Neurobiology of Dopamine in Schizophrenia

Olivier Guillin* & Marc Laruelle*†

Departments of Psychiatry* and Radiology†, Columbia University College of Physicians and Surgeons, New York, NY

Received 29th July © Cellscience 2005

1. Introduction

Schizophrenia is a severe and chronic mental illness, associated with high prevalence (about 1% of the general population). Symptoms of schizophrenia typically emerge during adolescence or early adulthood. They are usually classified as either positive, negative or cognitive symptoms. Positive symptoms include: hallucinations, delusion and severe thought disorganization. Negative symptoms are a group of deficits comprising many dimensions such as affect (flattening), volition (apathy), speech (poverty), pleasure (anhedonia), and social life (withdrawal). Cognitive symptoms, such as deficits in attention and memory, are prominent features of the illness.

While the etiology and pathophysiology of schizophrenia remain unclear, a large body of evidences suggest that alterations in several neurotransmitters systems (e.g. dopamine, glutamate, GABAergic, serotonin) are involved in the pathophysiological processes leading to the expression of these symptoms. Among these, the dopamine (DA) system has received most attention.

The involvement of DA in the pathophysiology and treatment of schizophrenia has been the subject of intense research efforts over the last fifty years. The first formulation of the DA hypothesis of schizophrenia proposed that hyperactivity of DA transmission was responsible for the core or “positive” symptoms (hallucinations, delusions) observed in this disorder (Carlsson and Lindqvist 1963). This hypothesis was based on the correlation between
clinical doses of antipsychotic drugs and their potency to block DA D2 receptors (Creese et al. 1976; Seeman and Lee 1975) and by the psychotogenic effects of DA enhancing drugs (for review see Angrist and van Kammen 1984; for review see Lieberman et al. 1987a). Given the predominant localization of DA terminals and D2 receptors in subcortical regions such as the striatum and the nucleus accumbens, the classical DA hypothesis of schizophrenia was concerned mostly with these subcortical regions.

Over the years, the increasing awareness of the importance of enduring negative and cognitive symptoms in this illness and of their resistance to D2 receptor antagonism has led to a reformulation of this classical DA hypotheses. Functional brain imaging studies suggested that these symptoms might arise from altered prefrontal cortex (PFC) functions (for reviews see Knable and Weinberger 1997). A wealth of preclinical studies emerged documenting the importance of prefrontal DA transmission at D1 receptors (the main DA receptor in the neocortex) for optimal PFC performance (for review see Goldman-Rakic et al. 2000). Together, these observations led to the hypothesis that a deficit in DA transmission at D1 receptors in the PFC might be implicated in the cognitive impairments and negative symptoms of schizophrenia (Davis et al. 1991b; Weinberger 1987).

Thus, the current predominant view in that DA systems in schizophrenia might be characterized by an imbalance between subcortical and cortical DA systems: subcortical mesolimbic DA projections might be hyperactive (resulting in hyperstimulation of D2 receptors and positive symptoms) while mesocortical DA projections to the PFC might be hypoactive (resulting in hypostimulation of D1 receptors, negative symptoms and cognitive impairment). Furthermore, since the seminal work of Pycock et al. (1980), many laboratories have described reciprocal and opposite regulations between cortical and subcortical DA systems (for review see Tzschentke 2001). An abundant literature suggests that prefrontal DA activity exerts an inhibitory influence on subcortical DA activity (Deutch 1990; Karreman and Moghaddam 1996; Kolachana et al. 1995; Wilkinson 1997). From these observations, it has been proposed that, in schizophrenia, both arms of the DA imbalance model might be related, inasmuch as a deficiency in mesocortical DA function might translate into disinhibition of mesolimbic DA activity (Weinberger 1987).

Despite decades of effort to generate experimental data supporting these hypotheses, documentation of abnormalities of DA function in schizophrenia has been difficult. Postmortem studies measuring DA and its metabolites and DA receptors in the brains of patients with schizophrenia yielded inconsistent or inconclusive
results (for review see Davis et al. 1991b). Over the last few years, the development of new brain imaging methods based on the principle of endogenous competition enabled direct measurement of DA transmission at D2 receptor in the striatum (for review see Laruelle 2000). Combined with studies that documented increased striatal [18F]DOPA accumulation in schizophrenia, application of these new techniques to the study of schizophrenia provided new information into dysregulation in subcortical DA function in schizophrenia (for review see Weinberger and Laruelle 2001). Imaging studies have consistently demonstrated that schizophrenia is associated with increased presynaptic activity of DA neurons projecting to the striatum. Thus, the first arm of the dopaminergic imbalance hypothesis (hyperactivity in subcortical territory) has received strong support from imaging studies.

On the other hand, the second arm of this hypothesis (DA deficit in cortical projections) is still largely based on inferences from preclinical model or indirect clinical evidence. In contrast to the striatum, presynaptic DA function in the PFC is not at present accessible to noninvasive imaging techniques. D1 receptor availability is the only parameter of prefrontal DA function that is currently quantifiable in vivo with adequate reliability. Despite the limited information that this parameter provides to characterize DA function, recent PET imaging studies have described interesting relationships between alterations of D1 receptor availability and cognitive functions in schizophrenia (Abi-Dargham et al. 2002; Karlsson et al. 2002; Okubo et al. 1997).

The goal of this paper is to review current evidence for DA dysregulation in schizophrenia. Following a brief review of dopaminergic systems and receptors, pharmacological, postmortem and imaging data that implicate DA alterations in schizophrenia will be presented.

2. Dopaminergic system in the brain

2.1 Dopaminergic projections
Dopaminergic projections are classically divided into nigrostriatal, mesolimbic, and mesocortical systems (Lindvall and Björklund 1983). The nigrostriatal system projects from the substantia nigra (SN) to the dorsal striatum, and has been classically involved in cognitive integration, habituation, sensorimotor coordination, and initiation of movement. The mesolimbic system projects from the ventral tegmental area (VTA) to limbic structures such as ventral striatum, hippocampus, and amygdala. The mesocortical system projects from the VTA to cortical regions, mostly orbitofrontal, medial prefrontal and cingulate cortices, but also to the dorso-lateral prefrontal cortex (DLPFC), temporal, and parietal cortex. The mesolimbic and mesocortical systems are involved in regulation of motivation, attention, and reward (Mogenson et al. 1980).

Corticostriatal-thalamo-cortical loops are important targets of DA modulation. The general scheme of these loops involves projections from the cortex to striatum to the internal segment of the globus pallidum (GPi) or the SN pars reticulata (SNr) to thalamus and back to the cortex. These loops have been classified into “limbic” loops (medial prefrontal and orbitofrontal cortex - ventral striatum - ventral pallidum - mediodorsal thalamic nuclei - cortex), associative loops (DLPFC - head of the caudate – GPi/SNr – ventral anterior thalamic nuclei - cortex) and motor loops (premotor and motor areas - putamen and body of the caudate – GPi/SNr - ventral anterior thalamic nuclei back - cortex; Alexander et al. 1986; Ferry et al. 2000; Hoover and Strick 1993; Joel and Weiner 2000; Parent and Hazrati 1995a). The amygdala and hippocampus provide significant inputs to the ventral striatum, contributing to information integration into the limbic loop (Everitt et al. 1991; Grace 2000; Kunishio and Haber 1994; Pennartz et al. 1994). Animal studies suggest that the nucleus accumbens is the critical region in which both typical and atypical antipsychotic drugs exert their antipsychotic effects (Chiodo and Bunney 1983; Deucht et al. 1991; Robertson et al. 1994). It is important to note that these different corticostriatal-thalamo-cortical loops are not completely segregated parallel loops. While corticostriatal-thalamic loops do generally re-enter the cortical area that provides input to the striatal subregions involved in these loops, thus forming closed circuits and serving segregating processes, they also project back to other areas of the cortex, forming open circuits and serving integrative processes (Joel and Weiner 2000).
Within each loop the striatum output reaches the GPi/SNR via a direct pathway and via an indirect pathway that traverses the external segment of the globus pallidus (GPe) and the subthalamic nuclei (STN), both pathways providing antagonistic inputs to the GPi/SNr (Albin et al. 1989; DeLong et al. 1985; Gerfen 1992; Joel and Weiner 2000). The view of the antagonistic nature of the direct/stimulatory pathway versus the indirect/inhibitory pathway has been criticized as overly simplistic (Parent and Hazrati 1995b). Nevertheless, it is important to keep in mind that activation of medium spiny GABAergic neurons in the striatum by cortico-striatal glutamatergic afferents can provide both stimulatory or inhibitory influences on thalamo-cortical projections (Carlsson et al. 2001).

DA modulates the flow of information within these loops. In primates DA cells from the VTA project to the ventral striatum and cortex, the dorsal tier of the SN includes cells that project to all striatal regions and cortex, and the ventral tier of the SN does project widely throughout the dorsal striatum, but not to the cortex (for review, see Haber and Fudge 1997). The striatum provides GABA projections back to the VTA and SN. Projections from the VST to midbrain DA neurons are not restricted to the VTA and dorsal tier of the SN (where DA neurons projecting to the VST are located), but also terminate in the ventral tier of SN (where DA neurons projecting to the dorsal striatum are located). Based on these observations Haber proposed that the DA system provides a bridge by which information circulating in the ventral limbic cortico-striatal-thalamo-cortical loops spirals along nigro-striatal loops and feeds into the cognitive and sensorimotor loops, translating drives into actions (Haber and Fudge 1997; Haber et al. 2000).

2.2. Dopaminergic receptors
The advent of molecular biology techniques in the late eighties enabled the cloning of these two receptors (Bunzow et al. 1988; Dearry et al. 1990; Monsma et al. 1990; Zhou et al. 1990), as well as three newer DA receptors, termed D3, D4 and D5 receptors (Sokoloff et al. 1990; Sunahara et al. 1991; Tiberi et al. 1991; Van Tol et al. 1991). On the basis of their sequence homologies, the five DA receptor subtype were classified into two categories (Table 1), a D1-like family (including D1 and D5 receptors), and a D2-like family (D2, D3 and D4 receptors, for reviews, see Civelli et al. 1993; Gingrich and Caron 1993; Sokoloff et al. 1995). This classification is also coherent with the initial distinction of D1 and D2 receptors on the basis of their signaling system, i.e. their coupling to Gs and Gi proteins respectively and opposite effects on adenylyl cyclase (Kebabian and Calne 1979; Spano et al. 1978). D2-like family receptors are both postsynaptic receptors and presynaptic autoreceptors (Diaz et al. 2000; Missale et al. 1998; Palermo-Neto 1997).

Table 1. The D1-like and D2-like family of dopamine receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>D1-like</th>
<th>D2-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence homology</td>
<td>60%</td>
<td>50-70%</td>
</tr>
<tr>
<td>Gene organization</td>
<td>Intronless genes</td>
<td>Genes with intron</td>
</tr>
<tr>
<td>Transduction</td>
<td>Stimulate adenylyl cyclase</td>
<td>Inhibit adenylyl cyclase</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Moderate to low affinity for antipsychotics</td>
<td>High to moderate affinity for antipsychotics</td>
</tr>
</tbody>
</table>

DA receptors differ in their regional localization in the human brain (for reviews see Joyce and Meador-Woodruff 1997; Meador-Woodruff et al. 1996). D1 receptors show a widespread neocortical distribution, including the prefrontal cortex, and are also present at high concentration within the striatum. D5 receptors are concentrated in the hippocampus and entorhinal cortex. D2 receptors are concentrated in the striatum, with low concentration in medial temporal structures (hippocampus, entorhinal cortex, amygdala) and thalamus. The concentration of D2 receptors in
the prefrontal cortex is extremely low. D₃ receptors are present in the striatum, where their concentration is particularly high in the ventral striatum. D₄ receptors are present in the prefrontal cortex and hippocampus, but have not been detected in the striatum (Lahti et al. 1998).

In the striatum D₂ receptors are principally expressed within enkephalin-rich GABAergic neurons that participate in the indirect pathways, while D₁ receptors are most abundant in dynorphin/ substance P containing GABAergic neurons that contribute to the direct pathways (Gerfen 1992; Hersch et al. 1995; Le Moine et al. 1991; Le Moine et al. 1990). In rodents, D₃ receptors are expressed in the Island of Calleja and in medium-sized spiny neurons of the rostral and ventromedial shell of nucleus accumbens (Diaz et al. 1995), while D₃ receptor distribution in the striatum is more widespread in humans (Gurevich et al. 1997). The magnitude of the segregation versus co-expression of D₁ and D₂ receptors in striatal neurons is still a matter of debate (Surmeier et al. 1992; Surmeier et al. 1996). In the VST D₃ receptors colocalize preferentially on neurons expressing D₁ receptors, substance P, dynorphin and/or neurotensin (Diaz et al. 1995; Ridray et al. 1998) and TrkB, the high affinity site for the Brain-derived Neurotrophic Factor (BDNF, Guillin et al. 2001). In the shell of accumbens, activation of D₁ and D₃ receptor results in a synergistic enhancement of substance P gene expression (Ridray et al. 1998). In view of the high degree of coexpression of the two receptor subtypes in medium-sized spiny neurons within this region, it seems likely that the synergism occurs at the single-cell level and reflects the MAP kinase pathway of the D₃ receptor signaling pathway being augmented by the cAMP pathway of the D₁ receptor. The segregation of D₂ and D₁ receptors on different and antagonistic pathways might account for the fact that activation of these receptors is often synergistic at the behavioral level (for example stimulation of both D₁ and D₂ receptors stimulate locomotion), while their effects on intracellular signaling (e.g. adenylate cyclase activity) are opposite in many regards. For example, stimulation of D₁ and D₂ receptors increases or decreases DARPP32 phosphorylation, induces or blocks c-fos expression, promotes or inhibit N-methyl-D-aspartate (NMDA) receptor function, respectively (Dunah and Standaert 2001; Konradi 1998; Leveque et al. 2000; Nguyen et al. 1992; Nishi et al. 1997). Thus, activation of D₂ receptors by DA might provide an inhibitory influence to the indirect pathway and activation of D₁ receptors by DA might provide a stimulatory influence on the direct pathway. Both effects are expected to result in stimulation of thalamo-cortical neurons.
However, the action of DA on target neurons should not be viewed in terms of simple excitation or inhibition. Unlike classical “fast” transmitters, DA does not directly gate ion channels, but stimulation of DA G-protein linked receptor induces a cascade of intracellular signaling that results in modifying the response of the cells to other transmitters. DA is neither “inhibitory” or “excitatory”, but its action will depend on the state of the neurons at the time of the stimulation (Yang et al. 1999). Cortical glutamatergic (GLU) afferents and DA projections converge on GABAergic medium spiny neurons in the striatum, usually on dendritic shafts and spines (for review, see Kotter 1994; Smith and Bolam 1990; for review, see Starr 1995). At this convergence point, DA has potent modulatory effects on GLU transmission ((for review, see Cepeda and Levine 1998; Konradi and Heckers 2003; for review, see Nicola et al. 2000). Overall, D₂ receptor stimulation inhibits NMDA-mediated GLU transmission and long term potentiation (LTP), and D₁ receptor stimulation facilitates GLU transmission and LTP (Centonze et al. 2001; Levine et al. 1996). The effect of D₂ receptor stimulation on GLU transmission involves both pre- and post-synaptic effects: D₂ stimulation inhibits GLU release, and reduces the excitability of medium spiny neurons (Cepeda et al. 2001; Cepeda and Levine 1998; Leveque et al. 2000; Nicola et al. 2000; Onn et al. 2000; Peris et al. 1988; West and Grace 2002). In contrast, D₁ receptor stimulation generally promotes NMDA function and medium spiny neuron excitability, more specifically when the cells are in a depolarized “upstate”, due to the convergence of excitatory inputs (Dunah and Standaert 2001; Flores-Hernandez et al. 2002; Hernandez-Lopez et al. 1997; Marti et al. 2002; Morari et al. 1994; West and Grace 2002; Wilson and Kawaguchi 1996).

In the prefrontal cortex, D₁/₅ receptors are localized both on pyramidal cells (dendritic spines and shafts) and on axonal terminals of non-dopaminergic neurons (Smiley et al. 1994), while some data suggest that D₄ receptors might be localized on GABAergic interneurons (Mrzljak et al. 1996). DA modulates pyramidal cell excitability, both directly and via GABAergic interneurons (Yang et al. 1999). Recent data suggest that DA differently affects GABAergic activity in the PFC via D₁-like or D₂-like mechanisms, whereas D₁/₅ and D₂/₄ receptor stimulation enhance or inhibits GABAergic activity, respectively. Here again, it has been proposed that DA increases the signal-to-noise ratio of glutamatergic afferents (Seamans et al. 2001).

3. Evidence supporting alterations of DA systems in schizophrenia.


3.1.1. Aversive pharmacological effects.

The psychotogenic effect of amphetamine and other DA enhancing drugs such as methylphenidate and L-DOPA is a cornerstone of the classical DA hypothesis of schizophrenia. Two sets of observations are relevant to this issue.
First, repeated exposure to high doses of psychostimulants in non-schizophrenic subjects might gradually induce paranoid psychosis. This well documented observation shows that a sustained increase in DA activity is psychotogenic. Second, low doses of psychostimulants that are not psychotogenic in healthy subjects might induce or worsen psychotic symptoms in patients with schizophrenia. This observation indicates that patients with schizophrenia have an increased vulnerability to the psychotogenic effects of DA enhancing drugs.

Amphetamine-induced psychosis in non schizophrenic subjects. Although mentioned in 1938 (Young and Scoville 1938), amphetamine-induced psychosis was not clearly recognized as a possible consequence of chronic amphetamine use until 1958 upon the publication of a 42 cases monograph by Connell (1958). In this paper, Connell provided the "classical" definition of amphetamine psychosis, as "a paranoid psychosis with ideas of references, delusions of persecution, auditory and visual hallucinations in the setting of a clear sensorium" and concluded that "the mental picture may be indistinguishable from acute or chronic paranoid schizophrenia" (Connell 1958).

In the early seventies several studies experimentally induced amphetamine psychosis in non-schizophrenic amphetamine-abusers in order to better document the clinical pattern of this syndrome (Angrist and Gershon 1970; Bell 1973; Griffith et al. 1968). These experiments formally established that sustained psychostimulant exposure can produce paranoid psychosis in non-schizophrenic individuals. This reaction does not occur in the context of a delirium since subjects maintain a clear sensorium during the episode, and are able to recollect the episode after its resolution. Since these studies were performed before the conceptualization of the symptoms of schizophrenia into positive and negative (Crow 1980), they did not formally assess negative symptoms. These papers only include anecdotal reports of emotional blunting, withdrawal or alogia, thereby suggesting that sustained and excessive stimulation of DA systems does not consistently induce what are now defined as the “negative” symptoms of schizophrenia.

Psychotogenic effects of amphetamine in schizophrenic patients. A number of studies (reviewed by Lieberman et al. 1987b) provided evidence that patients with schizophrenia, as a group, display increased sensitivity to the psychotogenic effects of acute psychostimulant administration. In other terms, some but not all patients with schizophrenia present emergence or worsening of psychotic symptoms after acute exposure to psychostimulants at doses that do not induced psychosis in healthy subjects. The psychotic response appears to be state dependent. First, patients who responded with a psychotic reaction to a psychostimulant challenge during an acute episode failed to show such a response when they were in remission. Second, the propensity to present a psychotic reaction to a psychostimulant challenge is predictive of relapse upon antipsychotic discontinuation. Thus, the clinical response to stimulants might “reveal” an active phase of the illness that is not readily identifiable by the clinical
symptomatology in the absence of a psychostimulant administration.

3.1.2. Therapeutic pharmacological effects.

Since the recognition in 1952 of the antipsychotic properties of chlorpromazine (Delay et al. 1952) antipsychotic medications have fundamentally altered the course and the prognosis of schizophrenia. They have proven effective at reducing the severity of symptoms and preventing episodes of illness exacerbation. To date D2 receptor antagonism is the only pharmacological property shared by all antipsychotic drugs. The clinical dose of these drugs is related to their affinity for D2 receptors. D2 receptor antagonism appears both necessary and sufficient for antipsychotic action (as demonstrated by the selective D2 receptor antagonist amisulpride). The fact that patients with schizophrenia improve following administration of D2 receptor antagonists is one of the few irrefutable pieces of evidence in schizophrenia (Weinberger 1987).

D2 receptor blockade by antipsychotic drugs has been confirmed by a large number of imaging studies (reviewed in Talbot and Laruelle 2002). In general, these studies failed to observe a relationship between the degree of D2 receptor occupancy and the quality of the clinical response. However, most studies reported doses achieving more than 50% occupancy. The minimum occupancy required for a therapeutic response remains somewhat uncertain. Two studies performed with low doses of relatively selective D2 receptor antagonists (haloperidol and raclopride) suggest that a minimum of 50% occupancy is required to observe a rapid clinical response (Kapur et al. 2000; Nordstrom et al. 1993). Imaging studies have repeatedly confirmed the existence of a striatal D2 receptor occupancy threshold (about 80%) above which extrapyramidal symptoms (EPS) are likely to occur (Farde et al. 1992). Thus, these data suggest the existence of a therapeutic window between 50 and 80% striatal D2 receptor occupancy. Within this window, the relationship between occupancy and response is unclear, presumably because the variability in endogenous DA (Frankle et al. 2004). Furthermore, the occupancy threshold required for therapeutic effects might differ among drugs.

The introduction of a second generation of antipsychotic (SGA) drugs since the early nineties has not fundamentally altered the prominence of D2 receptor antagonism in the current treatment of schizophrenia. Most SGAs also potently interact with other receptors, such as the serotonin 5HT2A receptors, but the possibility to achieve an "atypical" profile with a pure D2 receptor antagonist such as amisulpride indicates that serotonin pharmacological effects are not absolutely required to produce this effect.

On the other hand, imaging studies have generally reported lower occupancies of striatal D2 receptors at therapeutic doses of SGAs compared to first generation antipsychotic drugs (FGAs). This seems to be especially true for
 amisulpride, clozapine, and quetiapine, which provide 50-60% D₂ receptor occupancy range at clinically effective doses (for review and references, see Abi-Dargham and Laruelle 2005). In contrast studies with FGAs often reported occupancies exceeding 75%. Thus a parsimonious hypothesis to account for the SGA superiority is that, in general, clinical results obtained after moderate occupancies (50-75%) are better than after high occupancies (75-100%), and that, for a variety of reasons, SGAs tend to maintain lower occupancies than FGAs. The alternate hypothesis is that the D₂ receptor occupancy required for therapeutic effects is lower in SGAs than FGAs. Should the alternate hypothesis be true the mechanisms responsible for the gain in the occupancy/efficacy relationship of SGAs remain to be fully elucidated.

A potentially important synergistic effect of 5HT₂A and D₂ receptor antagonism is to increase prefrontal DA, an effect not observed with selective D₂ or 5HT₂A receptor antagonists administered alone (Gessa et al. 2000; Ichikawa et al. 2001; Melis et al. 1999; Pehek and Yamamoto 1994; Youngren et al. 1999). This effect might be mediated by the stimulation of 5HT₁A receptors as it is blocked by 5HT₁A antagonists and is also observed following the combination of 5HT₁A receptor agonism and D₂ receptor antagonism (Ichikawa et al. 2001; Rollema et al. 2000). Aripiprazole, clozapine, quetiapine and ziprasidone are also 5HT₁A partial agonists, and this additional property might also contribute to their ability to increase prefrontal DA. As discussed below, a decreased prefrontal DA function might contribute to the cognitive deficits present in patients with schizophrenia, and it is possible that an increase in prefrontal DA induced by SGAs might mediate some of the modest cognitive improvements induced by these drugs (Keefe et al. 1999). However it is unclear whether this increase in prefrontal DA, documented as an acute response in animal studies, is sustained during the course of treatment in patients with schizophrenia.

3.2. Post-mortem studies

The discovery of the antipsychotic effect of D₂ receptor blockade inspired numerous postmortem studies seeking to determine whether schizophrenia was associated with altered parameters of DA transmission. These postmortem studies have for the most part failed to provide definitive answers, partly because of the confounding effects of antemortem antipsychotic treatment.

**Tissue DA and HVA.** Direct measures of tissue content of DA and its metabolites have failed to demonstrate consistent and reproducible abnormalities (for review see Davis et al. 1991a; Reynolds 1989). It should be noted, however, that some studies have reported higher DA levels in tissue samples from patients with schizophrenia in subcortical regions such as caudate (Owen et al. 1978), nucleus accumbens (Mackay et al. 1982) or amygdala (Reynolds 1983).
**D2 receptors.** Increased density of striatal D2 receptors in patients with schizophrenia has been a consistent finding in a large number of postmortem studies (Cross et al. 1983; Dean et al. 1997; Hess et al. 1987; Joyce et al. 1988; Knable et al. 1994; Lahti et al. 1996; Lee et al. 1978; Mackay et al. 1982; Marzella et al. 1997; Mita et al. 1986; Owen et al. 1978; Reynolds et al. 1987; Ruiz et al. 1992; Seeman et al. 1987; Seeman et al. 1993; Seeman et al. 1984; Sumiyoshi et al. 1995). Because chronic neuroleptic administration upregulates D2 receptor density (Burt et al. 1977) it is likely that these postmortem findings are related to prior neuroleptic exposure rather than to the disease process per se. In light of these very consistent results with [3H]spiperone, it is interesting to note that the striatal binding of [3H]raclopride has been reported to increased in many studies (Dean et al. 1997; Marzella et al. 1997; Ruiz et al. 1992; Sumiyoshi et al. 1995), but normal in several others (Knable et al. 1994; Lahti et al. 1996; Seeman et al. 1993), even in patients exposed to neuroleptic drugs prior to death. This observation suggests that the increase in [3H]raclopride binding is of lower magnitude than the one of [3H]spiperone binding. This discrepancy might simply reflect the observation that, for reasons that are not currently understood, antipsychotic drugs upregulate more [3H]spiperone than [3H]raclopride binding to D2 receptors (Schoots et al. 1995; Tarazi et al. 1997).

**D3 receptors.** A significant increase in D3 receptor number in VST samples from patients with schizophrenia who were off neuroleptics at the time of death has been reported in one study (Gurevich et al. 1997). In contrast, in patients who had been treated with neuroleptics up to the time of death, D3 receptors levels did not differ significantly from those of controls (Gurevich et al. 1997). These data were interpreted as indicating that antipsychotics downregulate the D3 receptor in schizophrenic patients who otherwise have a higher density of this receptor in the VST. The D3 receptor gene expression is under the control of the neurotrophin BDNF, which is synthesized either in the VTA or the prefrontal cortex, and is released into the VST where it maintains the expression of the D3 receptor (Guillin et al. 2001). One study (Takahashi et al. 2000) have shown increased and two decreased (Hashimoto et al. 2005; Weickert et al. 2003) BDNF levels in the brain of patients with schizophrenia. D3 receptors are upregulated in the presence of a hyperdopaminergic tone (Bordet et al. 1997; Fauchey et al. 2000; Guillin et al. 2001; Le Foll et al. 2002) under the control of the BDNF, the synthesis of which is in turn under the control of the activity of neurons projecting from the PFC or the VTA in the VST.

**D4 receptors.** Based on ligand subtraction techniques, several studies have reported increased D4-like receptors in schizophrenia (Marzella et al. 1997; Murray et al. 1995; Seeman et al. 1993; Sumiyoshi et al. 1995). These findings were not confirmed by other studies using the same technique (Lahti et al. 1996; Reynolds and Mason 1994), nor by a study using [3H]NGD 94-1, a selective D4 ligand (Lahti et al. 1998). Moreover, the hypothesis that clozapine might act by blocking the D4 receptor was not supported by a clinical trial with the D4 selective agent L745,870 (Kramer et al. 1997).
**D1 receptors.** Striatal D1 receptors have generally been reported to be unaltered in schizophrenia (Joyce et al. 1988; Pimoule et al. 1985; Reynolds and Czudek 1988; Seeman et al. 1987), although one study reported decreased density (Hess et al. 1987). In the prefrontal cortex, one study reported no changes (Laruelle et al. 1990), and one reported a non-significant increase (Knable et al. 1996).

**DA transporters (DAT).** A large number of studies have reported unaltered DA transporter density (DAT) in the striatum of patients with schizophrenia (Chinaglia et al. 1992; Czudek and Reynolds 1989; Hirai et al. 1988; Joyce et al. 1988; Knable et al. 1994; Pearce et al. 1990).

**Tyrosine hydroxylase (TH) immunolabeling.** A recent and interesting postmortem finding regarding DA parameters in patients with schizophrenia is the observation that there is a decrease in TH labeled axons in layer 3 and 6 of the entorhinal cortex (EC) and in layer 6 of the PFC, a finding suggesting that schizophrenia might be associated with deficit in DA transmission in the EC and PFC (Akil et al. 2000; Akil et al. 1999). This finding was clearly unrelated to pre-mortem neuroleptic exposure. Benes et al. (1997) observed no significant changes in TH positive varicosities in the DLPFC. In the anterior cingulate region (layer 2), these authors observed a significant shift in the distribution of TH varicosities from large neurons to small neurons.

In conclusion, post-mortem measurements of indices of DA transmission generated a number of consistent observations in the striatum: 1. The binding of radioligand to D2-like receptors in the striatum of patients with schizophrenia is increased, but the magnitude of this increase varies with the type of radioligands used, and it difficult to exclude the contribution of pre-mortem antipsychotic exposure in this set of findings ; 2. Striatal DAT and D1 receptor density is unaffected in schizophrenia. Several interesting observations such as increase in D3 receptors in the ventral striatum and alteration in TH immunolabeling in several cortical regions do not appear to be consequences of pre-mortem neuroleptic exposure, but these findings have yet to be independently confirmed.

### 3.3. Imaging studies

#### 3.3.1. Striatal DA function

The development of PET and SPECT imaging techniques in the late 1980s made possible, for the first time, the examination of DA function in vivo in patients with schizophrenia who had never been exposed to antipsychotic drugs.

**Striatal D2 and D1 receptors.** Striatal D2 receptor density in schizophrenia has been extensively studied with PET
and SPECT imaging (Abi-Dargham et al. 1998b; Abi-Dargham et al. 2000c; Blin et al. 1989; Breier et al. 1997a; Crawley et al. 1986; Hietala et al. 1994b; Knable et al. 1997; Laruelle et al. 1996a; Martinot et al. 1991a; Martinot et al. 1990b; Pilowsky et al. 1994a; Wong et al. 1986a; Yang et al. 2004). Meta-analysis of these studies reveals a small (12%) but statistically significant elevation of striatal D2 receptors in untreated patients with schizophrenia (Table 2). No clinical correlates of increased D2 receptor binding parameters could be identified. Studies performed with butyrophenones (n = 7) show an effect size of 0.96 ± 1.05, significantly larger than the effect size observed with other ligands (benzamides and lisuride, n = 11, 0.19 ± 0.25, p = 0.02). This difference might be due to differences in vulnerability of the binding of these tracers to endogenous DA, and elevation of endogenous DA in schizophrenia (Seeman 1988; Seeman et al. 1989). Interestingly, the fact that D2 receptor levels are increased in healthy monozygotic twins compared to dizygotic twins of patients with schizophrenia has lead to the conclusion that the caudate DA D2 receptor up-regulation is related to a genetic risk factor for schizophrenia (Hirvonen et al. 2005). Imaging studies of D1 receptors have consistently failed to detect abnormalities of D1 receptor availability in the striatum of patients with schizophrenia (Abi-Dargham et al. 2002; Karlsson et al. 2002; Okubo et al. 1997).
Striatal DOPA decarboxylase activity. The eight studies which have reported rates of DOPA decarboxylase activity in patients with schizophrenia using $^{[18]}$F]DOPA or $^{[11]}$C]DOPA radiotracers are summarized in Table 3. Six out of eight studies reported an increased accumulation of DOPA in the striatum of patients with schizophrenia (Dao-Castellana et al. 1997a; Elkashef et al. 2000; Hietala et al. 1999b; Hietala et al. 1995; Lindstrom et al. 1999; McGowan et al. 2004; Meyer-Lindenberg et al. 2002; Reith et al. 1994a), one reported no change (Dao-Castellana et al. 1997a), and one study reported reduced $^{[18]}$F]DOPA striatal uptake (Elkashef et al. 2000).

Table 2. Imaging studies of striatal D2 receptor parameters in drug naive and drug free patients with schizophrenia

<table>
<thead>
<tr>
<th>Class radiotracer</th>
<th>Radiotracer</th>
<th>Study</th>
<th>n Controls</th>
<th>n Patients (DN/DF)a</th>
<th>Method</th>
<th>Outcome</th>
<th>Controls (n, mean ± SD)b</th>
<th>Patients (n, mean ± SD)b</th>
<th>p</th>
<th>Effect sizec</th>
<th>Ratio SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopa tomeses</td>
<td>$^{[1]}$CJNMSP</td>
<td>(Wong et al. 1986b)</td>
<td>11</td>
<td>15 (10/5)</td>
<td>Kinetic</td>
<td>$S_m$</td>
<td>100 ± 50</td>
<td>253 ± 105</td>
<td>&lt;0.05</td>
<td>3.06</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td>$^{[7]}$FCJPI</td>
<td>(Crawley et al. 1996)</td>
<td>8</td>
<td>16 (12/4)</td>
<td>Ratio</td>
<td>$S/C$</td>
<td>100 ± 14</td>
<td>111 ± 12</td>
<td>&lt;0.05</td>
<td>0.79</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>$^{[7]}$FCJPI</td>
<td>(Blin et al. 1999)</td>
<td>8</td>
<td>8 (8/0)</td>
<td>Ratio</td>
<td>$S/C$</td>
<td>100 ± 14</td>
<td>104 ± 14</td>
<td>ns</td>
<td>0.28</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>$^{[7]}$FCJPI</td>
<td>(Martino et al. 1990a)</td>
<td>12</td>
<td>12 (0/12)</td>
<td>Ratio</td>
<td>$S/C$</td>
<td>100 ± 11</td>
<td>101 ± 15</td>
<td>ns</td>
<td>0.14</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJNMSP</td>
<td>(Hietala et al. 1993)</td>
<td>17</td>
<td>10 (8/2)</td>
<td>Kinetic</td>
<td>$S_m$</td>
<td>100 ± 80</td>
<td>173 ± 143</td>
<td>0.08</td>
<td>0.91</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJNMSP</td>
<td>(Nordstrom et al. 1995)</td>
<td>7</td>
<td>7 (7/0)</td>
<td>Kinetic</td>
<td>$S_m$</td>
<td>100 ± 25</td>
<td>133 ± 63</td>
<td>ns</td>
<td>1.33</td>
<td>2.30</td>
</tr>
<tr>
<td>Benzamides</td>
<td>$^{[1]}$CJRaclopride</td>
<td>(Farde et al. 1990)</td>
<td>20</td>
<td>19 (10/9)</td>
<td>Equilib.</td>
<td>$S_m$</td>
<td>100 ± 29</td>
<td>107 ± 18</td>
<td>ns</td>
<td>0.23</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJRaclopride</td>
<td>(Hietala et al. 1994a)</td>
<td>10</td>
<td>13 (0/13)</td>
<td>Equilib.</td>
<td>$S_m$</td>
<td>100 ± 22</td>
<td>112 ± 43</td>
<td>ns</td>
<td>0.55</td>
<td>1.99</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJIBZM</td>
<td>(Pilowsky et al. 1994b)</td>
<td>20</td>
<td>20 (17/3)</td>
<td>Ratio</td>
<td>$S/FC$</td>
<td>100 ± 8</td>
<td>99 ± 7</td>
<td>ns</td>
<td>-0.07</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJIBZM</td>
<td>(Laruelle et al. 1996b)</td>
<td>15</td>
<td>15 (1/14)</td>
<td>Equilib.</td>
<td>$BP$</td>
<td>100 ± 26</td>
<td>115 ± 33</td>
<td>ns</td>
<td>0.56</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJIBZM</td>
<td>(Paxible et al. 1997)</td>
<td>16</td>
<td>21 (12/0)</td>
<td>Equilib.</td>
<td>$BP$</td>
<td>100 ± 20</td>
<td>97 ± 38</td>
<td>ns</td>
<td>-0.12</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJRaclopride</td>
<td>(Brooks et al. 1997b)</td>
<td>12</td>
<td>11 (6/5)</td>
<td>Equilib.</td>
<td>$BP$</td>
<td>100 ± 18</td>
<td>100 ± 30</td>
<td>ns</td>
<td>0.02</td>
<td>1.69</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJIBZM</td>
<td>(Abi-Dargham et al. 1999a)</td>
<td>15</td>
<td>15 (2/13)</td>
<td>Equilib.</td>
<td>$BP$</td>
<td>100 ± 20</td>
<td>102 ± 49</td>
<td>ns</td>
<td>0.09</td>
<td>2.30</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJIBZM</td>
<td>(Abi-Dargham et al. 2000b)</td>
<td>18</td>
<td>18 (8/10)</td>
<td>Equilib.</td>
<td>$BP$</td>
<td>100 ± 13</td>
<td>104 ± 14</td>
<td>ns</td>
<td>0.33</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>$^{[1]}$CJIBZM</td>
<td>(Yang et al. 2004)</td>
<td>12</td>
<td>11 (1/1)</td>
<td>Ratio</td>
<td>$S/C$</td>
<td>100 ± 11</td>
<td>101 ± 11</td>
<td>ns</td>
<td>0.09</td>
<td>1</td>
</tr>
<tr>
<td>Ergot Alk.</td>
<td>$^{[7]}$FCLevostemide</td>
<td>(Martino et al. 1991b)</td>
<td>14</td>
<td>19 (10/9)</td>
<td>Ratio</td>
<td>$S/C$</td>
<td>100 ± 10</td>
<td>104 ± 12</td>
<td>ns</td>
<td>0.45</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>$^{[7]}$FCLevostemide</td>
<td>(Martino et al. 1994)</td>
<td>10</td>
<td>10 (2/0)</td>
<td>Ratio</td>
<td>$S/C$</td>
<td>100 ± 10</td>
<td>100 ± 13</td>
<td>ns</td>
<td>0.00</td>
<td>1.29</td>
</tr>
</tbody>
</table>

a DN = drug naive; DF = drug free. b Mean normalized to mean of control subjects. c Effect size calculated as (Mean patients - mean controls) / SD controls.
Three studies involved first-episode schizophrenia and all three showed an increase of DOPA in the striatum (Hietala et al. 1999b; Hietala et al. 1995; Lindstrom et al. 1999). Interestingly, a recent study observed a relationship between poor prefrontal activation during the Wisconsin Card Sorting task and elevated \([^{18}\text{F}]\text{DOPA}\) accumulation in the striatum, suggesting a link between alteration of the dorsolateral prefrontal cortex function and increased striatal DA activity in schizophrenia (Meyer-Lindenberg et al. 2002). In rats, as in anesthetized pigs, increases in AADC activity \textit{in vitro} and \textit{in vivo} have been reported following acute treatment with DA antagonists.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study</th>
<th>n Controls</th>
<th>n Patients (DN/DF/T)a</th>
<th>Radiotracer (i/challenge)</th>
<th>Method</th>
<th>Outcome</th>
<th>Controls (n, mean ± SD)b</th>
<th>Patients (n, mean ± SD)b</th>
<th>p</th>
<th>Effect sizec</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOPA accumulation</td>
<td>(Keth et al. 1994b)</td>
<td>13</td>
<td>5 (4/0/1)</td>
<td>([^{18}\text{F}]\text{DOPA})</td>
<td>Kinetic</td>
<td>k3</td>
<td>100 ± 23</td>
<td>120 ± 15</td>
<td>&lt;0.05</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>(Hietala et al. 1995)</td>
<td>7</td>
<td>7 (7/0/0)</td>
<td>([^{18}\text{F}]\text{DOPA})</td>
<td>Graphical</td>
<td>k4</td>
<td>100 ± 11</td>
<td>117 ± 20</td>
<td>&lt;0.05</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>(Du-Castellana et al. 1997b)</td>
<td>7</td>
<td>6 (2/4/0)</td>
<td>([^{18}\text{F}]\text{DOPA})</td>
<td>Graphical</td>
<td>k4</td>
<td>100 ± 11</td>
<td>103 ± 40</td>
<td>ns</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>(Lindstrom et al. 1999)</td>
<td>10</td>
<td>12 (10/2)</td>
<td>([^{11}\text{C}]\text{DOPA})</td>
<td>Graphical</td>
<td>k4</td>
<td>100 ± 17</td>
<td>113 ± 12</td>
<td>&lt;0.05</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>(Hietala et al. 1999a)</td>
<td>13</td>
<td>10 (10/0/0)</td>
<td>([^{18}\text{F}]\text{DOPA})</td>
<td>Graphical</td>
<td>k4</td>
<td>100 ± 14</td>
<td>115 ± 28</td>
<td>&lt;0.05</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>(Elbasi et al. 2000)</td>
<td>13</td>
<td>19 (0/9/10)</td>
<td>([^{18}\text{F}]\text{DOPA})</td>
<td>Ratio</td>
<td>k4</td>
<td>100±11.7</td>
<td>92.4 ± 9.7</td>
<td>&lt;0.05</td>
<td>-0.65</td>
</tr>
<tr>
<td></td>
<td>(Meyer-Lindenberg et al. 2002)</td>
<td>6</td>
<td>6 (0/6/0)</td>
<td>([^{18}\text{F}]\text{DOPA})</td>
<td>Graphical</td>
<td>k4</td>
<td>100±9.7</td>
<td>119±9.7</td>
<td>&lt;0.02</td>
<td>1.96</td>
</tr>
<tr>
<td>Amphetamine-induced DA</td>
<td>(McGovern et al. 2004)</td>
<td>12</td>
<td>16 (0/0/16)</td>
<td>([^{18}\text{F}]\text{DOPA})</td>
<td>Graphical</td>
<td>k4</td>
<td>100±9.3</td>
<td>115±8.2</td>
<td>0.001</td>
<td>1.6</td>
</tr>
<tr>
<td>release</td>
<td>(Laruelle et al. 1996b)</td>
<td>15</td>
<td>15 (2/13/0)</td>
<td>([^{123}\text{I}]\text{IEZM}/\text{amphetamine})</td>
<td>Equilibrium</td>
<td>Delta BP</td>
<td>100 ± 113</td>
<td>271 ± 221</td>
<td>&lt;0.05</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td>(Breiter et al. 1997b)</td>
<td>18</td>
<td>18 (8/10.0)</td>
<td>([^{11}\text{C}]\text{raclopride}/\text{amphetamine})</td>
<td>Equilibrium</td>
<td>Delta BP</td>
<td>100 ± 43</td>
<td>175 ± 82</td>
<td>&lt;0.05</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td>(Abi-Dargham et al. 1998a)</td>
<td>16</td>
<td>21 (1/20.0)</td>
<td>([^{123}\text{I}]\text{IEZM}/\text{amphetamine})</td>
<td>Equilibrium</td>
<td>Delta BP</td>
<td>100 ± 88</td>
<td>194 ± 145</td>
<td>&lt;0.05</td>
<td>1.07</td>
</tr>
<tr>
<td>Baseline DA concentration</td>
<td>(Abi-Dargham et al. 2000b)</td>
<td>18</td>
<td>18 (8/10/0)</td>
<td>([^{123}\text{I}]\text{IEZM}/\text{AMPT})</td>
<td>Equilibrium</td>
<td>Delta BP</td>
<td>100 ± 78</td>
<td>211 ± 122</td>
<td>&lt;0.05</td>
<td>1.43</td>
</tr>
<tr>
<td>BAT density</td>
<td>(Laakso et al. 2000)</td>
<td>9</td>
<td>9 (9/0/0)</td>
<td>([^{18}\text{F}]\text{CFT})</td>
<td>Ratio</td>
<td>S/C</td>
<td>100 ± 12</td>
<td>101 ± 13</td>
<td>&lt;0.05</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>(Laruelle et al. 2000a)</td>
<td>22</td>
<td>22 (2/20.0)</td>
<td>([^{123}\text{I}]\text{CIT})</td>
<td>Equilibrium</td>
<td>EP</td>
<td>100 ± 17</td>
<td>93 ± 20</td>
<td>&lt;0.05</td>
<td>-0.43</td>
</tr>
<tr>
<td></td>
<td>(Hei et al. 2003)</td>
<td>12</td>
<td>12 (12/0.0)</td>
<td>([^{99}\text{mTc}]\text{TRODAT})</td>
<td>Ratio</td>
<td>100 ± 18</td>
<td>104 ± 21</td>
<td>ns</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) DN = drug naive; DF = drug free; T = treated with antipsychotics \(^b\) Mean normalized to mean of control subjects. 

\(^c\) Effect size calculated as (Mean patients - mean controls) / SD controls.
(Cho et al. 1997; Danielsen et al. 2001; Zhu et al. 1993). Conversely acute treatment with the DA agonist apomorphine decreases $^{11}$C-DOPA influx in monkeys (Torstenson et al. 1998). Evidence for such effects in humans however is extremely limited. In humans decreased $^{18}$F-DOPA uptake has been reported in patients with schizophrenia following subchronic treatment with haloperidol (Grunder et al. 2003), suggesting that chronic neuroleptic administration will tend to decrease AADC activity and hence DA synthesis. Interestingly, acute administration of antipsychotics increases DA neurons firing whereas chronic administration decreases the number of spontaneously active DA neurons in the rat substantia nigra (Grace 1991), suggesting that the different effects of antipsychotics on AADC activity in the living brain could reflect such phenomena.

**Striatal amphetamine-induced DA release.** The decrease in $^{11}$C-raclopride and $^{123}$IIBZM *in vivo* binding following acute amphetamine challenge has been well validated as a measure of the change in D$_2$ receptor stimulation by DA due to amphetamine-induced DA release (for review, see Laruelle 2000). Three out of three studies (Abi-Dargham et al. 1998b; Breier et al. 1997a; Laruelle et al. 1996a) showed that the amphetamine-induced decrease in $^{11}$C-raclopride or $^{123}$IIBZM binding is elevated in untreated patients with schizophrenia compared to well matched controls (Table 3). A significant relationship was observed between the magnitude of this effect and transient induction or worsening of positive symptoms.

This exaggerated response of the DA system to amphetamine was observed in both first episode/drug naive patients and previously treated patients (Laruelle et al. 1999), but was larger in patients experiencing an episode of illness exacerbation than in patients in remission at the time of the scan (Laruelle et al. 1999). This exaggerated DA reactivity did not appear to be a nonspecific effect of stress, as higher self reports of anxiety before the experiments were not associated with larger effect of amphetamine on $^{123}$IIBZM binding. Furthermore, nonpsychotic subjects with unipolar depression, who reported levels of anxiety similar to the schizophrenic patients at the time of the scan, showed normal amphetamine-induced displacement of $^{123}$IIBZM (Parsey et al. 2001).

These findings have generally been interpreted as reflecting an increase in synaptic DA following amphetamine in the schizophrenic group. Another interpretation of these observations would be that schizophrenia is associated with increased affinity of D$_2$ receptors for DA.

**Baseline occupancy of striatal D$_2$ receptors by DA.** In rodents acute depletion of synaptic DA is associated with an acute increase in the *in vivo* binding of $^{11}$C-raclopride or $^{123}$IIBZM to D$_2$ receptors (for review, see Laruelle 2000). The increased binding is observed *in vivo* but not *in vitro*, indicating that it is not due to receptor upregulation (Laruelle et al. 1997), but to removal of endogenous DA and unmasking of D$_2$ receptors previously occupied by DA. A similar acute DA depletion technique paired with D$_2$ receptor imaging in humans using AMPT,
has been developed to assess the degree of occupancy of D₂ receptors by DA (Laruelle et al. 1997). In schizophrenia, there was a higher occupancy of D₂ receptors by DA in patients experiencing an episode of illness exacerbation, compared to healthy controls (Table 3) (Abi-Dargham et al. 2000b). Again assuming normal affinity of D₂ receptors for DA, the data are consistent with higher synaptic DA levels in patients with schizophrenia. Higher synaptic DA levels in patients with schizophrenia were predictive of a good therapeutic response of these symptoms following six weeks of treatment with atypical antipsychotic medications (Abi-Dargham et al. 2000b).

**DAT transporters.** Three imaging studies (Table 3) have confirmed the *in vitro* observation of normal striatal DAT density in schizophrenia ((Laakso et al. 2000; Laruelle et al. 2000b). In addition, no association between amphetamine-induced DA release and DAT density was found (Laruelle et al. 2000b), suggesting that the increased presynaptic output revealed by the studies reviewed above is not due to higher terminal density.

**Vesicular monoamine transporter:** Using the radiotracer [¹¹C]DTBZ, (Taylor et al., 2000) were not able to show any difference in vesicular monoamine transporter BP in patients with schizophrenia compared to healthy subjects.

### 3.3.2. Prefrontal DA function and schizophrenia

Indirect evidence supports the hypothesis that a deficit in prefrontal DA function might contribute to prefrontal impairment in schizophrenia. Abundant preclinical evidences have documented the importance of prefrontal DA function for cognition (for review see Goldman-Rakic 1994; Goldman-Rakic et al. 2000). This important role has been recently confirmed in humans by the repeated observation that the carriers of the high activity allele of cathecol-O-methyltransferase (COMT), an enzyme involved in DA metabolism, display lower performance in various cognitive tasks compared to carriers of the allele that induces lower concentration of DA in PFC (for review, see Goldberg and Weinberger 2004). Clinical studies have suggested a relationship between low cerebrospinal fluid homovanillic acid, a measure reflecting low DA activity in the prefrontal cortex and poor performance at tasks involving working memory in schizophrenia (Kahn et al. 1994; Weinberger et al. 1988). Administration of DA agonists might have beneficial effects on the pattern of prefrontal activation measured with PET during these tasks (Daniel et al. 1991; Dolan et al. 1995). While these observations are consistent with the hypothesis of a hypodopaminergic state in the PFC of patients with schizophrenia, they do not constitute direct evidence.

The only parameter of DA transmission that is currently quantifiable with noninvasive *in vivo* studies is D₁ receptor availability. Three PET studies of prefrontal D₁ receptor availability in patients with schizophrenia have recently been published. Two studies were performed with [¹¹C]SCH 23390. The first reported decreased[¹¹C]SCH 23390 BP in the PFC (Okubo et al. 1997), and the other reported no change (Karlsson et al. 2002). One study was
performed with [$^{11}$C]NNC 112 (Abi-Dargham et al. 2002), and reported increased [$^{11}$C]NNC 112 BP in the dorsolateral prefrontal cortex (DLPFC), and no change in other regions of the prefrontal cortex such as the medial prefrontal cortex (MPFC) or the orbitofrontal cortex. In patients with schizophrenia, increased [$^{11}$C]NNC 112 binding in the DLPFC was predictive of poor performance on a working memory task (Abi-Dargham et al. 2002). Many potential factors, including patient heterogeneity and differences in the boundaries of the sampled regions, might account for these discrepancies. However, severity of deficits at tasks involving working memory were reported to be associated with both decreased PFC [$^{11}$C]SCH 23390 BP in one study (Okubo et al. 1997) and increased PFC [$^{11}$C]NNC 112 BP in another one (Abi-Dargham et al. 2000a), suggesting that both alterations might reflect a common underlying deficit.

Because of the prevalent view that schizophrenia is associated with a deficit in prefrontal DA activity, the impact of acute and subchronic DA depletion on the in vivo binding of [$^{11}$C]SCH 23390 and [$^{11}$C]NNC 112 is highly relevant to the interpretation of these data (Guo et al. 2001). Acute DA depletion does not affect the in vivo binding of [$^{11}$C]NNC 112, but results in decreased in vivo binding of [$^{3}$H]SCH 23390, a paradoxical response that might be related to a DA depletion-induced translocation of D1 receptors from the cytoplasmic to cell surface compartment (Dumartin et al. 2000; Laruelle 2000; Scott et al. 2002). In contrast, chronic DA depletion is associated with increased in vivo [$^{11}$C]NNC 112 binding, presumably reflecting a compensatory upregulation of D1 receptors. Interestingly, chronic DA depletion did not result in enhanced in vivo binding of [$^{3}$H]SCH 23390, an observation maybe related to opposite effects of receptors upregulation and externalization.

Thus, the increase in DLPFC [$^{11}$C]NNC 112 BP observed in schizophrenia might be related to a compensatory, although inefficient upregulation of D1 receptors following sustained DA depletion, and it is conceivable that such an upregulation might not be detectable with [$^{11}$C]SCH 23390. Studies with both radiotracers on the same patients are required to clarify this issue.

6. Conclusions
Over the last ten years, major advances have taken place in documenting alterations of DA systems in schizophrenia. The development of new imaging methods aiming at measuring presynaptic activity in striatal DA afferents provides convergent data supporting the hypothesis that schizophrenia is associated with hyperactivity of subcortical transmission at D2 receptors. These results are consistent with the known mode of action of current antipsychotic treatment (D2 receptor blockade), with the psychotogenic effects of sustained stimulation of DA function by psychostimulants, and with the “classical” DA hypothesis of schizophrenia derived from these observations. In addition, these results suggest that the DA hyperactivity of subcortical systems is episodic in nature, and account for only some aspects of positive symptomatology.

On the other hand, imaging methods might suggest that hypodopaminergia in the DLPFC contributes to the pathophysiology of cognitive symptoms endured by patients with schizophrenia, but the development of non-invasive techniques to measure DA presynaptic activity in the cortex will be needed to directly test this hypothesis.

REFERENCES


Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles L, Weiss R, Cooper T, Mann JJ, Van Heertum R, Gorman J, Laruelle M. (2000b) Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc. Natl. Acad. Sci. USA 97:8104-
Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M. (2000c) Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci U S A 97:8104-8109


Bell DS. (1973) The experimental reproduction of amphetamine psychosis. Arch Gen Psychiatry 29:35-40


Czudek C, Reynolds GP. (1989) [3H] GBR 12935 binding to the dopamine uptake site in post-mortem brain tissue in schizophrenia. J Neural Transm 77:227-230


Deutch A, Clark WA, Roth RH. (1990) Prefrontal cortical dopamine depletion enhances the responsiveness of the mesolimbic dopamine neurons to stress. Brain Res 521:311-315


implications. Psychopharmacology (Berl) 175:473-480

Gerfen CR. (1992) The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. Annu Rev Neurosci 15:285-320


Knable MB, Hyde TM, Herman MM, Carter JM, Bigelow L, Kleinman JE. (1994) Quantitative autoradiography of dopamine-D1...
receptors, D2 receptors, and dopamine uptake sites in postmortem striatal specimens from schizophrenic patients. Biol Psychiatry 36:827-835


Knable MB, Weinberger DR. (1997) Dopamine, the prefrontal cortex and schizophrenia. J. Psychopharmacol. 11:123-131


Lieberman JA, Kane JM, Alvir J. (1987a) Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology 91:415-433


Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. (1998) Dopamine receptors: from structure to function. Physiological Reviews 78:189


Reynolds GP. (1983) Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. Nature 305:527-529


Reynolds GP, Mason SL. (1994) Are striatal dopamine D4 receptors increased in schizophrenia? J Neurochem 63:1576-1577


Seeman P. (1988) Brain dopamine receptors in schizophrenia: PET problems. Arch Gen Psychiatry 45:598-600


D4 receptor with high affinity for the antipsychotic clozapine. Nature 350:610-614


preferentially increases dopamine release in the rhesus monkey prefrontal cortex compared with the caudate nucleus. Neuropsychopharmacology 20:403-412
