SPECT imaging in young patients with schizophrenia

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Summary and conclusions
The project “SPECT imaging in young patients with schizophrenia” was started to investigate different aspects of the central dopaminergic neurotransmission system in schizophrenic patients with a first or second psychotic episode. SPECT (single photon emission computed tomography) is a nuclear medicine technique, which is used to image functional processes in the body after administration of a radioligand. In this project, both postsynaptic and presynaptic aspects of the dopaminergic neurotransmission system were studied, as well as specific side effects of antipsychotic medication. The postsynaptic dopamine system was studied by focusing on the dopamine D<sub>2</sub> receptor occupancy by two recently introduced antipsychotic drugs (Part 1). The presynaptic dopamine system was studied by imaging dopamine transporter densities in patients with schizophrenia and in controls, and by focusing on tardive dyskinesia, a specific side effect of antipsychotic medication (Part 2). In addition, with respect to side effects, the muscarinic receptor occupancy of two recently developed antipsychotics was determined (Part 3).

Part 1
Dopamine receptor occupancy by antipsychotic medication

Part one focuses on the postsynaptic dopamine D<sub>2</sub> receptor. A literature overview of the large number of SPECT and PET (Positron Emission Tomography) imaging studies concerning dopamine D<sub>2</sub> receptor occupancy by antipsychotic medication is presented in Chapter 2. This overview shows that most antipsychotics induce a high occupancy of the D<sub>2</sub> receptors in the striatum, with the exception of clozapine and possibly quetiapine.

A minimum level of 60% D<sub>2</sub> receptor occupancy was found to be required to induce an antipsychotic effect, and above 80% D<sub>2</sub> receptor
occupancy the incidence of extrapyramidal side effects increases (Farde et al., 1992; Nyberg et al., 1995; Kapur et al., 1996).

Several previous reports have shown that olanzapine and risperidone, two new antipsychotic drugs, both show a low incidence of extrapyramidal side effects.

In order to find a possible explanation for the low extrapyramidal side effects, and to determine the difference in D<sub>2</sub> receptor occupancy between both antipsychotics, we assessed the D<sub>2</sub> receptor occupancy with [<sup>123</sup>I]-IBZM SPECT and rated the side effects of young patients treated with olanzapine or risperidone. In agreement with these previous studies, we also found that both recently developed antipsychotics showed a low incidence of extrapyramidal side effects. Moreover, we showed that there was no significant difference in D<sub>2</sub> receptor occupancy between the two groups under study (Chapter 3). In addition, we observed that risperidone treatment was related to high levels of prolactin, in contrast to olanzapine. The most likely explanation for this finding would be that this is due to a higher occupancy of dopamine receptors. However, as we found no difference in dopamine receptor occupancy between olanzapine and risperidone, an alternative hypothesis was suggested, stressing the different affinities of olanzapine and risperidone for the 5HT<sub>2c</sub> receptor (Leysen et al., 1998). Olanzapine, as opposed to risperidone, is a strong 5HT<sub>2c</sub> receptor antagonist, and blocking this specific receptor results in suppression of prolactin release. This may explain why the high prolactin levels are found in risperidone, and not in olanzapine.

Apart from extrapyramidal side effects, we studied the subjective experience of patients with schizophrenia treated with antipsychotics. We found a positive correlation between subjective experience and D<sub>2</sub> receptor occupancy in patients treated with moderate doses of olanzapine or risperidone (Chapter 4). This means that patients with a higher D<sub>2</sub> receptor occupancy, although with low rates on classical side effect rating scales, showed worse subjective experience. Therefore, subjective
experience may be more sensitive to D\(_2\) receptor occupancy than extrapyramidal symptoms. Further analysis of these data, specifically looking at the sub-scales of the subjective experience rating scales, showed a strong correlation between negative subjective experience and D\(_2\) receptor occupancy. These results look promising and resulted in the planning of a forthcoming larger study.

**General considerations regarding dopamine D\(_2\) receptor imaging with \[^{123}\text{I}\]-IBZM SPECT**

A number of limitations should be taken into account when discussing dopamine receptor SPECT imaging studies. The foremost critique on these studies is the brain region that is studied. As the highest density of dopamine receptors is situated in the striatum, almost all dopamine receptor imaging studies, both PET and SPECT, focus on this region. However, it is thought that in schizophrenia, dopamine abnormalities in the limbic cortical areas are of more importance for understanding symptomatology than abnormalities in the striatum. This general consideration has been under discussion since the introduction of dopamine neuroimaging. However, the finding of a lower threshold for antipsychotic action of antipsychotic medication, and studies suggesting a higher striatal dopamine release in patients, and especially the relationship to illness phase (Laruelle et al., 1999), show that imaging studies in the striatum are representative of the limbic dopaminergic system.

Recently, a new radioligand with higher affinity for the D\(_2\) receptor than \[^{123}\text{I}\]-IBZM was introduced, \[^{123}\text{I}\]-epidepride, enabling visualisation of also extrastriatal dopamine receptors (Bigliani et al., 1999, 2000; Stephenson et al., 2000;). These studies showed a substantial occupancy of receptors in the temporal cortex by antipsychotics, and suggest limbic selectivity in atypical antipsychotics. The availability of this and other radioligands, with higher affinity for the dopamine receptor than
[\textsuperscript{\textit{123}}}I]-IBZM, enables imaging of extrastriatal dopamine receptors. This may shed a new light on the basic question of changes in dopamine receptors in schizophrenia.

A second limitation is the selectivity of the radioligand. Apart from affinity for the dopamine D\textsubscript{2} receptor, [\textsuperscript{\textit{123}}}I]-IBZM also has affinity for the dopamine D\textsubscript{3} receptor. However, the density of D\textsubscript{3} receptors in the striatum is much lower than that of D\textsubscript{2} receptors, so that the contribution of D\textsubscript{3} receptor binding to the striatal [\textsuperscript{\textit{123}}}I]-IBZM SPECT measurement is probably negligible (Murray et al., 1994).

A third limitation of the methods of imaging dopamine receptor occupancy, is the comparison of data from patients treated with antipsychotics with data from normal controls. Ideally, one would compare the patient before and during antipsychotic treatment. This would minimise the error from the natural variance in dopamine receptor density. However, since no large difference was found in dopamine receptor density between patients with schizophrenia and healthy controls, and because of the practical and ethical problem of withdrawing antipsychotics for a number of weeks to make a baseline scan, nearly all dopamine receptor occupancy imaging studies are carried out by comparing patient data with data from controls.

A very recent discovery with potential impact on dopamine receptor imaging is the finding of distinct function of two isoforms of the dopamine D\textsubscript{2} receptor, namely D\textsubscript{2S} (D\textsubscript{2} short) and D\textsubscript{2L} (D\textsubscript{2} long) (Usiello et al., 2000). It was found that D\textsubscript{2L} acts mainly at postsynaptic sites, and D\textsubscript{2S} serves presynaptic autoreceptor functions. It was suggested that haloperidol has its extrapyramidal side effects through the D\textsubscript{2L} receptor, and, therefore, that drugs which could discriminate between D\textsubscript{2L} and D\textsubscript{2S} in vivo could lead to more effective treatment with fewer extrapyramidal side effects. In addition, the development of new radioligands to analyse these isoforms of the dopamine receptor would be of value to study the role of these isoforms in the pathophysiology of schizophrenia.
In conclusion, the large and growing number of studies on the occupancy of dopamine receptors by antipsychotic medication shows that dopamine receptor SPECT imaging is a valuable tool. This imaging technique improved the insight into the psychopharmacological effect of antipsychotic medication and is therefore important for the introduction of treatment guidelines, the development and evaluation of new antipsychotic medication and for further research concerning the subjective experience of individual patients with schizophrenia.

Part 2

The presynaptic Dopamine transporter

Part two focuses on the presynaptic dopamine system, covering the dopaminergic nerve terminal from which dopamine is released and where reuptake of dopamine is performed by the dopamine transporter. Two types of dopamine imaging studies found indications for changes in the presynaptic dopamine system in patients with schizophrenia. Using the amphetamine-challenge paradigm, it was found that patients with schizophrenia have a higher release of endogenous dopamine after stimulation with amphetamine (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998). Secondly, it was found that the uptake of $^{18}$F-DOPA, was increased in patients with schizophrenia (Reith et al., 1994; Hietala et al., 1995, 1999). These findings could be explained by a higher number of dopamine nerve terminals in schizophrenia. Our aim was to elucidate whether the number of dopaminergic nerve terminals was increased in schizophrenic patients, to explain both the higher amphetamine-induced dopamine release and the higher uptake of $^{18}$F-DOPA.

However, to properly study the density of dopamine transporters, it first had to be determined whether antipsychotic medication had an effect on the binding of the SPECT radioligand [$^{123}$I]-FP-CIT to dopamine trans-
porters. In our study, in which we used a rat model, it was shown that neither antipsychotic drugs nor dopaminomimetic medication had an effect on \([^{[123]}I]\)-FP-CIT binding in the rat striatum (Chapter 5). Therefore, antipsychotic medication was not withdrawn in our study comparing young patients with schizophrenia with controls. However, to exclude all possible effects of medication, also a subgroup was included with patients who had never been treated with antipsychotic medication at the moment of SPECT imaging. Using \([^{[123]}I]\)-FP-CIT SPECT, we found no significant difference in dopamine transporter density between patients and controls (Chapter 6).

At the time of that investigation, others published a study with a similar conclusion: the over-activity of the dopamine system is not likely to be explained by an increased number of dopamine transporters (Laakso et al., 2000; Laruelle et al., 2000). It appears that the increased \(^{18}\)F-DOPA uptake and higher dopamine release in patients with schizophrenia may better be explained by an over-activity of the dopamine system, than by an increased number of dopaminergic terminals.

**Dopamine transporters and gender**

In two studies, we investigated the influence of gender on dopamine transporter density in healthy controls. This work was done in addition to the \([^{[123]}I]\)-FP-CIT SPECT study in patients with schizophrenia, in which an effect of gender on dopamine transporter density was found. In combination with the intriguing difference between men and women in the occurrence and course of schizophrenia, this finding was studied in a larger group. In one study, we assessed the effect of age and gender on dopamine transporter density (Chapter 7). In this \([^{[123]}I]\)-FP-CIT SPECT study, we found that healthy females have a slightly but significantly higher striatal dopamine transporter density than males. A second finding was that the density of dopamine transporters decreases with age in healthy controls, a finding confirming earlier studies.

In a second study on the effect of gender on dopamine transporter density, we used a different SPECT radioligand, \([^{[123]}I]\)-\(\beta\)-CIT, to image both
the dopamine and serotonin transporter in healthy controls. We found a significantly higher density of both dopamine and serotonin transporters in women than in men and observed a relationship between the serotonin and dopamine system in healthy controls (Chapter 8). The observed gender differences may have implications for dopamine imaging studies and for diseases with an established gender difference, such as schizophrenia, but also for dopamine-related disorders, such as addiction. Since an imbalance between the dopamine and serotonin system may play a role in the pathophysiology of schizophrenia, it would be of interest to further investigate this relationship (Kapur and Remington, 1996).

Dopamine transporters and tardive dyskinesia

Tardive dyskinesia is a severe extrapyramidal side effect of antipsychotic medication. One hypothesis on the pathophysiology of tardive dyskinesia is the free-radical hypothesis (Lohr et al., 1988). According to this theory, tardive dyskinesia is a neurodegenerative process, with neuronal damage in the basal ganglia. Prolonged treatment with antipsychotic medication increases the dopamine metabolism and turnover. In this process free radicals are generated. This excessive production of free radicals could lead to neuronal membrane instability and dopaminergic cell death. To test the free-radical hypothesis of tardive dyskinesia in vivo, we investigated the density of the dopaminergic nerve terminal in patients with tardive dyskinesia using $[^{123}\text{I}]$FP-CIT SPECT (Chapter 9). We found no change in $[^{123}\text{I}]$FP-CIT binding in the striatum in patients with tardive dyskinesia compared to normal controls. This finding is in line with a large randomised clinical trial on the efficacy of the free radical scavenger vitamin E. That study found no evidence for efficacy of vitamin E in the treatment of tardive dyskinesia (Adler et al., 1999). A recently more dominating theory on the pathophysiology of tardive dyskinesia is the dopaminergic hypersensitivity theory, which explains tardive dyskinesia by an upregulation of dopamine D$_2$ receptors as a result of the chronic blockade by antipsychotic medication. Interestingly, this theory was
supported by a very recent study that showed an upregulation of striatal dopamine receptors in patients treated with antipsychotics, with the highest upregulation in patients with tardive dyskinesia (Silvestri et al., 2000).

General considerations regarding dopamine transporter imaging
Dopamine transporter imaging has recently been made widely available by the registration of a new radioligand, DaTSCAN, formerly called \([^{123}\text{I}]-\text{FP-CIT}\). This radioligand is designed for clinical studies in patients with dopaminergic degeneration such as Parkinson’s disease. However, there is one limitation that can be relevant in fundamental research. \([^{123}\text{I}]-\text{FP-CIT}\) is not strictly selective for the dopamine transporter, as also binds to the serotonin transporter. Because serotonin transporter density in the striatum is only a fraction of the dopamine transporter density, this will not be of great influence clinically. However, in fundamental studies a small serotonergic effect cannot be completely ruled out when studying striatal \([^{123}\text{I}]-\text{FP-CIT}\) binding.

Part 3
Muscarinic receptor occupancy
Apart from the dopaminergic system, we evaluated side effects related to the occupancy of muscarinic receptors by the antipsychotic drugs olanzapine and risperidone (Chapter 10). In vitro studies showed that olanzapine induces a high occupancy of muscarinic receptors, in contrast with risperidone, which shows hardly any affinity for muscarinic receptors. In our study, we used \([^{123}\text{I}]-\text{IDEX}\), a radioligand derived from dexetimide, which is an anticholinergic drug used e.g. in patients with Parkinson’s disease. SPECT imaging 8 hours after injection of \([^{123}\text{I}]-\text{IDEX}\) resulted in clear binding patterns with high activity in the striatum and cortex in
healthy volunteers. In schizophrenic patients treated with olanzapine the \([^{123}\mathrm{I}]\)-IDEX binding in all brain regions was dramatically decreased, compared to controls. This is thought to reflect a substantial occupancy of muscarinic receptor by olanzapine, and is in line with in vitro data.

Unexpectedly, patients treated with risperidone showed a significantly lower \([^{123}\mathrm{I}]\)-IDEX binding in the striatum than controls. However, in vitro studies showed that risperidone had a very low affinity for muscarinic receptors in the striatum (Schotte et al., 1996). Therefore, it is possible that the lower \([^{123}\mathrm{I}]\)-IDEX binding is not an effect of risperidone. Another explanation for the lower \([^{123}\mathrm{I}]\)-IDEX binding is that muscarinic receptor density in patients with schizophrenia is lower than in controls. This has also been suggested in another recent SPECT study (Raedler et al., 2000) and in recent post-mortem studies (Crook et al., 1999, 2000). Therefore, schizophrenia per se may also explain the lower \([^{123}\mathrm{I}]\)-IDEX binding in schizophrenic patients with risperidone. This interesting finding requires further study, especially with antipsychotic-naive patients, to exclude any medication effect.

**General Conclusion**

Several studies were performed in this project “SPECT imaging in young patients with schizophrenia”, mostly concerning the central dopaminergic system. SPECT imaging was found to be a non-invasive, reliable tool to investigate the central dopamine system in young patients with schizophrenia. The presynaptic and postsynaptic properties of this system can be adequately studied with various radioligands.

The dopamine hypothesis of schizophrenia, since its development in the middle of the 20th century, has, surprisingly, remained of interest (Davis et al., 1991). That this is remarkable is due to the many attempts to falsify this hypothesis. An overwhelming number of studies, stressing the
interaction of neurotransmitter systems (e.g. the serotonin system (Lieberman et al., 1998), and the cholinergic system (Tandon, 1999)) have put the hypothesis under fire, but have not falsified it.

The beneficial effect of antipsychotic drugs, which are all dopamine receptor antagonists, is a major basis for the dopamine hypothesis. Furthermore, the psychotogenic effect of dopamine agonists is still a relevant argument in favour of the dopamine hypothesis. The dopamine hypothesis therefore remains the most important hypothesis in schizophrenia.

In this project, we focused on side effects of antipsychotics and on the presynaptic dopamine system. Our presynaptic study in patients with schizophrenia, however, showed no changes in the presynaptic dopamine transporter density, and seems not to support the dopamine hypothesis. However, when we place our finding alongside those from other recent studies on the presynaptic dopamine system, it is well in line with the latest theory of a hypersensitive dopamine system, that supports an increased dopamine release, despite a normal number of dopaminergic nerve terminals (Duncan et al., 1999).

A fundamental aspect of schizophrenia is the variety of symptoms and course of the disease. Therefore, a specification of symptoms, or degree of illness, of patients under study would be a clarifying contribution to imaging studies. A larger number of patients in a study would make it possible to make analyses of sub-groups, for example of patients with predominantly negative symptoms.

Another characteristic aspect of schizophrenia is the age of onset, which is in most patients during adolescence. The majority of SPECT and PET studies in schizophrenia is performed in young patients. This group of patients is studied with the emphasis on the short lifetime period of treatment with antipsychotic medication, or the antipsychotic-naive state of these patients, but not on specific first episode aspects. As in these studies, and since both dopamine receptors and transporters decline with
age, we decided to include only young patients in a small age range. In addition, in we also included a subgroup of antipsychotic-naive patients. Assessment of typical clinical aspects of this young patient group was not the aim of our project. However, in the debate as to whether the disease process in schizophrenia involves only neurodevelopmental pathology, or also a progressive neurodegenerative component, the comparison of aspects of the dopamine system in first episode and in chronic patients with schizophrenia would be highly interesting.

A general remark on all schizophrenia imaging studies is that even studies that show significant differences between patients with schizophrenia and healthy controls always have a large overlap in group outcome, therefore, to date, no diagnosis can be made by scanning the individual patient (fig. 1).
Figure 1. The effect of amphetamine on \[^{123}\text{I}]\text{IBZM}\) binding in healthy controls and in untreated patients with schizophrenia. The y-axis shows the percentage decrease in \[^{123}\text{I}]\text{IBZM}\) binding potential induced by amphetamine, which is a measure of the increased occupancy of D\textsubscript{2} receptors by dopamine following the challenge. (M. Laruelle et al. Biological Psychiatry 1999; 46:56-72, reprinted with permission).

The combination of dopamine SPECT with other imaging modalities, such as Magnetic Resonance Spectroscopy (MRS) will probably have greater success in providing additional insight into the pathophysiology of this invalidating disease. For example, the finding of a correlation between D\textsubscript{2} receptor density in the striatum and prefrontal neuronal pathology, a combined \[^{123}\text{I}]\text{IBZM}\) SPECT and MRS study (Bertolino et al., 1999) may well set a trend for imaging strategies.

Finally, no total picture of schizophrenia will be possible with neuroimaging alone. Only in co-operation with other fields, e.g.
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neuropsychology, neurochemistry, and pharmacology, we will acquire more insight, resulting in a more fundamental treatment than the antipsychotic medication now prescribed. Symptom suppression with fewer side effects is a major step in the treatment of schizophrenia, but more fundamental knowledge on the pathophysiological processes that underlie the profound neuropsychiatric disturbances in schizophrenia may ultimately lead to a causal therapy.

References


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SUMMARY AND CONCLUSIONS

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