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Dopamine and Schizophrenia

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1. INTRODUCTION

Schizophrenia is a severe and pervasive illness afflicting approx 1% of the general population. The symptoms of schizophrenia have classically been subdivided in positive and negative symptoms. Positive symptoms refer to features that occur as a result of the disease, and include hallucinations (especially auditory) and delusions. Negative symptoms are features that are normally present but are reduced or absent as a result of the disease and include avolition, anhedonia, inattentiveness, and social withdrawal *(1)*. In more recent years it has become clear that this division in positive and negative symptoms is too simplistic. Using a factor analytical approach, Liddle investigated the symptomatology of stable schizophrenic patients and found three independent clusters of symptoms *(2)*: (1) *reality distortion*, which includes hallucinations and delusions; (2) *psychomotor poverty*, which includes poverty of speech, flat affect, and decreased spontaneous movements, and (3) *disorganization*, which include disorders of the form of thought and inappropriate affect.

Schizophrenia usually develops around or shortly after puberty, with a somewhat younger onset of age in males than in females. In some, though not in all cases, females have a second smaller peak shortly after menopause sets in *(3)*. This strongly suggests that hormones, such as estrogens, might have a protective influence. This would also explain why the course of schizophrenia in young females is usually somewhat more benign. With respect to the development of positive and negative symptoms, there is evidence that the negative symptoms develop prior to the positive symptoms. Thus, young children usually show disturbances in attention and social behavior several years prior to the development of the positive psychotic symptoms *(4,5)*.

2. THE ETIOLOGY OF SCHIZOPHRENIA

Although the etiology is not yet fully elucidated, there is ample evidence that genetic factors play an important role. This is illustrated by family, twin, and adoption studies *(6)*, where there is a clear correlation between concordance rates and the percentage of genes shared with an individual with schizophrenia. However, these studies have also shown that the genetics of schizophrenia are highly complex and cannot be described with simple Mendelian inheritance. Moreover, in spite of many molecular genetic studies,

From: *Dopamine and Glutamate in Psychiatric Disorders*
Edited by: W. J. Schmidt and M. E. A. Reith © Humana Press Inc., Totowa, NJ

the gene (or genes) involved in schizophrenia have not been identified. It would be beyond the scope of this paper to analyze all the genetic linkage studies, but linkage has been shown between schizophrenia and regions on chromosomes 1q, 5q, 6p, 8p, 10p, 13q, and 22q *(7,8)*. However, many other studies have failed to replicate this *(9)*. In a recent study, for example, the entire genome of 301 families with at least two schizophrenic family members was screened using 396 polymorphic markers. This led to scan with an average spacing of 10 centiMorgans. In spite of this very extensive genetic analysis, only one region with specific linkage to schizophrenia was found [on chromosome 10 (10p14)], which had not been identified in other genome-wide scans before *(10)*. The lack of a single gene that is clearly and unequivocally linked to schizophrenia suggests that more than one gene is involved. Moreover, it is highly likely that schizophrenia is a heterogeneous disease, with different subtypes that may be linked to different genes, making replication studies difficult.

In spite of the large amount of evidence that genes play a role in schizophrenia, there is also ample evidence that such factors only induce a predisposition and cannot, by themselves, explain the occurrence of schizophrenia. This is most clearly illustrated in the concordance rate of monozygotic twins, which is approx 50%, thus much lower than 100%. This implies that nongenetic factors must also play a role in ultimately determining the occurrence of schizophrenia. In recent years many epidemiological studies have been performed to try and elucidate these environmental factors. It appears that both early and late environmental factors can increase the risk of developing schizophrenia. Among the early environmental risk factors are *prenatal stress factors* such as famine *(11)*, unwantedness of a pregnancy *(12)*, and death of a spouse during pregnancy *(13)*, *perinatal stress factors*, such as obstetric complications, especially low Apgar scores *(14)*, and *early postnatal factors*, such as rearing in an urban environment *(15)*, immigration *(16,17)*, and parental loss *(18)*. In addition to these early environmental factors, there is evidence that environmental factors later in life may increase the risk of developing schizophrenia, including stressful life events *(19,20)* and cannabis use *(21–23)*.

Thus, schizophrenia seems to be a result of a combination of genetic and early-life and late-life environmental factors, and it appears to be the *interaction* between genes and environment that ultimately leads to the development of this severe disease. Mednick, for instance, studied genetic high-risk subjects and found that one of the most important factors predicting the outbreak of schizophrenia was early maternal separation *(24)*. Likewise, obstetric complications seems to occur especially in high-risk subjects *(25)*.

3. THE PATHOLOGY OF SCHIZOPHRENIA

As with the etiology, the pathology of schizophrenia is still an enigma. In general, the brains of patients with schizophrenia are smaller, with larger ventricles and gyri and smaller cortical volumes *(26,27)*. In addition to these more global deficits, a number of specific, though more subtle neuropathological findings have been reported. These focus predominantly on the hippocampal formation *(28–31)* and the prefrontal cortex *(32–34)*. Deficits have also been described in many other brain areas, including the cerebellum, basal ganglia, thalamus, and cingulate cortex *(26)*.

4. DOPAMINE AND SCHIZOPHRENIA

The most prominent neurochemical entity related to schizophrenia is, without any doubt, dopamine. In fact, the dopamine hypothesis consists of two separate parts: (1) *the*

dopamine hypothesis of schizophrenia and (2) *the dopamine hypothesis of antipsychotic drugs*. The first states that the symptoms of schizophrenia are owing to an increased dopamine transmission, whereas the second states that the therapeutic effects of antipsychotic drugs result from their inhibitory action on the dopamine transmission. Even though these arguments are often considered to be two sides of the same coin, there is no *a priori* reason for this. It is quite possible that the primary disturbance in schizophrenia is located upstream of the dopaminergic terminal regions (such as the aforementioned prefrontal cortex or the hippocampus), but that this disturbance can be modified at this lower level by dopamine antagonists. For that purpose the two hypotheses will be discussed separately in the remainder of this chapter.

4.1. The Dopamine Hypothesis of Antipsychotics

Although it is often suggested that the dopamine hypothesis of antipsychotic drugs was originally proposed by Carlsson and Lindqvist in 1963, this is actually not correct. In fact, in their original biochemical study these authors found an increase in both dopamine and noradrenaline metabolites after the administration of chlorpromazine and haloperidol. Indeed, the authors concluded that antipsychotics work through an interactions with the catecholamines, dopamine, and/or noradrenaline *(35)*. In fact, it was van Rossum in 1966 who showed that all antipsychotics were able to reverse the behavioral effects of levodopa, and he therefore suggested that the therapeutic effect of antipsychotics is related to their dopamine receptor-blocking properties *(36)*. About 10 yr later two independent studies were published showing that there was a good correlation between the dopamine blockade and the therapeutic dose of antipsychotic drugs *(37,38)*. Although these results have generally been taken to "prove" that the therapeutic effects of antipsychotics are indeed solely because of blockade of dopamine D_2 receptors, there is also evidence that the D_2 receptor alone cannot explain the effectiveness of antipsychotics.

Especially the introduction of the so-called atypical antipsychotics has challenged the validity of the dopamine receptor hypothesis. These drugs, such as clozapine, risperidone, olanzapine, and quetiapine, induce much less extrapyramidal (parkinsonian-like) side effects than the classical antipsychotics such as chlorpromazine and haloperidol. Because these side effects are directly related to the blockade of D_2 receptors in the caudate–putamen, this suggests that the atypical antipsychotics do not induce an overall blockade of D_2 receptors. These findings have led to the regional selectivity hypothesis, which states that classical and atypical antipsychotics have a differential effect on the various dopaminergic systems. Electrophysiological studies on clozapine, haloperidol, and various other compounds indeed suggested that classical antipsychotics block dopaminergic activity in both the mesolimbic and nigrostriatal system, whereas atypical antipsychotics only affect the mesolimbic system *(39,40)*. Although the hypothesis appears attractive, and would leave the overall dopamine hypothesis of antipsychotics intact, there are a few problems. First of all, it has been suggested that the differences between haloperidol and clozapine are an artifact, as it could not be observed in nonanesthetized animals *(41,42)*. Moreover, in freely moving rats, haloperidol and clozapine did not differentially affect dopamine release in the terminal regions of the nigrostriatal and mesolimbic system *(43)*. Finally, most of the novel atypical antipsychotics, such as olanzapine, ziprasidone, and risperidone, fail to show this regional selectivity *(44)*.

The dopamine hypothesis of antipsychotic drugs predicts that in therapeutically effective doses all antipsychotics should block the D_2 receptors to a similar extent. With the advent

of the position emission tomography (PET) scan technology, it has become possible to investigate this in living patients, and the results appear to be in violation of this prediction. Most antipsychotics need approx 60–80% D_2 receptor occupancy to be therapeutically effective. However, the atypical antipsychotics clozapine and quetiapine were found to be therapeutically effective at doses that blocked only about 25–35% of the D_2 receptors *(45)*. It seems difficult to explain this with the hypothesis that only the dopamine D_2 receptors are relevant for the therapeutic effects. It seems much more likely that at least for clozapine and quetiapine other receptors are also involved in the therapeutic effects. Indeed, the atypical antipsychotics are known to bind to a large number of different receptors *(46)*.

Recently an alternative theory again focusing exclusively on the role of dopamine receptors has been proposed *(47)*. The authors proposed that the essential difference between classical and atypical antipsychotics is the speed with which the atypical antipsychotics detaches from the dopamine receptor (k_{-1}). This can be calculated with the formula $K_A = k_1/k_{-1}$, in which K_A is the affinity constant and k_1 is the association constant, i.e. the speed with which the drug binds to the receptor. In general this k_1 is more or less constant for most drugs, including all antipsychotic drugs. This implies that k_{-1} is dependent only on the affinity. Drugs with a low affinity will have a high $k_{-1}$and thus will rapidly dissociate from the receptor. Kapur and Seeman argue that this explains the apparent low level of binding of clozapine and quetiapine in PET scan studies. Moreover, they argue that because of this rapid dissociation, the risk for inducing extrapyramidal side effects is lowered because these drugs do not induce a permanent blockade of the D_2 receptor. However, there are several arguments against this hypothesis. First of all, the fast dissociation rate of atypical antipsychotics (and hence the low affinity) is compensated for by increasing the dose, which should lead to an equally strong blockade as with the more potent classical antipsychotics. Secondly, it would imply that all atypical antipsychotics have a low affinity and that all antipsychotics with a low affinity are atypical. Neither of these assumptions appear to be correct. Atypical antipsychotics such as sertindole and risperidone have a high affinity for the D_2 receptors. Likewise, classical antipsychotics such as chlorpromazine have a very low affinity for the D_2 receptors. Finally, the hypothesis is unable to explain why the low-potency drug clozapine is effective in patients resistant to higher-potency antipsychotic drugs *(48)*.

In summary, although there is clear evidence for a role of dopamine in the therapeutic effects of antipsychotics, it is difficult to explain the available data solely on the basis of the blockade of D_2 receptors. Especially the finding that some patients are resistant to one antipsychotic yet respond favorably to others, strongly suggests that nondopamine receptors also play a role. At present it is unclear which receptor(s) this could be.

4.2. The Dopamine Hypothesis of Schizophrenia

One of the first indications that schizophrenia may be related to an increased activity of the dopaminergic system came from the seminal work of Connell on amphetamine-induced psychosis *(49)*. His results clearly showed that humans can develop schizophrenia-like symptoms when they receive amphetamine. Because amphetamine is (predominantly) an indirect dopamine agonist, enhancing release and blocking reuptake, this suggested that an increased dopamine transmission was somehow responsible for the schizophrenia-like symptoms. Later studies showed that other dopamine agonists like levodopa *(50)*

and methamphetamine *(51)* can also induce psychotic symptoms in nonschizophrenia patients. In addition to the effects in nonpsychotic patients, amphetamine also exacerbates existing symptoms in schizophrenic patients *(52)*, suggesting that an increased dopamine transmission is somehow related to the occurrence of psychotic symptoms.

Over the years, the dopamine hypothesis has been modified many times. The most important modification came with the observation that dopamimetics tend to induce only positive symptoms and are less effective in inducing negative symptoms. Likewise antipsychotics have only limited effect against the negative symptoms. This led to the idea that only the positive symptoms are related to dopamine *(53)*. A further modification came with the realization that negative symptoms can even *improve* with dopamimetics *(54–56)*. This led to the idea that negative symptoms may be related to a reduction in dopamine. Since positive symptoms (related to an increased dopaminergic transmission) and negative symptoms (related to a decreased dopaminergic transmission) can co-occur in the same patients, this implies that different dopaminergic systems must be involved in these symptoms.

The central question is, therefore, is there evidence for an increased and a decreased dopamine transmission in schizophrenic patients? The simplest way to measure this is by analyzing postmortem tissue. This material is most easily accessible and allows a detailed neurochemical analysis, with a very high spatial resolution. An important confounding factor is that virtually all patients with schizophrenia have at one point in time or another been treated with antipsychotics, and most of them have been treated with these drugs for a prolonged period of time, often up to many years. Because antipsychotics affect the dopaminergic system (as mentioned earlier), this might lead to erroneous conclusions. Moreover, postmortem studies give a static picture, and will never be able to give information about the dynamics of the dopaminergic system. Finally, people with schizophrenia develop the disease at a relatively young age and can live with it for 30–50 yr or more. In other words, postmortem changes will also reflect adaptation of the body to many decades of the disease. In vivo measures of dopaminergic activity would be able to circumvent most of these problems, especially if they could be done in drug-naive, first-episode patients. Because it is impossible to describe all the studies that have investigated the dopaminergic system in schizophrenia, we will focus on the most important results that have been obtained.

4.2.1. Is There Evidence for a Hyperdopaminergic State in Schizophrenia?

Figure 1 gives a schematic representation of the dopaminergic synapse, showing the different levels at which alterations in dopaminergic transmission can occur. Both pre- and postsynaptic processes may contribute to the development of a hyperdopaminergic state. Increased levels of dopamine have been described in several regions of postmortem brains of schizophrenic patients, including the caudate nucleus *(57)*, the nucleus accumbens *(58)*, and the amygdala *(59)*. In addition tyrosine hydroxylase (TH, the rate-limiting enzyme in the dopamine synthesis) levels were increased in the caudate putamen *(60,61)*. Moreover, there is in vivo evidence of an increased activity of the other synthesizing enzyme dopa-decarboxylase in schizophrenia patients *(62–64)*. Differences have also been observed in the capacity of dopaminergic cells to reuptake released dopamine. Thus both the K_M and the V_{max} of the high-affinity dopamine transporter (DAT) system in synaptosomes were significantly increased in the nucleus accumbens, but not the frontal

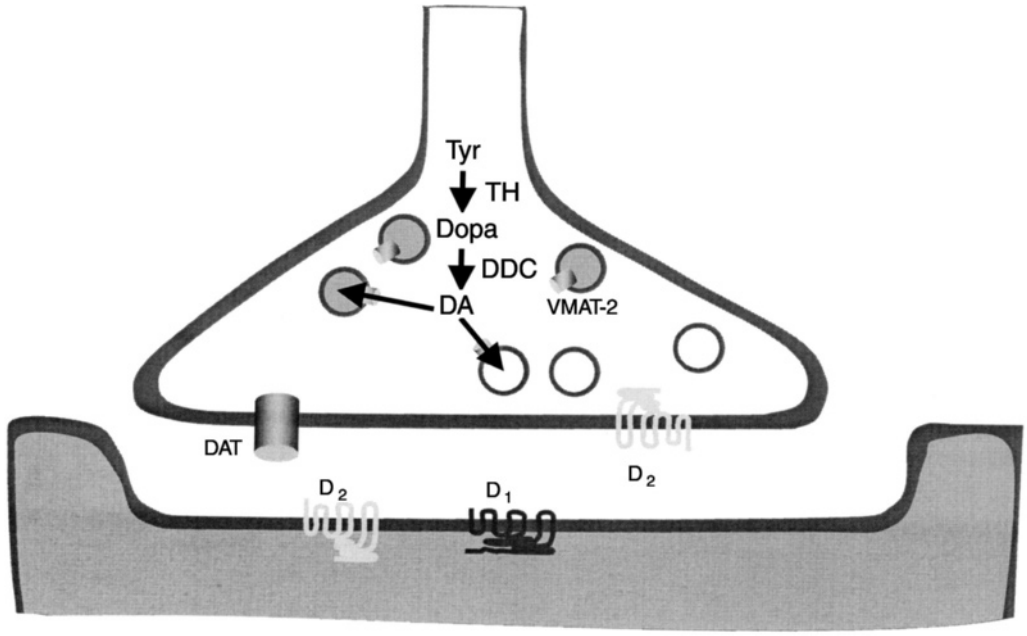

Fig. 1. A simplified representation of the dopaminergic synapse. The dopaminergic receptors are designated as families: D_1 (encompassing the D_1 and D_5 receptor) and D_2 (encompassing D_2, D_3 and D_4) Tyr; tyrosine; DA; dopamine; TH; tyrosine hydroxylase; DDC; dopa-decarboxylase; DAT; dopamine transporter; VMAT-2; vesicular monoamine transporter-2.

cortex of schizophrenic patients *(65)*, suggestive of an increased reuptake in schizophrenic patients. On the other hand, no change *(66)* or decreases *(67)* in the total number of reuptake sites in the striatum have also been described. In vivo studies using the PET technique failed to find alterations in DAT binding *(68,69)*. Interestingly, when using the ligand [^{11}C]DTBZ (dihydrotetrabenazine) a small but significant increase was found in the brainstem of schizophrenic patients. DTBZ specifically labels the vesicular monoamine transporter (VMAT-2), responsible for uptake of the monoamines into the storage and release vesicles *(70)*. Although it is not yet clear whether this is related to dopaminergic or noradrenergic neurons, it was shown many years ago that the [^{3}H]dopamine uptake in platelet storage granules was significantly increased in acute schizophrenic patients *(71)*. Because this effect could be reversed by reserpine, it suggests that this uptake carrier may be similar to the vesicular transporter in the brain. This might imply that also in the brain of schizophrenic patients more dopamine is taken up in storage vesicles, and hence more dopamine may be released on stimulation of the cells.

With respect to the involvement of postsynaptic processes in the development of hyperdopaminergia, most of the studies have concentrated on the dopamine receptors in various brain regions. Dopamine is known to bind to at least five different receptors belonging to two families. The D_1 family is composed of the D_1 and the D_5 receptors, whereas the D_2 family consists of the D_2, D_3, and D_4 receptors. Moreover, the D_2 receptor can exist in at least three different forms depending on the size of the third intracellular loop: D_{2short}, D_{2long}, and $D_{2longer}$ *(72)*. Unfortunately, selective ligands for the specific

receptor subtypes are not yet available. Therefore most studies have been limited to investigating the D_1 or the D_2 family of receptors, without being able to distinguish between the individual subtypes.

In several recent meta-analyses, the dopamine receptor–binding studies were evaluated *(73–75)*. These studies all concluded that there was support for the assumption that D_2 receptors are elevated in a subgroup of schizophrenic patients. However, they also provided evidence that postmortem studies usually led to larger differences between schizophrenics and controls than in vivo measures, suggesting that some of the increase in dopamine D_2 binding is owing to antipsychotics treatment. Alternatively, one might speculate that the number of D_2 receptors increase with progression of the illness, since most in vivo studies have been performed on drug-naive patients in an early stage of the disease. According to the meta-analysis, brain region and ligand used also significantly affect the outcome of dopamine-binding studies. The effect of brain region points to a nonhomogenous increase in D_2 binding in the brain of schizophrenic patients. Indeed, athough there is ample evidence that D_2 receptors' density is increased in the caudate putamen of schizophrenic patients, especially in postmortem tissue *(61,76,77)*, increases in other brain regions are much less evident. Thus Ruiz and colleagues did not find alterations in [^{3}H]raclopride binding in the frontal cortex *(76)*. The situation is even less clear in the nucleus accumbens. Whereas some find an increase in D_2 binding *(66)*, others find no differences *(78,79)*. The effect of choice of binding ligand on the effect size points to a differential distribution of different types of dopamine receptors in schizophrenic patients. Indeed, some have reported upregulation of D_4 receptors in schizophrenia *(79,80)*, though others have failed to be able to replicate this *(81)*. Recently an increase in mRNA for one of the dopamine D_2 receptors ($D_{2longer}$) has been described in the frontal cortex *(72)*. Because neither the second messenger system nor the function of this D_2 receptor subtype has yet been elucidated, it is unclear what the functional consequences of this increase in mRNA is.

The development of selective PET ligands for the dopamine receptors has led to a large number of studies in antipsychotic-free or even antipsychotic-naïve patients. The first papers using PET showed that drug-free and drug-naïve patients with schizophrenia have increased number of D_2 receptors in the caudate putamen *(82,83)*. Since then many more papers have been published using a variety of ligands. The results have been mixed, though most have been unable to find a difference between schizophrenic patients and controls *(84–87)*. Interestingly, the D_2-binding data of the individual patients in the last study seemed to fall into two groups, one with D_2 levels in the normal range and one with levels above the normal range. This suggests that there may be a subgroup of patients with increased D_2 levels within the schizophrenic population.

A distinct disadvantage of the first generation of PET ligands, such as [^{11}C]methylspiperone or [^{11}C]raclopride, is that they did not bind strongly to the D_2 receptors. Thus they were unable to detect dopamine receptors outside of the basal ganglia. The development of more specific ligands such as FLB457 has made it possible to also investigate extrastriatal dopamine receptors. However, so far, no clear-cut increases in extrastriatal D_2 receptors have been observed.

A final approach for studying the dopaminergic system is by using challenges to activate this system. Such studies are especially useful in investigating the dynamicity and reactivity of the dopaminergic cells. The previously mentioned increased activity of dopa-decarboxylase in combination with the increased activity of the VMAT-2 suggests

that the presynaptic dopaminergic terminals of schizophrenic patients contain more releasable dopamine than normal. One way to evaluate this is by treating patients and controls with amphetamine followed by the administration of a positron-emitting D_2 ligand, such as [^{11}C]raclopride. If amphetamine induces a stronger release of dopamine in schizophrenic patients, one would expect to see a more rapid reduction in raclopride binding, as more endogenous ligand competes with this PET ligand. Such an increased presynaptic release of dopamine has indeed been observed in the caudate–putamen in at least three different studies *(88–90)*. Interestingly, this increased responsiveness of the dopaminergic system was observed at the onset of the illness and during acute exacerbations but not when the patients were in remission *(91)*. A recent study provided strong evidence that this increased release of dopamine was present not only after stimulation with amphetamine, but also at baseline *(92)*. The authors pretreated controls and antipsychotic-free/naïve schizophrenic patients with α-methyl-para-tyrosine (αMpT), which blocks the TH activity thereby selectively depleting the cells of dopamine. In addition, they used the single photon emission computerized tomography (SPECT) to visualize the striatal D_2 receptor occupancy. The authors showed that, although the D_2 binding between the controls and the schizophrenic patients was not different at baseline, the increase in binding after αMpT was more than twice as large in schizophrenic patients compared to controls (19% vs 9%). Thus, all these data strongly suggest that there is an increased presynaptic dopaminergic activity and release in the caudate putamen of schizophrenic patients.

Studies using direct dopamine agonists, such as apomorphine, provided evidence of an increased sensitivity of the postsynaptic receptors. Thus the apomorphine-induced increase in plasma levels of growth hormone was much stronger in schizophrenic patients than controls *(93)*. Likewise apomorphine activated the regional cerebral blood flow in the anterior cingulate cortex *(94)* and decreased the glucose utilization in the caudate–putamen *(95)* to a much stronger degree in schizophrenic patients than in healthy volunteers. Interestingly, not all effects of apomorphine are upregulated. The apomorphine-induced increase in plasma ACTH and cortisol appears to be blunted in schizophrenic patients *(96,97)*.

Taking all these data together there is now, approx 45 yr after the original papers on the induction of psychotic symptoms after amphetamine use, direct evidence of a hyperfunctioning on the dopaminergic system in schizophrenia. This is most evident at the subcortical level, predominantly at the level of the basal ganglia. However, one should be aware of the fact that extrastriatal dopaminergic systems have not been investigated in any great detail yet. It might therefore be possible that other areas (including the nucleus accumbens) may also exhibit signs of hyperdopaminergia.

4.2.2. Is There Evidence for a Hypodopaminergic State in Schizophrenia?

As discussed above, several authors have linked the occurrence of negative symptoms to a reduced activity of the dopaminergic system. This would imply that the brains of schizophrenic patients should also show signs of hypodopaminergia. Because positive and negative symptoms can co-occur within the same patients *(1)*, the dopaminergic hypoactivity should be located outside of the basal ganglia.

Postmortem analysis of the brains of schizophrenic patients indeed found signs of a hypodopaminergic state, especially in cortical regions. Reductions in TH immunoreactivity

were found in area 9 of the prefrontal cortex, especially in layer 6 *(98)*, as well as in the entorhinal cortex *(99)*. In addition, there is a reduction in the number of DATs in the prefrontal cortex *(98)*. Less evidence has been obtained with respect to reductions in dopamine receptors. Whereas some authors found a reduction in D_1 binding in the prefrontal cortex *(100,101)*, this was not confirmed by others *(102)*. In addition, there were no differences in mRNA levels for D_1 receptors *(103)*, and a recent in vivo studies also failed to show differences in D_1 binding *(104)*. Recently a decrease in levels of the DARPP-32 protein was found in the prefrontal cortex of schizophrenic patients *(105)*. DARPP-32 is specifically localized in neurons containing dopamine receptors and controls the physiological characteristics of these neurons, as stimulation of dopamine D_1 receptors phosphorylates (and activates) DARPP-32 and stimulation of D_2 receptors dephosphorylates (and deactivates) DARPP-32. Whether this reduction is the result of a reduction in the number of dopamine-containing neurons or in the amount of peptide per cells remains to be investigated. With respect to other receptors, a reduction in mRNA levels for the D_3 and D_4 receptors has been observed in the orbitofrontal cortex *(103)*. Likewise, using [^{11}C]FLB457, a reduction in D_2 binding was observed in antipsychotic-naïve schizophrenic patients in the anterior cingulate cortex, as well as a strong tendency for a reduction in the thalamus *(106)*.

In summary, although much less investigated, the brains of schizophrenic patients also shows signs of hypodopaminergia, especially in frontal and temporal cortical regions, including the prefrontal, the anterior cingulate, and the entorhinal cortex.

5. INTEGRATION

Although the relevance of dopamine for schizophrenia has long been recognized, it was not until recently that hard biochemical evidence for a dysregulation of the dopaminergic system has been demonstrated in schizophrenic patients. Although there is still some controversy and much more confirmatory work needs to be done, the overall consensus is that schizophrenic patients have both a hyperactive subcortical dopaminergic system and a hypoactive cortical dopaminergic system. One important question that has not been solved yet is whether all patients suffer from this dopaminergic imbalance or whether some patients have predominantly a hyperactivity and others primarily a hypoactivity. As was mentioned above, the hyperactivity is primarily related to the occurrence of positive symptoms and the hypoactivity to the negative symptoms. Because both can occur in the same patients, both a hyperactivity and a hypoactivity should co-occur, though so far this has not been investigated.

There is, however, ample animal evidence that these two states can co-occur within the same rat. Already in 1980, Pycock and colleagues showed that lesioning of the prefrontal cortical dopaminergic system led to an upregulation of the subcortical dopaminergic system, including the nucleus accumbens and the striatum *(107,108)*. Since then, these findings have been replicated and extended many times, and all data point to a tonic inhibitory control of prefrontal dopamine on subcortical dopaminergic terminal fields. Removing this inhibitory control leads to an enhanced accumbal dopaminergic response to stress *(109)*, an effect predominantly mediated via cortical D_1 receptors *(110)*. Moreover, partial lesions also enhance the responsiveness to naturally reinforcing stimuli, such as highly palatable food and sex-related olfactory cues *(111)*. Thus, the data clearly

indicate that a reduction in cortical dopamine can co-occur with an increase in subcortical dopamine. It is not clear, however, whether these two are always causally related to each other. Given the independence of negative and positive symptoms in schizophrenia, it should be assumed that a reduction in prefrontal dopamine can also occur independent of an increase in subcortical dopamine.

Overall the data clearly point to a dysregulation of the dopaminergic system in schizophrenia, especially a hyperreactive striatal dopaminergic system. The in vivo studies clearly have shown that both the basal dopamine release (measured by the binding of raclopride after treatment with the TH inhibitor αMpT), as well as the amphetamine-induced dopamine release is enhanced in schizophrenic patients. In this respect it is important to realize that there are different pools of dopamine within the terminal region *(112)*. In general, a distinction is made between the so-called readily releasable pool (stored in vesicles close to the plasma membrane), and the so-called storage pool (stored in vesicles farther away from the plasma membrane; *see also* Fig. 1). Because both TH and dopa-decarboxylase occur in the cytosol, dopamine also occurs freely in a so-called cytosolic pool *(113)*. Newly synthesized dopamine accumulates preferentially in the readily releasable pool, which explains why this pool is so sensitive for αMpT *(114)*. The storage vesicles are thought to contain a much larger amount of dopamine, and this pool is more sensitive to reserpine *(112)*. Reserpine binds to the VMAT-2, which is responsible for sequestering dopamine into the vesicles. As mentioned above, schizophrenic patients are more sensitive to the effects of αMpT *(92)*, indicating a larger readily releasable pool of dopamine in these patients. These data would fit with the increased activity of both TH and DOPA-decarboxylase in schizophrenic patients. Moreover, it might also explain the higher sensitivity to amphetamine. Amphetamine is known to have multiple action of the dopaminergic system *(115)*. First of all, it binds to the DAT, where it works as a false substrate and is taken up into the presynaptic terminal. This stimulates a process called reverse transport (RT), where the DAT transports cytosolic dopamine out of the cell, instead of into it. In addition amphetamine can enter the presynaptic terminal through diffusion. Following the entry of amphetamine into the cell, it also enters the vesicles where it causes a change in pH, which subsequently leads to a leakage of dopamine from the vesicles into the cytosol, which can act as a substrate for RT. It is not clear whether amphetamine depletes both vesicular pools, but the work in DAT knockout mice shows that the readily releasable pool is certainly affected *(115)*. In summary, these data seem to indicate that especially the readily releasable and cytosolic compartment of the dopaminergic system are hyperactive in schizophrenic patients. Whether the storage pool is also altered has not been investigated in great detail yet, though some studies showed increases in the amount of VMAT-2 in schizophrenic patients *(70,71)*.

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