SPECT imaging in young patients with schizophrenia
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Citation for published version (APA):
Lavalaye, J. (2001). SPECT imaging in young patients with schizophrenia

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Dopamine receptor occupancy by antipsychotic medication, an overview of SPECT and PET research receptor

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Tijdschrift voor Psychiatrie: in press
Summary

By means of literature search, an overview of neuroimaging research on dopamine $D_2$ receptor occupancy by antipsychotic medication has been framed. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) techniques are useful to determine the occupancy of dopamine receptors by antipsychotic drugs in vivo. Clozapine and possibly quetiapine appear to result in low $D_2$ receptor occupancy though being effective. These techniques have led to a better insight in the relation between dosages of antipsychotic drugs, therapeutic effect, and the occurrence of extrapyramidal side effects.

Introduction

Although the efficacy of antipsychotic medication has been established, there is no conclusive explanation for their pharmacological effects. Occupancy of dopamine receptors in the brain is a property of all antipsychotic drugs, and is supposed to be the primary mechanism of action.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are research techniques from nuclear medicine, in which (patho-) physiological processes can be visualised by means of radio-labelled substances (radioligands). Specific radioligands bind to specific receptors. The administered dose is very low and does not induce any clinical effect. The gamma-camera or PET camera detects gamma radiation which is then transformed into an image. The radiation load a subject receives with these techniques is comparable to that of a CT scan.

PET offers higher resolution than SPECT and the possibility of absolute quantification, however PET is expensive and limited available.
A clear overview of differences between SPECT and PET was previously published in this journal (Louwerens and Korf, 1994).

Dopamine receptors are divided into subgroups. Most prevalent and most studied is the D₂ receptor, to which antipsychotic medication binds most. Verhoeff (Verhoeff, 1999) gives an overview of studies concerning other dopamine receptor subtypes.

In this article we give a concise overview of the imaging research that has been performed on dopamine D₂ receptor occupancy by antipsychotic medication.

Methods

Literature concerning SPECT and PET research on dopamine receptor occupancy by antipsychotic medication was collected via Ovid Medline from 1966 to 2000 (keywords: antipsychotics, SPECT, PET, dopamine and antipsychotic brand names) and by means of references in articles.

Results

The D₂ receptor occupancy by antipsychotic medication as found in SPECT and PET studies is presented in Table 1.
<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Dose</th>
<th>Dopamine D&lt;sub&gt;2&lt;/sub&gt; receptor occupancy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>variable</td>
<td>85 to 90%</td>
<td>(Farde et al., 1986)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Over 65%</td>
<td>Various studies</td>
</tr>
<tr>
<td>Clozapine</td>
<td>300-600 mg</td>
<td>40 to 65%</td>
<td>(Farde et al., 1989)</td>
</tr>
<tr>
<td></td>
<td>300-600 mg</td>
<td>38-63%</td>
<td>(Farde et al., 1992)</td>
</tr>
<tr>
<td></td>
<td>125-600 mg</td>
<td>20-67%</td>
<td>(Nordström et al., 1995)</td>
</tr>
<tr>
<td></td>
<td>175-900 mg</td>
<td>18 to 80%</td>
<td>(Pickar et al., 1996)</td>
</tr>
<tr>
<td></td>
<td>75-900 mg</td>
<td>16-66%</td>
<td>(Kapur et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>300-600 mg</td>
<td>20-49%</td>
<td>(Tauscher et al., 1999)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10-20 mg</td>
<td>Lower than classical AP</td>
<td>(Pilowsky et al., 1996)</td>
</tr>
<tr>
<td></td>
<td>10-20 mg</td>
<td>68-84% comparable with risperidone</td>
<td>(Nordström et al., 1998)</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>68%</td>
<td>(Dresel et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>5-30 mg</td>
<td>63-85%</td>
<td>(Lavalaye et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>10-25 mg</td>
<td>43-84%, comparable with risperidone, higher than clozapine</td>
<td>(Kapur et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>5-60 mg</td>
<td>clozapine</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>6 mg</td>
<td>75-80%</td>
<td>(Farde et al., 1995)</td>
</tr>
<tr>
<td></td>
<td>2, 4 and 6 mg</td>
<td>66, 73 and 79% comparable with classical AP</td>
<td>(Kapur et al., 1995)</td>
</tr>
<tr>
<td></td>
<td>4-14 mg</td>
<td>64 and 74%, (8 mg lower than 20 mg haloperidol)</td>
<td>(Busatto et al., 1995)</td>
</tr>
<tr>
<td></td>
<td>3 and 8 mg</td>
<td>60-90%, equal to 4-20 mg</td>
<td>(Küfferle et al., 1996)</td>
</tr>
<tr>
<td></td>
<td>1,5-10 mg</td>
<td>haloperidol</td>
<td>(Knable et al., 1997)</td>
</tr>
<tr>
<td></td>
<td>2-8 mg</td>
<td>76%</td>
<td>(Lavalaye et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>2-12 mg</td>
<td>63-89%</td>
<td>(Kapur et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>3 and 6 mg</td>
<td>72 and 82%</td>
<td>(Nyberg et al., 1999)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300-700 mg</td>
<td>Lower than 30% comparable with risperidone and olanzapine</td>
<td>(Küfferle et al., 1997)</td>
</tr>
<tr>
<td></td>
<td>450 mg</td>
<td>44%</td>
<td>(Gefvert et al., 1998)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40 mg</td>
<td>comparable with risperidone and olanzapine</td>
<td>(Bench et al., 1996)</td>
</tr>
</tbody>
</table>

Table 1. Overview of dopamine D<sub>2</sub> receptor occupancy by antipsychotic medication determined by SPECT and PET imaging.
Dosages and D₂ receptor occupancy

The relation between dosage and D₂ receptor occupancy of both classical and atypical antipsychotic medication is described as a saturation hyperbole. Increasing low doses resulted in a high rise in D₂ receptor occupancy, while high doses showed no further rise (Nordström et al., 1993; Kapur et al., 1999).

Clinical effects and D₂ receptor occupancy

With classical antipsychotic medication it was determined whether the absence of a clinical effect was caused by lower dopamine receptor occupancy in non-responders. In multiple studies it was found that the occupancy is equal in both responders and non-responders, and therefore non-response is not likely to be explained by a lack of D₂ receptor occupancy (Wolkin et al., 1989; Geaney et al., 1992; Pilowsky et al., 1993). Nordström and co-workers (Nordström et al., 1993) found no clinical effect at very low D₂ receptor occupancy (as low as 35%).

Extrapyramidal side effects, subjective experience and D₂ receptor occupancy

Extrapyramidal side effects (EPS) occur at higher doses of classical antipsychotics. A PET study showed an average D₂ receptor occupancy of 74% in patients with no EPS, and of 82% in patients with EPS (Farde et al., 1992). This difference in receptor occupancy between patients with and without EPS was later confirmed (Scherer et al., 1994). It is suggested that D₂ receptor occupancy of classical antipsychotics has to stay below 80% to prevent EPS.

Furthermore, a higher D₂ receptor occupancy in patients with olanzapine or risperidone is correlated with a worse subjective experience (de Haan et al., 2000).
Low dosage of antipsychotic medication

Dosages in recent studies are often lower in recent studies than in the beginning of the 1980's. One study found no clinical difference in patients that were treated with both 5 and 20 mg olanzapine, with a high D₂ receptor occupancy at 20 mg (60 vs. 83%, respectively) (Raedler et al., 1999). In a study with 2 mg of haloperidol, a D₂ receptor occupancy of 53-74% was found, at which most patients showed clinical improvement. (Kapur et al., 1996). Partly because of these high D₂ receptor occupancies, lower dosages are now recommended (Heinz et al., 1996; de Haan and Maksmovic, 1999).

Discussion

SPECT and PET imaging can be used to determine the occupancy of dopamine receptors by antipsychotic medication in vivo. These techniques improved the insight into the correlation between dosages of antipsychotics, clinical effects, and the occurrence of extrapyramidal side effects. These imaging techniques are therefore important for the introduction of treatment guidelines and the development and evaluation of new antipsychotic medication.

It is sometimes hard to compare dopamine receptor occupancy studies due to the differences in radioligand and in method of analysis. However, an important finding is that results from different groups are more or less comparable.

A clinically relevant finding is that an increase in dose at low doses induces a high increase in D₂ receptor occupancy, whereas an already high D₂ receptor occupancy hardly increases when doses are further increased. A direct application of PET studies is an advice to administer risperidone in a 4 mg dose, to induce a D₂ receptor occupancy of 70-80% (Nyberg et al., 1999). Moreover, on account of neuro-imaging studies
there is a recent plead for equivalent dosages when switching from haloperidol to risperidone (Remington et al., 1998).

The working mechanism of antipsychotics remains unclear. Because the $D_2$ receptor occupancy is not different in responders and non-responders, this occupancy may not be the only reason for the effect of antipsychotics in all schizophrenic patients.

Clozapine, and possibly quetiapine, appeared to induce a lower $D_2$ receptor occupancy, and are effective antipsychotic drugs. New radio-ligands for the determination of binding to other receptors such as the serotonin receptor, the dopamine $D_1$ receptor, the muscarinic and GABA receptors can be used in future to unravel the complex working mechanism of antipsychotic drugs.

References


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European Journal of Nuclear Medicine, 26, 862-868.


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