Neurochemical Imaging in Schizophrenia

Nina Urban and Anissa Abi-Dargham

Contents

Abstract Recent advances in the development and applications of neurochemical brain imaging methods have improved the ability to study the neurochemistry of the living brain in normal processes as well as psychiatric disorders. In particular, positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used to determine neurochemical substrates of schizophrenia and to uncover the mechanism of action of antipsychotic medications. The growing availability of radiotracers for monoaminergic neurotransmitter synthesis, transporters and receptors, has enabled the evaluation of hypotheses regarding neurotransmitter function in schizophrenia derived from preclinical and clinical observations.

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This chapter reviews the studies using neurochemical brain imaging methods for (1) detection of abnormalities in indices of dopamine and serotonin transmission in patients with schizophrenia compared to controls, (2) development of new tools to study other neurotransmitters systems, such as gamma-aminobutyric acid (GABA) and glutamate, and (3) characterization of target occupancy by antipsychotic drugs, as well as its relationship to efficacy and side effects.

As more imaging tools become available, this knowledge will expand and will lead to better detection of disease, as well as better therapeutic approaches.

Keywords Neurochemical imaging techniques · Dopamine · Serotonin · Gamma-amino butyric acid (GABA) · Glutamate · Occupancy

1 Introduction

The introduction of neuroimaging techniques in the 1960s has revolutionized the study of the biology of psychiatric disorders. Functional imaging techniques including neurochemical/molecular imaging such as single photon emission computerized tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS) have advanced our understanding of the pathophysiology of schizophrenia and other psychiatric disorders. This chapter summarizes current insights gained from application of molecular imaging techniques to the study of schizophrenia.

Prior to the advent of in vivo imaging, postmortem studies were the mainstay for developing an understanding of the neurochemical alterations in schizophrenia (for review, see Benes 2000). Postmortem studies have limitations; in particular, they do not allow exploring the functional aspect of neurochemical transmission. On the other hand, PET and SPECT allow direct or indirect measurement of neurotransmitter systems in living patients and can be used to explore alterations in neurotransmitter systems suggested by postmortem studies, as well as examine their clinical correlates.

Neuroreceptor imaging research in schizophrenia can be largely divided into (1) studies of pathophysiology and (2) studies of pharmacology. Pathophysiology studies examine neuroreceptor binding under baseline conditions, competition between the radioligand and endogenous neurotransmitters at the binding site to assess neurotransmitter release, as well as activity of enzymes. Pharmacology studies explore the mechanism of action for the existing treatments utilized in this disorder, by measuring dose-dependent occupancy of the drug in question at different receptor-binding sites. Insights from pharmacological studies are invaluable for improving psychiatric management and recently PET has become an increasingly used tool in the development of new psychiatric medications. Here, we will consider studies of both pathophysiology and pharmacology with PET and

SPECT, and discuss the application of these techniques to drug development relevant to schizophrenia.

2 Brief Overview of Neurochemical Imaging Techniques

The objective of PET or SPECT neuroreceptor imaging is to obtain quantitative information regarding the distribution of the target molecules in the living human brain. These studies involve the injection of a radioactively labeled tracer (radioligand) that binds specifically to the protein of interest, usually specific neuroreceptors or transporters (Laruelle et al. 1994). Relative to SPECT, PET allows visualizing a larger number of candidate targets in the brain and produces higher quality images due to higher resolution (better "signal-to-noise ratio") and sensitivity of the scanner. PET is also more quantitatively informative because tissue attenuation can be more accurately measured with PET technology and the associated radioisotopes than with SPECT. On the other hand, SPECT uses longer acting isotopes, allowing shipments of radioisotopes bypassing the need for an on-site cyclotron. In addition, when near-equilibrium methods of analysis can be applied, SPECT can be used to assess a relatively large number of subjects (Laruelle et al. 1994).

A crucial step for PET and SPECT technology is the synthesis of radiotracers. To be successfully used for in vivo molecular imaging, the chemical properties of a radiotracer must fall within a narrow range of appropriate combinations of lipophilicity, receptor affinity and selectivity, specificity, reversibility, and toxicity. The most commonly used positron emitting sources for PET imaging are carbon-11 ($[^{11}C]$) and fluoride-18 ($[^{18}F]$) (for in-depth review, see Townsend 2004). Radiotracer production has been the rate-limiting step in terms of exploring new targets in the brain. There are tracers for dopaminergic and serotonergic sites, but very few for sites outside of these systems that are available for use in humans. Once produced successfully, the radiotracer is injected into a vein, travels throughout the body, crosses the blood–brain barrier (BBB), and binds to the receptor (referred to as *specific binding*). The radiotracer also binds to other nonreceptor proteins in the brain (termed *nonspecific binding*).

Several factors must be taken into account in order to form accurate conclusions about receptor parameters. The activity recorded by the scanner in areas of the brain represents a combination of specifically bound, nonspecifically bound, and unbound or free radioligand. The free and nonspecifically bound radioligand are referred to as nondisplaceable binding or compartment. The proportions represented by each of these parts are time varying and interdependent. Additionally, peripheral clearance, regional cerebral blood flow, and transport of the radiotracer across the BBB influence the radioactivity profile over time and can vary significantly from subject to subject. Analysis of neuroreceptor studies requires model-based methods that relate the observed time activity in the region of interest (ROI)

to the plasma time activity curve over the time course of the scan through a defined mathematical model (i.e., receptor parameter estimation is based on fitting data to a model of the underlying kinetics of ligand uptake in the brain). A variety of model-based methods have been developed (for in-depth review, see Slifstein and Laruelle 2001). The outcome measure that can be derived in neuroreceptor imaging studies is called the binding potential (BP), a term introduced by Mintun et al. (1984). It is proportional to the ratio B_{max}/K_D. The constant of proportionality differs according to the method of analysis used. K_D (nM) is the radioligand equilibrium dissociation constant and B_{max} (nM; receptor density) is the number of binding sites. In vitro, derivation of the affinity, $1/K_D$, and B_{max} is possible by using a radioactively labeled tracer, and varying the concentration of unlabeled tracer to obtain a range of receptor occupancies. In vivo studies of this type are difficult to perform in humans, as they would require multiple scans and pharmacological concentrations of the radioligand. With the very small concentrations of radioligand used in human PET studies ("tracer dose"), K_D and B_{max} cannot be measured separately. The outcome measure most often reported for PET studies is the "specific to nonspecific partition coefficient," BP_{ND} (unitless) (Fig. 2):

$$BP_{ND} = f_{ND} B_{max}/K_D.$$

Here, the constant of proportionality f_{ND} is the fraction of freely dissolved and nonspecifically bound radioligand that is freely dissolved in brain tissue. Measurement of BP_{ND} does not require measurement of arterial plasma concentration of the radioligand. Two other forms of BP that do require arterial plasma to be measured are BP_P:

$$BP_P = f_P B_{max}/K_D,$$

where f_P is the fraction of unmetabolized radioligand in arterial plasma that is not protein bound, and BP_F:

$$BP_F = B_{max}/K_D.$$

BP_F can be derived from BP_P if f_P has been measured. The choice of outcome measure is partly dictated by the experimental design – whether or not arterial plasma samples are collected – but it is also important to recognize that the outcome measures refer to different free pools of radioligand: free radioligand in the brain in the case of BP_{ND}, and in the arterial plasma in the cases of BP_P and BP_F. Ideally, all three measures provide equivalent information, but there can be differences across study groups in either free pool, leading to BP differences due to the proportionality constant rather than the receptor-related quantities B_{max} and K_D. Thus, it is important that investigators rule out these confounds in the analysis of their studies. Also, prior to the publication of the consensus nomenclature in Innis et al. (2007), the term BP was used interchangeably for any of the three outcome measures; in older literature, the particular choice must be inferred by context if it has not been made

explicit. In the remainder of this chapter, the term BP is used exclusively, but can refer to any of these outcome measures.

The major disadvantages of PET and SPECT are the radiation exposure involved, limiting the number of scans which a subject may have, and the dependence of the technique on the availability of appropriate radioligands to label molecules of interest.

3 Imaging Neurotransmitter Systems

Exploration of the basic pathophysiology of schizophrenia includes studies of receptor or transporter expression in schizophrenia compared to controls, activity of enzymatic processes, and in vivo measures of neurotransmitter release. The majority of neuroreceptor studies in schizophrenia research focus on the dopamine (DA) and the serotonin (5-hydroxytryptamine – 5-HT) system, owing to both the radiotracers available for use, and current theories on the etiology of schizophrenia (for review, see Abi-Dargham 2007; Guillin et al. 2007).

3.1 Dopamine

Striatal DA activity, largely via DA D2 receptors (D2R), regulates response inhibition, temporal organization of information, and motor performance, while cortical DA transmission via DA D1 receptors (D1R) is likely affecting the maintenance and representation of ongoing behavior (Cropley et al. 2006).

Here, mostly studies with combined D2/D3 antagonist radiotracers are considered, as the lack of D3-selective radioligands has limited exploration of the functional role of the D3 receptors in the brain. Similarly, studies examining D1Rs do not distinguish between D1 and D5 as the radiotracers are not selective for one versus the other (Missale et al. 1998). In this chapter, we use D2R to refer to both D2 and D3 receptors and D1R to refer to both D1 and D5, unless indicated otherwise.

3.1.1 Striatal DA Parameters

D2 Receptors

Baseline Striatal D2 Receptor Density

Initial SPECT and PET ligand studies in schizophrenia focused on determining the number of DA receptors at baseline compared to controls, as the apparent overactivity of the DA system in patients with schizophrenia could be explained

by an increased numbers of striatal DA receptors. By now, there has been an abundance of studies investigating striatal D2Rs in patients with schizophrenia, both treated and medication naïve, with varying results: The findings of the first studies were inconsistent, with some reporting increased D2R binding in schizophrenia (Crawley et al. 1986; Pearlson et al. 1993; Tune et al. 1993, 1996; Wong et al. 1986) and others no difference from controls (Abi-Dargham et al. 1998; Breier et al. 1997; Farde et al. 1990; Hietala et al. 1994; Martinot et al. 1991). Studies of medication-naïve patients with schizophrenia, using the PET D2R ligands [^{11}C]raclopride (Breier et al. 1997; Farde et al. 1990; Hietala et al. 1994; Talvik et al. 2006), [^{11}C]*N*-methylspiperone ([^{11}C]NMSP) (Nordstrom et al. 1995b; Okubo et al. 1997; Wong et al. 1986), and [^{76}Br]lisuride (Martinot et al. 1991, 1994) and the SPECT ligands [^{123}I]iodobenzamide ([^{123}I]IBZM) (Knable et al. 1997b; Laruelle et al. 1996; Parellada et al. 2004; Yang et al. 2004) and [^{76}Br]bromospiperone (Blin et al. 1989; Martinot et al. 1990), did not yield consistent results. Farde et al. (1990) found no general difference between groups, but patients had significant hemispheric asymmetry in D2R densities in the putamen.

Seeman and Seeman (1988) proposed to explain the discrepant results among studies with the differences in the sensitivities of different ligands to the effects of endogenous DA. There is a significantly larger effect size of studies employing butyrophenone radiotracers compared to radiotracers from other chemical families (benzamides and lisuride) (Laruelle 1998). If endogenous DA competes with the radioligand for the receptor, higher levels of DA will reduce BP for ligands that are more readily displaced by DA (such as [^{11}C]raclopride), thereby reducing the estimate of total D2R numbers. An alternative explanation is that discrepancies could be due to small sample size leading to underpowered studies. Thus, meta-analyses were performed to attempt to derive conclusions. Several meta-analyses (Kestler et al. 2001; Laruelle 1998; Weinberger and Laurelle 2001; Zakzanis and Hansen 1998) showed an overall modest (10–20%) elevation in striatal D2R density in schizophrenia. This increase is independent of the effects of antipsychotic drugs, as it was observed in drug-naïve patients (e.g., Wong et al. 1986). It is also regionally specific, as these increases are not seen in the extrastriatal regions (Buchsbaum et al. 2006; Suhara et al. 2002; Takahashi et al. 2006; Talvik et al. 2006). This increase could be genetically determined, as one SPECT study in drug-naïve patients with schizophrenia using [^{123}I]epidepride suggested: No significant differences in BP values were observed between patients and controls, but a significant correlation between frontal D2R BP values and positive symptoms in male patients with schizophrenia was found, as well as higher frontal BP values in male compared to female patients (Glenthoj et al. 2006). A twin study of patients with schizophrenia and their unaffected twins showed that monozygotic co-twins had increased caudate D2R density compared with unaffected dizygotic co-twins and healthy controls, and D2R BP was associated with a poor performance on cognitive tasks involving corticostriatal pathways (Hirvonen et al. 2005).

DA Release: Pharmacological Challenge Studies

Elevated baseline D2R is too small in magnitude to present a sufficient explanation for the increased dopaminergic tone in schizophrenia. For this reason, it was suspected that transmitter release might be abnormal. Pharmacological manipulations that induce DA release from the presynaptic dopaminergic neuron (e.g., amphetamine) allow evaluation of DA presynaptic activity or storage capacity. The released DA competes with the radioligand at the receptor and leads to a reduction in D2R radiotracer binding upon repeated scanning. The difference between baseline and postchallenge BP is considered to be an indirect index of DA transmission (Laruelle 2000; Laruelle et al. 1996). These interactions are present in rodents, nonhuman primates, and humans (for review, see Laruelle 2000). Combined microdialysis and imaging experiments in primates demonstrated that the magnitude of the ligand displacement correlated with the magnitude of the increase in amphetamine-induced intrasynaptic DA (Laruelle et al. 1997), suggesting that challenge studies provide an appropriate measure of the changes in synaptic DA levels. Agonist-induced receptor internalization may contribute to this effect, but the exact contribution of competition versus internalization to the resulting change in BP in vivo is difficult to assess (Ginovart 2005).

Studies using this approach have found evidence of roughly doubled radioligand displacement in patients with schizophrenia compared with controls (Abi-Dargham et al. 1998; Kestler et al. 2001; Laruelle et al. 1996). This was independent of the radioligand or imaging modality employed (Abi-Dargham et al. 1998; Laruelle et al. 1996).

Among patients, elevated amphetamine-induced DA release was associated with transient exacerbation of positive psychotic symptoms (Laruelle et al. 1996). The increased amphetamine-induced DA release was observed both in first episode, drug-naïve patients and in those previously treated with antipsychotic drugs. First episode patients and those who were experiencing an episode of illness exacerbation at the time of the scan showed relatively larger amphetamine-induced DA release, while patients in remission appeared no different from controls, although numerically higher (Laruelle et al. 1999). Thus, patients with schizophrenia are on average more sensitive to the DA-releasing effects of amphetamine compared with controls, but this hyperdopaminergic state is malleable and may reflect either an acute illness phase or a risk for relapse (Laruelle et al. 1999). Older literature has demonstrated that patients whose symptoms worsened following amphetamine or methylphenidate administration were more prone to relapse than those whose symptoms did not worsen (Lieberman et al. 1994).

Baseline DA Release

Amphetamine challenge imaging studies have the disadvantage of measuring changes in synaptic DA transmission following a nonphysiological stimulus and do not provide any information about synaptic DA levels at baseline. In rodents, acute depletion of synaptic DA is associated with an acute increase in the in vivo

binding of [^{11}C]raclopride or [^{123}I]IBZM to D2Rs (Laruelle 2000). As increased expression of the receptor was not observed in vitro, increased radiotracer binding cannot be due to receptor upregulation, but to removal of endogenous DA and unmasking of D2Rs. Our group (Abi-Dargham et al. 2000) used an acute DA depletion paradigm in humans involving administration of oral alpha-methyl-*para*-tyrosine (AMPT), a tyrosine hydroxylase inhibitor, over 48 h, to assess the degree of occupancy of D2Rs by endogenous DA at baseline. We administered AMPT prior to estimating D2R density in patients with schizophrenia and control subjects with the SPECT tracer [^{123}I]IBZM. D2R availability after AMPT administration increased significantly more in patients than in control subjects (19 vs. 9%), consistent with the hypothesis that these patients have higher baseline levels of intrasynaptic DA. As further evidence for a striatal hyperdopaminergic state, AMPT administration led to an acute reduction in positive symptoms, and a higher level of intrasynaptic DA at baseline was predictive of rapid clinical response of positive symptoms to treatment (Abi-Dargham et al. 2000). Another study employing the depletion paradigm found that compared to healthy controls, D2R availability to the ligand [^{123}I]epidepride after DA depletion in patients correlated significantly with dysphoric symptom scores on the positive and negative symptom scale (PANSS) (Fujita et al. 2000).

Striatal D1 Receptors

The majority of imaging studies (Abi-Dargham et al. 2002; Karlsson et al. 2002; Okubo et al. 1997) have reported unaltered levels of striatal D1R in unmedicated patients with schizophrenia. Only one PET study with the D1R radioligand [^{11}C] SCH 23390 found reduced striatal D1R density in patients when compared to healthy controls and unaffected co-twins of the patients (Hirvonen et al. 2006). Yet, the finding of unchanged striatal D1 levels in the majority of the in vivo studies is consistent with the results of most postmortem studies (Seeman et al. 1987). One source of discrepancy may be the presence of differences in volumes between groups. Volume loss results in a larger fraction of partial volume effects in smaller structures compared to larger structures, leading to erroneous decreases in receptor BP measures which can be corrected by using partial volume correction methods (Rousset et al. 1998, 2008).

Dopamine Transporters

All data reviewed so far are consistent with higher DA output in striatal regions of patients with schizophrenia, which could also be explained by increased density of DA terminals. As striatal dopamine transporter (DAT) is exclusively localized on DA terminals, measurement of this receptor provides an indirect assessment of their density. Several studies have addressed this question by measuring binding of DAT radiotracers in patients with schizophrenia (Hsiao et al. 2003; Laakso et al. 2000,

2001; Laruelle et al. 2000; Lavalaye et al. 2001; Schmitt et al. 2005; Yoder et al. 2004). No differences in DAT binding between groups were reported for studies with either medication-free or medication-naïve patients at the time of scanning. A later study, however, found a significant correlation between DAT and D2R availability in the patient but not in the healthy control group and an inverse correlation between DAT and D2R availability and the extent of positive symptoms (Schmitt et al. 2008). When performed with currently medicated patients, varying results were found: no difference (Yoder et al. 2004), decreased (Laakso et al. 2001; Mateos et al. 2007), and also increased DAT binding (Sjoholm et al. 2004). Yet, the majority of evidence does not support increased presynaptic DA output in schizophrenia as a function of higher DA terminal density at baseline, which is consistent with postmortem studies (Laruelle et al. 2000) and a study evaluating the vesicular monoamine transporter type 2 (VMAT2) in the striatum: No difference between schizophrenic patients and control groups was found using the PET ligand [^{11}C] dihydrotetrabenazine ([^{11}C]DTBZ) (Taylor et al. 2000).

DA Synthesis

Presynaptic striatal dopaminergic function can be assessed using radiolabeled levodopa (L-dopa) or fluorodopa (F-dopa), which is converted to DA and stored in striatal DA nerve terminals. This provides an index of the synthesis of DA in the presynaptic terminals of striatal dopaminergic neurons (Moore et al. 2003).

The majority of studies in patients with schizophrenia using this technique to date have reported elevated presynaptic DA synthesis capacity in schizophrenia (Hietala et al. 1995, 1999; Howes et al. 2009; Lindstrom et al. 1999; McGowan et al. 2004; Meyer-Lindenberg et al. 2002), with moderate-to-large effect sizes. Two other studies, both in chronic patients, reported either a small but not significant elevation (Dao-Castellana et al. 1997) or a small reduction in L-dopa levels (Elkashef et al. 2000). All the studies that investigated patients during episodes of acute psychosis at the time of PET scanning found elevated presynaptic striatal DA availability (Hietala et al. 1995, 1999; Howes et al. 2009; Lindstrom et al. 1999) with relevant effect size (Howes et al. 2007). This is one of the most widely replicated brain dopaminergic abnormalities in schizophrenia.

Between 22 and 31% of individuals meeting clinical criteria for a high risk of psychosis, the "prodromal stage," develop a psychotic illness, predominantly schizophrenia, within 12 months, and 35% do so after 2.5 years of follow-up (Cannon et al. 2008). Prodromal patients also show an increase in striatal [^{18}F] F-dopa accumulation, which is positively correlated with more severe symptoms as it approaches the levels seen in patients with schizophrenia (Howes et al. 2009). Striatal [^{18}F]F-dopa was elevated in patients with prodromal symptoms of schizophrenia to an intermediate degree compared with that in patients with schizophrenia, confirming that DA overactivity predates the onset of schizophrenia (Howes et al. 2009). Elevated presynaptic striatal dopaminergic function is found also in other schizophrenia spectrum patients, such as schizotypal personality

disorder (Abi-Dargham et al. 2004) and in relatives of patients with schizophrenia (Huttunen et al. 2008).

3.1.2 Extrastriatal Dopamine

D2 Receptors

Until recently, research has been hampered by the lack of suitable radioligands for detection of the low-density D2R DA receptor populations in the limbic and cortical DA systems that may be implicated in the pathophysiology of schizophrenia. The first generation of D2R ligands ([^{11}C]NMSP, [^{11}C]raclopride, [^{123}I]IBZM) enabled imaging of only striatal D2Rs. The recent introduction of high-affinity D2R radiotracers ([^{123}I]epidepride, [^{18}F]fallypride, [^{11}C]FLB 457) made visualization of extrastriatal D2Rs possible. Because of the low density of extrastriatal D2Rs (Hall et al. 1994) and therefore the low signal-to-noise ratio, radiotracers with high affinity or low nonspecific binding are required, such as [^{18}F]fallypride or [^{11}C]FLB 457 (K_D = 0.20 nM) (Halldin et al. 1995; Slifstein et al. 2004).

Several PET or SPECT studies have examined extrastriatal D2R levels in schizophrenia with the new generation of tracers. All have reported a decrease or no change in radiotracer (Buchsbaum et al. 2006; Suhara et al. 2002; Talvik et al. 2003; Tuppurainen et al. 2003; Yasuno et al. 2004b) binding in schizophrenia compared to controls. The most recent evaluation with [^{18}F]fallypride, however, found increased D2R levels in the substantia nigra bilaterally and decreased levels were seen in the left medial thalamus (Kessler et al. 2009) (Fig. 1) illustrates D2R binding in striatal and extrastriatal regions with [^{18}F]fallypride.

Extrastriatal D1 Receptors

Dopaminergic transmission in the prefrontal cortex (PFC) is mainly mediated by D1R, and D1R dysfunction has been linked to cognitive impairment and negative symptoms in schizophrenia (see review Tamminga 2006). Imaging studies of D1R present conflicting results: reduced D1R density measured with PET and [^{11}C]SCH 23390 was found to be related to the severity of negative symptoms and cognitive impairment (Okubo et al. 1997). A correlation between negative symptoms and [^{11}C]SCH 23390 binding in the frontal cortex persisted even when no significant difference in D1R binding in medication-naïve patients with schizophrenia compared to controls was found (Karlsson et al. 2002). Our group used [^{11}C] NNC 112 to investigate cortical D1R and found increased levels (Abi-Dargham et al. 2002). The increase correlated with cognitive impairment, which may be interpreted as the result of a compensatory upregulation in D1R density to chronic low levels of DA stimulation (Abi-Dargham and Moore 2003).

These differences in findings may be explained by different properties of the radiotracers: Guo et al. (2003) evaluated the effect of acute and subchronic DA

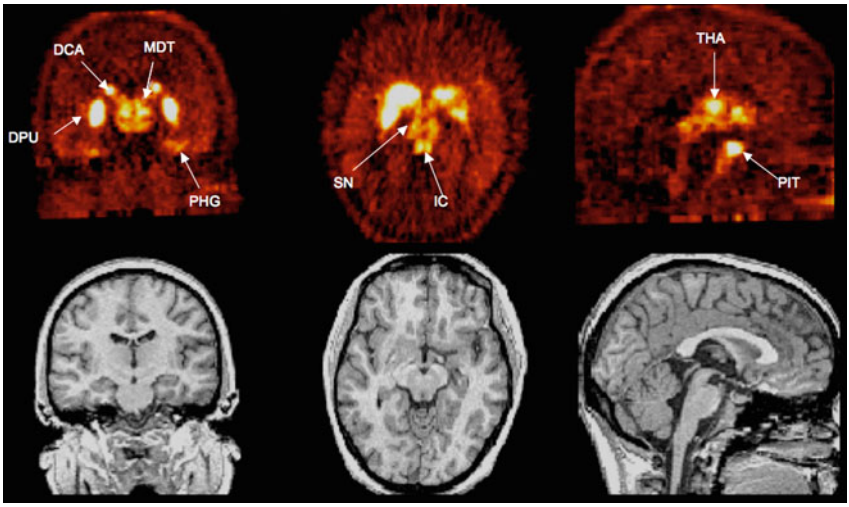

Fig. 1 PET scan in one subject under baseline conditions with coregistered structural MRI, showing activity distribution from 10 to 60 min following injection of the D2R antagonist [^{18}F] fallypride. Relatively more activity is seen in striatal compared to extrastriatal areas (dorsal caudate – DCA and dorsal putamen – DPU are shown), where concentration of D2R receptors is 10–20-fold higher. Extrastriatal binding is highest in mediodorsal thalamus (MDT), posterior hippocampal gyrus (PHG), substantia nigra (SN), inferior colliculus (IC), thalamus (THA), and pituitary gland (PIT)

depletion on the in vivo binding of [^{11}C]NNC 112 and [^{3}H]SCH 23390 in rats and found that in vivo binding of these radiotracers is differentially affected by changes in endogenous DA tone. Further studies in patients are required to clarify the exact role of D1R in schizophrenia, particularly because both tracers also bind to serotonergic 5-HT2A receptors (Ekelund et al. 2007) to a significant degree, resulting in lack of D1R selectivity in cortical areas (Slifstein et al. 2007).

3.2 Serotonin

The hypothesis that serotonin (or 5-HT) may be involved in the pathogenesis of schizophrenia was initially based on the observation of the structural similarity between serotonin and the hallucinogenic drug lysergic acid diethylamide (LSD) (Aghajanian and Marek 2000; Gaddum 1957). Postmortem studies have described alterations of 5-HT2A receptors (5-HT2AR), serotonin transporter (SERT), and above all, 5-HT1A receptors (5-HT1AR) (Gurevich and Joyce 1997; Sumiyoshi et al. 1996), and serotonin has been implicated in negative symptoms of schizophrenia (Meltzer and Sumiyoshi 2008). Cerebrospinal fluid studies and pharmacological challenges also suggest a deficit in serotonergic function in the cortex of patients with schizophrenia (Borg 2008; Sedvall 1990). 5-HT2AR antagonism appears to have beneficial effects on both positive and negative symptoms of the

illness (Abi-Dargham 2007). 5-HT2AR antagonists are proposed to reduce negative symptoms in schizophrenia through activation of midbrain DA projections to the limbic system and cerebral cortex: activation of ventral tegmental area (VTA) neurons by 5-HT2AR antagonists might provide a basis for their effect on improvement of negative symptoms (Ugedo et al. 1989), as VTA DA neurons and their projections are involved in drive and reward (Bozarth 1986). Positive symptoms could be reduced by attenuation of DA phasic activity via blockade of 5-HT2A-stimulated tyrosine hydroxylase activity (Abi-Dargham et al. 1997; Bozarth 1986). Given the relatively recent development of radiotracers to study 5-HTAR, only a limited amount of data from imaging studies is available.

3.2.1 5-HT2A Receptors

The majority of postmortem studies have reported decreased 5-HT2AR in the PFC (Arora and Meltzer 1991; Burnet et al. 1996; Dean and Hayes 1996; Joyce et al. 1993; Laruelle et al. 1993). When comparing 5-HT2AR and serotonin uptake sites in PFC and occipital cortex of patients with schizophrenia, chronic schizoaffective disorder, nonpsychotic suicide victims, and controls, 5-HT2AR density was decreased in the PFC of chronic psychotic patients dying of natural causes, as opposed to the other groups (Laruelle et al. 1993). All but one (Ngan et al. 2000; using [^{18}F]setoperone) in vivo PET studies in drug-naïve or drug-free patients with schizophrenia reported normal cortical 5-HT2AR binding in the PFC, using various ligands: [^{11}C]*N*-methylspiperone (Okubo et al. 2000), [^{18}F]setoperone (Lewis et al. 1999; Trichard et al. 1998), and [^{18}F]altanserin (Erritzoe et al. 2008). Erritzoe et al. reported increased 5-HT2AR binding in the caudate nucleus (Erritzoe et al. 2008), a finding that requires further confirmation, especially in light of the low density of the 5-HT2AR in this brain region.

3.2.2 5-HT1A Receptors

The most consistent abnormality of 5-HT parameters reported in postmortem studies in schizophrenia is an increase in the density of 5-HT1AR in prefrontal cortical regions, including the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate, and motor regions (Hashimoto et al. 1991; Joyce et al. 1993). More recently, three PET studies examined 5-HT1AR levels in vivo using [^{11}C]WAY 100635 in patients with schizophrenia and healthy controls (Frankle et al. 2006; Tauscher et al. 2002; Yasuno et al. 2004a). Frankle et al. (2006) did not detect differences in 5-HT1AR binding, whereas Tauscher et al. (2002) reported increased binding in the temporal lobe and Yasuno et al. (2004a) found decreased binding in the amygdala. A significant negative correlation was observed between BP in the amygdala and the negative and depression/anxiety symptom scores on a subscale of the PANSS (Yasuno et al. 2004a). The lack of consistency with postmortem findings may relate to the different resolutions of the different techniques. Some

postmortem studies show more pronounced increase in 5-HT1AR density within superficial cortical layers (Gurevich and Joyce 1997), while others show no difference while exploring specific cellular locations within the PFC (Cruz et al. 2004). With the currently available PET technology, it is not possible to explore differences in receptor density specific to cortical layers.

3.2.3 Serotonin Transporters

The role of the SERT is the inactivation of 5-HT via uptake into the presynaptic nerve terminals. Initially, SPECT studies in humans using the SERT radiotracer [^{123}I]β-CIT were limited to imaging the midbrain. [^{11}C]McN 5652 was the first PET radiotracer successfully developed as a SERT-specific ligand, but lately a newer ligand with higher specific to nonspecific binding (Huang et al. 2002) has been in use to explore SERT density in schizophrenia: [^{11}C]DASB proved of advantage for measurement of SERT in regions with moderate density, such as the limbic regions (Frankle et al. 2004b). A study evaluating ten brain regions, including the striatum, midbrain, amygdala, hippocampus, and anterior cingulate cortex found no difference in SERT density between subjects with schizophrenia and controls (Frankle et al. 2005). A limitation of this tracer is the ability to reliably quantify SERT in cortical regions, where SERT density is low (Frankle et al. 2004b).

3.3 Gamma-Aminobutyric Acid

A significant body of preclinical findings suggests deficiency of GABAergic neurotransmission in the PFC in schizophrenia (for review, see Lewis 2000). Upregulation of GABA-A receptor-binding activity is observed throughout most subregions of the hippocampus (Benes et al. 1997). In vivo evaluation of GABAergic systems in schizophrenia was initially limited to assessment of benzodiazepine (BDZ) receptor densities with SPECT and [^{123}I]iomazenil, and none of the studies comparing patients with schizophrenia to controls reported significant regional differences (Abi-Dargham et al. 1999; Busatto and Pilowsky 1995; Busatto et al. 1997; Verhoeff et al. 1999), contrary to postmortem findings. However, alterations of GABAergic systems in schizophrenia might be restricted to certain cortical layers or classes of GABAergic cells that are beyond the resolution of current imaging techniques (Benes et al. 1997). A recently developed technique may allow to measure acute GABA fluctuations in patients with schizophrenia in vivo: The increase in the affinity of GABA-A receptors in the presence of increased GABA levels, as suggested by preclinical work, can be detected as an increase in the binding of GABA-A BDZ-receptor site-specific radioligands. Acute elevation in GABA levels was achieved through the blockade of the GABA membrane transporter (GAT1) in a PET study with [^{11}C]flumazenil. In healthy controls, this

resulted in significant increases in [^{11}C]flumazenil BP compared to baseline in cortical regions (Frankle et al. 2009). This new technique may be applied in future studies to measure in vivo the responsivity of GABA transmission in patients with schizophrenia compared to controls.

3.4 *N*-Methyl-D-Aspartic Acid and Glutamate

The *N*-methyl-D-aspartic acid (NMDA) receptor hypofunction hypothesis of schizophrenia arose from the observation that subanesthetic doses of dissociative anesthetic drugs such as phencyclidine (PCP) and ketamine, both noncompetitive antagonists at the NMDA receptor, reliably induce the hallucinations, delusions, cognitive impairments, brain functional abnormalities, and, most notably, negative symptoms of schizophrenia in normal subjects (Krystal et al. 1994; Olney and Farber 1995; Vollenweider and Geyer 2001). The primary target may be NMDA receptors expressed on GABAergic interneurons in the thalamus and basal forebrain (Olney and Farber 1995) and action may be mediated through excess glutamate release and hyperactivity at non-NMDA glutamate receptors (Aghajanian and Marek 2000). Both drugs bind to an intrachannel site of the NMDA receptor and prevent calcium influx into the cell (Anis et al. 1983). The binding site's physical location complicates the development of suitable PET and SPECT radiotracers for this site (Waterhouse 2003). To date, one study used [^{123}I]CNS 1261, an intrachannel NMDA receptor SPECT ligand, and showed significant reductions in relative NMDA receptor binding in the left hippocampus in medication-free, but not antipsychotic-treated, patients with schizophrenia compared to healthy subjects (Pilowsky et al. 2006). Other studies have explored the effects of NMDA antagonists on indices of dopaminergic function and showed that S-ketamine increased DA release in the striatum, as evidenced by decreased [^{11}C]raclopride BP after ketamine administration (Vollenweider et al. 2000), and potentiated the effect of amphetamine-induced DA release in healthy volunteers to levels similar to those observed in patients with schizophrenia (van Berckel et al. 2006). On the other hand, chronic ketamine users had alterations in cortical D1R of similar direction and magnitude to one of the reports of D1R alterations observed in schizophrenia (Guo et al. 2003; Kapur et al. 1999). These findings from imaging studies suggest that the glutamate and DA dysregulations in schizophrenia may be interrelated and potentiate each other, forming a vicious circle.

4 Occupancy Studies (Pharmacological Studies)

The most widespread use of neuroreceptor imaging in schizophrenia over the last decade has been the assessment of receptor occupancy achieved by typical and atypical antipsychotic drugs. The main focus has been on D2R occupancy, particularly in the striatum, but 5-HT2AR, 5-HT1AR, and D1R occupancy have also been

studied (Abi-Dargham and Laruelle 2005; Frankle 2007; Frankle and Laruelle 2002; Kapur et al. 1999; Nyberg et al. 1998). PET and SPECT imaging are used not only to assess the in vivo properties of currently marketed drugs, but also to help with the development of new medications for psychiatric conditions. Overall, many insights into the mechanisms of action of antipsychotics have been gained from brain imaging studies, as we will illustrate and summarize below.

4.1 DA Receptor Occupancy

4.1.1 D2 Receptor Occupancy

Implications for Treatment

Currently, most antipsychotics are administered empirically according to clinical dose-finding studies, in which arbitrarily selected doses are tested to find the most efficient dose range in a patient population. Imaging studies have consistently shown that all categories of antipsychotic drugs induced a marked occupancy of D2R at clinical doses and a threshold exists above which extrapyramidal side effects (EPS) are likely to occur (±80%). Farde et al. (1992) demonstrated that treatment of patients with schizophrenia with a range of antipsychotic medications resulted in blockade of 65–90% of striatal D2Rs, and that patients with acute EPS had higher levels of D2R occupancy. The minimum striatal D2 occupancy required for antipsychotic efficacy is less clearly defined, but occupancy above the EPS threshold does not appear to confer additional benefit: Clinical studies with haloperidol do not point to an advantage of doses exceeding 5 mg/day, which corresponds to ±80% occupancy.

Another question of clinical relevance is whether poor response to treatment can be explained by inadequate blockade of D2R. In this regard, "nonresponders" show little improvement despite high D2R occupancy rates (Kapur et al. 2000; Wolkin et al. 1989).

The onset of antipsychotic action appears to occur early (Leucht et al. 2005), but is dependent on the degree of striatal D2R occupancy (Agid et al. 2007). Low doses of selective D2R antagonists like haloperidol and raclopride require 50–60% occupancy for a rapid clinical response (Kapur et al. 2000; Nordstrom et al. 1993b), and D2 occupancy during the first 2 days predicts the nature of response over the next 2 weeks (Catafau et al. 2006).

PET studies helped to investigate the mechanisms that underlie clozapine's superior efficacy. Clozapine was the first "atypical antipsychotic" and three main hypotheses have been proposed: high 5-HT2/D2R binding ratio, loose binding to D2R, and regional specificity (Abi-Dargham and Laruelle 2005). In clozapine-treated patients with schizophrenia, the mean D2R occupancy was 47% (range 20–67%). It was also the first antipsychotic found to have a very high 5-HT2R occupancy in schizophrenia (range 84–94%) even at low doses (Farde et al. 1992;

Nordstrom et al. 1993a, 1995a). At high plasma concentrations, clozapine can induce high extrastriatal DA D2R occupancy, as found with [^{11}C]FLB 457 (Takano et al. 2006). Higher in vivo binding to cortical D2R than in the basal ganglia is suggested as an indicator of favorable profile (Xiberas et al. 2001) but has not been shown to relate to therapeutic effect, while striatal D2R occupancy has been related to therapeutic effects in more than one study with other atypical antipsychotics (Agid et al. 2007; Kegeles et al. 2008).

Studies evaluating the next two atypical antipsychotic medications, risperidone and olanzapine, found that therapeutically effective doses of risperidone blocked 46% to over 90% of striatal D2R (Knable et al. 1997a). In a study with [^{123}I]IBZM SPECT in patients treated with olanzapine, Raedler et al. observed a range of 33–81% D2 receptor blockade at 5 mg and 56–97% at 20 mg. No significant increase in EPS was found when patients' medication was increased from the lower to the higher olanzapine dose (Raedler et al. 1999). Sparing of substantia nigra and VTA D2R occupancy, demonstrated with [^{18}F] fallypride, was proposed to contribute to the low incidence of EPS in olanzapine-treated patients (Kessler et al. 2005) although many alternative explanations can be offered, the most parsimonious being low striatal D2R occupancy followed by anticholinergic blockade. Both risperidone and olanzapine in clinical dosages lead to levels of D2R occupancy that are comparable to those observed with low dosages of "typical" antipsychotics (Bressan et al. 2003; Knable et al. 1997a), but higher than with clozapine.

The striatal D2R occupancy of atypical antipsychotics ranges from 81% with risperidone to 30% with quetiapine (rank order: risperidone > olanzapine > clozapine > quetiapine) (Heinz et al. 1996). From the observed degree of elevation of synaptic DA levels in antipsychotic-naïve patients, Laruelle et al. (2005) have estimated that antipsychotic medications would need to occupy 48% of the D2R to normalize DA transmission. The fact that patients are generally treated with dosages of medication that result in 60–80% D2R blockade, and higher with standard dosing of typical antipsychotics, means that their DA tone is being maintained at slightly lower levels than those found in unmedicated healthy subjects (Frankle et al. 2004a). Ongoing D2R blockade and reduced DA tone may contribute to the dysphoria, secondary negative symptoms, and depression experienced by some patients even in the absence of EPS (Mizrahi et al. 2007).

More recently, ziprasidone has been demonstrated to result in levels of D2R occupancy similar to risperidone and olanzapine (Mamo et al. 2004; Vernaleken et al. 2008).

The advent of partial agonists may offer a way to achieve substantial D2R occupancy with a lesser impact on subjective well-being (Mamo et al. 2006). Aripiprazole at clinical doses occupies about 90% of its target receptor in the brain (Grunder et al. 2008). Occupancy levels are slightly higher in extrastriatal than striatal regions (Kegeles et al. 2008 see Fig. 2).

Quetiapine shows a transiently high D2R occupancy, which decreases to very low levels by the end of the dosing interval. Quetiapine's low D2R occupancy can explain its lack of EPS and some have speculated that its transient D2R occupancy may be sufficient for its antipsychotic effect (Kapur and Seeman 2001; Tauscher-Wisniewski et al. 2002).

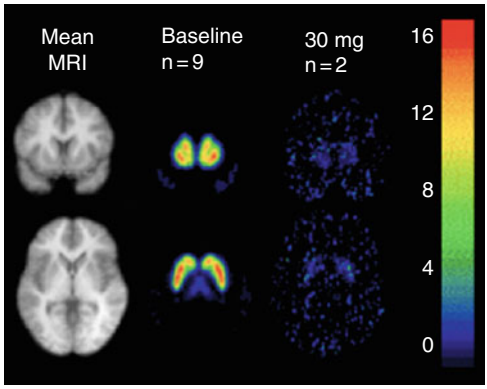

Fig. 2 Parametric map of BP_{ND} of the dopamine D2R antagonist [^{18}F]fallypride, computed for nine unmedicated subjects (*baseline*), showing activity distribution in striatal regions summed over 240 min (*middle*). Coregistered structural MRI are on the *left*. On the *right*, parametric map for two subjects treated with 30 mg of aripiprazole daily. The image after [^{18}F] fallypride injection was summed over 120 min. Aripiprazole reached over 90% receptor occupancy at this dose

4.1.2 D1 Receptor Occupancy

Exploring the effects of antipsychotic medications on extrastriatal D1Rs has become of interest because of its implications for cognitive deficits in schizophrenia (Goldman-Rakic and Selemon 1997). Several small clinical trials with D1R antagonists have proved ineffective in reducing psychotic symptoms (Karlsson et al. 1995). Imaging studies of D1R occupancy have explored antipsychotic binding in the striatum of clozapine (33–59%), typical antipsychotics (0–44%), olanzapine (43%), quetiapine (12%), and risperidone (25%) (Farde et al. 1992; Nordstrom et al. 1995a). When comparing atypical antipsychotics for D1R occupancies studied with PET and [^{11}C]SCH 23390, mean striatal occupancies ranged from 55% with clozapine to 12% with quetiapine (rank order: clozapine > olanzapine > risperidone > quetiapine). The ratio of striatal D1/D2R occupancy was significantly higher for clozapine (0.88) relative to olanzapine (0.54), quetiapine (0.41), or risperidone (0.31) (Tauscher et al. 2004). D1R occupancy does not seem to contribute to the therapeutic effect of these drugs, as they are all D1R antagonists. Currently D1R agonists are under experimental testing.

4.2 Serotonin Occupancy

4.2.1 5-HT2A Receptor Occupancy

A fair number of recent imaging studies measured 5-HT2AR occupancy achieved by atypical medications in vivo, but information on the binding of typical antipsychotic medications to the 5-HT2AR in human subjects is very limited. Nordstrom et al. (1995b) used [^{11}C]NMSP to image the 5-HT2AR in patients with schizophrenia on clozapine. The receptor occupancy values were high despite the wide range

of clozapine serum levels at the time of the scan (120–1,060 ng/ml); when compared to antipsychotic-naïve patients with schizophrenia, the 5-HT2AR occupancy ranged from 84 to 94%. Other studies have also revealed high levels of 5-HT2AR occupancy for risperidone. Greater than 80% occupancy was reported in a small sample of seven subjects taking 3 mg/day of risperidone (Nyberg et al. 1999). At 6 mg/day of risperidone, the 5-HT2AR occupancy was 95%. 5-HT2AR occupancy rates are associated with favorable treatment for depressive symptoms within schizophrenia and improvement of cognitive function (Kasper et al. 1999). It has been suggested that blockade of serotonin 5-HT2A/2C receptors may be responsible for the lower EPS observed when patients are treated with atypical antipsychotics (Heinz et al. 1996), but at high D2R occupancy levels, 5-HT2A/2C receptor antagonism is not sufficient to prevent EPS (Knable et al. 1997a), since the threshold of D2R occupancy associated with EPS is not markedly different between these drugs and the ones devoid of 5-HT2AR antagonism (Kapur et al. 1998; Knable et al. 1997a; Nyberg et al. 1998, 1999).

4.2.2 5-HT1A Receptor Occupancy

The atypical antipsychotic medications aripiprazole, clozapine, quetiapine, and ziprasidone all have a degree of agonist activity at the 5-HT1AR (Bantick et al. 2004b). Studies using [^{11}C]WAY 100635 to assess the degree of occupancy of clozapine and ziprasidone at that receptor in schizophrenia have been unsuccessful in detecting occupancy (Bantick et al. 2004a). Aripiprazole was found to have a mean occupancy of 16.4% in the temporal and frontal regions (range 0 to 39% and −2 to 43%, respectively) of patients. There was no correlation between dose (between 10 and 30 mg daily for 4 weeks) and 5-HT1AR occupancy (Mamo et al. 2007). Preclinical studies demonstrate that activation of this receptor can increase DA release in the PFC (for review, see Meltzer et al. 2003). Clinically, several small studies have shown that the addition of 5-HT1AR agonists, such as tandospirone and buspirone, to D2R antagonist medications improves negative and cognitive symptoms in schizophrenia (Sumiyoshi et al. 2001a, b). The presence of a pharmacological effect in the absence of detectable occupancy, or with minimal occupancy, is not unusual for full agonists, and has been described previously in other systems. The reasons may relate to the fact that an antagonist is used to label the sites, binding to both high- and low-affinity configurations of the receptor, while the agonist binds only to the fraction of those in the high-affinity state (Leff 1995).

5 Future Directions

The search for new and improved antipsychotic agents with more focus on neurotransmitters other than DA is an active area of research (for review, see Stone and Pilowsky 2007). Future drug development and research into the etiopathogenesis will focus on further identifying and manipulating the upstream factors that converge on the dopaminergic system (Howes and Kapur 2009). This process

will unravel new mechanisms that can be used as therapeutic targets. PET can speed the process of drug discovery by (1) aiding in identifying these mechanisms of pathology, (2) providing rapid screening of new drugs with early fast decisions about which drugs are suitable to move into clinical testing, and (3) guiding dose selection. The availability of new tracers for transmitter systems that have not been studied to date will greatly facilitate this process.

Thus, neurochemical imaging has played a major role in advancing our knowledge of the pathology and treatment of schizophrenia and will continue to do so as technology improves and widens in scope.

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