

# Neuropharmacology of dopamine receptors: Implications in neuropsychiatric diseases

Frank I. Tarazi

## الدوائيات العصبية للمستقبلات الدوبامينية: تأثيراتها في الأمراض العصب - نفسية

فرانك طرزي

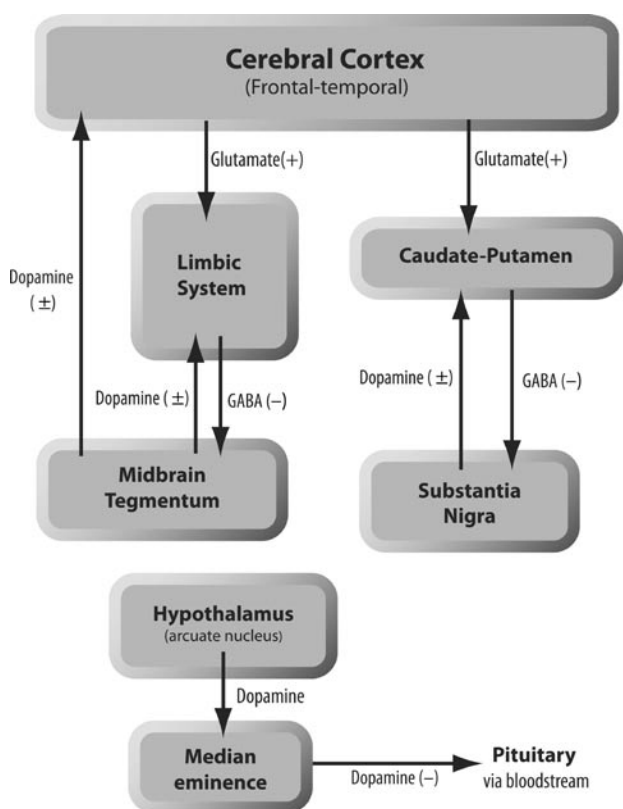
**الملخص:** تجمعت في السنين الأخيرة معلومات هائلة تخص العلوم العصبية وعلم أدوية الجهاز العصبي للمستقبلات الدوبامينية في الجهاز العصبي المركزي للتدبيات. أستنسخ كثير من الجزيئات الدوبامينية، وتم تحديد المورثات و تتابع الهضمين وتشكيلها. تم توصيف التوزيع التشريحي لها في مخ الثدييات و تحدد تأثيرها الدوائي. وحصل تقدم نحو تطوير ربيطات محددة و مرشحات عقارية لمختلف مستقبلات الدوبامين. حفزت هذه الإكتشافات الجديدة دراسات ماقبل السريرية والسريرية لسبر الدوائيات العصبية لمستقبلات الدوبامين لمختلف الأمراض العصب - نفسية ومن ضمنها الفصام، داء باركنسن، وممرض فرط الحركة. فلذلك يبدو أنه من المناسب حاليا أن نستعرض جوانب مختلفة لهذه المنطقة من الدائيات العصبية قبل السريرية وعلاقتها بالأمراض العصب - نفسية.

**ABSTRACT.** There has been an extraordinary recent accumulation of information concerning the neurobiology and neuropharmacology of dopamine (DA) receptors in the mammalian central nervous system. Many new DA molecular entities have been cloned, their gene, peptide sequences and structures have been identified, their anatomical distributions in the mammalian brain described, and their pharmacology characterized. Progress has been made toward developing selective ligands and drug-candidates for different DA receptors. The new discoveries have greatly stimulated preclinical and clinical studies to explore the neuropharmacology of DA receptors and their implications in the neuropathophysiology of different neuropsychiatric diseases including schizophrenia, Parkinson's disease and attention-deficit hyperactivity disorder. Accordingly, it seems timely to review the salient aspects of this specialized area of preclinical neuropharmacology and its relevance to clinical neuropsychiatry.

**Key words:** antipsychotics, ADHD, basal ganglia, dopamine receptors, Parkinson's disease, schizophrenia

**D**OPAMINE (DA) IS A MAJOR NEUROTRANSMITTER within the mammalian central nervous system (CNS). DA-containing neurons arise mainly from DA cell bodies in the substantia nigra and ventral tegmental area in mid-brain region, and are organized into four major subsystems [Figure 1]:<sup>1-6</sup> (i) the *nigrostriatal* system involving neurons projecting from the substantia nigra pars compacta to the caudate-putamen of the basal ganglia. This is the major DA system in the brain as it accounts for about 70% of the total DA in the brain, and its degeneration makes a major contribution to the pathophysiology of Parkinson's disease; (ii) the *mesolimbic* system that

originates in the midbrain tegmentum and projects to the nucleus accumbens septi and lateral septal nuclei of the basal forebrain as well as the amygdala, hippocampus, and the entorhinal cortex, all of which are considered components of the limbic system and so are of particular interest for the pathophysiology of idiopathic psychiatric disorders; (iii) the *mesocortical* system, which also arises from neuronal cell bodies in the tegmentum which project their axons to the cerebral cortex, particularly the medial prefrontal regions; (iv) the *tuberoinfundibular* pathway, which is a neuroendocrinological pathway arising from the arcuate and other nuclei of the hypothalamus and ending



**Figure 1.** Schematic organisation of the four major dopamine systems in the brain.<sup>2</sup>

in the median eminence of the inferior hypothalamus. DA released in this system exerts regulatory effects in the anterior pituitary and inhibits the release of prolactin.

DA mediates its neurochemical and physiological actions via membrane receptor proteins. DA receptors are found on postsynaptic neurons in brain regions that are DA-enriched. In addition, they reside presynaptically on DA neuronal cell bodies and dendrites in the midbrain as well as on their terminals in the forebrain. Stimulation of these 'autoreceptors' inhibits DA synthesis by blocking the activity of tyrosine hydroxylase, the rate-limiting enzymatic step in catecholamine synthesis. In addition, DA autoreceptor activation blocks DA release from presynaptic membrane-enclosed storage vesicles, and significantly attenuate the firing rate of the DA neurons.<sup>7,8</sup> All DA receptor proteins belong to a superfamily of large peptides that are coupled to G-proteins and modified by attached carbohydrate, lipid-ester or phosphate groups. They are characterized by having seven hydrophobic transmembrane-spanning regions, as well as a functionally critical third intracytoplasmic loop that interacts with G-proteins and other effector molecules to mediate the physiological

and neurochemical effects of the receptors.<sup>2-5</sup>

The DA receptors were originally differentiated into two major types.<sup>9</sup> This was mainly based on the presence or absence of ability of DA to stimulate adenylyl cyclase and produce the second-messenger molecule cyclic-AMP (cAMP) to distinguish receptor types D<sub>1</sub> and D<sub>2</sub>. D<sub>1</sub> receptors were characterized initially as mediating the stimulation of cAMP production. D<sub>2</sub> receptors, which inhibit the production of cAMP, were pharmacologically characterized based on the ability of only some DA agents to block adenylyl cyclase activity, and on the ability of catecholamines including DA to inhibit the release of prolactin *in vivo* and *in vitro* in a cAMP-independent fashion.<sup>10</sup> Applications of recent technical advances in molecular genetics have greatly facilitated the isolation and characterization of novel DA receptors, D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub>, with different anatomical localization from traditional D<sub>1</sub> or D<sub>2</sub> receptors. Based upon their pharmacological profiles, including their effects on different signal transduction cascades, these receptors are currently divided into two families: the D<sub>1</sub>-like family, which includes D<sub>1</sub> and D<sub>5</sub> receptors, and the D<sub>2</sub>-like family which includes D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors.<sup>11-13</sup>

## MOLECULAR BIOLOGY OF DOPAMINE RECEPTORS

### DOPAMINE D<sub>1</sub>-LIKE FAMILY

#### D<sub>1</sub> receptors

The DA D<sub>1</sub> receptor is the most abundant DA receptor in the central nervous system. The D<sub>1</sub> receptor gene, which lacks any introns, encodes a protein that extends for 446 amino acids.<sup>14</sup> The human gene has been localized to chromosome 5 [Table 1].<sup>15</sup> D<sub>1</sub> receptors show characteristic ability to stimulate adenylyl cyclase and generate inositol 1,4,5-trisphosphate (IP<sub>3</sub>) and diacylglycerol via the activation of phospholipase C.<sup>16,17</sup> D<sub>1</sub> receptors are highly expressed in basal ganglia followed by cerebral cortex, hypothalamus and thalamus. In striatal neurons of the basal ganglia, the mRNA for D<sub>1</sub> receptors has been colocalized with mRNA for DARPP-32 (a DA- and cyclic-AMP-regulated phosphoprotein of molecular mass 32,000 daltons, or 32 kD), suggesting that DARPP-32 may contribute to the actions of D<sub>1</sub> receptors.<sup>18-19</sup>

#### D<sub>5</sub> receptors

The intronless D<sub>5</sub> receptor gene encodes a protein that extends for 477 amino acids [Table 1].<sup>20</sup> The protein has an overall 50% homology with the D<sub>1</sub> receptor and 80% if only the seven transmembrane segments are considered. The gene encoding the human D<sub>5</sub> protein is located at

**Table 1.** Properties of dopamine receptors

Type	Amino acids	Chromosome (human)	Highest tissue sites	Selective agonists	Selective antagonists	Effectors
<b>D<sub>1</sub> like receptors</b>						
<b>D<sub>1</sub></b>	446 (h) 446 (r)	5	Basal ganglia Nucleus accumbens Cerebral cortex	Hydroxybenzazepines A-68930 CY-208-245 Dihyrexidines	Halobenzazepines (SCH- 23390) Thioxanthenes	AC(+) PLC(+)
<b>D<sub>5</sub></b>	477 (h) 475 (r)	4	Hippocampus Thalamus	Hydroxybenzazepines	Halobenzazepines	AC(+)
<b>D<sub>2</sub> like receptors</b>						
<b>D<sub>2</sub></b>	443 (h)	11	Anterior pituitary, Basal ganglia	Ergolines Hydroxyaporphines Aminotetralins	Benzamides Butyrophenones Phenothiazines	AC(-) PLC(-); AA(+) K <sup>+</sup> channels(+) Ca <sup>2+</sup> channels (-)
<b>D<sub>3</sub></b>	400 (h) 444 (r)	3	Islands of Calleja, Olfactory Tubercle Cerebellum	(+)-7-OH-DPAT (+)-PD-128,907	Nafadotride S-14297	AC(-) (?)
<b>D<sub>4</sub></b>	387 (h) (& variants) 368(r)	11	Frontal cortex,  Hippocampus, Amagdyla	CP-226,269 PD-106,077	L-745,870 U-101,387 RBI-257 NGD-94-1	AC(-) AA(+)

Peptide length varies with species (h=human, r=rat); chromosome number are for human.

AA=arachidonic acid; AC=adenylyl cyclase; PI=phosphatidyl inositol cycle; PLC=phospholipase C; K<sup>+</sup> channels = potassium channels; Ca<sup>2+</sup> channels = calcium channels; (+) = activation; (-) = inhibition.

(?) indicates a tentatively proposed, or weak, association.

the short arm of chromosome 4, the same region where the Huntington disease gene has been located.<sup>21</sup> It is unknown, however, if there is any functional interaction between the two genes. Molecular studies identified two D<sub>5</sub>-like pseudogenes that extend for 154 amino acids and show 90% homology to the D<sub>5</sub> receptor genomic sequence. These pseudogenes, however, contain stop codons in their coding regions that prevent them from expressing functional receptors. The functions of these pseudogenes, which appear so far to be specific to humans, are not yet known.<sup>22</sup>

Expression of D<sub>5</sub> mRNA is unique and limited to the hippocampus and parafascicular nucleus of the thalamus,<sup>23</sup> a thalamic nucleus involved in pain perception, suggesting that D<sub>5</sub> receptors may be involved in the thalamic processing of painful stimuli.<sup>24</sup> D<sub>5</sub> receptors, like D<sub>1</sub> receptors, appear to interact with G-proteins and can stimulate adenylyl cyclase, with relatively high affinity for DA and D<sub>1</sub>-selective agonists [Table 1].<sup>20</sup>

#### DOPAMINE D<sub>2</sub>-LIKE FAMILY

##### D<sub>2</sub> receptors

The DA D<sub>2</sub> receptor was the first DA receptor to be cloned.<sup>25</sup> The D<sub>2</sub> receptor gene encodes a protein that extends for 415 amino acids [Table 1]. Similar to other G-protein coupled receptors, the D<sub>2</sub> gene product has seven transmembrane segments, but in contrast to D<sub>1</sub>-like receptors, the third cytoplasmic domain is long and the carboxyl terminus is short. Unlike the D<sub>1</sub>-like receptor genes, the D<sub>2</sub> receptor gene contains seven introns that are spliced out during mRNA transcription.<sup>26</sup> The gene encoding this receptor was found to reside on q22-q23 of human chromosome 11.<sup>27</sup> D<sub>2</sub> receptors are involved in several signal transduction cascades, including inhibition of cAMP production,<sup>28</sup> inhibition of phosphoinositide turnover,<sup>29</sup> activation of potassium channels, and potentiation of arachidonic acid release [Table 1].<sup>30</sup>

D<sub>2</sub> receptors are highly expressed in basal ganglia, nucleus accumbens septi, and ventral tegmental area.<sup>31</sup>

Molecularly, D<sub>2</sub> receptor protein exists in two isoforms derived from the same gene by alternative RNA splicing which occurs during the maturation of the D<sub>2</sub> receptor pre-mRNA.<sup>32</sup> Both isoforms (known as D<sub>2L</sub> and D<sub>2S</sub>) vary within each species by the presence or less frequent absence of a 29-amino acid sequence in the third cytoplasmic domain of the D<sub>2</sub> receptor peptide chain. Pharmacologically, both isoforms exhibit nearly similar profiles in terms of their affinities to different D<sub>2</sub>-selective agents, and both inhibit adenylyl cyclase activity. However, they display an opposite regulatory response to DA treatment: DA induces up-regulation of D<sub>2L</sub> isoform and down-regulation of D<sub>2S</sub> isoform.<sup>33</sup>

#### D<sub>3</sub> receptors

The D<sub>3</sub> receptor gene contains five introns and encodes a 446 amino acid protein.<sup>34</sup> The gene encoding this receptor resides on chromosome 3 [Table 1].<sup>35</sup> The D<sub>3</sub> receptors bear close structural and pharmacological similarities to the D<sub>2R</sub> and, like the genes for D<sub>2</sub> receptor variants, D<sub>3</sub> mRNA also occurs in longer and shorter spliced forms generated from the same gene.<sup>36</sup> Distribution of D<sub>3</sub> mRNA indicated that these receptors are mainly expressed in subcortical limbic regions including islands of Calleja, nucleus accumbens septi and olfactory tubercle, with low levels of expression in the basal ganglia [Table 1].<sup>31</sup> Surprisingly, D<sub>3R</sub> mRNA has also been found in neurons of the cerebellum, which may regulate eye-movements.<sup>37</sup> The status of the D<sub>3</sub> molecular entity as a functional receptor remains uncertain since it neither couples to G-proteins nor consistently transduces an effector mechanism.<sup>34,38</sup> However, the structural similarity with D<sub>2</sub> receptor raises the possibility that D<sub>3</sub> receptor may also inhibit adenylyl cyclase activity in its normal cellular setting. More recent studies reported that D<sub>3</sub> receptors might mediate positive regulatory influences of DA on production of the peptide neurotensin.<sup>39</sup>

#### D<sub>4</sub> receptors

The human D<sub>4</sub> receptor gene contains four introns and encodes a 387 amino acid protein.<sup>40</sup> The overall homology of the D<sub>4</sub> receptor to the D<sub>2</sub> and D<sub>3</sub> receptors is about 41% and 39% respectively, but this homology increases to 56% for both receptors when only the transmembrane spanning segments are considered. The gene encoding the human D<sub>4</sub> protein is located at the tip of the short arm of chromosome 11.<sup>41</sup> Histoprobes for its mRNA localized this gene product in non-extrapyramidal regions of human brain including hippocampus and frontal cerebral cortex.<sup>42</sup> Like the D<sub>2</sub> receptors, stimulation of the D<sub>4</sub> receptors can inhibit adenylyl cyclase activity and activate release of

arachidonic acid in brain neurons [Table 1].<sup>43</sup>

Human, but not primate or rodent, D<sub>4</sub> receptors are known to occur in several genomic polymorphic variants that contain from two to eleven repeats of a 48 base-pair segment expressed in the third cytoplasmic domain.<sup>44</sup> Two, four and seven repeats (designated as D<sub>4.2</sub>, D<sub>4.4</sub> and D<sub>4.7</sub>) are the most common D<sub>4</sub> alleles. These variants may contribute to the pathophysiology of certain neuropsychiatric disorders or their improved treatment.<sup>4</sup>

#### DISTRIBUTION OF DOPAMINE RECEPTORS IN BASAL GANGLIA

The basal ganglia consist of five interconnected subcortical nuclei including the striatum (caudate nucleus and putamen), globus pallidus, subthalamic nucleus, and substantia nigra *pars compacta* and *pars reticulata*.<sup>45–47</sup> The medium spiny neurons, which constitute 90–95% of the neurons in the striatum, receive the bulk of the incoming excitatory input from the cerebral cortex. These neurons send their projections through two major striatal output pathways. The direct or *striatonigral* pathway, where striatal neurons project to the internal segment of the globus pallidus and the substantia nigra *pars reticulata* and the indirect or *striatopallidal* pathway where striatal neurons project to the external segment of the globus pallidus, then to the subthalamic nucleus and terminate in the substantia nigra *pars reticulata*. The latter region sends projections to the ventral anterior, ventral lateral and mediodorsal thalamic nuclei, which in turn provide an excitatory input to the cerebral cortex.<sup>45–47</sup>

In the striatum, the majority of D<sub>1</sub> receptors are expressed on striatonigral neurons, whereas D<sub>2</sub> receptors are predominately localized to striatopallidal neurons.<sup>46,47</sup> Some D<sub>4</sub> receptors are co-expressed with the excitatory glutamate NMDA receptors, on terminals of glutamatergic corticostriatal projections innervating striatum, as well as on medium spiny neurons in striatum.<sup>48</sup> Both D<sub>2</sub> and D<sub>3</sub> subtypes are found on terminals of dopaminergic nigrostriatal neurons projecting from substantia nigra *pars compacta* to striatum.<sup>49</sup>

The basal ganglia are involved in programming and initiation of movement, particularly slow movements, and in motor memory and retrieval. Abnormalities in DA neurotransmission in the basal ganglia nuclei and/or their projecting targets have been linked to attention-deficit hyperactivity disorder (ADHD) and schizophrenia.<sup>1,2,50</sup> In addition, disorders of the basal ganglia may produce restricted and rigid movements as in Parkinson's disease or uncontrollable and involuntary movements as in Huntington's disease.<sup>51</sup>

## DOPAMINE RECEPTORS AND NEUROPSYCHIATRIC DISEASES

DA receptors have been implicated in a variety of neuropsychiatric disorders, most notably in schizophrenia, Parkinson's disease and attention-deficit hyperactivity disorder (ADHD). Other brain disorders in which DA receptors are involved or dopaminergic drugs have a therapeutic role are Huntington's chorea, Tourette's syndrome, and hyperprolactanemia.

### SCHIZOPHRENIA

Schizophrenia is one of the most common neuropsychiatric diseases affecting 1% of the general population. This rate is fairly uniform throughout the world, even though the environmental and socio-economical factors vary among different countries. Additional 2–3% of the general population has schizotypal personality disorder, which is a milder form of the disease.<sup>52–55</sup> The symptoms of schizophrenia start to develop in late adolescence or early adulthood. The 'positive' symptoms include thought disorder, perceptual disturbances, visual and auditory hallucinations and delusions while the 'negative' symptoms include loss of executive functions such as planning and working memory, neglect of hygiene, social isolation and withdrawal from interaction with other people.<sup>52–55</sup>

Genetic studies suggested that genetic factors play an important role in the pathophysiology of schizophrenia. Monozygotic twins, who have identical genome, show a concordance rate of about 40–50%, but in dizygotic twins, the rate drops to only 15%.<sup>55–57</sup> These rates, however, indicate that genetic predisposition alone is insufficient to produce the disease, and that other neurochemical and environmental factors also contribute to the development of the disease. Injuries in the normal development of human brain including maldevelopment of the anatomical organization and connectivity of cortical afferents innervating the limbic regions may contribute to neurobiological substrates for schizophrenia.<sup>58</sup> Disturbances in the concentrations and subsequent alterations in the neurotransmission of different neurotransmitters, including DA, serotonin and glutamate, in different cortical and limbic and extrapyramidal pathways have been also proposed to underlie the pathophysiology of schizophrenia.<sup>59–61</sup>

### Treatment of Schizophrenia

Treatment of schizophrenia and other idiopathic psychotic disorders was revolutionized by the serendipitous discovery of chlorpromazine (*phenothiazine* derivative) and haloperidol (*butyrophenone* derivative) in the 1950s. This was followed by introduction of other effective antipsy-

chotic compounds including *thioxanthenes* (clopexitol, flupentixol, and thiothixene), *benzepines* (loxapine, clothiapine and zotepine), *diphenylbutylpiperidines* (spiperones), *indolones* (molindone and oxyperline) and other heterocyclic compounds.<sup>1,2</sup> Virtually, all of these drugs, which collectively are known as *typical* antipsychotic drugs, reduce DA neuronal activity, reverse the psychotic symptoms induced by psychostimulants such as amphetamine and cocaine, and block DA D<sub>2</sub> receptors in a direct correlation with their antipsychotic efficacy.<sup>1,2,62,63</sup>

Typical antipsychotics are effective in alleviating the positive symptoms of schizophrenia. However, their effectiveness is limited and non-specific as they fail to significantly improve the cognitive deficits and negative symptoms of schizophrenia. Moreover, treatment with these medications is commonly associated with neurological extrapyramidal and endocrinological side effects, of both acute and delayed nature.<sup>1,2</sup> *Parkinsonism*, a syndrome with similar symptoms to Parkinson's disease, is the most frequent acute side effect. Other acute side effects include *dystonia* (sustained contraction of orofacial muscles), *akathisia* (motor restlessness with anxiety and agitation), and *galactorrhea* (excessive lactation). These side effects are the result of D<sub>2</sub> receptor blockade in either the striatum or pituitary gland.<sup>1,2</sup> A potentially life-threatening adverse effect of antipsychotic drug treatment is known as *neuroleptic malignant syndrome*.<sup>64,65</sup> It is characterized by muscle rigidity, dystonia, unstable pulse, blood pressure, fever, and elevated serum concentrations of muscle proteins (creatine kinase, myoglobin). The syndrome has been attributed to D<sub>2</sub> receptor blockade by typical antipsychotic agents, but its pathophysiology remains obscure, and may involve hypothalamic and brainstem dysfunction as well as extrapyramidal motor effects mediated by the basal ganglia.

Long-term treatment of schizophrenic patients with typical antipsychotic agents has been also associated with *tardive dyskinesia*, a delayed-onset hyperkinetic movement disorder that is often irreversible even after drug discontinuation.<sup>1,2</sup> The most characteristic features of this syndrome are abnormal movements of the mouth, face, extremities, and trunk. DA receptor supersensitivity that results from antipsychotic-induced blockade and upregulation of D<sub>2</sub> receptors,<sup>66,67</sup> an imbalance in D<sub>1</sub>/D<sub>2</sub> receptor densities in striata of medicated schizophrenic patients,<sup>10</sup> or a disruption in  $\gamma$ -amino butyric acid (GABA) neurotransmission in the basal ganglia may contribute to the development of tardive dyskinesia.<sup>68,69</sup>

All these side effects prompted the search for novel drugs with less risk of the adverse effects of typical

antipsychotics, but similar or even superior antipsychotic effects. This led to the introduction of several new drugs, classified as *atypical* antipsychotic drugs. The current prototype 'atypical' antipsychotic agent is clozapine (clozaril®), a dibenzodiazepine derivative. Several basic and clinical studies have provided substantial evidences that clozapine exhibit superior antipsychotic effectiveness over standard antipsychotics, especially in improving negative symptoms and cognitive deficits in schizophrenia. Clozapine is also effective in treatment-resistant schizophrenia, and other poorly responsive primary psychotic disorders, along with its very limited profile of extrapyramidal side effects or hyperprolactinemia.<sup>1,2,70,71</sup>

The pharmacological basis of the unusual clinical properties of this unique agent remains unclear. Clozapine interacts high or moderate potency at a wide range of neurotransmitter receptors including serotonergic (5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>), acetylcholinergic (muscarinic M<sub>1</sub>–M<sub>4</sub>), adrenergic ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta_2$ ), and histaminic (H<sub>1</sub>) receptors. In contrast, it has only moderate affinity for both DA D<sub>1</sub> and D<sub>2</sub> DA receptors.<sup>1,2,70–72</sup> Clozapine has greater affinity for serotonin 5-HT<sub>2A</sub> than DA D<sub>2</sub> receptors and this receptor-interaction pattern may contribute to its low risk of extrapyramidal side effects.<sup>73</sup>

Clozapine also displays somewhat greater affinity for D<sub>4</sub> than other DA receptors, suggesting that these receptors may represent potential sites of action of clozapine and perhaps other antipsychotic agents.<sup>40,74–76</sup> Post mortem brain tissue studies reported that D<sub>4</sub> receptors are increased in the striata of medicated schizophrenic patients.<sup>77,78</sup> In addition, laboratory studies found that repeated administration of clozapine, as well as other typical and atypical antipsychotics increased the abundance of D<sub>4</sub> receptors in rat striatum and nucleus accumbens septi.<sup>79–82</sup> These agents also up-regulated D<sub>2</sub> receptors in rodent and primate prefrontal cortex but had little or no effect on D<sub>1</sub> or D<sub>3</sub> receptors.<sup>79–83</sup> These findings support the view that D<sub>4</sub> receptors in striatum and nucleus accumbens, as well as D<sub>2</sub> receptors in prefrontal cortex are common sites where both typical and atypical antipsychotics mediate their beneficial therapeutic effects.<sup>1,2</sup> In contrast, typical neuroleptics, but not clozapine, also increased D<sub>2</sub> receptor binding and expression in rat and monkey striatum.<sup>79–83</sup> This selective increase in D<sub>2</sub> receptor labelling in the striatum may contribute to the development of neurological side effects typical of standard antipsychotics.<sup>1,2</sup> Lack of effect of typical and atypical antipsychotic agents on D<sub>1</sub> and D<sub>3</sub> receptors suggest that these receptors are less likely to be involved in the mechanisms of antipsychotic drug actions.<sup>1,2</sup>

Despite its favourable characteristics, clinical use of

clozapine is complicated by its high risk of potentially fatal bone marrow toxicity, agranulocytosis.<sup>1,70,84,85</sup> Patients on clozapine are required to undergo regular monitoring of their complete blood count to ensure that the development of agranulocytosis is detected early. In addition, clozapine has other adverse effects, including dose-dependent risk of epileptic seizures, excessive sedation, significant weight-gain, and a higher incidence of hypertension and type II diabetes mellitus.<sup>1,70,84,85</sup> These side effects collectively left the door opened for developing novel antipsychotic medications with less adverse risk than clozapine, but comparable antipsychotic effects.

Several newer agents have emerged. Among them are clozapine analogues olanzapine (Zyprexa®) and quetiapine (Seroquel®), the benzisoxazole derivative risperidone (Risperidal®) and its analogue ziprasidone (Geodon®).<sup>1,2,84,86</sup> Like clozapine, these compounds have multiple sites of molecular interaction, and greater affinity for serotonin 5-HT<sub>2A</sub> than DA D<sub>2</sub> receptors, which again may contribute to their benign extrapyramidal profile.<sup>1,2,84,86</sup> These newer agents have undergone extensive pharmacological and behavioural characterization in animals,<sup>86–88</sup> and their therapeutic effects were assessed in many clinical trials.<sup>1,85</sup> Despite the favourable clinical profile of most of the second generation of antipsychotic drugs, and their effectiveness in treating psychotic symptoms of schizophrenia, they are also associated with different adverse side effects. With the remarkable exception of clozapine, and perhaps quetiapine, other atypical antipsychotic agents have brought only *relative* avoidance of side effects on central neural control of posture and movement, urging continued searches for novel principles of developing novel antipsychotic drugs.<sup>1,85</sup>

#### PARKINSON'S DISEASE

Parkinson's disease (PD) develops later in life with the average age of onset of 60 years. PD patients suffer from disturbances of movements (akinesia), increased muscle tone (rigidity), tremor (4–5 per second at rest), and postural defects, along with speech and writing problems. These symptoms progress with a gradual exacerbation along with the progress of the disease.<sup>89</sup> Cognitive deficits and psychiatric disturbances are also common in patients with PD. The main cognitive deficits include disturbances in memory, fluency, visuospatial and construction abilities accompanied by dementia.<sup>90</sup> The most common psychiatric disturbances include depression, anxiety, mania and psychosis. PD is observed in more than 1% of individuals over the age of 65.<sup>91</sup> Genetics may also play a role in the aetiology of PD, but perhaps less prominent than that of

schizophrenia. Recent studies have found that mutations in three different proteins (*alpha-synuclein*, *parkin* and *UCHL1*) can lead to autosomal dominant form of the disease.<sup>92,93</sup>

The pathological hallmark of PD is the specific degeneration of more than 80% of the nigrostriatal dopaminergic neurons and the appearance of intracellular inclusions known as *Lewy bodies*.<sup>94,95</sup> This results in a profound depletion of DA in the substantia nigra pars compacta, caudate nucleus, putamen, and causes an increase in striatal D<sub>2</sub> receptor levels. The loss of striatal DA will decrease the inhibitory activity of nigrothalamic projections, which in turn will increase the activity of the thalamocortical neurons leading to the excitation of motor cortex and spinal motor neurons. The end results will be increased contraction of both flexors and extensors at the same time causing cogwheel rigidity and movement disorder.<sup>51,89</sup>

The discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can reduce the DA levels in the brain by selectively degenerating the nigrostriatal dopaminergic pathway, and producing a clinical syndrome similar to PD, helped to develop a useful animal model for PD and stimulated new approaches to investigating its pathophysiology and therapy.<sup>96,97</sup> MPTP is converted by monoamine oxidase B to MPP<sup>+</sup> (1-methyl-4-phenyl pyridinium) which is taken up by the DA neurons via presynaptic DA transporters. MPP<sup>+</sup> is then accumulated in the mitochondria where it inhibits complex I of the mitochondrial electron transport chain. This blocks the process of oxidative phosphorylation and generates toxic free radicals, which in turn attacks the integrity of cell cytoskeleton and eventually leads to cell death.<sup>96-98</sup>

#### *Treatment of Parkinson's disease*

The simplest way to replace depleted DA would be to administer DA itself. However, DA does not cross the blood brain barrier and therefore its direct administration is ineffective. Levodopa (L-3,4-dihydroxyphenyl alanine; L-DOPA) is the immediate precursor of DA which readily crosses blood brain barrier and is converted to DA by decarboxylation within the remaining few intact dopaminergic neurons.<sup>99</sup> Administration of levodopa, at least early in the course of the disease, significantly improved tremor, rigidity and motor-impairment in PD patients.<sup>89,99</sup> It should be noted, however, that the peripheral tissue conversion of levodopa to DA by aromatic amino acid decarboxylase permits only a small percentage of levodopa to reach the brain. Therefore, it is necessary to co-administer with levodopa, selective inhibitors of peripheral decarboxylase enzyme activity that do not cross the blood brain barrier,

such as carbidopa (Sinemet<sup>®</sup>) or benserazide (Madopar<sup>®</sup>) to profoundly increase the availability of levodopa in the brain.<sup>100,101</sup>

Long-term therapy of levodopa is complicated by the fact that the beneficial effects of levodopa start to wear off and patients start to experience response fluctuations with each dose of levodopa despite maintaining the same treatment regimen.<sup>102,103</sup> Later, patients start to show the 'on/off phenomenon' in which sudden periods of tremors and rigidity alternate with periods of mobility. Increasing the dose and frequency administration of levodopa can improve this situation, but this increases the risk of dyskinesias and excessive and involuntary movements.<sup>102,103</sup> In addition, patients may experience dopaminergic psychosis. The novel atypical antipsychotic agents, such as clozapine or quetiapine, have been shown to be effective in improving levodopa-induced psychosis.<sup>104</sup>

Inhibitors of the enzyme monoamine oxidase (MAO) represent another class of drugs for the treatment of PD. Two isoenzymes of MAO (MAO-A and MAO-B) oxidize monoamines. MAO-B is the predominant form in the striatum and is responsible for the oxidative metabolism of striatal DA.<sup>105</sup> Deprenyl (Eldepryl<sup>®</sup>), also known as selegiline, is a selective MAO-B inhibitor that irreversibly inhibits MAO and slows the breakdown of DA in the striatum. A combination of deprenyl and levodopa is useful in prolonging the effects of levodopa and in reducing the 'on/off' effects.<sup>106</sup> Currently, deprenyl is considered as one of the drugs of choice for treatment of early or mild PD.<sup>107</sup> However, in more advanced PD patients, deprenyl may accelerate the motor and cognitive side effects of levodopa therapy. Metabolites of deprenyl include amphetamine and methamphetamine, which can cause insomnia, anxiety and mood elevation in treated PD patients.<sup>89</sup>

An alternative to levodopa or deprenyl therapy is the use of direct DA receptor agonists. These drugs are more specific in their actions and can selectively target one or more DA receptor subtype, in contrast to the non-selective effects of levodopa or deprenyl. In addition, these agonists are well absorbed orally, have longer duration of actions than levodopa and are more effective in the management of fluctuations in motor activity.<sup>108</sup> Four DA receptor agonists are available for treatment of PD: the standard agents, bromocriptine (Parlodel<sup>®</sup>) and pergolide (Permax<sup>®</sup>), and the more recently introduced agonists, ropinirole (Requip<sup>®</sup>) and pramipexole (Mirapex<sup>®</sup>).<sup>89,108</sup> Bromocriptine is strong D<sub>2</sub> receptor agonist with partial antagonistic activity at D<sub>1</sub> receptors, while pergolide is an active agonist on both DA receptor subtypes. Ropinirole and pramipexole are active agonists at D<sub>2</sub>/D<sub>3</sub> sites with negligible activity at D<sub>1</sub> sites.<sup>89,108</sup>

Despite the progress in PD pharmacotherapy, many medications tend to lose their beneficial effects after long-term administration. Alternative therapies try to restore DA function by means of intracerebral tissue grafts. One approach focuses on transplanting adrenal medulla tissue either into a lateral ventricle or into the striatum itself.<sup>109</sup> Another approach is to implant fetal substantia nigra tissue with the anticipation that new DA neurons will grow, sprout and restore the lost nigrostriatal dopaminergic connectivity. This approach, however, remains controversial due to its ethical implications.<sup>110</sup> A third approach involves the use of xenografts, that is tissue grafts obtained from other species like pigs or monkeys, although the clinical outcome of these grafts have not been well established.<sup>111</sup> Neurosurgical intervention to selectively lesion the inner segment of globus pallidus (also known as pallidotomy) has been also utilised in treatment of PD. However, because of the risk of permanent damage to the brain, this treatment remains as the last resort.<sup>112</sup>

#### ATTENTION-DEFICIT HYPERACTIVITY DISORDER

ADHD is a neuropsychiatric condition characterized by inattention, impulsivity and inappropriate behavioural hyperactivity, typically associated with impaired academic and social functioning in school-aged children.<sup>50</sup> Several studies have implicated environmental and psychosocial factors, such as pregnancy and delivery complications, marital distress, family dysfunction and low social class as predisposing risk factors for ADHD.<sup>50,113</sup> The neuroanatomical networks involving frontal cortex and basal ganglia are proposed to be critically involved in the pathophysiology of ADHD.<sup>114,115</sup> Neuroimaging studies found that frontal cortex, caudate and globus pallidus were smaller in children diagnosed with ADHD compared to normal controls.<sup>116,117</sup> In addition, a functional deficit was detected in the putamen of children with ADHD relative to normal peers.<sup>118</sup> These findings provide a compelling support for the suggested dysfunction in fronto-subcortical pathways in patients diagnosed with ADHD.<sup>119</sup>

Molecular genetic studies have identified a genetic linkage between ADHD and an allele of DA transporter using a family based association study.<sup>120,121</sup> This association has been supported by the development of genetically altered mice that lack functional DA transporters. Such mice displayed a hyperdopaminergic state that included spontaneous hyperactivity similar to ADHD.<sup>122</sup> In addition, an association of D<sub>4</sub> receptor polymorphism and clinical ADHD has been also reported.<sup>75,76,123,124</sup> This association involves increased incidence of a 7-repeat allele (receptor type D<sub>4.7</sub>) coding for a 16-amino acid sequence in the

functionally critical third intracytoplasmic loop of the D<sub>4</sub> receptor in patients diagnosed with ADHD compared to normal controls. Additional support for possible involvement of D<sub>4</sub> receptors in ADHD is provided by recent findings that transgenic mice lacking D<sub>4</sub> receptors show increased sensitivity to psychostimulants and increased metabolic turnover of striatal DA compared to wild type mice.<sup>125</sup>

#### TREATMENT OF ADHD

Psychostimulants are considered the first line of treatment for ADHD, since the pathophysiology of ADHD involves deficiency in DA neurotransmission. The most widely used compounds in this class include methylphenidate (Ritalin®), amphetamines (Adderall® and Dexedrine®) and pemoline (Cylert®).<sup>126,127</sup> These compounds, which enhance DA neurotransmission, increase synaptic DA by inhibiting the reuptake of DA into presynaptic vesicles (methylphenidate, amphetamines and pemoline) or by releasing presynaptic DA into synaptic cleft.<sup>126-128</sup> Although these compounds are quite effective in alleviating the symptoms of ADHD and in improving attention and academic performance ADHD patients, they are associated with different side effects. Most notable, all these medications are considered controlled substances of potential abuse. In addition, they cause insomnia, anorexia, jitteriness, and headaches. Moreover, pemoline can cause hepatitis and liver toxicity, and so monitoring liver functions is essential for patients on pemoline.<sup>126-128</sup>

Antidepressants follow psychostimulants as the second line of choice for treatment of ADHD. The tricyclic antidepressants (TCAs), such as imipramine, desipramine, venlafaxine and atomoxetine, block the reuptake of monoamine neurotransmitters, especially norepinephrine.<sup>126-129</sup> TCAs are effective in controlling abnormal behaviours and reducing cognitive impairment in ADHD patients. They are also useful if depression or anxiety symptoms co-exist with ADHD.<sup>126-129</sup> Antihypertensive drugs such as clonidine and guanfacine are also used for treatment of ADHD in young patients. They are particularly effective against aggressiveness and sleep disturbances. However, cardiovascular monitoring of patients on these medications is recommended.<sup>126-128</sup>

Finally, recent reports have suggested that selective DA D<sub>4</sub> receptor antagonists may provide much-needed innovative treatments for ADHD. Motor hyperactivity observed in juvenile rats with neonatal 6-hydroxydopamine lesions, a laboratory model for ADHD, was reversed in dose-dependent manner by highly selective D<sub>4</sub> antagonists, and worsened by selective D<sub>4</sub> agonists.<sup>130</sup> A direct correlation



was also observed between motor hyperactivity in lesioned rats and increases in D<sub>4</sub> receptor levels in rat caudate-putamen.<sup>130</sup> These findings provided behavioural and pharmacological evidences for the suggested genetic association between D<sub>4</sub> receptor alleles and ADHD.<sup>75,76,123,124</sup> It is still premature to judge the effectiveness of D<sub>4</sub>-antagonists in treatment of ADHD. Post-mortem studies on brain tissue from patients diagnosed with ADHD are still needed to clarify the role of D<sub>4</sub> receptors in its neuropathology or pathophysiology. In addition, selective D<sub>4</sub>-antagonists should be tested in clinical trials to determine their safety and effectiveness for treatment of ADHD.<sup>75,76</sup>

### CONCLUSIONS

The new neuropharmacology of DA receptors and their effectors stimulates renewed interest in many aspects relevant to DA neurotransmission, including the molecular control of the DA synthesis and release, as well as the rational development of novel CNS drugs. The advances in molecular biology have revealed the presence of two classical DA receptors (D<sub>1</sub> and D<sub>2</sub>) as well as novel gene products that present novel DA receptors (D<sub>3</sub>, D<sub>4</sub>, D<sub>5</sub>). Clarification of the sites of expression of classical and novel DA receptor mRNAs and proteins in mammalian brain, characterization of their effector systems, and the identification of novel chemical or drug molecules selective for each receptor subtype have rapidly advanced the understanding of these novel DA receptors. Such understanding is relevant to the pathophysiology of major neuropsychiatric diseases, including schizophrenia, Parkinson's disease and ADHD, as well as to understanding the mechanisms of action and side effects of many drugs currently used in treatment of these disorders. The exciting neuropharmacological leads reviewed here should open new avenues of research on the preclinical aspects of different DA receptor subtypes, and should lead to innovative principles guiding discovery of novel drugs for improved treatment of neuropsychiatric diseases.

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