

## Neurobiology of Dopamine in Schizophrenia

Olivier Guillin\* & Marc Laruelle\*† 

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

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### 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.

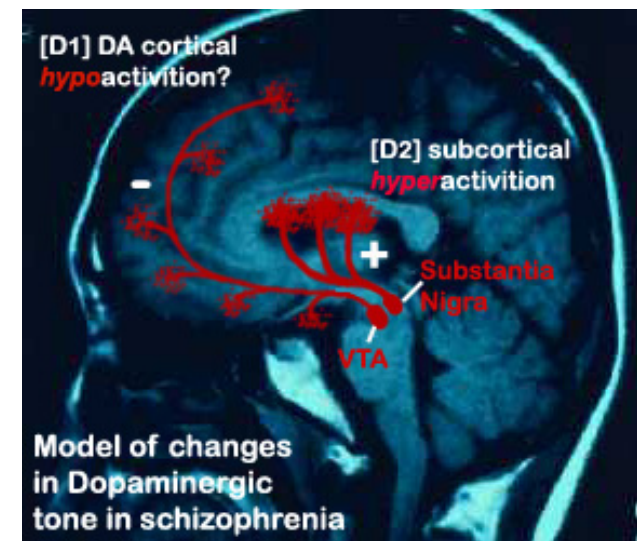
While the etiology and pathophysiology of schizophrenia remain unclear, a large body of evidences suggest that alterations in several neurotransmitters systems (e.g. dopamine, glutamate, GABAergic, serotonin) are involved in the pathophysiological processes leading to the expression of these symptoms. 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 D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>1</sub> 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 D<sub>1</sub> 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 D<sub>2</sub> receptors and positive symptoms) while mesocortical DA projections to the PFC might be hypoactive (resulting in hypostimulation of D<sub>1</sub> 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

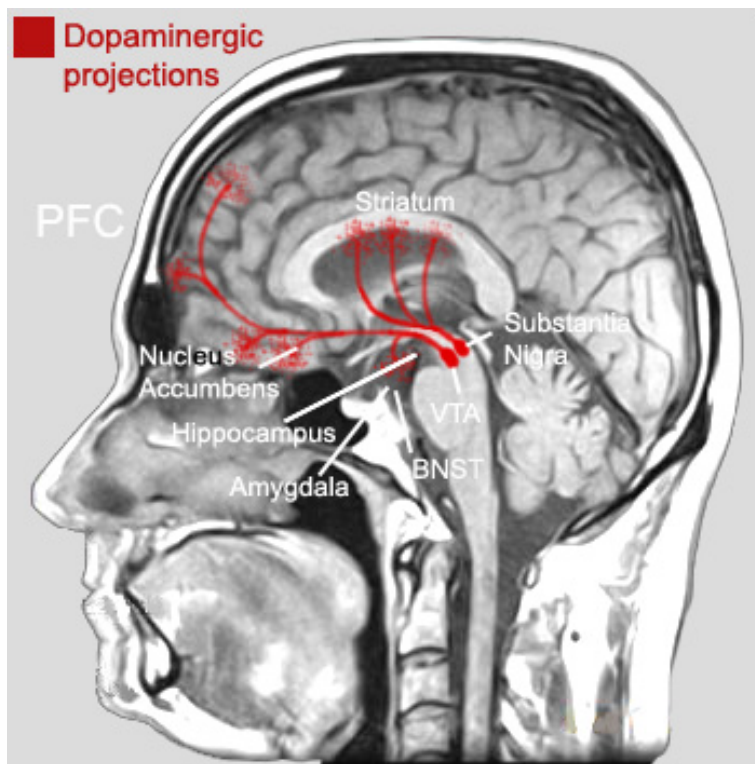
results (for review see Davis *et al.* 1991b). Over the last few years, the development of new brain imaging methods based on the principle of endogenous competition enabled direct measurement of DA transmission at D<sub>2</sub> receptor in the striatum (for review see Laruelle 2000). Combined with studies that documented increased striatal [<sup>18</sup>F]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. D<sub>1</sub> 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 D<sub>1</sub> 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 in nigro-striatal, mesolimbic and mesocortical systems (Lindvall and Björklund 1983). The nigro-striatal 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).

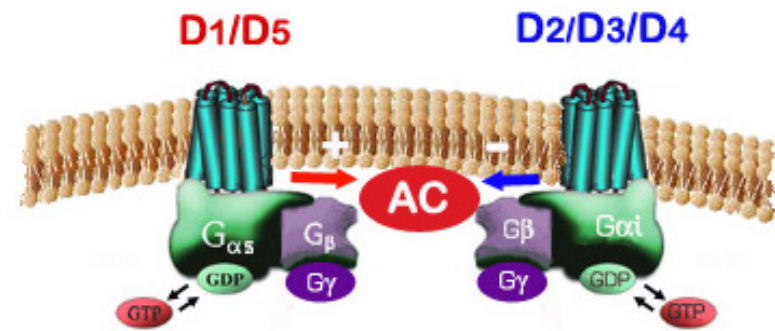
Cortico-striatal-thalamo-cortical loops are important targets of DA modulation. The general scheme of these loops involves projections from the cortex to striatum to the internal segment of the globus pallidum (GPi) or the SN pars reticulata (SNr) to thalamus and back to the cortex. These loops have 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; Deutch *et al.* 1991; Robertson *et al.* 1994). It is important to note that these different cortico-striatal-thalamo-cortical loops are not completely segregated parallel loops. While cortico-striatal-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 D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub> 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 D<sub>1</sub>-like family (including D<sub>1</sub> and D<sub>5</sub> receptors), and a D<sub>2</sub>-like family (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> 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 D<sub>1</sub> and D<sub>2</sub> receptors on the basis of their signaling system, i.e. their coupling to G<sub>s</sub> and G<sub>i</sub> proteins respectively and opposite effects on adenylyl cyclase (Kebabian and Calne 1979; Spano *et al.* 1978). D<sub>2</sub>-like family receptors are both postsynaptic receptors and presynaptic autoreceptors (Diaz *et al.* 2000; Missale *et al.* 1998; Palermo-Neto 1997).



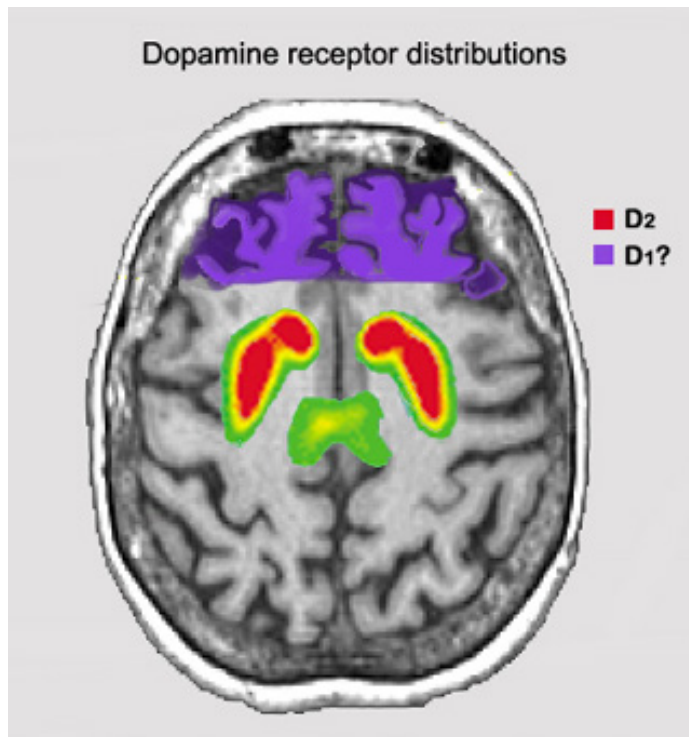
**Antagonistic coupling of D<sub>1</sub>-like and D<sub>2</sub>-like receptors to Adenylyl Cyclase (AC)**

**Table 1. The D<sub>1</sub>-like and D<sub>2</sub>-like family of dopamine receptors**

Receptor	D <sub>1</sub> -like		D <sub>2</sub> -like		
	D <sub>1</sub>	D <sub>5</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>
Sequence homology	60%		50-70%		
Gene organization	Intronless genes		Genes with intron		
Transduction	Stimulate adenylyl cyclase		Inhibit adenylyl cyclase		
Pharmacology	Moderate to low affinity for antipsychotics		High to moderate affinity for antipsychotics		

DA receptors differ in their regional localization in the human brain (for reviews see Joyce and MeadorWoodruff 1997; Meador-Woodruff *et al.* 1996). D<sub>1</sub> receptors show a widespread neocortical distribution, including the prefrontal cortex, and are also present at high concentration within the striatum. D<sub>5</sub> receptors are concentrated in the hippocampus and entorhinal cortex. D<sub>2</sub> receptors are concentrated in the striatum, with low concentration in medial temporal structures (hippocampus, entorhinal cortex, amygdala) and thalamus. The concentration of D<sub>2</sub> receptors in

the prefrontal cortex is extremely low. D<sub>3</sub> receptors are present in the striatum, where their concentration is particularly high in the ventral striatum. D<sub>4</sub> receptors are present in the prefrontal cortex and hippocampus, but have not been detected in the striatum (Lahti *et al.* 1998).



In the striatum D<sub>2</sub> receptors are principally expressed within enkephalin-rich GABAergic neurons that participate in the indirect pathways, while D<sub>1</sub> 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, D<sub>3</sub> 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 D<sub>3</sub> receptor distribution in the striatum is more widespread in humans (Gurevich *et al.* 1997). The magnitude of the segregation versus co-expression of D<sub>1</sub> and D<sub>2</sub> receptors in striatal neurons is still a matter of debate (Surmeier *et al.* 1992; Surmeier *et al.* 1996). In the VST D<sub>3</sub> receptors colocalize preferentially on neurons expressing D<sub>1</sub> 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 D<sub>1</sub> and

D<sub>3</sub> 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 D<sub>3</sub> receptor signaling pathway being augmented by the cAMP pathway of the D<sub>1</sub> receptor. The segregation of D<sub>2</sub> and D<sub>1</sub> 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 D<sub>1</sub> and D<sub>2</sub> receptors stimulate locomotion), while their effects on intracellular signaling (e.g. adenylate cyclase activity) are opposite in many regards. For example, stimulation of D<sub>1</sub> and D<sub>2</sub> receptors increases or decreases DARP32 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 D<sub>2</sub> receptors by DA might provide an inhibitory influence to the indirect pathway and activation of D<sub>1</sub> 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, D<sub>2</sub> receptor stimulation inhibits NMDA-mediated GLU transmission and long term potentiation (LTP), and D<sub>1</sub> receptor stimulation facilitates GLU transmission and LTP (Centonze *et al.* 2001; Levine *et al.* 1996). The effect of D<sub>2</sub> receptor stimulation on GLU transmission involves both pre- and post-synaptic effects: D<sub>2</sub> 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, D<sub>1</sub> 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, D<sub>1/5</sub> 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 D<sub>4</sub> 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 D<sub>1</sub>-like or D<sub>2</sub>-like mechanisms, whereas D<sub>1/5</sub> and D<sub>2/4</sub> receptor stimulation enhance or inhibit 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. Pharmacological evidence.**

##### **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 D<sub>2</sub> receptor antagonism is the only pharmacological property shared by all antipsychotic drugs. The clinical dose of these drugs is related to their affinity for D<sub>2</sub> receptors. D<sub>2</sub> receptor antagonism appears both necessary and sufficient for antipsychotic action (as demonstrated by the selective D<sub>2</sub> receptor antagonist amisulpride). The fact that patients with schizophrenia improve following administration of D<sub>2</sub> receptor antagonists is one of the few irrefutable pieces of evidence in schizophrenia (Weinberger 1987).

D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>2</sub> receptor antagonism in the current treatment of schizophrenia. Most SGAs also potently interact with other receptors, such as the serotonin 5HT<sub>2A</sub> receptors, but the possibility to achieve an "atypical" profile with a pure D<sub>2</sub> 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 D<sub>2</sub> 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% D<sub>2</sub> 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 D<sub>2</sub> 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 5HT<sub>2A</sub> and D<sub>2</sub> receptor antagonism is to increase prefrontal DA, an effect not observed with selective D<sub>2</sub> or 5HT<sub>2A</sub> 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 5HT<sub>1A</sub> receptors as it is blocked by 5HT<sub>1A</sub> antagonists and is also observed following the combination of 5HT<sub>1A</sub> receptor agonism and D<sub>2</sub> receptor antagonism (Ichikawa *et al.* 2001; Rollema *et al.* 2000). Aripiprazole, clozapine, quetiapine and ziprasidone are also 5HT<sub>1A</sub> 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 D<sub>2</sub> 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 ante-mortem 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).

**D<sub>2</sub> receptors.** Increased density of striatal D<sub>2</sub> 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 D<sub>2</sub> 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 [<sup>3</sup>H]spiperone, it is interesting to note that the striatal binding of [<sup>3</sup>H]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 [<sup>3</sup>H]raclopride binding is of lower magnitude than the one of [<sup>3</sup>H]spiperone binding. This discrepancy might simply reflect the observation that, for reasons that are not currently understood, antipsychotic drugs upregulate more [<sup>3</sup>H]spiperone than [<sup>3</sup>H]raclopride binding to D<sub>2</sub> receptors (Schoots *et al.* 1995; Tarazi *et al.* 1997).

**D<sub>3</sub> receptors.** A significant increase in D<sub>3</sub> 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, D<sub>3</sub> receptors levels did not differ significantly from those of controls (Gurevich *et al.* 1997). These data were interpreted as indicating that antipsychotics downregulate the D<sub>3</sub> receptor in schizophrenic patients who otherwise have a higher density of this receptor in the VST. The D<sub>3</sub> 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 D<sub>3</sub> 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. D<sub>3</sub> 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.

**D<sub>4</sub> receptors.** Based on ligand subtraction techniques, several studies have reported increased D<sub>4</sub>-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 [<sup>3</sup>H]NGD 94-1, a selective D<sub>4</sub> ligand (Lahti *et al.* 1998). Moreover, the hypothesis that clozapine might act by blocking the D<sub>4</sub> receptor was not supported by a clinical trial with the D<sub>4</sub> selective agent L745,870 (Kramer *et al.* 1997).

**D<sub>1</sub> receptors.** Striatal D<sub>1</sub> 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 D<sub>2</sub>-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 D<sub>1</sub> receptor density is unaffected in schizophrenia. Several interesting observations such as increase in D<sub>3</sub> 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 D<sub>2</sub> and D<sub>1</sub> receptors.** Striatal D<sub>2</sub> 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 D<sub>2</sub> receptors in untreated patients with schizophrenia (Table 2). No clinical correlates of increased D<sub>2</sub> receptor binding parameters could be identified. Studies performed with butyrophenones (n = 7) show an effect size of  $0.96 \pm 1.05$ , significantly larger than the effect size observed with other ligands (benzamides and lisuride, n = 11,  $0.19 \pm 0.25$ ,  $p = 0.02$ ). 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 D<sub>2</sub> receptor levels are increased in healthy monozygotic twins compared to dizygotic twins of patients with schizophrenia has led to the conclusion that the caudate DA D<sub>2</sub> receptor up-regulation is related to a genetic risk factor for schizophrenia (Hirvonen *et al.* 2005). Imaging studies of D<sub>1</sub> receptors have consistently failed to detect abnormalities of D<sub>1</sub> receptor availability in the striatum of patients with schizophrenia (Abi-Dargham *et al.* 2002; Karlsson *et al.* 2002; Okubo *et al.* 1997).

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

Class radiotracer	Radiotracer	Study	n Controls	n Patients (DN/DF) <sup>a</sup>	Method	Outcome	Controls (n, mean ± SD) <sup>b</sup>	Patients (n, mean ± SD) <sup>b</sup>	P	Effect size <sup>c</sup>	Ratio SD
Butyrophenones	[ <sup>11</sup> C]NMSP	(Wong et al. 1986b)	11	15 (10/5)	Kinetic	B <sub>max</sub>	100 ± 50	253 ± 105	<0.05	3.06	2.10
	[ <sup>76</sup> Br]SPI	(Crawley et al. 1986)	8	16 (12/4)	Ratio	S/C	100 ± 14	111 ± 12	<0.05	0.79	0.86
	[ <sup>76</sup> Br]SPI	(Blin et al. 1989)	8	8 (0/8)	Ratio	S/C	100 ± 14	104 ± 14	ns	0.28	1.00
	[ <sup>76</sup> Br]SPI	(Martinot et al. 1990a)	12	12 (0/12)	Ratio	S/C	100 ± 11	101 ± 15	ns	0.14	1.41
	[ <sup>11</sup> C]NMSP	(Tune et al. 1993)	17	10 (8/2)	Kinetic	B <sub>max</sub>	100 ± 80	173 ± 143	0.08	0.91	1.79
	[ <sup>11</sup> C]NMSP	(Nordstrom et al. 1995)	7	7 (7/0)	Kinetic	B <sub>max</sub>	100 ± 25	133 ± 63	ns	1.33	2.30
Benzamides	[ <sup>11</sup> C]Raclopride	(Farde et al. 1990)	20	18 (18/0)	Equilib.	B <sub>max</sub>	100 ± 29	107 ± 18	ns	0.23	0.63
	[ <sup>11</sup> C]Raclopride	(Hietala et al. 1994a)	10	13 (0/13)	Equilib.	B <sub>max</sub>	100 ± 22	112 ± 43	ns	0.55	1.99
	[ <sup>123</sup> I]IBZM	(Pilowsky et al. 1994b)	20	20 (17/3)	Ratio	S/FC	100 ± 8	99 ± 7	ns	-0.07	0.82
	[ <sup>123</sup> I]IBZM	(Laruelle et al. 1996b)	15	15 (1/14)	Equilib.	BP	100 ± 26	115 ± 33	ns	0.56	1.25
	[ <sup>123</sup> I]IBZM	(Knable et al. 1997)	16	21 (1/20)	Equilib.	BP	100 ± 29	97 ± 38	ns	-0.12	1.31
	[ <sup>11</sup> C]Raclopride	(Breier et al. 1997b)	12	11 (6/5)	Equilib.	BP	100 ± 18	100 ± 30	ns	0.02	1.69
	[ <sup>123</sup> I]IBZM	(Abi-Dargham et al. 1998a)	15	15 (2/13)	Equilib.	BP	100 ± 20	102 ± 49	ns	0.09	2.30
	[ <sup>123</sup> I]IBZM	(Abi-Dargham et al. 2000b)	18	18 (8/10)	Equilib.	BP	100 ± 13	104 ± 14	ns	0.33	1.11
	[ <sup>123</sup> I]IBZM	(Yang et al. 2004)	12	11 (11/0)	Ratio	S/C	100 ± 11	101 ± 11	ns	0.09	1
Ergot Alk.	[ <sup>76</sup> Br]Lisuride	(Martinot et al. 1991b)	14	19 (10/9)	Ratio	S/C	100 ± 10	104 ± 12	ns	0.45	1.21
	[ <sup>76</sup> Br]Lisuride	(Martinot et al. 1994)	10	10 (2/8)	Ratio	S/C	100 ± 10	100 ± 13	ns	0.00	1.29

<sup>a</sup> DN = drug naive; DF = drug free. <sup>b</sup> Mean normalized to mean of control subjects. <sup>c</sup> Effect size calculated as (Mean patients - mean controls) / SD controls

**Striatal DOPA decarboxylase activity.** The eight studies which have reported rates of DOPA decarboxylase activity in patients with schizophrenia using [<sup>18</sup>F]DOPA or [<sup>11</sup>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 [<sup>18</sup>F]DOPA striatal uptake (Elkashef *et al.* 2000).

Table 3. Imaging studies of striatal presynaptic DA parameters in drug naive and drug free patients with schizophrenia

Parameter	Study	n Controls	n Patients (DN/DF/T) <sup>a</sup>	Radiotracer (challenge)	Method	Outcome	Controls (n, mean ± SD) <sup>b</sup>	Patients (n, mean ± SD) <sup>b</sup>	p	Effect size <sup>c</sup>
<b>DOPA accumulation</b>	(Reith et al. 1994b)	13	5 (4/0/1)	[ <sup>18</sup> F]DOPA	Kinetic	k <sub>3</sub>	100 ± 23	120 ± 15	<0.05	0.91
	(Hietala et al. 1995)	7	7 (7/0/0)	[ <sup>18</sup> F]DOPA	Graphical	K <sub>i</sub>	100 ± 11	117 ± 20	<0.05	1.54
	(Dao-Castellana et al. 1997b)	7	6 (2/4/0)	[ <sup>18</sup> F]DOPA	Graphical	K <sub>i</sub>	100 ± 11	103 ± 40	ns	0.30
	(Lindstrom et al. 1999)	10	12 (10/2)	[ <sup>11</sup> C]DOPA	Graphical	K <sub>i</sub>	100 ± 17	113 ± 12	<0.05	0.77
	(Hietala et al. 1999a)	13	10 (10/0)	[ <sup>18</sup> F]DOPA	Graphical	K <sub>i</sub>	100 ± 14	115 ± 28	<0.05	1.09
	(Elkashaf et al. 2000)	13	19 (0/9/10)	[ <sup>18</sup> F]DOPA	Ratio	K <sub>i</sub>	100 ± 11.7	92.4 ± 9.7	<0.05	-0.65
	(Meyer-Lindenberg et al. 2002)	6	6 (0/6/0)	[ <sup>18</sup> F]DOPA	graphical	K <sub>i</sub>	100 ± 9.7	119 ± 9.7	<0.02	1.96
(Mc Gowan et al. 2004)	12	16 (0/0/16)	[ <sup>18</sup> F]DOPA	graphical	K <sub>i</sub>	100 ± 9.3	115 ± 8.2	0.001	1.6	
<b>Amphetamine- induced DA release</b>	(Laruelle et al. 1996b)	15	15 (2/13/0)	[ <sup>123</sup> I]IBZM/ amphetamine	Equilibrium	Delta BP	100 ± 113	271 ± 221	<0.05	1.51
	(Breier et al. 1997b)	18	18 (8/10/0)	[ <sup>11</sup> C]raclopride/ amphetamine	Equilibrium	Delta BP	100 ± 43	175 ± 82	<0.05	1.73
	(Abi-Dargham et al. 1998a)	16	21 (1/20/0)	[ <sup>123</sup> I]IBZM/ amphetamine	Equilibrium	Delta BP	100 ± 88	194 ± 145	<0.05	1.07
<b>Baseline DA concentration</b>	(Abi-Dargham et al. 2000b)	18	18 (8/10/0)	[ <sup>123</sup> I]IBZM/ AMP T	Equilibrium	Delta BP	100 ± 78	211 ± 122	<0.05	1.43
<b>DAT density</b>	(Laakso et al. 2000)	9	9 (9/0/0)	[ <sup>18</sup> F]CFT	Ratio	S/C	100 ± 12	101 ± 13	<0.05	0.11
	(Laruelle et al. 2000a)	22	22 (2/20/0)	[ <sup>123</sup> I]CIT	Equilibrium	BP	100 ± 17	93 ± 20	<0.05	-0.43
	(Hsiao et al. 2003)	12	12 (12/0/0)	[ <sup>99m</sup> Tc]TRODAT	Ratio	S/Occ	100 ± 18	104 ± 21	ns	0.22

<sup>a</sup> DN = drug naive; DF = drug free; T = treated with antipsychotics <sup>b</sup> Mean normalized to mean of control subjects.

<sup>c</sup> 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 [<sup>18</sup>F]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 *in vitro* and *in vivo* have been reported following acute treatment with DA antagonists

(Cho *et al.* 1997; Danielsen *et al.* 2001; Zhu *et al.* 1993). Conversely acute treatment with the DA agonist apomorphine decreases [<sup>11</sup>C]-DOPA influx in monkeys (Torstenson *et al.* 1998). Evidence for such effects in humans however is extremely limited. In humans decreased [<sup>18</sup>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 [<sup>11</sup>C]raclopride and [<sup>123</sup>I]IBZM *in vivo* binding following acute amphetamine challenge has been well validated as a measure of the change in D<sub>2</sub> 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 [<sup>11</sup>C]raclopride or [<sup>123</sup>I]IBZM 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 [<sup>123</sup>I]IBZM 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 [<sup>123</sup>I]IBZM (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<sub>2</sub> receptors for DA.

***Baseline occupancy of striatal D<sub>2</sub> receptors by DA.*** In rodents acute depletion of synaptic DA is associated with an acute increase in the *in vivo* binding of [<sup>11</sup>C]raclopride or [<sup>123</sup>I]IBZM to D<sub>2</sub> 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<sub>2</sub> receptors previously occupied by DA. A similar acute DA depletion technique paired with D<sub>2</sub> receptor imaging in humans using AMPT,

has been developed to assess the degree of occupancy of D<sub>2</sub> receptors by DA (Laruelle *et al.* 1997). In schizophrenia, there was a higher occupancy of D<sub>2</sub> 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 D<sub>2</sub> 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 [<sup>11</sup>C]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 catechol-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 D<sub>1</sub> receptor availability. Three PET studies of prefrontal D<sub>1</sub> receptor availability in patients with schizophrenia have recently been published. Two studies were performed with [<sup>11</sup>C]SCH 23390. The first reported decreased [<sup>11</sup>C]SCH 23390 BP in the PFC (Okubo *et al.* 1997), and the other reported no change (Karlsson *et al.* 2002). One study was

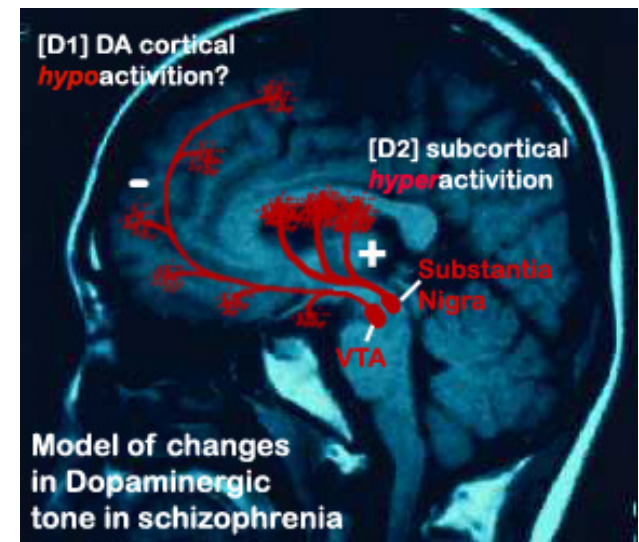
performed with [ $^{11}\text{C}$ ]NNC 112 (Abi-Dargham *et al.* 2002), and reported increased [ $^{11}\text{C}$ ]NNC 112 BP in the dorsolateral prefrontal cortex (DLPFC), and no change in other regions of the prefrontal cortex such as the medial prefrontal cortex (MPFC) or the orbitofrontal cortex. In patients with schizophrenia, increased [ $^{11}\text{C}$ ]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 [ $^{11}\text{C}$ ]SCH 23390 BP in one study (Okubo *et al.* 1997) and increased PFC [ $^{11}\text{C}$ ]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 [ $^{11}\text{C}$ ]SCH 23390 and [ $^{11}\text{C}$ ]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 [ $^{11}\text{C}$ ]NNC 112, but results in decreased *in vivo* binding of [ $^3\text{H}$ ]SCH 23390, a paradoxical response that might be related to a DA depletion-induced translocation of  $\text{D}_1$  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* [ $^{11}\text{C}$ ]NNC 112 binding, presumably reflecting a compensatory upregulation of  $\text{D}_1$  receptors. Interestingly, chronic DA depletion did not result in enhanced *in vivo* binding of [ $^3\text{H}$ ]SCH 23390, an observation maybe related to opposite effects of receptors upregulation and externalization.

Thus, the increase in DLPFC [ $^{11}\text{C}$ ]NNC 112 BP observed in schizophrenia might be related to a compensatory, although inefficient upregulation of  $\text{D}_1$  receptors following sustained DA depletion, and it is conceivable that such an upregulation might not be detectable with [ $^{11}\text{C}$ ]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 D<sub>2</sub> receptors. These results are consistent with the known mode of action of current antipsychotic treatment (D<sub>2</sub> 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, Gil R, Krystal J, Baldwin R, Seibyl J, Bowers M, van Dyck C, Charney D, Innis R, Laruelle M. (1998a) Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am. J. Psychiatry* 155:761-767

Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M. (1998b) Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* 155:761-767

Abi-Dargham A, Laruelle M. (2005) Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. *Eur Psychiatry* 20:15-27

Abi-Dargham A, Martinez D, Mawlawi O, Simpson N, Hwang DR, Slifstein M, Anjilvel S, Pidcock J, Guo NN, Lombardo I, Mann JJ, Van Heertum R, Foged C, Halldin C, Laruelle M. (2000a) Measurement of striatal and extrastriatal dopamine D<sub>1</sub> receptor binding potential with [<sup>11</sup>C]NNC 112 in humans: validation and reproducibility. *J Cereb Blood Flow Metab* 20:225-243

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M. (2002) Prefrontal dopamine D<sub>1</sub> receptors and working memory in schizophrenia. *J Neurosci* 22:3708-3719

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 D<sub>2</sub> 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
- Akil M, Edgar CL, Pierri JN, Casali S, Lewis DA. (2000) Decreased density of tyrosine hydroxylase-immunoreactive axons in the entorhinal cortex of schizophrenic subjects. *Biol Psychiatry* 47:361-370
- Akil M, Pierri JN, Whitehead RE, Edgar CL, Mohila C, Sampson AR, Lewis DA. (1999) Lamina-specific alterations in the dopamine innervation of the prefrontal cortex in schizophrenic subjects. *Am J Psychiatry* 156:1580-1589
- Albin RL, Young AB, Penney JB. (1989) The functional anatomy of basal ganglia disorders. *Trends Neurosci* 12:366-375
- Alexander GE, DeLong MR, Strick PL. (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9:357-381
- Angrist B, van Kammen DP. (1984) CNS stimulants as a tool in the study of schizophrenia. *Trends Neurosci.* 7:388-390
- Angrist BM, Gershon S. (1970) The phenomenology of experimentally induced amphetamine psychosis-Preliminary observation. *Biol. Psychiatry* 2:95-107
- Bell DS. (1973) The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry* 29:35-40
- Blin J, Baron JC, Cambon H, Bonnet AM, Dubois B, Loc'h C, Maziere B, Agid Y. (1989) Striatal dopamine D2 receptors in tardive dyskinesia: PET study. *J Neurol Neurosurg Psychiatry* 52:1248-1252
- Bordet R, Ridray S, Carboni S, Diaz J, Sokoloff P, Schwartz JC. (1997) Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. *Proc Natl Acad Sci U S A* 94:3363-3367
- Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D. (1997a) Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci U S A* 94:2569-2574
- Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, deBartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D. (1997b) Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: Evidence from a novel positron emission tomography method. *Proc. Natl. Acad. Sci. USA* 94:2569-2574
- Bunzow JR, Van Tol HH, Grandy DK, Albert P, Salon J, Christie M, Machida CA, Neve KA, Civelli O. (1988) Cloning and expression of a rat D2 dopamine receptor cDNA. *Nature* 336:783-787

- Burt DR, Creese I, Snyder SH. (1977) Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain. *Science* 196:326-328
- Carlsson A, Lindqvist M. (1963) Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol. Toxicol.* 20:140-144
- Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. (2001) Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* 41:237-260
- Centonze D, Picconi B, Gubellini P, Bernardi G, Calabresi P. (2001) Dopaminergic control of synaptic plasticity in the dorsal striatum. *Eur J Neurosci* 13:1071-1077
- Cepeda C, Hurst RS, Altemus KL, Flores-Hernandez J, Calvert CR, Jokel ES, Grandy DK, Low MJ, Rubinstein M, Ariano MA, Levine MS. (2001) Facilitated glutamatergic transmission in the striatum of D2 dopamine receptor-deficient mice. *J Neurophysiol* 85:659-670
- Cepeda C, Levine MS. (1998) Dopamine and N-methyl-D-aspartate receptor interactions in the neostriatum. *Dev Neurosci* 20:1-18
- Chinaglia G, Alvarez FJ, Probst A, Palacios JM. (1992) Mesostriatal and mesolimbic dopamine uptake binding sites are reduced in Parkinson's disease and progressive supranuclear palsy: a quantitative autoradiographic study using [<sup>3</sup>H]mazindol. *Neuroscience* 49:317-327
- Chiodo LA, Bunney BS. (1983) Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. *J Neurosci* 3:1607-1619
- Cho S, Neff NH, Hadjiconstantinou M. (1997) Regulation of tyrosine hydroxylase and aromatic L-amino acid decarboxylase by dopaminergic drugs. *Eur J Pharmacol* 323:149-157
- Civelli O, Bunzow JR, Grandy DK. (1993) Molecular diversity of the dopamine receptors. *Annu Rev Pharmacol Toxicol* 33:281-307
- Connell PH. (1958) Amphetamine psychosis. London: Chapman and Hill
- Crawley JC, Owens DG, Crow TJ, Poulter M, Johnstone EC, Smith T, Oldland SR, Veall N, Owen F, Zanelli GD. (1986) Dopamine D2 receptors in schizophrenia studied *in vivo*. *Lancet* 2:224-225
- Creese I, Burt DR, Snyder SH. (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 19:481-483
- Cross AJ, Crow TJ, Ferrier IN, Johnstone EC, McCreadie RM, Owen F, Owens DG, Poulter M. (1983) Dopamine receptor changes in schizophrenia in relation to the disease process and movement disorder. *J Neural Transm Suppl* 18:265-272

- Crow TJ. (1980) Molecular pathology of schizophrenia: more than one disease process? Br. Med. J. 280:66-68
- Czudek C, Reynolds GP. (1989) [<sup>3</sup>H] GBR 12935 binding to the dopamine uptake site in post-mortem brain tissue in schizophrenia. J Neural Transm 77:227-230
- Daniel DG, Weinberger DR, Jones DW, Zigun JR, Coppola R, Handel S, Bigelow LB, Goldberg TE, Berman KF, Kleinman JE. (1991) The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. J Neurosci 11:1907-1917
- Danielsen EH, Smith D, Hermansen F, Gjedde A, Cumming P. (2001) Acute neuroleptic stimulates DOPA decarboxylase in porcine brain *in vivo*. Synapse 41:172-175
- Dao-Castellana MH, Paillere-Martinot ML, Hantraye P, Attar-Levy D, Remy P, Crouzel C, Artiges E, Feline A, Syrota A, Martinot JL. (1997a) Presynaptic dopaminergic function in the striatum of schizophrenic patients. Schizophr Res 23:167-174
- Dao-Castellana MH, Paillere-Martinot ML, Hantraye P, Attar-Levy D, Remy P, Crouzel C, Artiges E, Feline A, Syrota A, Martinot JL. (1997b) Presynaptic dopaminergic function in the striatum of schizophrenic patients. Schizophrenia Res. 23:167-174
- Davis KL, Kahn RS, Ko G, Davidson M. (1991a) Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 148:1474-1486
- Davis KL, Kahn RS, Ko G, Davidson M. (1991b) Dopamine in schizophrenia: a review and reconceptualization. Am. J. Psychiatry 148:1474-1486
- Dean B, Pavey G, Opeskin K. (1997) [<sup>3</sup>H]raclopride binding to brain tissue from subjects with schizophrenia: methodological aspects. Neuropharmacology 36:779-786
- Dearry A, Gingrich JA, Falardeau P, Freneau RT, Jr., Bates MD, Caron MG. (1990) Molecular cloning and expression of the gene for a human D1 dopamine receptor. Nature 347:72-76
- Delay J, Deniker P, Harl J. (1952) Therapeutic use in psychiatry of phenothiazine of central elective action (4560 RP). Ann Med Psychol Paris:112-117
- DeLong MR, Crutcher MD, Georgopoulos AP. (1985) Primate globus pallidus and subthalamic nucleus: functional organization. J Neurophysiol 53:530-543
- 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
- Deutch AY, Moghaddam B, Innis RB, Krystal JH, Aghajanian GK, Bunney BS, Charney DS. (1991) Mechanisms of action of atypical antipsychotic drugs. Implications for novel therapeutic strategies for schizophrenia. Schizophr Res 4:121-156

- Diaz J, Levesque D, Lammers CH, Griffon N, Martres MP, Schwartz JC, Sokoloff P. (1995) Phenotypical characterization of neurons expressing the dopamine D3 receptor in the rat brain. *Neuroscience* 65:731-745
- Diaz J, Pilon C, Le Foll B, Gros C, Triller A, Schwartz JC, Sokoloff P. (2000) Dopamine D3 receptors expressed by all mesencephalic dopamine neurons. *J Neurosci* 20:8677-8684
- Dolan RJ, Fletcher P, Frith CD, Friston KJ, Frackowiak RS, Grasby PM. (1995) Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* 378:180-182
- Dumartin B, Jaber M, Gonon F, Caron MG, Giros B, Bloch B. (2000) Dopamine tone regulates D1 receptor trafficking and delivery in striatal neurons in dopamine transporter-deficient mice. *Proc Natl Acad Sci U S A* 97:1879-1884
- Dunah AW, Standaert DG. (2001) Dopamine D1 receptor-dependent trafficking of striatal NMDA glutamate receptors to the postsynaptic membrane. *J Neurosci* 21:5546-5558
- Elkashef AM, Doudet D, Bryant T, Cohen RM, Li SH, Wyatt RJ. (2000) 6-(18)F-DOPA PET study in patients with schizophrenia. *Positron emission tomography. Psychiatry Res* 100:1-11
- Everitt BJ, Morris KA, O'Brien A, Robbins TW. (1991) The basolateral amygdala-ventral striatal system and conditioned place preference: further evidence of limbic-striatal interactions underlying reward-related processes. *Neuroscience* 42:1-18
- Farde L, Nordström AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. (1992) Positron emission tomography analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Arch. Gen. Psychiatry* 49:538-544
- Farde L, Wiesel F, Stone-Elander S, Halldin C, Nordström AL, Hall H, Sedvall G. (1990) D2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [<sup>11</sup>C]raclopride. *Arch Gen Psychiatry* 47:213-219
- Fauchey V, Jaber M, Caron MG, Bloch B, Le Moine C. (2000) Differential regulation of the dopamine D1, D2 and D3 receptor gene expression and changes in the phenotype of the striatal neurons in mice lacking the dopamine transporter. *Eur J Neurosci* 12:19-26
- Ferry AT, Ongur D, An X, Price JL. (2000) Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. *J Comp Neurol* 425:447-470
- Flores-Hernandez J, Cepeda C, Hernandez-Echeagaray E, Calvert CR, Jokel ES, Fienberg AA, Greengard P, Levine MS. (2002) Dopamine enhancement of NMDA currents in dissociated medium-sized striatal neurons: role of D1 receptors and DARPP-32. *J Neurophysiol* 88:3010-3020
- Frankle WG, Gil R, Hackett E, Mawlawi O, Zea-Ponce Y, Zhu Z, Kochan LD, Cangiano C, Slifstein M, Gorman JM, Laruelle M, Abi-Dargham A. (2004) Occupancy of dopamine D2 receptors by the atypical antipsychotic drugs risperidone and olanzapine: theoretical

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

Gessa GL, Devoto P, Diana M, Flore G, Melis M, Pistis M. (2000) Dissociation of haloperidol, clozapine, and olanzapine effects on electrical activity of mesocortical dopamine neurons and dopamine release in the prefrontal cortex. *Neuropsychopharmacology* 22:642-649.

Gingrich JA, Caron MG. (1993) Recent advances in the molecular biology of dopamine receptors. *Annu Rev Neurosci* 16:299-321

Goldberg TE, Weinberger DR. (2004) Genes and the parsing of cognitive processes. *Trends Cogn Sci* 8:325-335

Goldman-Rakic P. (1994) Working memory dysfunction in schizophrenia. *J.Neuropsychiatry Clin.Neurosci.* 6:348

Goldman-Rakic PS, Muly EC, 3rd, Williams GV. (2000) D(1) receptors in prefrontal cells and circuits. *Brain Res Brain Res Rev* 31:295-301

Grace AA. (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* 41:1-24

Grace AA. (2000) Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Res Brain Res Rev* 31:330-341

Griffith JJ, Oates J, Cavanaugh J. (1968) Paranoid episodes induced by drugs. *J. Am. Med. Assoc.* 205:39

Grunder G, Vernaleken I, Muller MJ, Davids E, Heydari N, Buchholz HG, Bartenstein P, Munk OL, Stoeter P, Wong DF, Gjedde A, Cumming P. (2003) Subchronic haloperidol downregulates dopamine synthesis capacity in the brain of schizophrenic patients *in vivo*. *Neuropsychopharmacology* 28:787-794

Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P. (2001) BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature* 411:86-89

Guo N, Hwang D, Abdellhadi S, Abi-Dargham A, Zarahn E, Laruelle M. (2001) The effect of chronic DA depletion on D1 ligand binding in rodent brain. *Soc Neurosc Abst* 27

Gurevich EV, Bordelon Y, Shapiro RM, Arnold SE, Gur RE, Joyce JN. (1997) Mesolimbic dopamine D3 receptors and use of antipsychotics in patients with schizophrenia. A postmortem study. *Arch Gen Psychiatry* 54:225-232

Haber SN, Fudge JL. (1997) The primate substantia nigra and VTA: integrative circuitry and function. *Crit Rev Neurobiol* 11:323-342

- Haber SN, Fudge JL, McFarland NR. (2000) Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 20:2369-2382
- Hashimoto T, Bergen SE, Nguyen QL, Xu B, Monteggia LM, Pierri JN, Sun Z, Sampson AR, Lewis DA. (2005) Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. *J Neurosci* 25:372-383
- Hernandez-Lopez S, Bargas J, Surmeier DJ, Reyes A, Galarraga E. (1997) D1 receptor activation enhances evoked discharge in neostriatal medium spiny neurons by modulating an L-type Ca<sup>2+</sup> conductance. *J Neurosci* 17:3334-3342
- Hersch SM, Ciliax BJ, Gutekunst CA, Rees HD, Heilman CJ, Yung KK, Bolam JP, Ince E, Yi H, Levey AI. (1995) Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. *J Neurosci* 15:5222-5237
- Hess EJ, Bracha HS, Kleinman JE, Creese I. (1987) Dopamine receptor subtype imbalance in schizophrenia. *Life Sci* 40:1487-1497
- Hietala J, Syvalahti E, Vilkmann H, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Eronen E, Ruotsalainen U, Salokangas RK. (1999a) Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophrenia Res.* 35:41-50
- Hietala J, Syvalahti E, Vilkmann H, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Eronen E, Ruotsalainen U, Salokangas RK. (1999b) Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophrenia Res* 35:41-50
- Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Kirvela O, Ruotsalainen U, *et al.* (1995) Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet* 346:1130-1131
- Hietala J, Syvalahti E, Vuorio K, Nagren K, Lehikoinen P, Ruotsalainen U, Rakkolainen V, Lehtinen V, Wegelius U. (1994a) Striatal D2 receptor characteristics in neuroleptic-naive schizophrenic patients studied with Positron Emission Tomography. *Arch. Gen. Psychiatry* 51:116-123
- Hietala J, West C, Syvalahti E, Nagren K, Lehikoinen P, Sonninen P, Ruotsalainen U. (1994b) Striatal D2 dopamine receptor binding characteristics *in vivo* in patients with alcohol dependence. *Psychopharmacology (Berl)* 116:285-290
- Hirai M, Kitamura N, Hashimoto T, Nakai T, Mita T, Shirakawa O, Yamadori T, Amano T, Noguchi-Kuno SA, Tanaka C. (1988) [<sup>3</sup>H]GBR-12935 binding sites in human striatal membranes: binding characteristics and changes in parkinsonians and schizophrenics. *Jpn J Pharmacol* 47:237-243
- Hirvonen J, van Erp TG, Huttunen J, Aalto S, Nagren K, Huttunen M, Lonnqvist J, Kaprio J, Hietala J, Cannon TD. (2005) Increased caudate dopamine D2 receptor availability as a genetic marker for schizophrenia. *Arch Gen Psychiatry* 62:371-378

Hoover JE, Strick PL. (1993) Multiple output channels in the basal ganglia. *Science* 259:819-821

Hsiao MC, Lin KJ, Liu CY, Tzen KY, Yen TC. (2003) Dopamine transporter change in drug-naive schizophrenia: an imaging study with 99mTc-TRODAT-1. *Schizophr Res* 65:39-46

Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY. (2001) 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. *J Neurochem* 76:1521-1531.

Joel D, Weiner I. (2000) The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 96:451-474

Joyce JN, Lexow N, Bird E, Winokur A. (1988) Organization of dopamine D1 and D2 receptors in human striatum: receptor autoradiographic studies in Huntington's disease and schizophrenia. *Synapse* 2:546-557

Joyce JN, MeadorWoodruff JH. (1997) Linking the family of D-2 receptors to neuronal circuits in human brain: Insights into schizophrenia. *Neuropsychopharmacology* 16:375-384

Kahn RS, Harvey PD, Davidson M, Keefe RS, Apter S, Neale JM, Mohs RC, Davis KL. (1994) Neuropsychological correlates of central monoamine function in chronic schizophrenia: relationship between CSF metabolites and cognitive function. *Schizophr Res* 11:217-224.

Kapur S, Zipursky R, Jones C, Remington G, Houle S. (2000) Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 157:514-520

Karlsson P, Farde L, Halldin C, Sedvall G. (2002) PET study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. *Am J Psychiatry* 159:761-767

Karreman M, Moghaddam B. (1996) The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. *J. Neurochem.* 66:589-598

Kebabian JW, Calne DB. (1979) Multiple receptors for dopamine. *Nature* 277:93-96

Keefe RS, Silva SG, Perkins DO, Lieberman JA. (1999) The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull* 25:201-222

Knable MB, Egan MF, Heinz A, Gorey J, Lee KS, Coppola R, Weinberger DR. (1997) Altered dopaminergic function and negative symptoms in drug-free patients with schizophrenia. [<sup>123</sup>I]-iodobenzamide SPECT study. *Br J Psychiatry* 171:574-577

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, Hyde TM, Murray AM, Herman MM, Kleinman JE. (1996) A postmortem study of frontal cortical dopamine D1 receptors in schizophrenics, psychiatric controls, and normal controls. *Biol. Psychiatry* 40:1191-1199

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

Kolachana BS, Saunders R, Weinberger D. (1995) Augmentation of prefrontal cortical monoaminergic activity inhibits dopamine release in the caudate nucleus: an *in vivo* neurochemical assessment in the rhesus monkey. *Neurosciences* 69:859-868

Konradi C. (1998) The molecular basis of dopamine and glutamate interactions in the striatum. *Adv Pharmacol* 42:729-733

Konradi C, Heckers S. (2003) Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. *Pharmacol Ther* 97:153-179

Kotter R. (1994) Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum. *Prog Neurobiol* 44:163-196

Kramer MS, Last B, Getson A, Reines SA. (1997) The effects of a selective D4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia. D4 Dopamine Antagonist Group. *Arch Gen Psychiatry* 54:567-572

Kunishio K, Haber SN. (1994) Primate cingulostriatal projection: limbic striatal versus sensorimotor striatal input. *J Comp Neurol* 350:337-356

Laakso A, Vilkmann H, Alakare B, Haaparanta M, Bergman J, Solin O, Peurasaari J, Rakkolainen V, Syvalahti E, Hietala J. (2000) Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. *Am J Psychiatry* 157:269-271

Lahti RA, Roberts RC, Cochrane EV, Primus RJ, Gallager DW, Conley RR, Tamminga CA. (1998) Direct determination of dopamine D4 receptors in normal and schizophrenic postmortem brain tissue: a [<sup>3</sup>H]NGD-94-1 study. *Mol Psychiatry* 3:528-533

Lahti RA, Roberts RC, Conley RR, Cochrane EV, Mutin A, Tamminga CA. (1996) D2-type dopamine receptors in postmortem human brain sections from normal and schizophrenic subjects. *Neuroreport* 7:1945-1948

Laruelle M. (2000) Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J. Cereb. Blood Flow Metab.* 20:423-451

Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. (1999) Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry* 46:56-72

- Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, Seibyl J, Baldwin R, Innis R. (2000a) Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [<sup>123</sup>I]beta-CIT. *Biol Psychiatry* 47:371-379
- Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, Seibyl J, Baldwin R, Innis R. (2000b) Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [<sup>123</sup>I]beta-CIT. *Biol Psychiatry* 47:371-379
- Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB. (1996a) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A* 93:9235-9240
- Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, De Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB. (1996b) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug free schizophrenic subjects. *Proc. Natl. Acad. Sci. USA* 93:9235-9240
- Laruelle M, Casanova M, Weinberger D, Kleinman J. (1990) Postmortem study of the dopaminergic D1 receptors in the dorsolateral prefrontal cortex of schizophrenics and controls. *Schizophrenia Res* 3:30-31
- Laruelle M, DSouza CD, Baldwin RM, Abi-Dargham A, Kanes SJ, Fingado CL, Seibyl JP, Zoghbi SS, Bowers MB, Jatlow P, Charney DS, Innis RB. (1997) Imaging D-2 receptor occupancy by endogenous dopamine in humans. *Neuropsychopharmacology* 17:162-174
- Le Foll B, Frances H, Diaz J, Schwartz JC, Sokoloff P. (2002) Role of the dopamine D3 receptor in reactivity to cocaine-associated cues in mice. *Eur J Neurosci* 15:2016-2026
- Le Moine C, Normand E, Bloch B. (1991) Phenotypical characterization of the rat striatal neurons expressing the D1 dopamine receptor gene. *Proc Natl Acad Sci U S A* 88:4205-4209
- Le Moine C, Tison F, Bloch B. (1990) D2 dopamine receptor gene expression by cholinergic neurons in the rat striatum. *Neurosci Lett* 117:248-252
- Lee T, Seeman P, Tourtellotte WW, Farley IJ, Hornykeiwicz O. (1978) Binding of 3H-neuroleptics and 3H-apomorphine in schizophrenic brains. *Nature* 274:897-900
- Leveque JC, Macias W, Rajadhyaksha A, Carlson RR, Barczak A, Kang S, Li XM, Coyle JT, Huganir RL, Heckers S, Konradi C. (2000) Intracellular modulation of NMDA receptor function by antipsychotic drugs. *J Neurosci* 20:4011-4020
- Levine MS, Li Z, Cepeda C, Cromwell HC, Altemus KL. (1996) Neuromodulatory actions of dopamine on synaptically-evoked neostriatal responses in slices. *Synapse* 24:65-78
- Lieberman JA, Kane JM, Alvir J. (1987a) Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology* 91:415-433

- Lieberman JA, Kane JM, Sarantakos S, Gadaleta D, Woerner M, Alvir J, Ramos-Lorenzi J. (1987b) Prediction of relapse in schizophrenia. Arch. Gen. Psychiatry 44:597-603
- Lindstrom LH, Gefvert O, Hagberg G, Lundberg T, Bergstrom M, Hartvig P, Langstrom B. (1999) Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. Biol Psychiatry 46:681-688
- Lindvall O, Björklund A. (1983) Dopamine- and norepinephrine-containing neuron systems: their anatomy in the rat brain. In: Chemical Neuroanatomy (Emson P, ed), New York: Raven Press, pp 229-255
- Mackay AV, Iversen LL, Rossor M, Spokes E, Bird E, Arregui A, Creese I, Synder SH. (1982) Increased brain dopamine and dopamine receptors in schizophrenia. Arch Gen Psychiatry 39:991-997
- Marti M, Mela F, Bianchi C, Beani L, Morari M. (2002) Striatal dopamine-NMDA receptor interactions in the modulation of glutamate release in the substantia nigra pars reticulata *in vivo*: opposite role for D1 and D2 receptors. J Neurochem 83:635-644
- Martinot J-L, Peron-Magnan P, Huret J-D, Mazoyer B, Baron J-C, Boulenger J-P, C. Lh, B. M, Caillard V, H. L, Syrota A. (1990a) Striatal D2 dopaminergic receptors assessed with positron emission tomography and 76-Br-bromospiperone in untreated patients. Am J Psychiatry 147:346-350
- Martinot JL, Paillere-Martinot ML, Loc'h C, Hardy P, Poirier MF, Mazoyer B, Beaufils B, Maziere B, Allilaire JF, Syrota A. (1991a) The estimated density of D2 striatal receptors in schizophrenia. A study with positron emission tomography and 76Br-bromolisuride. Br J Psychiatry 158:346-350
- Martinot JI, Paillère-Martinot ML, Loc'h C, Hardy P, Poirier MF, Mazoyer B, Beaufils B, Mazière B, Alliaire JF, Syrota A. (1991b) The estimated density of D2 striatal receptors in schizophrenia. A study with positron Emission tomography and 76Br-bromolisuride. Br. J. Psychiatry 158:346-350
- Martinot JL, Paillère-Martinot ML, Loch'H C, Lecrubier Y, Dao-Castellana MH, Aubin F, Allilaire JF, Mazoyer B, Mazière B, Syrota A. (1994) Central D2 receptors and negative symptoms of schizophrenia. Br. J. Pharmacol. 164:27-34
- Martinot JL, Peron-Magnan P, Huret JD, Mazoyer B, Baron JC, Boulenger JP, Loc'h C, Maziere B, Caillard V, Loo H, *et al.* (1990b) Striatal D2 dopaminergic receptors assessed with positron emission tomography and [76Br]bromospiperone in untreated schizophrenic patients. Am J Psychiatry 147:44-50
- Marzella PL, Hill C, Keks N, Singh B, Copolov D. (1997) The binding of both [<sup>3</sup>H]nemonapride and [<sup>3</sup>H]raclopride is increased in schizophrenia. Biol Psychiatry 42:648-654
- McGowan SW, Lawrence A, Sale T, Queded D, Grasby PM. (2004) Presynaptic dopaminergic dysfunction in medicated schizophrenic patients. Arch Gen Psychiatry 61:134-142

- Meador-Woodruff JH, Damask SP, Wang J, Haroutunian V, Davis KL, Watson SJ. (1996) Dopamine receptor mRNA expression in human striatum and neocortex. *Neuropsychopharmacology* 15:17-29
- Melis M, Diana M, Gessa GL. (1999) Clozapine potently stimulates mesocortical dopamine neurons. *Eur J Pharmacol* 366:R11-13.
- Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, Weinberger DR, Berman KF. (2002) Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci* 5:267-271
- Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. (1998) Dopamine receptors: from structure to function. *Physiological Reviews* 78:189
- Mita T, Hanada S, Nishino N, Kuno T, Nakai H, Yamadori T, Mizoi Y, Tanaka C. (1986) Decreased serotonin S2 and increased dopamine D2 receptors in chronic schizophrenics. *Biol Psychiatry* 21:1407-1414
- Mogenson GJ, Jones DL, Yim CY. (1980) From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 14:69-97
- Monsma FJ, Jr., Mahan LC, McVittie LD, Gerfen CR, Sibley DR. (1990) Molecular cloning and expression of a D1 dopamine receptor linked to adenylyl cyclase activation. *Proc Natl Acad Sci U S A* 87:6723-6727
- Morari M, O'Connor WT, Ungerstedt U, Fuxe K. (1994) Dopamine D1 and D2 receptor antagonism differentially modulates stimulation of striatal neurotransmitter levels by N-methyl-D-aspartic acid. *Eur J Pharmacol* 256:23-30
- Mrzljak L, Bergson C, Pappy M, Huff R, Levenson R, Goldman-Rakic PS. (1996) Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. *Nature* 381:245-248
- Murray AM, Hyde TM, Knable MB, Herman MM, Bigelow LB, Carter JM, Weinberger DR, Kleinman JE. (1995) Distribution of putative D4 dopamine receptors in postmortem striatum from patients with schizophrenia. *J Neurosci* 15:2186-2191
- Nguyen TV, Kosofsky BE, Birnbaum R, Cohen BM, Hyman SE. (1992) Differential expression of c-fos and zif268 in rat striatum after haloperidol, clozapine, and amphetamine. *Proc Natl Acad Sci U S A* 89:4270-4274
- Nicola SM, Surmeier J, Malenka RC. (2000) Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. *Annu Rev Neurosci* 23:185-215
- Nishi A, Snyder GL, Greengard P. (1997) Bidirectional regulation of DARPP-32 phosphorylation by dopamine. *J Neurosci* 17:8147-8155
- Nordstrom AL, Farde L, Eriksson L, Halldin C. (1995) No elevated D2 dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [<sup>11</sup>C]N-methylspiperone [see comments]. *Psychiatry Res* 61:67-83

- Nordstrom AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, Uppfeldt G. (1993) Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatry* 33:227-235
- Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M. (1997) Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* 385:634-636
- Onn SP, West AR, Grace AA. (2000) Dopamine-mediated regulation of striatal neuronal and network interactions. *Trends Neurosci* 23:S48-56
- Owen F, Cross AJ, Crow TJ, Longden A, Poulter M, Riley GJ. (1978) Increased dopamine-receptor sensitivity in schizophrenia. *Lancet* 2:223-226
- Palermo-Neto J. (1997) Dopaminergic systems. Dopamine receptors. *Psychiatr Clin North Am* 20:705-721
- Parent A, Hazrati LN. (1995a) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev* 20:91-127
- Parent A, Hazrati LN. (1995b) Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev* 20:128-154
- Parsey RV, Oquendo MA, Zea-Ponce Y, Rodenhiser J, Kegeles LS, Prapat M, Cooper TB, Van Heertum R, Mann JJ, Laruelle M. (2001) Dopamine D(2) receptor availability and amphetamine-induced dopamine release in unipolar depression. *Biol Psychiatry* 50:313-322
- Pearce RK, Seeman P, Jellinger K, Tourtellotte WW. (1990) Dopamine uptake sites and dopamine receptors in Parkinson's disease and schizophrenia. *Eur Neurol* 30 Suppl 1:9-14
- Pehek EA, Yamamoto BK. (1994) Differential effects of locally administered clozapine and haloperidol on dopamine efflux in the rat prefrontal cortex and caudate-putamen. *J Neurochem* 63:2118-2124
- Pennartz CM, Groenewegen HJ, Lopes da Silva FH. (1994) The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioural, electrophysiological and anatomical data. *Prog Neurobiol* 42:719-761
- Peris J, Dwoskin LP, Zahniser NR. (1988) Biphasic modulation of evoked [<sup>3</sup>H]D-aspartate release by D-2 dopamine receptors in rat striatal slices. *Synapse* 2:450-456
- Pilowsky LS, Costa DC, Ell PJ, Verhoeff NP, Murray RM, Kerwin RW. (1994a) D2 dopamine receptor binding in the basal ganglia of antipsychotic-free schizophrenic patients. An <sup>123</sup>I-IBZM single photon emission computerised tomography study. *Br J Psychiatry* 164:16-26

- Pilowsky LS, Costa DC, Ell PJ, Verhoeff NPLG, Murray RM, Kerwin RW. (1994b) D2 dopamine receptor binding in the basal ganglia of antipsychotic-free schizophrenic patients. An I-<sup>123</sup>-IBZM single photon emission computerized tomography study. *Br. J. Psychiatry* 164:16-26
- Pimoule C, Schoemaker H, Reynolds GP, Langer SZ. (1985) [<sup>3</sup>H]SCH 23390 labeled D1 dopamine receptors are unchanged in schizophrenia and Parkinson's disease. *Eur J Pharmacol* 114:235-237
- Pycock CJ, Kerwin RW, Carter CJ. (1980) Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. *Nature* 286:74-77
- Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, Bachneff S, Cumming P, Diksic M, Dyve SE, *et al.* (1994a) Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc Natl Acad Sci U S A* 91:11651-11654
- Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, Bachneff S, Cumming P, Diksic M, Dyve SE, Etienne P, Evans AC, Lal S, Shevell M, Savard G, Wong DF, Chouinard G, Gjedde A. (1994b) Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc. Natl. Acad. Sci. USA* 91:11651-11654
- Reynolds GP. (1983) Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. *Nature* 305:527-529
- Reynolds GP. (1989) Beyond the dopamine hypothesis. The neurochemical pathology of schizophrenia. *Br J Psychiatry* 155:305-316
- Reynolds GP, Czudek C. (1988) Status of the dopaminergic system in post-mortem brain in schizophrenia. *Psychopharmacol Bull* 24:345-347
- Reynolds GP, Czudek C, Bzowej N, Seeman P. (1987) Dopamine receptor asymmetry in schizophrenia. *Lancet* 1:979
- Reynolds GP, Mason SL. (1994) Are striatal dopamine D4 receptors increased in schizophrenia? *J Neurochem* 63:1576-1577
- Ridray S, Griffon N, Mignon V, Souil E, Carboni S, Diaz J, Schwartz JC, Sokoloff P. (1998) Coexpression of dopamine D1 and D3 receptors in islands of Calleja and shell of nucleus accumbens of the rat: opposite and synergistic functional interactions. *Eur J Neurosci* 10:1676-1686
- Robertson GS, Matsumura H, Fibiger HC. (1994) Induction patterns of Fos-like immunoreactivity in the forebrain as predictors of atypical antipsychotic activity. *J Pharmacol Exp Ther* 271:1058-1066
- Rollema H, Lu Y, Schmidt AW, Sprouse JS, Zorn SH. (2000) 5-HT(1A) receptor activation contributes to ziprasidone-induced dopamine release in the rat prefrontal cortex. *Biol Psychiatry* 48:229-237.
- Ruiz J, Gabilondo AM, Meana JJ, Garcia-Sevilla JA. (1992) Increased [<sup>3</sup>H] raclopride binding sites in postmortem brains from schizophrenic violent suicide victims. *Psychopharmacology (Berl)* 109:410-414

- Schoots O, Seeman P, Guan HC, Paterson AD, Van Tol HH. (1995) Long-term haloperidol elevates dopamine D4 receptors by 2-fold in rats. *Eur J Pharmacol* 289:67-72
- Scott L, Kruse MS, Forssberg H, Brismar H, Greengard P, Aperia A. (2002) Selective up-regulation of dopamine D1 receptors in dendritic spines by NMDA receptor activation. *Proc Natl Acad Sci U S A* 99:1661-1664
- Seamans JK, Gorelova N, Durstewitz D, Yang CR. (2001) Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. *J Neurosci* 21:3628-3638.
- Seeman P. (1988) Brain dopamine receptors in schizophrenia: PET problems. *Arch Gen Psychiatry* 45:598-600
- Seeman P, Bzowej NH, Guan HC, Bergeron C, Reynolds GP, Bird ED, Riederer P, Jellinger K, Tourtellotte WW. (1987) Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's, and Huntington's diseases. *Neuropsychopharmacology* 1:5-15
- Seeman P, Guan HC, Niznik HB. (1989) Endogenous dopamine lowers the dopamine D2 receptor density as measured by [<sup>3</sup>H]raclopride: implications for positron emission tomography of the human brain. *Synapse* 3:96-97
- Seeman P, Guan HC, Van Tol HH. (1993) Dopamine D4 receptors elevated in schizophrenia. *Nature* 365:441-445
- Seeman P, Lee T. (1975) Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* 188:1217-1219
- Seeman P, Ulpian C, Bergeron C, Riederer P, Jellinger K, Gabriel E, Reynolds GP, Tourtellotte WW. (1984) Bimodal distribution of dopamine receptor densities in brains of schizophrenics. *Science* 225:728-731
- Smiley JF, Levey AI, Ciliax BJ, Goldman-Rakic PS. (1994) D1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: predominant and extrasynaptic localization in dendritic spines. *Proc Natl Acad Sci U S A* 91:5720-5724
- Smith AD, Bolam JP. (1990) The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. *Trends Neurosci* 13:259-265
- Sokoloff P, Diaz J, Levesque D, Pilon C, Dimitriadou V, Griffon N, Lammers CH, Martres MP, Schwartz JC. (1995) Novel dopamine receptor subtypes as targets for antipsychotic drugs. *Ann N Y Acad Sci* 757:278-292
- Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. (1990) Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. *Nature* 347:146-151
- Spano PF, Govoni S, Trabucchi M. (1978) Studies on the pharmacological properties of dopamine receptors in various areas of the central nervous system. *Adv Biochem Psychopharmacol* 19:155-165

- Starr MS. (1995) Glutamate/dopamine D1/D2 balance in the basal ganglia and its relevance to Parkinson's disease. *Synapse* 19:264-293
- Sumiyoshi T, Stockmeier CA, Overholser JC, Thompson PA, Meltzer HY. (1995) Dopamine D4 receptors and effects of guanine nucleotides on [<sup>3</sup>H]raclopride binding in postmortem caudate nucleus of subjects with schizophrenia or major depression. *Brain Res* 681:109-116
- Sunahara RK, Guan HC, O'Dowd BF, Seeman P, Laurier LG, Ng G, George SR, Torchia J, Van Tol HH, Niznik HB. (1991) Cloning of the gene for a human dopamine D5 receptor with higher affinity for dopamine than D1. *Nature* 350:614-619
- Surmeier DJ, Eberwine J, Wilson CJ, Cao Y, Stefani A, Kitai ST. (1992) Dopamine receptor subtypes colocalize in rat striatonigral neurons. *Proc Natl Acad Sci U S A* 89:10178-10182
- Surmeier DJ, Song WJ, Yan Z. (1996) Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. *J Neurosci* 16:6579-6591
- Takahashi M, Shirakawa O, Toyooka K, Kitamura N, Hashimoto T, Maeda K, Koizumi S, Wakabayashi K, Takahashi H, Someya T, Nawa H. (2000) Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. *Mol Psychiatry* 5:293-300
- Talbot PS, Laruelle M. (2002) The role of *in vivo* molecular imaging with PET and SPECT in the elucidation of psychiatric drug action and new drug development. *Eur Neuropsychopharmacol* 12:503-511
- Tarazi FI, Florijn WJ, Creese I. (1997) Differential regulation of dopamine receptors after chronic typical and atypical antipsychotic drug treatment. *Neuroscience* 78:985-996
- Tiberi M, Jarvie KR, Silvia C, Falardeau P, Gingrich JA, Godinot N, Bertrand L, Yang-Feng TL, Fremeau RT, Jr., Caron MG. (1991) Cloning, molecular characterization, and chromosomal assignment of a gene encoding a second D1 dopamine receptor subtype: differential expression pattern in rat brain compared with the D1A receptor. *Proc Natl Acad Sci U S A* 88:7491-7495
- Torstenson R, Hartvig P, Langstrom B, Bastami S, Antoni G, Tedroff J. (1998) Effect of apomorphine infusion on dopamine synthesis rate relates to dopaminergic tone. *Neuropharmacology* 37:989-995
- Tune LE, Wong DF, Pearlson G, Strauss M, Young T, Shaya EK, Dannals RF, Wilson AA, Ravert HT, Sapp J, et al. (1993) Dopamine D2 receptor density estimates in schizophrenia: a positron emission tomography study with 11C-N-methylspiperone. *Psychiatry Research* 49:219-237
- Tzschentke TM. (2001) Pharmacology and behavioral pharmacology of the mesocortical dopamine system. *Prog Neurobiol* 63:241-320.
- Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, Civelli O. (1991) Cloning of the gene for a human dopamine

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

Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. (2003) Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. *Mol Psychiatry* 8:592-610

Weinberger DR. (1987) Implications of the normal brain development for the pathogenesis of schizophrenia. *Arch. Gen. Psychiatry* 44:660-669

Weinberger DR, Berman KF, Chase TN. (1988) Mesocortical dopaminergic function and human cognition. *Ann N Y Acad Sci* 537:330-338

Weinberger DR, Laruelle M. (2001) Neurochemical and neuropharmacological imaging in schizophrenia. In: *Neuropharmacology - The Fifth Generation of Progress* (Davis KL, Charney DS, Coyle JT *et al.*, eds): Lippincott, Williams, and Wilkins

West AR, Grace AA. (2002) Opposite influences of endogenous dopamine D1 and D2 receptor activation on activity states and electrophysiological properties of striatal neurons: studies combining *in vivo* intracellular recordings and reverse microdialysis. *J Neurosci* 22:294-304

Wilkinson LS. (1997) The nature of interactions involving prefrontal and striatal dopamine systems. *J Psychopharmacol* 11:143-150

Wilson CJ, Kawaguchi Y. (1996) The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. *J Neurosci* 16:2397-2410

Wong DF, Wagner HN, Jr., Tune LE, Dannals RF, Pearlson GD, Links JM, Tamminga CA, Broussolle EP, Ravert HT, Wilson AA, *et al.* (1986a) Positron emission tomography reveals elevated D2 dopamine receptors in drug-naïve schizophrenics. *Science* 234:1558-1563

Wong DF, Wagner HN, Tune LE, Dannals RF, Pearlson GD, Links JM, Tamminga CA, Broussolle EP, Ravert HT, Wilson AA, Toung JK, Malat J, Williams JA, O'Tuama LA, Snyder SH, Kuhar MJ, Gjedde A. (1986b) Positron Emission Tomography reveals elevated D2 dopamine receptors in drug-naïve schizophrenics. *Science* 234:1558-1563.

Yang CR, Seamans JK, Gorelova N. (1999) Developing a neuronal model for the pathophysiology of schizophrenia based on the nature of electrophysiological actions of dopamine in the prefrontal cortex. *Neuropsychopharmacology* 21:161-194.

Yang YK, Yu L, Yeh TL, Chiu NT, Chen PS, Lee IH. (2004) Associated alterations of striatal dopamine D2/D3 receptor and transporter binding in drug-naïve patients with schizophrenia: a dual-isotope SPECT study. *Am J Psychiatry* 161:1496-1498

Young D, Scoville WB. (1938) Paranoid psychosis in narcolepsy and the possible dangers of benzedrine treatment. *Medical Clinics of North America* 22:637

Youngren KD, Inglis FM, Pivrotto PJ, Jedema HP, Bradberry CW, Goldman-Rakic PS, Roth RH, Moghaddam B. (1999) Clozapine

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

Zhou QY, Grandy DK, Thambi L, Kushner JA, Van Tol HH, Cone R, Pribnow D, Salon J, Bunzow JR, Civelli O. (1990) Cloning and expression of human and rat D1 dopamine receptors. Nature 347:76-80

Zhu MY, Juorio AV, Paterson IA, Boulton AA. (1993) Regulation of striatal aromatic L-amino acid decarboxylase: effects of blockade or activation of dopamine receptors. Eur J Pharmacol 238:157-164