Probing cortical sites of antipsychotic drug action with *in vivo* receptor imaging

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Imaging receptors using radioactive ligands has allowed direct determination of the sites of action of antipsychotic drugs. Initial studies relating antipsychotic drug efficacy to action at striatal dopamine D2-like receptors have recently been undermined. Developments in imaging extrastriatal dopamine D2-like receptors suggest rather that antagonism of these receptors in the temporal cortex is the common site of action for antipsychotic drugs, with occupancy at striatal receptors relating more closely to extrapyramidal side effects. Further work into dopamine receptor subtypes and other receptor groups such as serotonin and GABA neurotransmitters awaits the development of suitable probes, but there are some initial finding. Again a main site of antipsychotic drug action is at cortical levels with high degrees of cortical D1 and $5HT_{2a}$ receptor occupancy attained particularly by atypical antipsychotic drugs.

1. Introduction

Contemporary research increasingly suggests the cortex is a primary site of action of antipsychotic drugs. This selective review will show how developments in imaging neuroreceptors using radioactive-labelled ligands has implicated cortical dopamine D2-like receptors as important mediators for antipsychotic action. Other potential neurochemical targets in the cortex for antipsychotic drug discovery will be discussed with a particular emphasis on the role of in vivo receptor imaging in the development and testing of new hypotheses on the treatment of schizophrenia. The technical basis of in vivo receptor imaging by Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPET) will not be discussed here. The interested reader is referred to Murray and Ell [31].

2. In vivo dopamine receptor imaging and antipsychotic action

Early receptor imaging studies focussed on the action of antipsychotic drugs at striatal dopaminergic receptors. Theoretically this was driven by the hypothesis that dopaminergic hyperactivity underlies schizophrenic symptomatology (for a review of this theory see [9]). Technically, the dopamine receptor binding assays available for *in vitro* and *in vivo* studies only allowed an examination of the richly dopaminergic striatum. Initial *in vitro* studies suggested that antipsychotic drug efficacy correlated with action at striatal dopaminergic D2 receptors [10,17,39]. The earliest *in vivo* receptor imaging studies appeared to confirm these findings. Using PET, Farde et al. [11] found that twelve distinct classes of typical antipsychotic drugs all produced between 65–85% striatal D2 dopamine receptor blockade. Others have gone on to show that the degree of response to typical antipsychotics correlates with the level of striatal D2 occupancy [32].

However, the case for a striatal site of drug action has been undermined by two more recent findings. Firstly, several groups, using both PET and SPET *in vivo* imaging, failed to find a difference in the levels of striatal D2 occupancy between subjects who responded to typical antipsychotics and those who failed to respond [42, 54]. Secondly, many atypical antipsychotics do not rely on striatal D2 antagonism for their therapeutic effect. SPET and PET studies have shown a wide range of D2 occupancies (20–60%) associated with a favourable response to the highly effective atypical antipsychotic drug clozapine [11,40,41]. Others have extended these in vivo findings of low striatal occupancy at therapeutic doses in responders to other atypical antipsychotic drugs. Two studies of ^{131}IIBZM binding to striatal

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D2 dopaminergic receptors in schizophrenic subjects on a therapeutic dose of olanzapine (mean 12.5 mg a day) and quetiapine (300–700 mg/day) found rates of occupancy of approximately 60% for olanzapine and 24–28% for quetiapine [26,43]. Further research in this area suggests that olanzapine occupancy is dose-related, and clinical response has been associated with levels of 68–84% striatal D2 receptor occupancy [34]. Nevertheless, the main point, that clinical response can be obtained without high striatal D2 occupancy for many classes of antipsychotic drugs has been well demonstrated.

This also appears to hold true for typical antipsychotic drugs. In a PET study of eight schizophrenic subjects who received a low-dose haloperidol decanoate depot (20–50 mg), Nyberg et al. [36] found that D2 dopamine receptor occupancy at four weeks after drug administration was 52% (range 20–74%). There was a good clinical response with this moderate level of striatal dopaminergic blockade, suggesting continually high D2 dopaminergic occupancy is not necessary to control schizophrenic symptomatology.

Striatal D2 dopamine receptor occupancy does however relate closely to the unwanted effects of typical antipsychotic drugs. Imaging studies have consistently found that extra-pyramidal side effects appear when a high proportion (above 70–80%) of striatal D2 dopamine receptors are occupied [20,32].

Clearly other candidate sites for antipsychotic action need to be examined-particularly regions which may relate to the pathogenesis of schizophrenia. It has only recently been possible to image dopamine receptors in vivo in extrastriatal structures using the high affinity D2/D3 SPET radioligand ^{123}I epidepride [21] and the PET ligands ^{11}C FLB 457 and ^{76}Br FLB 457 [13,15].

Pilowsky et al. [44] used ^{123}I epidepride SPET to compare striatal and temporal cortical D2/D3 receptor occupancy rates for schizophrenic subjects on clozapine or a typical antipsychotic. As expected they found significantly lower occupancy of striatal D2/D3 receptors in the striatum of patients on clozapine, consistent with all previous PET and SPET studies. Importantly, they found no significant difference between the two treatment groups in D2/D3 occupancy in the temporal cortex: both groups showed high mean temporal ($> 70\%$) occupancy. This constituted the first in vivo receptor imaging evidence suggestive of a common site of action at D2/D3 dopamine receptors for typical and atypical drugs in the temporal cortex.

Expanding on this finding, Bigliani et al. [6,7] used ^{123}I epidepride to estimate D2/D3 dopamine receptor occupancy, and demonstrated that other typical and atypical antipsychotics (olanzapine and sertindole) had similar profiles of temporal cortical dopamine receptor antagonism. For the typical antipsychotics D2-like receptor blockade in the striatum showed a strong dose dependency with high saturation of available receptors at doses over 600 mg chlorpromazine equivalents. However there was complete blockade of D2-like receptors in the temporal cortex at all clinically efficacious doses down to 37.5 mg chlorpromazine equivalents. This near total D2-like receptor blockade in the temporal cortex at low doses of neuroleptics may explain the increasing evidence of therapeutic efficacy for low doses of typical antipsychotics [19].

A preliminary study of quetiapine, which has the lowest affinity in vitro of all the antipsychotic drugs for D2 receptors, showed the lowest levels of D2/D3 blockade in the striatum (approximately 30%) but still showed marked occupancy of about 60% for temporal D2/D3 receptors [49].

Using PET and a novel D2/D3 dopamine receptor radioligand (^{76}Br-FLB 457) another group have confirmed the finding of high occupancy by antipsychotics of temporal cortical D2/D3 dopamine receptors [56]. Again this held true for a range of antipsychotic drugs (haloperidol, clozapine and amisulpride).

There have been some conflicting findings. A PET study using the ligand [^{11}C] FLB 457 is not in agreement with the ^{123}I epidepride studies [15]. Although the study confirmed temporal D2 receptor occupancy in six schizophrenic patients who were responsive to haloperidol or clozapine, the levels of receptor occupancy were lower – haloperidol caused a 41–56% and clozapine a 27–47% occupancy in the temporal cortex. The reasons for the discrepant results are unclear, but could relate to factors such as differences in the biophysical properties of the radioisotopes used. However, the conflicting findings emphasise the need for careful replication of new findings in this rapidly developing field.

The case for a common cortical site of action on D2-like receptors as evinced by ^{123}I epidepride studies is consistent with findings from three other distinct methodologies. Firstly, in ex vivo binding studies, an animal is sacrificed after the administration of the antipsychotic drug of interest and the amount of the drug bound to the receptor is determined autoradiographically. Using this technique, the effects in rats of antipsychotics such as high dose amisulpride (40–80 mg/kg) and remoxipride on the binding of the radioactively labelled D2/D3 ligand raclopride

has been studied [22,45]. It has been shown that both drugs preferentially inhibit raclopride's binding to limbic rather than striatal areas. Typical neuroleptics such as haloperidol showed a similar potency for the displacement of raclopride from both the striatum and limbic systems. The common site of competitive antipsychotic binding (and therefore displacement of raclopride) was limbic.

Secondly, studies examining the effect of antipsychotic treatment on levels of mRNA for dopamine D2-like receptors in the post-mortem brain have also implicated a common effect on cortical, not striatal, structures. Lidow et al. [24,25] found that in non-human primates six months administration of eight classes of typical and atypical antipsychotic drugs given at doses recommended for humans all upregulated mRNA for D2 receptors in the cerebral cortex. Only six also upregulated striatal D2 receptor mRNA. The atypical drugs clozapine and olanzapine both showed cortical selectivity of this D2 dopamine receptor mRNA upregulation effect. A similar pattern of upregulation of mRNA for D2 dopamine receptors after has also been demonstrated in the rat brain using ^{125}I epidepride. Following two weeks of haloperidol (1.5 mg/kg) or clozapine (30 mg/kg) both drugs increased the binding sites for ^{125}I epidepride in the medial prefrontal and parietal cortex, with striatal upregulation occurring only in the group given haloperidol [16].

Finally, microdialysis studies have been used in live animals to examine regional differences in changes in dopamine metabolism induced by antipsychotic drugs. Following acute administration of a neuroleptic there is blockade of dopamine receptors, leading to a compensatory increase in dopamine cell firing and concomitant dopamine release and metabolism. Although many regions of the brain show an increase in dopaminergic activity with antipsychotic drugs, including the nucleus accumbens and the dorsolateral striatum, a recent review showed a common area of increased activity in the pre-frontal cortex, particularly for atypical agents [1].

Recently the dopamine receptor family has been more extensively characterised. It is now understood that the dopamine receptor family is composed of D1-like (D1 and D5) and D2-like (D2, D3 and D4) subdivisions and each member may be a target for antipsychotic drug action [25,51]. It is noteworthy that most of the research to dates has been carried out with ligands which bind to D3 dopamine receptors as well as the D2 receptor. Thus the specific contribution of each subtype to antipsychotic effect cannot yet be estimated. Some initial work has examined the binding of antipsychotic drugs to the D1 receptor using the PET ligand ^{11}C SCH23390. These studies suggest that the cortical D1 dopamine receptor is a site for atypical antipsychotic drug occupancy, with clozapine blocking between 36–59% D1 dopamine receptors compared to 0–44% binding found for typical neuroleptics [33]. Although open trials in schizophrenic subjects of specific D1 antagonists have shown little or no antipsychotic effect [2], D1 dopamine receptor antagonism may modulate the effects of D2-like receptor antagonism, exerting an indirect antipsychotic effect. The in vivo assessment of the contribution of the other dopamine receptor sub-types to antipsychotic action awaits the development of new neurochemical probes, such as the highly selective and specific ligands under development for the dopamine D4 receptor [38].

In summary, preliminary in vivo SPET and PET studies using high affinity D2/D3 specific radioligands support animal and human in vitro data suggesting antipsychotics share to some degree a common antagonism of D2-like dopaminergic receptors in limbic structures, particularly the temporal lobe.

3. Antipsychotic action related to other cortical neurotransmitters

Localising the site of antipsychotic action to cortical and limbic structures clearly cannot assume this activity is exclusively related to alteration of dopaminergic transmission. Several factors have generated interest in other neurotransmitter systems. Up to a third of schizophrenic patients respond poorly or not at all to selective D2 antagonists [23], and blockade of the D2 dopamine receptor has relatively little impact on the negative symptoms of schizophrenia [18]. There has therefore been increasing interest in the role of other neurotransmitter systems in both the pathogenesis of schizophrenia and as targets for antipsychotic action including the glutamate, serotonin and sigma receptor groups. These neuroreceptors are found in areas thought to contribute to the symptoms of schizophrenia, and some drugs active at these receptors have a pro or antipsychotic effect [27,29,47]. The serotonergic system has also been implicated by the demonstration of a relationship between different allelic forms of the $5HT_{2a}$ and $5HT_{2c}$ receptors and response to clozapine [48].

Direct determination in the living human subject of the association between antipsychotic activity and occupancy of different cortical receptor sites has been limited by the lack of specific ligands for many of the candidate receptor groups. However, some valuable initial steps have been made, specifically in the imaging of the serotonin and GABA receptor groups.

4. Serotonin receptors and antipsychotic drugs

In vivo imaging of serotonergic receptors has given new insights into both the contribution of serotonergic blockade to antipsychotic action and its possible role in determining the varying side effect profiles of antipsychotic drugs. Blockade of cortical $5HT_{2a}$ receptors has been consistently demonstrated for a wide range of antipsychotic drugs. A relatively early PET study by Nordstrom et al. [33] using the serotonergic ligand ^{11}C-N-methyl spiperone demonstrated high levels of frontal cortical serotonergic receptor blockade in patients treated with clozapine. A similar pattern has been shown in PET studies on subjects following the acute administration of the atypical antipsychotic agents risperidone and olanzapine [35].

These studies are limited by the non-specific nature of the ligands used. For example, ^{11}C-N methyl spiperone cannot distinguish between D2 dopamine and $5HT_{2a/c}$ receptors, limiting its ability to image the serotonergic system in dopamine rich areas. The development of a highly specific $5HT_{2A}$ receptor ligand ^{123}I-R-91150 for SPET studies has overcome some of these limitations and provided further evidence for common high (80–95%) cortical $5HT_{2a}$ receptor occupancy for patients treated with atypical antipsychotic drugs – clozapine, risperidone, olanzapine, sertindole – over a wide range of doses [7,52]. In contrast, the blockade of cortical 5 HT_{2a} receptors by typical antipsychotic agents was found in both PET and SPET studies to be dose dependent with moderate to high degrees of blockade occurring with high doses of typical neuroleptics [53].

The actual contribution of cortical serotonergic blockade to antipsychotic drug action is debatable. Certainly cortical $5HT_{2a}$ antagonism does not appear to be essential for the active therapeutic component. Several imaging studies have found high levels of $5HT_{2a}$ receptor occupancy with antipsychotic drugs at clinically subtherapeutic doses [12,14,19,33]. Others have demonstrated that rates of occupancy of $5HT_{2a}$ receptors do not correlate with scales measuring clinical improvement [7] and for some antipsychotic drugs such as sulpiride there is no evidence of any in vivo serotonergic blockade [53].

It is more likely that the different patterns of serotonergic blockade by typical and atypical antipsychotics may contribute to their side effect profiles. In particular, consistently high serotonergic blockade in conjunction with lower striatal dopaminergic receptor occupancy could partly account for the relative absence of extra-pyramidal side effects with atypical agents.

5. The GABA receptor complex: initial findings

The availability of a probe which acts as a antagonist at the benzodiazepine subunit of the $GABA_a$ receptor – ^{123}I iomazenil – has produced results in line with earlier anatomical studies suggesting subtle microanatomical abnormalities in the temporal cortex in schizophrenia [3,4]. Thus Busatto et al. [8] in a SPET study showed a correlation between the severity of positive symptoms of schizophrenia and binding of ^{123}I iomazenil in limbic regions. Research into antipsychotic drug modulation of GABAergic inhibitory transmission is yet another potential area for the application of neurochemical imaging to the better understanding and development of new drugs.

Continued progress in imaging other receptor groups awaits the development of new radioligands. For example, in imaging the NMDA receptor the lipophilicity of one of the main current probes ^{123}I MK801 has proble matically high levels of non-specific binding- a feature which may be overcome by the new ligand ^{123}I CNS 1261 [28,30]. Similarly, increasingly specific probes for subtypes of serotonin and sigma receptors and component parts of the GABA-benzodiazepine receptor are under development.

6. Conclusion

Several lines of evidence support the idea that antipsychotic efficacy may result from a complex interaction of drugs with many different receptor systems, in clinically and biologically heterogeneous groups of patients. The dopamine system remains a prominent candidate given the striking consensus in the literature showing all antipsychotic drugs studied and in clinical use have a common mode of action in their antagonism of cortical D2-like dopamine receptors. Disagreement

in the literature relates to the degree of this effect not its presence or absence.

Other neurotransmitter systems may act in concert with mandatory cortical D2-like receptor blockade to induce antipsychotic action. All of the neurotransmitters mentioned modulate dopaminergic transmission. GABAergic transmission has been shown to modulate dopaminergic transmission in the nigrostriatal pathway in animals [50,55] and a similar interaction of 5HT2 and D2 receptors has been demonstrated in autoradiographic receptor studies in animals [46].

Nonetheless, the relationship between antagonism of limbic cortical D2-like receptors and clinical response is indirect, and clearly there are subgroups of patients who show little, if any benefit from D2/D3 receptor antagonism. Identification of other receptor systems is a priority, to expand potential targets for drug development, most especially for treatment resistant individuals.

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