not be used in post-mortem human tissue or living human subjects. However, it is reasonable to assume that dopamine receptors couple to a similar repertoire of second messengers in human brain. At the molecular level dopamine receptors can have opposing actions, even though the final cellular response is similar. For example, in cell lines, arachidonate release was increased by both the dopamine D2 and D4 receptor subtypes, but required activation of protein kinase A for the dopamine D2 receptor and protein kinase C for the dopamine D4 receptor (Di Marzo et al., 1993; Chio et al., 1994; Lee et al., 2004). It has also recently been demonstrated that different dopamine receptor subtypes (i.e. D1 and D3) can form hetero-oligomers in cells and can cross phosphorylate each other (Lee et al., 2004; So et al., 2005). This means a dopamine D1 receptor agonist can elicit a dopamine D2 receptor-mediated cellular response and vice versa. Evidently, caution must be observed when extrapolating data derived from such studies to how the native receptors function in brain. But such interactions at the molecular level may explain the synergy found between, for example, dopamine D1 and D3 receptors and the dysfunction of such interactions observed in animal models of Parkinson’s disease (Ridray et al., 1998; Guigoni et al., 2005). An account of dopamine receptor signaling is not the purpose of this review and only second messengers that have been identified as having altered function in Parkinson’s disease or animal models of the disorder will be discussed here.

4.1. Dopamine receptor signaling in Parkinson’s disease

Receptor supersensitivity, leading to imbalance between the direct and indirect striatal output pathways, is believed to underlie some of the motor complications that occur following chronic treatment with L-DOPA or dopamine agonists (Obeso et al., 2000). Dopamine D2 receptor mediated effects in Parkinson’s disease and animal models of the disorder can be explained, at least in part, by the increase in receptor dopamine D2 receptor density which occurs following dopaminergic denervation of the striatum. In the absence of consistent alterations in the levels of receptor expression, altered functional responses of dopamine D1 receptors may result from changes in signaling mechanisms. This view is supported by a number of recent studies. Corvol et al. (2004) found an increase in G\textsubscript{olf} and G\textsubscript{\gamma}7 in putamen of post-mortem tissue from patients with Parkinson’s disease and in 6-OHDA-lesioned rats. In rats the increase in G\textsubscript{olf} was normalised by treatment with L-DOPA or a dopamine D1 receptor agonist but not by dopamine D2/D3 receptor agonist treatment, indicating that the alterations in G\textsubscript{olf} may underlie the dopamine D1 receptor supersensitivity seen in animal models of Parkinson’s disease. Another mechanism shown to underlie dopamine D1 receptor supersensitivity in the dopamine-depleted striatum is activation of the ERK1/2MAP kinase (extracellular signal-regulated kinase/mitogen-activated kinase) in neurons of the direct pathway (Gerfen et al., 2002). In normal brain the ERK1/2MAP kinase pathway is active in neurons of the indirect pathway and quiescent in those of the direct pathway. Abnormal striatal kinase or phosphatase activity, occurring as a result of the dopaminergic denervation, may underlie the altered levels of NMDA receptor subunit and cyclic AMP responsive element binding protein phosphorylation that have been linked to the mechanisms of persistence of motor complications in L-DOPA treated 6-hydroxydopamine lesioned rats (Oh et al., 1998, 1999; Dunah et al., 2000; Oh et al., 2003). This is supported by recent studies in MPTP-treated monkeys. Aubert et al. (2005) using agonist-induced [\textsuperscript{35}S]GTP\gammaS binding, demonstrated increased dopamine D1 receptor sensitivity and higher levels of cyclin-dependent kinase 5 and dopamine- and cAMP-regulated phosphoprotein of 32 kDa in striatum from dyskinetic animals. While Bezard et al. (2005) found increased arrestin 2 and G-protein-coupled receptor kinase expression that was accompanied by elevated ERK1/1 in MPTP-treated monkey striatum.
The alterations were normalised following L-DOPA treatment indicating that dopamine regulates expression of these enzymes.

4.2. Transcription factors and immediate early genes

Long-term alterations in the function of neurons (including altering levels of receptor expression) can be produced by altered rates of gene transcription, a process which is under the control of transcriptional regulatory proteins. Activation of a group of transcriptional regulatory proteins occurs within minutes of cellular stimulation and genes encoding these proteins are called immediate early genes, although not all immediate early genes are transcription factors (Morgan & Curran, 1989). Other transcription factors, such as cAMP response element binding protein (CREB), are present constitutively in the striatum. Berke et al. (1998) using differential display polymerase chain reaction techniques demonstrated that more than 30 (both novel and previously known) immediate early genes were induced following activation of the dopamine D1 receptor. The role of the majority of these genes is unknown, but levels of the same immediate early genes, such as c-fos, fosB, c-jun and zif268/Egr1 were altered in animal models of Parkinson’s disease and correlations have been made between such alterations and the motor complications of treatment with L-DOPA and dopamine agonists (Cenci, 2002; Gerfen, 2000).

4.3. Co-transmitters/neuropeptides

The GABAergic output pathways of the striatum can be differentiated based on the type of neuropeptide co-transporter they predominantly utilise. The dopamine D1 receptor bearing indirect pathway neurons contain substance P, preproenkephalin B derived opioids (e.g. dynorphin, leucine-enkephalin) and neurotensin, whereas the dopamine D2 receptor bearing neurons of the indirect pathway contain preproenkephalin A derived enkephalins (Gerfen et al., 1995; Le Moine & Bloch, 1995b; Aubert et al., 2000). Altered levels of neuropeptides, or their precursor peptides, have been measured in the basal ganglia of parkinsonian brain from patients dying with Parkinson’s disease and MPTP-treated primates. Such alterations may contribute to the postulated imbalance of neuronal activity between the striatal output pathways which is thought to underlie dyskinesia. Henry et al. (2003) found increased striatal preproenkephalin B mRNA in striatum from patients exhibiting motor complications, which was mainly associated with the predominantly dopamine D1 receptor bearing striatonigral neurons of the direct pathway. This supports earlier studies in animal models of Parkinson’s disease and L-DOPA-induced dyskinesia which suggested a possible mechanism for dyskinesia was elevated levels of peptides derived from pre-proenkephalin B in neurons of the direct pathway (Gerfen et al., 1990; Herrero et al., 1995; Henry et al., 1999; Morissette, 1999). This view is supported further by a recent study where Chen et al. (2005) found a positive correlation between dyskinesia and enhanced subtype-specific opioid receptor-stimulated G-protein activation in caudate nucleus, putamen and premotor cortex of dyskinetic, L-DOPA-treated MPTP-lesioned squirrel monkeys.

4.4. Receptor trafficking/internalization

Following continuous or repeated agonist stimulation, G-protein coupled receptors undergo agonist-induced desensitisation. The mechanisms of agonist-induced desensitisation have been most thoroughly investigated for α-adrenergic receptors (which are structurally similar to dopamine D1 receptors) and a general process of how G-protein coupled receptors undergo agonist-induced desensitization has been proposed. Namely, following agonist binding, the receptor is phosphorylated by a G-protein-coupled receptors kinase, which allows binding of an arrestin-like protein. Binding of the arrestin-like protein leads to uncoupling of the receptor from its G-protein, which decreases functional activity and promotes receptor internalization via clathrin-coated pits to the endosome. Once internalized the receptor is either resensitized by dephosphorylation and reinserted into the cell membrane or the receptor is degraded (Krupnick & Benovic, 1998). Studies in vitro using transfected cell lines have shown that this general process (achieved using a range of kinases or modulators of internalisation processes) also applies to the dopamine D1 (Ng et al., 1995; Gardner et al., 2001; Mason et al., 2002; Adlersberg et al., 2004; Kim et al., 2004) and D2 receptors (Kim et al., 2001; Kabbani et al., 2002; Namkung & Sibley, 2004). Furthermore, internalised dopamine D1 receptors have also been demonstrated in brain from patients dying with Parkinson’s disease and studies in animal models of the disorder indicate that dopaminergic treatment, rather than the lesion itself, is responsible for the altered neuronal localization of the receptors (Muriel et al., 1999). The inability of the dopamine D1 receptor agonist A-77636 to sustain an antiparkinsonian effect in vivo has been found to result from receptor desensitization due to a slow dissociation of the drug from the receptor (Blanchet et al., 1996; Lin et al., 1996). This highlights the importance of considering a drugs pharmacokinetics in the treatment of Parkinson’s disease and has relevance to the design and choice of drugs suitable for continuous dopamine receptor stimulation strategies (see below).

4.5. NMDA glutamate receptor interactions

Dopamine D1 and NMDA receptors are juxtaposed within the post-synaptic density on dendrites of striatal neurons and on the terminals of corticostriatal afferents and are functionally linked through their second messenger systems (Ariano et al., 1997). Consequently, activation of either receptor type can modify the function of the other. Altered phosphorylation of NMDA receptor subunits has been found in the striatum of 6-hydroxydopamine-lesioned rats treated with L-DOPA and these changes have been suggested to represent a molecular basis for persistence of dyskinesia (Oh et al., 1998, 1999; Dunah et al., 2000). The NMDA receptor has also been shown to regulate dopamine D1 function through direct protein–protein interactions. Stimulation of NMDA receptors can increase dopamine D1 receptor insertion into the cell membrane in cell lines and
cultured hippocampal neurons (Pei et al., 2004), while oligomerization between NMDA receptors and dopamine D1 receptors can prevent dopamine D1 receptor internalisation and desensitization following dopamine D1 receptor agonist stimulation (Fiorentini et al., 2003). The ability of NMDA receptors to modulate dopamine D1 receptor function may explain the ability of NMDA receptor antagonists to ameliorate motor side effects in Parkinson’s disease patients and animal models of the disorder (Papa et al., 1995; Blanchet et al., 1998; Metman et al., 1998; Blanchet et al., 1999; Loschmann et al., 2004).

5. Treatment strategies

Recognition of the dopamine receptor adaptations occurring in Parkinson’s disease and following treatment has not led to a treatment more effective than l-DOPA. No change observed so far has been unequivocally linked to motor complications and even if this was so, there is currently no means of targeting a population of receptors in a specific brain region with a systemically administered drug. With the exception of increased use of agonists with a preferential affinity (10-fold vs. the dopamine D2 receptor) for the dopamine D3 receptor (e.g. pramipexole, ropinirole) there have been no novel dopamine agonists introduced to treat Parkinson’s disease since the 1970s. The effectiveness of currently available dopamine agonists at reversing parkinsonian symptoms and the ability of them to cause unwanted motor side effects has been reviewed elsewhere (Jenner, 2003; Foley et al., 2004). The majority of dopamine agonists used to treat Parkinson’s disease have preferential selectivity for dopamine D2-like receptors. No selective dopamine D1 receptor agonists, despite them being effective at reversing symptoms in animal models of Parkinson’s disease, are available for clinical use because of toxicological and pharmacokinetic problems. The dopamine D3 receptor was postulated to play a greater role in cognitive and emotional functions than movement, because highest expression levels were found in limbic regions of the striatum (Sokoloff & Giros, 1992). Yet pramipexole and ropinirole are effective antiparkinsonian drugs, which suggests that the dopamine D3 receptor is involved in the control of movement. There are no dopamine agonists in clinical use which are selective for the dopamine D2 receptor and which have low affinity for the dopamine D3 receptor. However the novel compound sumanrole, which exhibits a 200-fold selectivity for the dopamine D2 receptor over the dopamine D3 receptor and which has very low affinity for dopamine D4 and D1 receptors, was recently shown to be effective at reversing motor symptoms in rodent and primate models of Parkinson’s disease and did not cause dyskinesia (McCall et al., 2005; Stephenson et al., 2005). The effectiveness of this compound in patients with Parkinson’s disease and whether it causes dyskinesia or/and psychiatric disturbances awaits assessment and it therefore remains unknown whether a selective dopamine D2 receptor agonist would be an effective antiparkinsonian agent with fewer side effects. The functional synergy between dopamine D1 and D2 receptors may underlie antiparkinsonian action of dopamine D2-like receptor agonists with preferential dopamine D3 receptor selectivity. This indicates that pursuit of selective dopamine D1 receptor agonists as a treatment for Parkinson’s disease is warranted and it would be interesting to determine whether chronic use of such drugs resulted in similar motor complications to l-DOPA and the dopamine agonists in current use. Unfortunately, while directly acting dopamine receptor agonists when used as a monotherapy to treat Parkinson’s disease are initially effective, the majority of patients require addition of l-DOPA after 5 years (Rascol et al., 2003). The reason why l-DOPA is superior to directly acting dopamine receptor agonists is not known, but is unlikely to be simply due to an action on all dopamine receptor subtypes, since combinations of dopamine receptor agonists are not as effective as l-DOPA, at least in advanced disease. Although in recent clinical trials, the novel mixed dopamine D1/D2/D3 agonist rotigotine has been shown to be an effective antiparkinsonian agent in early Parkinson’s disease (Jenner, 2005). Perhaps the difference is that directly acting dopamine receptor agonists stimulate dopamine receptors in brain regions where conversion of l-DOPA to dopamine is minimal. Alternatively, the superior therapeutic actions of l-DOPA could result from other mechanisms, such as increasing brain noradrenaline levels, increasing release of trace amines, or by acting as a neuromodulator or/and neurotransmitter (Misu & Goshima, 1993; Misu et al., 2003). The manner in which dopaminergic drugs are delivered, namely a continuous (i.e. more physiological) stimulation of striatal dopamine receptors currently holds the most promise for extending the useful therapeutic duration of l-DOPA and dopamine agonist treatment while minimizing the development of motor side effects (Chase, 2004). MPTP-treated marmosets treated with l-DOPA 4 times a day exhibit less dyskinesia than animals receiving the same total daily dose of l-DOPA in just 2 doses (Smith et al., 2005). Similarly, clinical trials have shown a benefit of continuous infusion of l-DOPA or dopamine agonists over pulsatile oral administration, but this method of drug delivery is not practical for everyday use by patients (Marion et al., 1896; Quinn et al., 1982; Obeso et al., 1987; Colzi et al., 1998; Stocchi et al., 2005). However, modified formulations of l-DOPA and novel methods of delivery may provide a means of emulating continuous infusion thereby avoiding the adverse effects associated with pulsatile oral administration. Can l-DOPA and dopamine receptor agonists ever be entirely replaced with drugs acting on other receptor types, or will such drugs only ever be adjuncts to dopaminergic treatments? Drugs acting on a wide range of neurotransmitter systems have been posited as potential adjuncts to l-DOPA treatment and some have proven to be effective at doing so in animal models of Parkinson’s disease (Brotchie, 1998). Studies in primate models of Parkinson’s disease have shown that the adenosine A2A receptor antagonist istradefylline (KW-6002) can reverse parkinsonian symptoms without worsening established dyskinesia (Kanda et al., 1998). Recently 2 small-scale clinical trials with istradefylline in patients with advanced Parkinson’s disease exhibiting motor fluctuations and peak-dose dyskinesia have been conducted. Hauser et al. (2003) found a reduced off-time with an increase in non-troublesome dyskinesia during on-time when istradefylline was given with an optimal doses of l-DOPA. While Bara-
Jimenez et al. (2003) found that istradefylline can potentiate and prolong the antiparkinsonian effect of a low dose of L-DOPA to that seen with an optimal dose of L-DOPA, with a concurrent 45% reduction in dyskinesia to that induced by an optimal dose of L-DOPA. Istradefylline therefore seems an acceptable adjunct to the treatment of advanced Parkinson’s disease with L-DOPA. Large-scale trials are necessary to confirm this and investigation as to whether it could be used as an effective monotherapy in early Parkinson’s, as animal studies indicate, is warranted (Wu & Frucht, 2005).

It is evident that chronic treatment with L-DOPA or dopamine agonists causes alterations in dopamine receptor signaling in addition to the changes observed in dopamine receptor expression levels. Targeting these alterations using kinase or phosphatase inhibitors may yield adjuncts to L-DOPA and dopamine agonist treatment which are able to reduce motor complications, thereby extending the useful time frame of dopaminergic treatments.

6. Conclusions

In Parkinson’s disease functional alterations in dopaminergic neurotransmission occur in the striatum and extrastriatal brain regions as a consequence of the dopaminergic neuron degeneration and chronic L-DOPA or dopamine agonist treatment. These changes, together with the continued degeneration of dopaminergic neurons, are believed to underlie the gradual failure in the effectiveness of treatment and development of motor and psychiatric side effects. The understanding of dopamine receptor function has expanded enormously since the recognition of their existence in brain and the realization of their importance in Parkinson’s disease in the early 1970s. But for patients with Parkinson’s disease, the pharmacological treatment options have not really changed since then. However, careful use of available dopaminergic drugs, together with novel non-dopaminergic antiparkinsonian agents, should allow better management of Parkinson’s disease symptoms and lead to an improved quality of life for patients with Parkinson’s disease.

Acknowledgment

Dr. Hurley is funded by the Parkinson’s Disease Society.

References


Gerfen, C. R. (1992). The neostriatal mosaic: multiple levels of compartmental organization. Trends Neurosci 15, 133–139.


