Recent Findings on Dopamine in the Pathophysiology of Schizophrenia

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The original dopamine hypothesis (Carlsson & Lindqvist, 1963 as cited in Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999) predicts a hyperactivity of dopamine transmission that is responsible for the symptoms of schizophrenia. The hypothesis was based upon clinical observations of the effects of antipsychotic medications, however, recent research aims to directly measure the dopamine system in the brains of schizophrenic patients. Postmortem and in vivo methods have found results beyond a constant hyperactive state predicted in the classical dopamine hypothesis. In addition, complex interactions of the dopamine system with other neurotransmitters have been implicated.

Schizophrenia is a debilitating disease that affects 1% of the population worldwide (Taber, Lewis, & Hurley, 2001). Theories of the causes of schizophrenia have covered a wide range from original sin to biological causes, such as heritability and abnormalities in the brain. The topic of brain abnormalities itself ranges from structural defects to neurochemical imbalances.

An individual’s life is significantly affected by the various symptoms of this devastating disease. Symptoms of schizophrenia range greatly from negative to positive symptoms. In 1980, Crow (as cited in Fowles, 1992, p. 312) coined and defined the terms Type I and Type II schizophrenia. Type I is characterized by the positive symptoms of delusions, hallucinations, and excited motor activity. Type II is characterized by the negative symptoms of “emotional and social withdrawal, blunted affect, apathy, and poverty of thought or speech” (Crow, 1980 as cited in Fowles, 1992, p. 311). Crow proposed that Type I schizophrenia indicates a neurochemical disturbance involving dopamine, whereas Type II schizophrenia reflects structural brain changes.

The dopamine hypothesis also predicts schizophrenia to be related to dopamine dysfunction. Van Rossum (1967, as cited in Farde, 1997, p. 157) postulated that the “symptoms of schizophrenia are associated with increased central dopaminergic neurotransmission.” The dopamine hypothesis was supported by clinical observations showing psychotic symptoms to be worsened by dopamine agonists (Randrup & Munkvad, 1967 as cited in Farde, 1997). However, new brain imaging technologies have enabled researchers to experimentally examine schizophrenic brains beyond clinical observations.

Brain imaging methods have been developed and used in both postmortem and in vivo studies. Postmortem studies utilize autoradiographic assays of brain tissue sections, in which dopamine receptor densities are measured with various radiotracers that bind to its specific receptor. Although postmortem studies have been useful in schizophrenia research,
they are greatly limited in evaluating effects of medication, age, or duration of illness on schizophrenia (Dean & Hussain, 2001; Laruelle et al., 2000). The in vivo method allows researchers to examine antipsychotic-naïve schizophrenic patients so that the side effects of antipsychotics will not obscure the true etiology of schizophrenia.

In vivo studies utilize radiotracers administered to individuals, who then undergo an imaging scan of either positron emission tomography (PET) or single photon emission computerized tomography (SPECT). The technology involved in these neurochemical brain imaging methods has greatly advanced in the past 20 years (Soares & Innis, 1999). Since its beginning in the early 1980s, neurochemical brain imaging has helped to clarify and refine the original dopamine hypothesis by allowing close examinations of pre-synaptic activity, intrasynaptic levels of dopamine, and post-synaptic receptors (Soares & Innis, 1999).

Pre-synaptic activity in neurons includes neurotransmitter synthesis and release. Intrasynaptic neurotransmitter levels are the amounts of neurotransmitter present in the synaptic cleft due to firing of the neurons. Lastly, post-synaptic receptors are the receptors on the post-synaptic membrane that are binding the neurotransmitters. The original dopamine hypothesis is not clear on which of these three aspects of neural transmission is dysfunctional (Soares & Innis, 1999; Taber, et al., 2001).

The purpose of this literature review is to examine the modifications and clarifications to the original dopamine hypothesis of schizophrenia made by recent postmortem and in vivo studies. The findings on pre-synaptic dopamine activity, intrasynaptic levels of dopamine, and dopamine receptors in studies of schizophrenic patients are discussed. In line with Crow’s (1980) proposed hypothesis, this focus on the dopaminergic system is associated therefore, with a focus on the positive symptoms of schizophrenia.

Dopamine

Pre-synaptic Abnormalities

Pre-synaptic activities that take place in neurons are neurotransmitter synthesis, release, and re-uptake. In dopamine, synthesis is controlled largely through the enzyme aromatic L-amino acid decarboxylase. Release and re-uptake of dopamine are controlled by dopamine transporters (DAT). These two functions, if impaired, could theoretically contribute to the dysfunctional dopaminergic transmission.

Synthesis. A vital part of the dopaminergic system is dopamine synthesis. Dopamine synthesis consists of the conversion of tyrosine to L-DOPA, which is converted to dopamine. This conversion process takes place pre-synaptically through enzymatic control. An increase in dopamine synthesis is therefore suspected to be involved in the pathophysiology of schizophrenia. Various brain imaging methodologies have been developed and used to investigate the enzyme activity in dopamine synthesis in schizophrenic patients, including the use of \([^{18}F]DOPA\) and \([^{11}C]DOPA\) radiotracers and amphetamine-challenge inducing dopamine release.

\([^{18}F]DOPA\) and \([^{11}C]DOPA\) are the radiotracer equivalents of L-DOPA, which is converted to dopamine by the enzyme aromatic
L-amino acid decarboxylase (Elkashef et al., 2000; Bjurling et al., 1990 as cited in Lindstrom et al., 1999). It had been shown in Gjedde et al., 1991 (as cited in Reith et al., 1994) that the rate constant of \[^{18}F\]DOPA metabolism is an accurate index of the activity of dopa decarboxylase. Reith et al. (1994), Hietala et al. (1995), Dao-Castellana et al. (1997), Lindstrom et al. (1999) and Elkashef et al. (2000) have conducted studies using this methodology and three of the five studies show a significant increase in presynaptic dopamine activity.

Reith et al. (1994) hypothesized that a decrease in baseline extracellular dopamine due to low cortical stimulation in schizophrenia leads to an increase in the activity of dopa decarboxylase. An important part of this study was their connection of increased dopamine-synthesizing enzyme activity with positive symptoms of schizophrenia. They looked at \[^{18}F\]DOPA uptake in the caudate nucleus and putamen through PET scanning in four groups: a control group of 13 healthy subjects, eight patients with complex partial seizures (CPS) without psychosis, five patients with CPS with psychosis, and five neuroleptic-naive schizophrenic patients. The metabolism of \[^{18}F\]DOPA was calculated as the value \(k_3\), which took into account the maximum velocity of the decarboxylation reaction, the half-saturation constant for \[^{18}F\]DOPA, and the \[^{18}F\]DOPA distribution volume in the brain. The \(k_3\) values of the caudate and putamen were found to be significantly higher in patients with schizophrenia and patients with CPS with psychosis compared to control subjects and patients with CPS without psychosis. The results first showed the hyperfunction of dopa decarboxylase in schizophrenia. The activity of dopa decarboxylase is the first irreversible step in dopamine synthesis. Although an increased activity of this enzyme does not signify increased dopamine synthesis per se, it plays a role in an overall pre-synaptic dopamine hyperactivity. Secondly, the results showed the connection of elevated dopa decarboxylase activity specifically with positive symptoms.

Hietala et al. (1995) reported results similar to those of Reith et al. (1994). This study also examined the caudate and putamen of schizophrenic patients with \[^{18}F\]DOPA and PET scanning. However, the subjects used were neuroleptic-naive schizophrenics, eliminating the questions of neuroleptic treatment effects on dopa decarboxylase activity. In their sample of seven patients with schizophrenia and eight healthy controls, they found a significantly higher \[^{18}F\]DOPA uptake, calculated as \(K_i\) values, in the putamen of schizophrenic subjects compared to controls. However, their results did not show a difference in the caudate of schizophrenics. This study also did not find a significant correlation between higher \[^{18}F\]DOPA uptake and positive symptoms or negative symptoms rated with the Positive and Negative Symptom Scale (PANSS). Although there was no formal correlation between elevated \[^{18}F\]DOPA uptake and positive symptoms, a schizophrenic subject with catatonic schizophrenia showed no increase in \[^{18}F\]DOPA uptake, and even had lower \[^{18}F\]DOPA uptake than controls. This implies that negative symptoms of schizophrenia, displayed as catatonia, are not
associated with elevated presynaptic dopamine function, whereas positive symptoms of schizophrenia are.

A more recent study by Lindstrom et al. (1999) used the radiotracer \([{\text{11}}^C}\)DOPA with the same theoretical framework as the two previous studies to measure dopamine turnover. \([{\text{11}}^C]\)DOPA has an advantage over \([{\text{18}}^F]\)DOPA in measuring dopamine turnover because it is not easily metabolized outside the blood-brain barrier, whereas \([{\text{18}}^F]\)DOPA is. Therefore, \([{\text{18}}^F]\)DOPA uptake calculations must correct for the metabolites entering the brain (Lindstrom et al., 1999). A second strength of this study was their schizophrenia sample group, made up of 12 schizophrenics, 10 of which were neuroleptic-naïve, eliminating the question of whether results were due to antipsychotic use. This study found significantly higher overall \(K_i\) values for the schizophrenia group mean compared to the control group mean. The effect was most prominent in the caudate nucleus, putamen, and the caudal medial prefrontal cortex. The increased \(K_i\) value in the medial prefrontal cortex has never been found in previous studies and has important implications in future research on dopaminergic functioning in the prefrontal cortex.

In contrast to Reith et al. (1994), Hietala et al. (1995), and Lindstrom et al. (1999), the works of Dao-Castellana et al. (1997) and Elkashef et al. (2000) did not find an increase in \([{\text{18}}^F]\)DOPA uptake. In Dao-Castellana et al., the \([{\text{18}}^F]\)DOPA uptake rate constant was also calculated and expressed in \(K_i\) values. They found no difference between the untreated schizophrenia group and control group \(K_i\) values in the caudate and putamen. However, several schizophrenia subjects did have higher \(K_i\) values compared to control subjects. In addition, lower \([{\text{18}}^F]\)DOPA metabolic rate values were obtained from catatonic schizophrenic subjects. It appears that Hietala et al. and Reith et al. did not have as great a number of catatonic cases as this study. The small number of subjects in Dao-Castellana et al. - six schizophrenic patients and seven control subjects - makes even a slightly larger number of catatonic schizophrenics the probable cause of discrepant results.

The study by Elkashef et al. (2000) found contrasting results of a significant decrease of \([{\text{18}}^F]\)DOPA uptake in the ventral striatum of drug-free schizophrenics and significant increase in the posterior cingulate of drug-free schizophrenics. However, although categorized as drug-free schizophrenics, subjects were medication-free for at most 56 days. These subjects were not medication-naive schizophrenics as were the subjects in Reith et al. (1994), Hietala et al. (1995), Dao-Castellana et al. (1997), and Lindstrom et al. (1999). Although there have been conflicting results apparently due to differences in subject selection, the consensus in these studies is that increased dopa decarboxylase activity could very likely be an up-regulatory mechanism in response to a deficiency of dopamine release (Elkashef et al., 2000; Lindstrom et al., 1999; Reith et al., 1994) from “corticostriatal glutamatergic projections from the prefrontal cortex” (Abi-Dargham et al., 2000, p. 8108; Reith et al., 1994, p. 11651). The increase in enzymatic activity would increase dopamine in the striatum, which is then
stored in vesicles or accumulated in a free cytoplasmic dopamine pool (Breier et al., 1997; Lindstrom et al., 1999). In light of these findings, increased dopamine decarboxylase activity would therefore lead to increased intracellular dopamine levels and decreased extracellular dopamine levels in tonic or non-firing periods.

Release and reuptake. A second possible pre-synaptic dysfunction that has been examined in schizophrenia is in dopamine transporters (DAT). Dopamine transporters function as releasers of dopamine from terminals into the synaptic cleft and as re-uptake carriers of dopamine in the synaptic cleft back into the terminals (Lavalaye et al., 2001; Soares & Innis, 1999). The \([^{18}F]DOPA\) and \([^{11}C]DOPA\) studies discussed previously (Hietala et al., 1995; Lindstrom et al., 1999; Reith et al., 1994) have generally suggested an increase in pre-synaptic dopamine activity. These related pre-synaptic dopamine studies and the question of whether there is an increased amount of dopamine terminals in schizophrenic patients have led researchers to explore dopamine transporter densities.

In the measurement of dopamine transporter densities, there have been postmortem and in vivo studies conducted. Knable et al. (1994) and Dean and Hussain (2001) conducted two post-mortem autoradiographic studies looking at dopamine transporter density. Knable et al. used \([^{3}H]2ß-carbomethoxy-3ß-(4-fluorophenyl)tropane\), or \([^{3}H]CFT\), autoradiography to measure the dopamine transporter density in the putamen, caudate, and nucleus accumbens of schizophrenic patients, controls, and a neuroleptic-treated control group that did not have schizophrenia. There was no significant differences in \([^{3}H]CFT\) binding between the three groups, therefore signaling no change in dopamine transporter density in schizophrenic patients (Knable et al., 1994).

Dean and Hussain (2001) used the radioligand \([^{3}H]mazindol\) in their measurement of dopamine transporter density in the caudate and putamen. They tested 13 schizophrenic patients and compared them to 13 age- and gender-matched control subjects. It was reported that schizophrenic patients had a significant decrease in \([^{3}H]mazindol\) binding of the striatum compared to controls. This suggests a decrease in DAT density in these schizophrenic patients. This result differs from what was found by Knable et al. (1994), who did not find an alteration in DAT density in schizophrenic subjects. The inconsistencies of postmortem findings in dopamine transporter density were cleared up through in vivo methods.

In vivo studies, using various radioligands and scanning techniques in schizophrenic patients, have also been conducted to examine dopamine transporter density. In vivo studies have advantages over postmortem studies for several reasons. First, postmortem samples are obtained from older subjects who died several decades after the active phases of schizophrenia, associated with positive symptoms and dopamine hyperactivity (Laruelle et al., 2000). Secondly, in vivo studies allow researchers to make clearer observations and correlations of the severity of symptoms, duration of illness, and neuroleptic use with dopamine transporter density.

Most in vivo studies have not found a decrease in DAT density.
This was found and demonstrated in three independent studies by Laruelle et al. (2000), Laakso et al. (2000), and Lavalaye et al. (2001). Laruelle et al. employed SPECT scanning and the radioligand $[^{123}I]$methyl 3ß-(4-iodophenyl)tropane-2ß-carboxylate, also known as $[^{123}I]$-CIT, which was shown by Laruelle et al. (1993, as cited in Laruelle et al., 2000) to selectively bind to DAT in the striatum. They tested 15 schizophrenic patients and 15 controls and found no significant difference between the two groups. Despite the non-significant results between the schizophrenic group and the control group, an important trend was found in the correlation between longer durations of illness and lower striatal DAT density.

A second in vivo DAT study done by Laakso et al. (2000) used the radioligand $[^{18}F]2ß$-carbo-methoxy-3ß-(4-fluorophenyl)tropane (or $[^{18}F]$CFT) and PET imaging. They studied the caudate and putamen DAT density in nine first-episode, neuroleptic-naive schizophrenic patients and matched controls. The results from this study showed that there was no significant difference in $[^{18}F]$CFT binding between the two groups in the caudate and the putamen. This study replicated the results of Laruelle et al. (2000) in finding no alteration in patients’ DAT density, and in finding a negative correlation in illness duration and DAT density.

A possible source of the inconsistency in postmortem studies’ results was the patients’ use of antipsychotic medication. It was argued that Dean and Hussain’s (2001) finding of decreased DAT density was due to the effects of antipsychotics. However, a recent in vivo study conducted by Lavalaye et al. (2001) attempted to discover the effects of medication on DAT density. Lavalaye et al. examined the DAT density in the striatum of antipsychotic-naive schizophrenic patients, patients currently on risperidone or olanzapine, patients that were previously treated with antipsychotics (AP) but currently antipsychotic-free, and control subjects. It was found through SPECT imaging and the radiotracer $N$-$ß$-fluoropropyl-2$ß$-carbomethoxy-3$ß$-[4-iodophenyl]tropane, or $[^{123}I]$FP-CIT, that there was no significant difference in DAT density in the entire striatum, caudate, and putamen between the groups studied (Lavalaye et al., 2001). This study demonstrates that antipsychotics do not affect dopamine transporter density because patients who were previously on AP, currently on AP, or AP-naive patients did not have differences in DAT density. Lavalaye et al. also replicated the findings of previous in vivo studies by finding no differences in schizophrenic patients’ and controls’ DAT density.

Although antipsychotic medication does not seem to affect dopamine transporter density, it has been found in several in vivo studies discussed previously (Laakso et al., 2000; Laruelle et al., 2000) that the duration of illness in schizophrenia is associated with a decrease in DAT density. This may be the main reason for the decrease in DAT density found in the results of Dean and Hussain (2001). The subjects examined in their postmortem study had a mean duration of illness of 45 ± 5.1 years. A recent study by Laakso et al. (2001) examined the DAT density of patients with chronic schizophrenia with PET imaging and $[^{18}F]$CFT in the caudate and putamen. The group of chronic schizophrenic subjects recruited...
DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

for this study had a median duration of illness of ten years, with the highest duration of 28 years. It was reported that there was a significant decrease of \[^{[18]}F\text{CFT}\] binding in the caudate and putamen in the schizophrenic compared to the control group. Specifically, there was a reduction of 11.4\% \[^{[18]}F\text{CFT}\] binding in the caudate and 11.6\% in the putamen of schizophrenic patients (Laakso et al., 2001). This shows a significant decrease in DAT density in chronic schizophrenia that has not been explicitly demonstrated in previous studies.

In light of the literature reviewed on the topic of dopamine transporter density, it has been shown that it is not a factor in the pathophysiology of schizophrenia. However, Laakso et al. (2001) has demonstrated a decrease in DAT density in chronic schizophrenia. It is hypothesized therefore, that this decrease may be due to a loss of dopaminergic neurons either from a prolonged hyperactive dopamine system, the progressive nature of schizophrenia, or a combination of both (Lieberman et al., 1990 as cited in Laakso et al., 2001).

Synaptic Abnormalities of Dopamine Levels

The increase in D2 transmission hypothesized in the dopamine hypothesis could possibly be associated with an increase in synaptic levels of dopamine. The increase in dopa decarboxylase activity from \[^{[14]}F\text{DOPA}\] and \[^{[11]}C\text{DOPA}\] studies has led researchers to wonder if the synaptic output by neurons is also increased (Abi-Dargham et al., 2000). In addition, rodent studies have found an increased dopamine concentration after the administration of amphetamine (Abi-Dargham et al., 2000). This led researchers to examine human synaptic dopamine concentrations first with the amphetamine challenge method and later through a dopamine depletion method. Amphetamine-challenge studies.

Amphetamine-challenge studies induce dopamine release because amphetamine is a dopamine agonist. Fischer and Cho (1979, as cited in Breier et al., 1997), Sulzer et al. (1995, as cited in Soares & Innis, 1999), and Giros et al. (1996, as cited in Soares & Innis, 1999) reported that amphetamine releases the cytoplasmic dopamine into the extracellular space through transporters, which are firing-independent mechanisms. It is hypothesized that in schizophrenia, amphetamine-induction causes higher dopamine release levels compared to non-schizophrenic individuals. This was established in the works of Laruelle et al. (1996), Abi-Dargham et al. (1998), and Breier et al. (1997). Laruelle et al. developed this methodology of studying amphetamine-induced dopamine transmission using single photon emission computerized tomography (SPECT) images and the radioligand \[^{[123]}I\text{(S)-(}-3\text{-iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide}\ or simply \[^{[123]}I\text{IBZM}\, which is a selective antagonist at D\text, and D\text, receptors. The procedure is as follows: a state of equilibrium of \[^{[123]}I\text{IBZM}\ binding is obtained through a bolus and constant infusion of \[^{[123]}I\text{IBZM}, a first SPECT scan shows the pre-amphetamine baseline \[^{[123]}I\text{IBZM}\ binding potentials, and after amphetamine injection a second SPECT scan shows a decrease in the post-amphetamine \[^{[123]}I\text{IBZM}\ binding potentials. Amphetamine causes an increase in the release of dopamine, which is believed to displace the \[^{[123]}I\text{IBZM bound to...}
receptors. By measuring the radioactivity of \([^{123}\text{I}]\text{IBZM}\) binding, dopamine release is found.

With this methodology, Laruelle et al. (1996) found that the "amphetamine-induced decrease in \([^{123}\text{I}]\text{IBZM}\) binding potential was significantly larger in schizophrenic patients (-19.5 ± 4.1%) than in controls (-7.6 ± 2.1%)" (p. 9237). This greater decrease in \([^{123}\text{I}]\text{IBZM}\) binding in schizophrenics demonstrates a greater amount of dopamine release that is displacing the \([^{123}\text{I}]\text{IBZM}\) in receptors. Another important finding of this study was the schizophrenic patients’ responses to amphetamine administration and the amount of decrease in \([^{123}\text{I}]\text{IBZM}\) binding potential they had. Laruelle et al. found within-subjects differences in the responses to amphetamine, ranging from improvements in positive symptoms, unaltered positive symptoms, and worsening of positive symptoms as evaluated by the PANSS. The six patients with an exacerbation of positive symptoms showed larger reductions in \([^{123}\text{I}]\text{IBZM}\) binding potential (-27.6 ± 6.4%) compared to the nine patients who did not experience a worsening of positive symptoms (-14.1 ± 4.6%) and the healthy controls (-7.6 ± 2.1%). This correlation shows the relationship between positive symptoms and dopamine hyperactivity.

Abi-Dargham et al. (1998) repeated the procedure by Laruelle et al. (1996) on a second cohort of 15 new schizophrenic subjects. Results of Laruelle et al. (1996) were successfully replicated. The first main finding was that amphetamine-induced dopamine release was significantly higher in patients than controls. Secondly, no controls experienced psychotic symptoms due to the amphetamine administration and the schizophrenic patients’ responses to amphetamine were heterogeneous. The patients suffering a worsening of positive symptoms had significantly higher amphetamine-induced dopamine release levels than patients without psychotic responses. Lastly, no significant correlations were found between negative symptoms and amphetamine-induced dopamine release.

Independent of Laurelle et al. (1996) and Abi-Dargham et al. (1998), Breier et al. (1997) conducted a study also measuring amphetamine-induced dopamine release in schizophrenia; however, different measurement techniques of PET and the radiotracer \([^{11}\text{C}]\text{raclopride}\) were used. This study first established the soundness of \([^{11}\text{C}]\text{raclopride}\) by finding that doubling the amphetamine dose caused a doubling in the mean striatal binding reductions. Breier et al. found two important results. First, schizophrenic patients showed greater amphetamine-induced reductions in \([^{11}\text{C}]\text{raclopride}\) striatal binding than control subjects, replicating previous findings of schizophrenia’s association with greater amphetamine-induced dopamine release.

Secondly, this study included both neuroleptic-naive and previously treated schizophrenic patients, allowing for the examination of possible differences between the two groups. It was found that there was no significant difference in amphetamine-induced binding changes between the two subgroups of schizophrenics. This result indicates that an increase in amphetamine-induced dopamine release is not due to previous neuroleptic treatment, but is
prevalent in both drug-naive and drug-treated schizophrenics.

**Baseline state studies.**
Although it has been demonstrated that people with schizophrenia are more sensitive by releasing more dopamine in amphetamine studies, researchers questioned if dopamine release is increased in schizophrenia in a non-challenged or baseline state (Abi-Dargham et al., 2000; Laruelle et al., 1997). Laruelle et al. developed a method to study baseline dopamine levels in an in vivo human brain. They looked specifically at dopamine occupancy in D2 receptors due to the many conflicting results in the study of these receptors.

The method measures the amount of free D2 receptors using the radioligand $[_{123}I]$IBZM in a first SPECT scan. Next, a synaptic dopamine depleter called alpha-methyl-para-tyrosine (AMPT), found to be safe with rapidly reversible effects in humans, is orally administered. A second SPECT scan is taken and the difference in $[_{123}I]$IBZM binding between the two scans reflects "the unmasking of D2 receptors previously occupied by dopamine" (Abi-Dargham et al., 2000, p. 8104). Therefore, it is thought that schizophrenia is associated with a higher dopamine release and occupation of D2 receptors in a baseline state in addition to the established amphetamine-challenged state. Through this method then, it is expected for schizophrenic patients to have a greater increase of $[_{123}I]$IBZM binding to D2 receptors after AMPT depletion due to AMPT unmasking more dopamine in schizophrenics than in normal subjects.

Abi-Dargham et al. (2000) used this dopamine depletion method in comparing eight antipsychotic-naive schizophrenic patients, ten antipsychotic-treated patients, and 18 matched controls. The striatal dopamine occupancy of D2 receptors was specifically examined through the binding of $[_{123}I]$IBZM. Abi-Dargham et al. reported a significant difference between schizophrenic patients and controls with patients having a higher D2 receptor availability after dopamine depletion, measured by the increase in $[_{123}I]$IBZM binding, than controls. The D2 receptor availability after depletion increased in control subjects by 9% ± 7% but increased in schizophrenic patients by 19% ± 7%. In addition, both antipsychotic-naive and antipsychotic-treated schizophrenic patients experienced a significant increase in D2 receptor availability compared to control subjects. The results did not show a significant correlation between D2 dopamine receptor occupancy and positive symptoms, however, a trend level of a correlation was found.

These data imply that schizophrenic individuals have a higher amount of dopamine occupying their D2 receptors, even without amphetamine-induction of dopamine release. This demonstrates a dysregulated dopaminergic system in schizophrenia with no pharmacological interventions. A limitation of this method was that an exact calculation of the amount of dopamine depleted with AMPT is not known, and is estimated at 70-80% (Abi-Dargham et al., 2000). Another limitation of this study was the resolution of SPECT imaging. It prevented the specific localization of the structures in the mesolimbic dopaminergic system. With a higher resolution SPECT camera, the examination of the nucleus accumbens and ventral striatum may give significant results in
the correlation between D2 receptor availability and an increase in the positive symptoms of schizophrenia (Abi-Dargham et al., 2000).

**Post-synaptic Abnormalities**

It has been hypothesized that "increased dopaminergic activity in schizophrenia has been attributed to abnormalities of dopamine receptors" (Knable et al., 1994, p. 828). Numerous studies have investigated multiple receptor site densities: D1 receptors, the popular D2 receptors, and recent research on D3 and D4 receptors. In the examination of receptors, both postmortem and radioligand methodologies have been employed.

D1 receptors. Knable et al. (1994) and Dean and Hussain (2001) conducted postmortem studies with the radioligand \[ ^{3}H \text{SCH} 23390 \] on the striatal tissue of schizophrenic patients and healthy controls. The similar procedures followed by the two studies both yielded no significant differences in D1 receptor density in the striatum of schizophrenics. These results are in agreement with other postmortem studies conducted by Cross et al. (1981, as cited in Knable et al., 1994), Seeman et al. (1987, as cited in Knable et al., 1994), and Reynolds and Czudek (1988, as cited in Dean & Hussain, 2001).

Although postmortem studies have found no alteration in D1 receptor density in the striatum of schizophrenic patients, in vivo studies with PET imaging has recently been utilized. \text{SCH} 23390 was labeled with \[^{11}C\] to produce a radiotracer that binds to D1-like receptors (Karlsson, Farde, Halldin, & Sedvall, 1993). The following in vivo studies discussed all used the radioligand \[^{11}C\text{SCH} 23390\). In a preliminary in vivo study by Karlsson, Farde, Halldin, Nordstrom, and Sedvall (1993), the putamens of five antipsychotic-naive schizophrenics were measured and compared with five healthy controls. The results showed that there was no significant difference between healthy and schizophrenic subjects in the D1 receptor binding in the striatum. A second in vivo study by Okubo et al. (1997) studied a larger sample of schizophrenic patients, with both antipsychotic-naive and drug-free subgroups. It was found that the density of D1 receptors in the striatum of schizophrenics was not significantly different between the two subgroups of schizophrenic patients and control subjects. A recent in vivo study by Karlsson et al. (2002) looked at the D1 receptor density and also found no significant alterations in the caudate and putamen in neuroleptic-naive schizophrenic patients compared to controls.

Karlsson et al. (2002) also found no significant difference in the density of D1 receptors in the prefrontal cortex. However, in the preliminary study by Karlsson et al. (1993), the variability of schizophrenic patients' prefrontal D1 receptor densities was great. In addition, the Okubo et al. (1997) study found a significant decrease of prefrontal D1 receptor density in both drug-naive and drug-free schizophrenic patients compared to control subjects. This difference in results by Karlsson et al. (2002) and Okubo et al. may have been the difference in the age of subjects, with Karlsson et al. having a younger mean age for the schizophrenia group than Okubo et al. had. Okubo et al. then controlled for these age differences and still observed a significant decrease in both subgroup subjects.
compared to control subjects in the prefrontal D1 receptor density. Significant decreases of D1 receptor densities were also observed for the anterior cingulate cortex after age control. In addition, Okubo et al. had a larger sample size than Karlsson et al. This implies that since neuroleptic-naive, and not only neuroleptic-treated patients, were significantly different from controls, decreases in prefrontal and anterior cingulate densities of D1 receptors are involved in the disease of schizophrenia itself.

This decrease in D1 receptor density found in the prefrontal cortex has stimulated research on the role that prefrontal cells have on dopaminergic activity. The results from Okubo et al. (1997) related to negative and cognitive symptoms of schizophrenia. Therefore Okubo et al. hypothesized that the decreased activity of dopamine, due to the reduction in D1 receptors in the prefrontal cortex induces the deficiencies in cognition and motor function seen in the negative symptoms of schizophrenia. Although this review focuses on the positive symptoms of schizophrenia, it is interesting to note that new research has elucidated the complexity of the dopaminergic system, with schizophrenia involving not only hyperactivity, but also a hypoactivity of dopamine. Knable et al. (1997, as cited in Goldman-Rakic, Muly, & Williams, 2000) has also demonstrated the connection between a dysfunctional dopamine system and the cognitive symptoms of schizophrenia. The interaction between prefrontal D1 receptors and pyramidal neurons has been demonstrated in a study by Smiley, Levey, Ciliax, and Goldman-Rakic (1991, as cited in Goldman-Rakic, Muly, & Williams, 2000).

The association of D1 receptors and dysfunctional cognition and motor skills of schizophrenics is further validated by the ineffectiveness of D1 receptor antagonists on eliminating positive symptoms. Karlsson, Smith, Farde, Harnryd, Sedvall, and Wisel (1995) studied the effects of SCH 39166, which is a potent D1 receptor antagonist, and found a lack of an antipsychotic effect. The antagonist may even have aggravated psychoses. This finding was replicated by Sedvall and Karlsson (1999). Wiesel et al. (1994, as cited in Sedvall et al., 1995), in a clinical pharmacological PET study, administered antipsychotics in vivo to human brains and did not find any occupancy of the medication in D1 receptors.

Although D1 receptors do not seem to play an important role in the actions of antipsychotics, a correlation was found in Dean and Hussain (2001) between D1 receptor density and D2 receptor density in schizophrenic patients. Further research should look at this connection. In addition, further research must be done to find a more selective radioligand that binds only to D1 receptors because the [\(^{11}\)C]SCH 23390 used in all studies is now known to also bind to 5-HT receptors (Knable et al., 1994; Okubo et al., 1997) and D5 receptors (Karlsson et al., 2002).

D2 receptors. D2 receptor abnormalities have long been the focus in the search for the etiology of schizophrenia. Research had centered on D2 receptors due to the clinical effects of antipsychotics that were found to mainly block D2 receptors. From these clinical observations, the dopamine
hypothesis, mentioned earlier, was postulated in which the symptoms of schizophrenia are related to an increased central dopaminergic activity, which may be associated with an increase in the number of dopamine receptors in schizophrenic patients (Farde, 1997; Farde et al., 1990; Hietala et al., 1994; Nordstrom, Farde, Eriksson, & Halldin, 1995). The research on D2 receptors has centered on the density of the receptors in striatal and extrastriatal regions, and in recent studies, the clinical effects of atypical antipsychotics on D2 receptors. Extensive research with postmortem schizophrenic brains had been conducted (Mackay et al., 1980 as cited in Nordstrom et al., 1995; Mito et al., 1984 as cited in Farde et al., 1990; Owen et al., 1978 as cited in Nordstrom et al., 1995; Seeman et al., 1984 as cited in Farde et al., 1990) and reported elevated D2 receptor density in schizophrenic patients compared to controls. However, animal studies have shown that long-term treatment with antipsychotics cause an increase in D2 receptor densities (Farde et al., 1990), and in postmortem studies, most patients had received medication during their entire lifetimes. Therefore, new brain imaging techniques allowed in vivo measurements of D2 receptor densities in neuroleptic-naive patients. Farde et al. (1990) examined D2 receptor density with \(^{11}\text{C}\)raclopride and replicated the results of Farde et al., with no significant difference found in the striatal D2 receptor densities of schizophrenic versus control subjects.

A study by Nordstrom et al. (1995) used a different radioligand, \(^{11}\text{C}\)N-methylspiperone (\(^{11}\text{C}\)NMSP) in their measurement of D2 receptor density. The study recruited a small sample of seven neuroleptic-naive schizophrenic patients and seven controls. Nordstrom et al. found no significant differences between \(^{11}\text{C}\)NMSP binding in control and schizophrenic subjects. Wong et al. (1997) used a similar methodology as Nordstrom et al. (1995), with \(^{11}\text{C}\)NMSP. However, the sample was larger with 22 antipsychotic-naive schizophrenic patients and included 14 bipolar individuals. Wong et al. found a significant increase in D2 receptor densities in the caudate of the seven psychotic bipolar individuals compared to the seven non-psychotic bipolar individuals and controls. In addition, the results showed an increase in the D2 receptor density in schizophrenic patients compared to controls. The results from Wong et al. are in contradiction to a majority of the other in vivo studies looking at D2 receptor density.

The majority of studies show no increase in D2 receptor density in the striatum of schizophrenic patients. Seeman and Kapur (2000) suggest that the inconsistency seen in Wong et al. (1997) may have resulted from the radioligand \(^{11}\text{C}\)NMSP that was used. In Seeman and Kapur, the difference between \(^{11}\text{C}\)NMSP and \(^{11}\text{C}\)raclopride and the effects on the measurement of receptor densities were discussed. An important point in Seeman and
Kapur’s discussion was that \[^{11}C\]raclopride binds to all forms of the D2 receptors, whereas \[^{11}C\]NMSP only binds to the monomer form of the D2 receptor. It was proposed that schizophrenic patients have all their D2 receptors in the form of a monomer, instead of in a variety of forms as in healthy controls. Therefore, using the radioligand \[^{11}C\]NMSP would result in a false increase in D2 receptors. In addition, Seeman et al. (1993) proposed that the increase in D2 receptor binding with \[^{11}C\]NMSP actually reflects an increase in D4 receptor density.

The lack of evidence of an increase in D2 receptor density in neuroleptic-naive schizophrenic patients shows that an increase in D2 receptor density is not involved in the etiology of schizophrenia and most likely results from antipsychotic treatment, which explains the increase observed in postmortem studies. A confirmation of this hypothesis was obtained in Silvestri et al. (2000) who compared the D2 receptor density in eight antipsychotic-naive and nine long-term antipsychotic treated schizophrenic patients. Silvestri et al. used the radioligand \[^{11}C\]raclopride and found that patients with long-term antipsychotic treatment had significantly higher D2 receptor densities than antipsychotic-naive schizophrenic patients. This increase was seen in both patients treated with traditional antipsychotics and patients treated with atypical antipsychotics. The increase in D2 receptor numbers after long-term antipsychotic treatment shows an up-regulation of D2 receptors. Up-regulation is the increase of receptor numbers present in post-synaptic membranes to compensate for the long-term blockade of dopamine by antipsychotic drugs.

Due to the insignificant increase in the D2 receptor density in the striatum of neuroleptic-naive schizophrenics, extrastriatal regions of the brain have recently been more closely examined. An important study by Suhara et al. (2002) examined the anterior cingulate cortex, prefrontal cortex, thalamus, parietal cortex, occipital cortex, and cerebellar cortex with the radioligand \[^{11}C\]FLB 457 and PET imaging. Suhara et al. found a significant decrease in D2 receptor density in the anterior cingulate cortex in schizophrenic patients compared to controls. Results also showed a significant negative correlation of binding potential values in the anterior cingulate with positive symptom scores, indicating that a higher level of endogenous dopamine in the anterior cingulate may be associated with positive symptoms. This relationship of the anterior cingulate and the positive symptoms of schizophrenia had been made previously by Silbersweig et al. (1995, as cited in Suhara et al., 2002) and Cleghorn et al. (1990, as cited in Suhara et al., 2002) through observations of increased activity in this area during auditory hallucinations in schizophrenic patients. The last important implication in this study was the hypothesis in Benes et al. (1991, as cited in Suhara et al., 2002) that neurons in the anterior cingulate cortex are mainly inhibitory interneurons that use GABA as an inhibitory neurotransmitter. The results of a decrease in D2 receptors in the anterior cingulate may suggest an “altered regulatory function of interneurons” taking away the ability to regulate dopamine.
release normally (Suhara et al., 2002, p. 26).

Other studies such as Benes et al. (1997, as cited in Wong, 2002) have also found alterations in the anterior cingulate cortex in schizophrenic patients. However, further research must be conducted to find evidence of these neurons in the anterior cingulate as being inhibitory interneurons.

In addition to recent studies of extrastriatal D2 receptor densities, the clinical effects of different types of antipsychotics are being examined. There are two types of antipsychotics, which are classified as typical or atypical antipsychotics. The main clinical differences between the two are that atypicals do not lead to extrapyramidal side effects and increased prolactin levels whereas typicals do (Kapur & Remington, 2001; Kapur & Seeman, 2001; Kapur, Zipursky, Jones, Remington, & Houle, 2000).

More importantly, imaging studies have shown that atypicals differ from typicals in their dissociation rates from D2 receptors. A study by Seeman and Tallerico (1999) found that atypical antipsychotic drugs, such as clozapine and quetiapine, are displaced by competing endogenous dopamine 100 times faster than the typical antipsychotics of haloperidol, chlorpromazine, and olanzapine.

Therefore, Kapur and Seeman (2001) conclude that a faster dissociation rate by atypicals leads to faster responses to dopamine surges seen in schizophrenia. This fast dissociation rate by atypicals plays a role in preventing extrapyramidal side effects as suggested by Burki (1986, as cited in Kapur & Seeman, 2001) who stated that “the low incidence of extrapyramidal side-effects is probably due to their [clozapine and fluperlapine] weak and relatively brief action on brain DA systems” (p. 365).

In addition to preventing extrapyramidal side effects, Kapur and Seeman (2001) also suggested that repeated transient blockade leads to the dopamine system becoming more sensitive to the effects of dopamine blockade, whereas continuous dopamine blockade leads to dopamine system up-regulation and tolerance. Therefore, in terms of types of antipsychotics, atypicals have a transient nature and long-term treatment with atypicals would not lead to up-regulation or increases in dopamine receptor densities. In fact, Kapur and Seeman suggest that atypicals would cause the dopamine system to respond more efficiently to atypical medication after long-term treatment.

D3 receptors. The role of D3 receptors is not well established due to the small amount of research on the topic. The existence of D3 and D4 receptors was discovered only in the late 1980s and early 1990s (Joyce, 2001). However, it has been determined that the D3 receptor is located mainly in the islands of Calleja, the nucleus accumbens, and the olfactory tubercle (Richtand, Woods, Berger, & Strakowski, 2001), therefore it has been suggested that the receptor functions are related to the mesolimbic rather than the nigrostriatal dopaminergic system (Sokoloff et al., 1990 as cited in Joyce, 2001). Because of D3 receptors’ relation to the mesolimbic dopamine system, its relevance to the psychotic symptoms of schizophrenia is particularly important and wanting for further research.

There have been several hypotheses proposed for the role
and functioning of D3 receptors. One hypothesis is that D3 receptors act as autoreceptors, modulating dopamine synthesis presynaptically (Shafer & Levant, 1998). In vivo studies have shown that a decrease in dopamine synthesis occurs when 7-OH-DPAT, a D3 agonist, is administered (Aretha et al., 1995, Gobert et al., 1995, Gainetdinov et al., 1996, Pugsley et al., 1995, all as cited in Shafer & Levant, 1998). Aretha et al. had also found the decrease in dopamine synthesis to be mainly in the nucleus accumbens and not the caudate. This finding suggests that D3 receptors are the modulating effectors because the nucleus accumbens has a large quantity of D3 receptors and the caudate has few D3 receptors. Therefore, a decrease in D3 autoreceptors would lead to an increase in dopamine synthesis and release.

A post-synaptic role of D3 receptors has also been proposed, where the psychotic symptoms of schizophrenia are associated with a post-synaptic sensitivity of D3 receptors to dopamine (Bordet et al., 1997 as cited in Joyce, 2001). The D3 receptor hypothesis proposed by Richtand, Woods, Berger, and Strakowski (2001) uses aspects of both hypotheses described above. Richtand et al. proposed a down regulation, or decrease in activity of dopamine D3 receptors after a continuous hyperdopaminergic state, as seen in schizophrenia. Ramsey and Woods (1997, as cited in Richtand et al., 2001) proposed that a stimulant-induced release of dopamine, such as that caused by amphetamine, would cause the D3 receptor to respond by returning to equilibrium. It was further hypothesized by Richtand et al. that a continuous hyperdopaminergic state will lead to D3 receptors increasing their homeostatic responses, and will eventually lead to D3 receptors decreasing their signals. In addition, Richtand et al. believe that this decrease in D3 receptor activity leads to the behaviors associated with schizophrenia.

A study by Flores, Barbeau, Quirion, and Srivastava (1996) looked at the effects of lesions of the ventral hippocampus (VH) on dopamine receptors and behaviors. Animals with lesions of the ventral hippocampus experience a hyperdopaminergic effect when exposed to amphetamines. Flores et al. found that the lesioned animals had a significant decrease in D3 receptor levels in the nucleus accumbens, the olfactory tubercle, and the islands of Calleja. The decrease in receptor level was even more drastic in rats that had had lesions for seven weeks than for rats with lesions for four weeks. This study shows that a prolonged hyperdopaminergic activity, as demonstrated with the seven-week lesioned rats, is also associated with a dramatic decrease in D3 receptors. In addition, Flores et al. found increased locomotor activity in the rats with the longer duration of lesioning compared to rats with no lesions or rats with the shorter duration of lesioning. This study supports the Richtand et al. (2001) hypothesis of a down regulation of D3 receptors and schizophrenic symptoms from a prolonged hyperdopaminergic state. Earlier studies similar to Flores et al. (1996) have found concurring results. For example, Wallace, Mactutus, and Booze (1996, as cited in Richtand et al., 2001) used cocaine to produce a hyperdopaminergic condition and found decreased amounts of D3 receptor proteins in the nucleus accumbens and increased locomotion response.
However, an important limitation to these animal studies is that only locomotion responses are looked at, due to the difficulty in measuring positive symptoms in animals. Therefore, it is still unknown whether psychotic symptoms are also brought about from the down regulation of D3 receptors. Future study of D3 receptors must also address the need for another possible selective D3 receptor radioligand to measure receptor density. The radioligands used currently are D3 receptor agonists, and the use of antagonist radioligands can examine existing hypotheses and the accuracy of findings in these hypotheses.

D4 receptors. D4 receptors are a part of the D2-like receptor family. The techniques used in the measurement of receptors are often unable to discriminate between the receptors in the same family. This leads to difficulties in research and interpretations of results (Marzella, Hill, Keks, Singh, & Copolov, 1997). Until better developed technology and radioligands are discovered, researchers must resort to what is available.

The research on D4 receptor density in schizophrenia has mainly used postmortem methods. The difficulty in finding a selective D4 receptor radioligand has forced researchers to use a unique method called the ‘‘pharmacologic subtraction’’ (Marzella et al., 1997, p. 649) method. This method uses two radioligands one of which is known to bind to D2, D3, and D4 receptors, and a second radioligand known to bind to D2 and D3 receptors. Through subtracting the second radioligand measurement from the first radioligand measurement, the D4 receptor binding is found (Marzella et al., 1997; Seeman, Guan, & Van Tol, 1993).

Seeman, Guan, and Van Tol (1993) used the radioligand [3H]emonapride to measure D2, D3, and D4 receptors, and the radioligand [3H]raclopride to measure D2 and D3 receptors. In addition, Seeman et al. added guanine nucleotide ‘‘to remove the interfering effect of endogenous dopamine on the binding of [3H]raclopride’’ (p. 441). The striatum of schizophrenic and control subjects were examined. The results showed a six-fold elevation of D4 receptors in schizophrenic patients’ striatum compared to controls.

A study by Marzella et al. (1997) used a similar ‘‘pharmacologic subtraction’’ method in which the radioligand [3H]emonapride measured D2, D3, and D4 receptors, and the radioligand [3H]raclopride measured D2 and D3 receptors. Caudate and putamen tissue from 15 schizophrenic patients and 15 age- and gender-matched controls were examined. The density of D4 receptors was significantly increased in schizophrenic individuals compared to controls, with a 2.6-fold increase in the patients.

These studies by Seeman et al. (1993) and Marzella et al. (1997) are in agreement with two other independent studies by Murray et al. (1995, as cited in Marzella et al., 1997) and Sumiyoshi et al. (1995, as cited in Marzella et al., 1997). However, the pharmacologic method has been criticized to overestimate D4 receptor density because ‘‘[3H]emonapride and [3H]raclopride have different affinities for the same dopamine receptors’’ (Marzella et al., 1997, p. 652). Secondly, postmortem studies have limitations in knowing the history of patients’ medication use and symptoms. Lastly, some
DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

researchers are unsure of the measurement of D4 receptors and refer to the increase as an increase in “D4-like sites” (Murray et al., 1995 as cited in Marzella et al., 1997). Some researchers even argue that D4-like sites, and not D4 receptors per se are increased in schizophrenia (Seeman & Van Tol, 1996 as cited in Marzella et al., 1997).

However, researchers acknowledge these limitations of the pharmacologic subtraction methodology and the need for a specific D4 receptor radioligand is recognized. Increased research in this area may prove extremely beneficial in the treatment of schizophrenia due to preliminary research by Van Tol et al. (1991, as cited in Marzella et al., 1997) showing that “the antipsychotic clozapine may influence D4 receptors in the alleviation of positive symptoms” (p. 649).

Conclusions

Implications of New Findings on the Original Dopamine Hypothesis

The original dopamine hypothesis relied mainly on clinical observations of the behaviors of schizophrenic patients after antipsychotic treatment without examinations of control subjects or direct measurements of brain activity. However, recent research findings have shed more light on the neurochemical etiologies of schizophrenia through their investigation of pre-synaptic activities, synaptic dopamine release, and post-synaptic densities of dopaminergic receptors. These recent findings have added to and modified the original dopamine hypothesis greatly.

Pre-synaptic abnormalities. An increased dopa decarboxylase enzyme activity is hypothesized as due to a deficiency of dopamine release from corticostriatal glutamatergic projections from the prefrontal cortex (Abi-Dargham et al., 2000; Reith et al., 1994). This hypothesis is important because it contradicts the original dopamine hypothesis that predicts hyperdopaminergic activity in schizophrenia at all times. With the findings from [18F]DOPA and [11C]DOPA studies, the belief that schizophrenia is associated with a constant hyperdopaminergic state is challenged because it appears that in non-firing periods, the synaptic dopamine level is actually low (Reith et al., 1994). In addition, an interaction of the glutamatergic system with the dopaminergic system has been proposed in the etiology of schizophrenia. This glutamate interaction will be further discussed in an upcoming section.

The dopamine transporter densities do not seem to play a part in the etiology of schizophrenia since a normal amount is present in neuroleptic-naive schizophrenic patients. However, DAT density appears to decrease as the illness progresses, as seen in Laakso et al. (2000) and Laruelle et al. (2000), possibly due to neuronal loss.

Synaptic abnormalities of dopamine levels. In contrast to the non-firing periods with low dopamine release, firing or “phasic” release of dopamine is increased in schizophrenia shown in Abi-Dargham et al. (2000) and Laruelle et al. (1997). These studies reinforce the hyperdopaminergic activity proposed by the original dopamine hypothesis by showing an increased dopamine release in neurons that are firing.
Post-synaptic abnormalities. D2 receptors were postulated by the original dopamine hypothesis (Soares & Innis, 1999) to be altered in schizophrenic patients. However, research has extended the possibility of post-synaptic abnormalities to other dopamine receptors discovered. The first main finding in receptor densities has been a decrease in D1 receptors in the prefrontal cortex and anterior cingulate, which is associated with the cognitive and motor dysfunctions in schizophrenia. Research in D1 receptors has shown that D1 receptor antagonists are not helpful to the actions of antipsychotics and may aggravate positive symptoms further.

Recent D2 receptor research has found surprising results. First, the hypothesized increase in D2 receptor density in the striatum postulated by the original dopamine hypothesis was not supported with in vivo studies of antipsychotic-naive schizophrenic patients (Farde et al., 1990; Hietala et al., 1994; Nordstrom et al., 1995). It does seem, however, that antipsychotics cause an increase in D2 receptors to compensate for the long-term blockade of dopamine (Silvestri et al., 2000). In addition, it was found that D2 receptor densities are decreased in the anterior cingulate cortex (Suhara et al., 2002), which was also associated with the positive symptoms of schizophrenia (Cleghorn et al., 1990, as cited in Suhara et al., 2002; Silbersweig et al., 1995, as cited in Suhara et al., 2002). The D2 receptors located at the anterior cingulate were also hypothesized to be interneurons that use GABA to inhibit dopamine release. This is a drastic addition to the original dopamine hypothesis, in which D2 receptors were only linked to the stimulation of dopamine release.

The examination of dopamine D3 receptors, although in its early stages, also brings surprising revisions to the dopamine hypothesis. The original dopamine hypothesis focused on D2 receptors’ connection with the positive symptoms of schizophrenia. However, Richtand et al. (2001) found that a continuous hyperdopaminergic state from neuronal firing leads to a decrease in D3 receptor activity, which causes psychotic symptoms associated with schizophrenia. This was further supported by Flores et al. (1996) who found that lesioning the ventral hippocampus which leads to a hyperdopaminergic state caused a dramatic decrease in the amount of D3 receptors in the nucleus accumbens, the olfactory tubercle, and the islands of Calleja. Therefore, in addition to the role of D2 receptors in the positive symptoms of schizophrenia, D3 receptors are also suspected to play an important role.

Lastly, D4 receptor research has not been definite in its findings due to the limitations of radioligands currently available. However, with the present studies by Marzella et al. (1997) and Seeman et al. (1993), it appears that there is an increase in D4 receptor density in schizophrenic patients, although its relevance to psychosis is not yet known.

Future Research in Interactions of the Dopaminergic System with Other Systems

Carlsson, Waters, Waters and Carlsson (2000) have pointed out that various neurotransmitters in the brain interact making it very likely that the dopaminergic system is not the only dysfunctional system in schizophrenia. Attention has been
DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

turned, specifically, to the glutamatergic and serotonergic systems and their role in the pathophysiology of schizophrenia. 

Glutamate-dopamine interaction. The role of glutamate on the pathophysiology of schizophrenia was first proposed due to the psychotic, schizophrenia-like effects of phencyclidine (PCP) (Carlsson et al., 2000). PCP is a powerful antagonist of the NMDA receptor, which is a glutamatergic receptor that is essential in controlling the conductance of calcium. Calcium influx triggers an intracellular calcium-dependent second messenger system, which is believed to “underlie complex neurophysiological phenomena” (Bressan & Pilowsky, 2000, p. 1724). In addition, rodent studies had demonstrated that striatal dopamine activity is regulated by glutamatergic projections from the prefrontal cortex (Taber & Fibiger, 1993 as cited in Bressan & Pilowsky, 2000). 

In vivo \[^{18}\text{F}\]DOPA and \[^{11}\text{C}\]DOPA human studies hypothesized that a deficiency of dopamine release in non-firing periods may be caused by corticostriatal glutamatergic projections from the prefrontal cortex in schizophrenia (Abi-Dargham et al., 2000; Bressan & Pilowsky, 2000). Grace (1991, 1993, as cited in Abi-Dargham et al., 2000) proposed the importance of glutamate and tonic release of dopamine by stating that “in schizophrenia, increased phasic activity of dopamine neurons might be secondary to decreased tonic activity due to deficits in prefrontal-striatal glutamatergic drive, which controls tonic release” (p. 8109). Therefore a glutamate hypofunction suggested in “the insufficiency in NMDA receptor density or function may underlie schizophrenia” (Bressan & Pilowsky, 2000, p. 1723). 

Clinical research has also suggested that atypical, and not typical, antipsychotics affect NMDA receptors (Goff & Coyle, 2001). However, the absence of radioligands for NMDA receptors have prevented in vivo investigations of the glutamate and dopamine interaction in schizophrenia (Bressan & Pilowsky, 2000). Additional research is needed in the investigation of glutamate and its relation to schizophrenia symptoms.

Serotonin-dopamine interaction. In addition to glutamate, serotonin has been hypothesized in several studies to influence dopamine transmission (Di Matteo, Di Giovanni, Di Mascio, & Esposito, 1999). The serotonin hypothesis of schizophrenia was actually postulated before the dopamine hypothesis by Gaddum’s finding (1953, as cited in Lewis et al., 1999) that the hallucinogenic LSD bound to serotonin receptors. 

Some researchers have postulated an inhibitory effect of serotonin on dopamine release (Kapur & Remington, 1996). However, there is a large number of different serotonin receptors, with major differences between the 5-HT1, 5-HT2, and 5-HT3 receptor classes (Kapur & Remington, 1996). An examination of just the 5-HT2 receptor density of schizophrenic patients has yielded inconsistent results (Lewis et al., 1999; Ngan, Yatham, Ruth, & Liddle, 2000; Verhoeff et al., 2000).

Due to the concentration of research on the dopaminergic system, much more research is needed for conclusions to be reached on the role of serotonin transmission on dopamine and schizophrenia. Carlsson et al. (2000) has suggested that
serotonin turnover could be measured in a similar method as dopamine turnover, through the radiolabelled precursor 5-hydroxytryptophan. The importance for additional research in serotonin and schizophrenia is seen in the observation that atypicals such as risperidone, act as 5-HT2 antagonists and alleviate extrapyramidal symptoms (Kapur & Remington, 1996). 

Future Developments in Brain Imaging Technology

Developments in specific radioligands would aid dramatically in the study of dopamine receptor densities. Certain radioligands currently used are not specific to one type of receptor and assumptions are made in studies that the radioligand is specifically binding to the desired receptor type. In the measurement of D1 receptors, a more specific radiotracer is needed to replace [\(^{11}\text{C}\)]SCH 23390, which is known to also bind to 5-HT, receptors (Knable et al., 1994; Okubo et al., 1997) and D5 receptors (Karlsson et al., 2002). In the measurement of striatal D2 receptors, there are inconsistent results due to the different binding properties of [\(^{11}\text{C}\)]raclopride and [\(^{11}\text{C}\)]NMSP. These discrepancies must be sorted out to gain an unambiguous conclusion of D2 receptor influence on the symptoms of schizophrenia. In addition, development of other radioligands is needed for accurate measurement of extrastriatal regions. Extrastriatal regions have low concentrations of D2 receptors (Farde et al., 1997), requiring radioligands that are more sensitive to binding. Lastly, in the measurement of D4 receptors, the subtraction method currently used by all studies needs to be replaced by a specific radioligand that binds only to D4 receptors. A specific radioligand that binds only to D4 receptors would provide a direct measurement of these receptors.

Further advances in the current brain imaging technology would be useful in solidifying the results and conclusions of past research. However, it is apparent that research conducted just in the past three decades has made many revisions to the original dopamine hypothesis of schizophrenia. Additional research is expected to expand our knowledge of the etiology of schizophrenia, and to incorporate the currently hypothesized effects of glutamate and serotonin.

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DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

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DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA


