Dopamine and antipsychotic drug action revisited

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The key event in the initiation of pharmacological responses is the formation of a complex between the ligand (or drug or molecule) and its site of action (Taylor & Insel, 1990). Competitive binding experiments ascertain how specific the interaction is between a ligand and its binding site by examining the ability of various compounds to compete with a radiolabelled reference probe for the site. The more potently a drug binds to the receptor, the more effective it is at competing for labelled sites. The greater the potency a drug has for the receptor, the lower the concentration required before all available receptor sites are occupied or blocked. This affinity (termed K_d or K_i) for the receptor is quantified in test-tube experiments and is a function of the rate of drug association and dissociation from the receptor. It is empirically measured as the concentration of drug required to block half the total receptor population. High-affinity drugs have low K_d values. These drugs are better at 'occupying' receptors. In living animals, including humans, receptor occupancy by drugs is also determined by the rate of association and dissociation of the drug from the receptors, the concentration of drug at the receptor and the concentration of endogenous neurotransmitter at the receptor (Strange, 2001). Rehearsing these dry pharmacological concepts is important to our understanding of antipsychotic drug action, in particular how dopamine is the 'comeback kid' for hypotheses of antipsychotic drug action, a lead candidate for antipsychotic drug discovery and relevant to the modern clinical management of schizophrenia. Here we shall discuss the dopamine hypothesis of drug action, review studies that have refined understanding of its relevance, and attempt to synthesise the current view with respect to clinical management.

DOPAMINERGIC PATHWAYS AND RECEPTOR PHYSIOLOGY

Dopamine is one of the principal modulatory neurotransmitters in the brain. Dopamine systems arise from two primary midbrain clusters, the ventral tegmental area (A10) and the substantia nigra (A9), which have discrete projections to mesolimbic, mesocortical and striatal regions of the brain. A separate tuberoinfundibular pathway runs from hypothalamic neurons to the pituitary gland. The dopamine receptor family separates into two major subtypes: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, D_4). Variants of the dopamine receptors exist with different DNA and amino acid sequences. Receptor cloning has identified two isoforms of the D_2 receptor (D_{2short} and D_{2long}), which are differentially localised in the brain. The neurochemical anatomy of dopamine differs in cortical and striatal regions, and it now appears that dopamine concentration, receptor regulation and D_2-like receptor subtype density vary greatly between striatal and extrastriatal regions (Lidow *et al*, 1998; Strange, 2001). Antipsychotic drugs are thought to achieve their main effects (both beneficial and unwanted) by acting on D_2 receptors.

DOPAMINE RECEPTORS AND ANTIPSYCHOTIC DRUG ACTION

The D_2 receptor blockade hypothesis

Without exception, effective antipsychotic drugs have at least some degree of antagonism of the dopamine D_2 receptors. The observation that antipsychotic drug affinity for the D_2 receptor and the average daily dose required to control symptoms were directly correlated (Peroutka & Snyder, 1980) led to confirmation that it was a major site of action of antipsychotic drugs (Creese *et al*, 1976; Seeman *et al*, 1976; Johnstone *et al*, 1978). These findings rationalised clinical observation and practice at the time. Efforts to treat partially or poorly responsive patients revolved around 'mega-dose' antipsychotic therapy, although many contemporaneous papers questioned the usefulness of this approach (Baldessarini *et al*, 1984; Van Putten & Marder, 1986). More D_2 receptor blockade was better, the theory went, and concomitant movement disorder (secondary to striatal D_2 receptor blockade) and hyperprolactinaemia (secondary to pituitary D_2 blockade) were an inevitable, if unfortunate, corollary of treatment.

Re-evaluation of the dopamine hypothesis of antipsychotic drug action

In the 1980s and 1990s the simple understanding that dopamine D_2 receptor blockade was linearly related to clinical response was reversed (as is so often the case in schizophrenia research) by powerful new research tools, which forced the re-evaluation of the role of D_2 receptors in antipsychotic drug action. These included receptor imaging *in vivo* with positron and single photon emission tomography (PET and SPET). One PET study showed that up to 12 different typical antipsychotic drugs had 65–85% occupancy at D_2 receptors in living patients (Farde *et al*, 1989). Subsequent studies revealed that the degree of D_2 receptor occupancy was directly correlated with the dose (or plasma level) of traditional antipsychotic drugs; but did D_2 receptor occupancy also correlate with clinical benefit?

Chinks in the 'dopamine hypothesis' armour appeared with the clear demonstration that some patients taking therapeutic doses of typical antipsychotic drugs not only failed to benefit from the treatment, but also had levels of central D_2 receptor blockade in excess of 90% (Wolkin *et al*, 1989; Pilowsky *et al*, 1993). This finding obviated pharmacokinetic explanations that poor clinical effect was the result of low brain penetration or increased wash-out of typical antipsychotic drugs in treatment-resistant individuals. Indeed, some patients who responded well to treatment showed remarkably low levels of D_2 receptor blockade (Pilowsky *et al*, 1993). These data contributed greatly to the consensus that high-dosage antipsychotic treatment was,

in the main, unhelpful in the treatment of poorly responsive schizophrenia (Thompson, 1994). Finally, clozapine, a therapeutically superior antipsychotic drug without extrapyramidal side-effects (and modest affinity for D_2 receptors *in vitro*) had consistently low levels of D_2 receptor blockade (ranging from 20% to 60%) in association with excellent clinical response, even in patients previously poorly responsive to standard or high-dosage typical antipsychotic drug therapy (Pilowsky *et al*, 1992).

This evidence prompted a careful reinterpretation of the importance of D_2 receptor blockade to therapeutic efficacy. Other receptor systems were probed as potential sites of antipsychotic drug action, and a call was made to abandon preconceived ideas of particular neurochemical profiles determining atypical drug activity until potential sites for drug discovery were better understood (Kerwin, 1994). Simple behavioural or clinical definitions of atypicality (low or no extrapyramidal symptoms or hyperprolactinaemia at therapeutically relevant doses) would preserve an open field for novel therapeutic targets. Most notable of these was the 5-hydroxytryptamine type 2 (5-HT_2) receptor subclass. Meltzer *et al* (1989) proposed, on the basis of drug affinity data, that the ratio of 5-HT_{2A} to D_2 receptor affinities was the major determinant of a drug's likelihood to behave as an atypical antipsychotic. Studies using PET and SPET found that many atypical antipsychotic drugs, including clozapine, olanzapine, risperidone and quetiapine, shared a strikingly high degree of 5-HT_{2A} receptor occupancy (>90%) over their entire dose range (Nordstrom *et al*, 1993*a*; Nyberg *et al*, 1993; Travis *et al*, 1998; Kapur *et al*, 1999; Jones *et al*, 2001). This is unsurprising given that olanzapine, risperidone and quetiapine were developed on the basis of their high 5-HT_{2A}:D_2 receptor affinity profiles. It appears from the results of further studies (particularly the failure of pure 5-HT_{2A} antagonists to show striking therapeutic effects) that 5-HT_{2A} receptor occupancy alone is unlikely to be sufficient to determine clinical efficacy for antipsychotic drugs (Kapur *et al*, 1999).

The central primacy of dopamine to antipsychotic action

The notion that D_2 receptor occupancy was central to therapeutic response never really went away. Compounds that lack even modest activity at these sites are therapeutically inactive. Nordstrom *et al* (1993*b*) and later Kapur *et al* (2000*a*) showed that symptom reduction and side-effect induction could be fitted to a threshold model of striatal D_2 receptor occupancy (at least in acutely relapsed patients and excluding excellent responders and treatment-resistant cases). In one study of 22 patients (5 women and 17 men) with first-episode schizophrenia, Kapur *et al* (2000*a*) demonstrated that striatal D_2 receptor occupancy values exceeding approximately 65% predicted clinical benefit, values exceeding 72% predicted hyperprolactinaemia, and values exceeding 78% predicted motor side-effects. For the clinician, maintaining patients within a therapeutic window of 7–15% D_2 receptor occupancy is not straightforward, especially when prescribing haloperidol, since doses as low as 2.5 mg of this drug result in a wide variation in striatal D_2/D_3 receptor occupancy (38–87%).

Furthermore, individual responses to similar degrees of D_2 receptor occupancy may vary, based on other as yet undefined pharmacogenetic characteristics and on the individual's underlying dopaminergic tone (Laruelle *et al*, 1996). It is pertinent to this point that hyperprolactinaemia occurred in 80% (4 out of 5) of the women and 24% (4 out of 17) of the men in the study by Kapur *et al* (2000*a*) despite similar levels of D_2 receptor occupancy. Melkersson *et al* (2000) reported that in a group of patients receiving long-term typical antipsychotic therapy, the women developed symptomatic hyperprolactinaemia at half the chlorpromazine equivalent dose of that in men (approximately 250 mg chlorpromazine equivalents).

Dopamine transmission is abnormal in schizophrenia

Post-mortem studies of D_2 receptors in schizophrenia were crucial to the genesis of the dopamine hypothesis. Increased striatal D_2 receptor density was reported by some authors (Lee & Seeman, 1980; Mackay *et al*, 1982), but these findings were questioned on the basis that the data were obtained by studying antipsychotic-treated patients. Classical antipsychotic therapy could, in itself, cause D_2 receptor upregulation (Clow *et al*, 1980). Imaging studies using PET and SPET could control for this confound by studying never-treated people with schizophrenia. These studies did not, on the whole, support increased striatal D_2 receptor density in schizophrenia (Farde *et al*, 1990; Martinot *et al*, 1990; Pilowsky *et al*, 1994), although the possibility that endogenous dopamine concentration was abnormal (Mackay *et al*, 1982; Reynolds, 1983) remained untested *in vivo*. Support for the central importance of dopaminergic antagonism in antipsychotic efficacy eventually came from [^{123}I]-iodobenzamide SPET data suggesting that dopamine transmission was indeed disrupted in schizophrenia. Using dynamic challenge paradigms, Laruelle *et al* (1996) demonstrated an aberrant response in people with schizophrenia to a drug that elevated dopamine levels. Following administration of amphetamine, mean occupancy of striatal D_2 receptors by amphetamine-stimulated endogenous dopamine release was approximately doubled in the patient group compared with the control group. This effect was more striking in the more acutely ill patients, although findings in many patients overlapped with those in controls. These data, replicated using a different PET technique (Breier *et al*, 1997), provided concrete proof of disturbed dopamine control, at least in some people with schizophrenia. Drawing on these and other data, Moore *et al* (1999) have thoughtfully argued that overactive phasic dopamine transmission in limbic regions (including the amygdala and nucleus accumbens) could account for misinterpretation of innocuous external stimuli (resulting in delusions) and improper filtering of perceptions (causing hallucinations). Blockade of D_2 receptors in these regions would help control the positive symptoms of schizophrenia. In cortical (especially frontal and prefrontal cortical) regions, these authors propose that tonic dopamine transmission is relatively underactive, resulting in disrupted executive function, poverty of thought, speech and action, and low motivation. Antipsychotic occupancy of D_2 receptors in these regions would worsen these negative features. This attractively parsimonious model synthesises available data and meshes with the finding that atypical antipsychotic drugs (particularly clozapine and quetiapine) exhibit cortically selective D_2 receptor occupancy (primarily temporal cortex, including amygdala and hippocampus) at clinically useful doses *in vivo* (Pilowsky *et al*, 1997; Lidow *et al*, 1998; Meltzer *et al*, 1999; Stephenson *et al*, 2000; Xiberas *et al*, 2001). This effect is not seen for standard

doses of typical antipsychotic drugs (Bigliani *et al*, 1999). Importantly, drugs with modest affinity for D_2 receptors exhibit this effect robustly across their whole dose range, whereas atypical drugs with higher affinity for the D_2 receptor (e.g. risperidone) display dose-dependent limbic selectivity (Xiberas *et al*, 2001; Bressan *et al*, 2003; Fig. 1).

These data could not be replicated by Talvik *et al* (2001), and full *in vivo* PET or SPET confirmation awaits further study. Nevertheless, regionally selective dopaminergic action of atypical antipsychotic drugs is supported by both electrophysiological and animal studies (Lidow *et al*, 1998; Strange, 2001).

How much D_2 blockade is too much?

The advent of antipsychotic drugs with very low affinity for dopamine D_2 receptors (most notably clozapine and quetiapine) begged the question whether D_2 receptor blockade was invariably required for antipsychotic efficacy. Imaging studies using PET reveal that striatal D_2 receptor occupancy by these drugs changes considerably over a 24 h period, even in steady state (Gefvert *et al*, 1998; Kapur *et al*, 2000*b*). Consideration of the D_2 receptor affinity and occupancy data relating to typical and atypical antipsychotic drugs led Kapur & Seeman (2001) to conclude that owing to low affinity for the D_2 receptor (driven, as these authors see it, by fast dissociation 'off' the receptor) clozapine and quetiapine exhibit transiently high D_2 receptor occupancy (not exceeding the threshold required to induce adverse movement or hormonal side-effects), which declines to very low levels over a 24 h period. This suggests that low-affinity drugs, with modest effects at D_2 receptors, may antagonise the system in a manner that preserves physiologically responsive endogenous dopamine transmission across a wide dose range (Kapur *et al*, 2000*b*). The effect may presumably also be achieved by higher-affinity drugs that are cleared rapidly from the synapse, or given at doses producing low synaptic concentrations of the drug (Strange, 2001). These data still do not explain the well-documented discrepancy between the rapid D_2 receptor blockade induced by antipsychotic drugs and the gradual remission of psychotic symptoms over several days or weeks. This delay could result from longer-term effects of antipsychotic drugs on brain plasticity, including (for example) synaptogenesis (Konradi & Heckers, 2001).

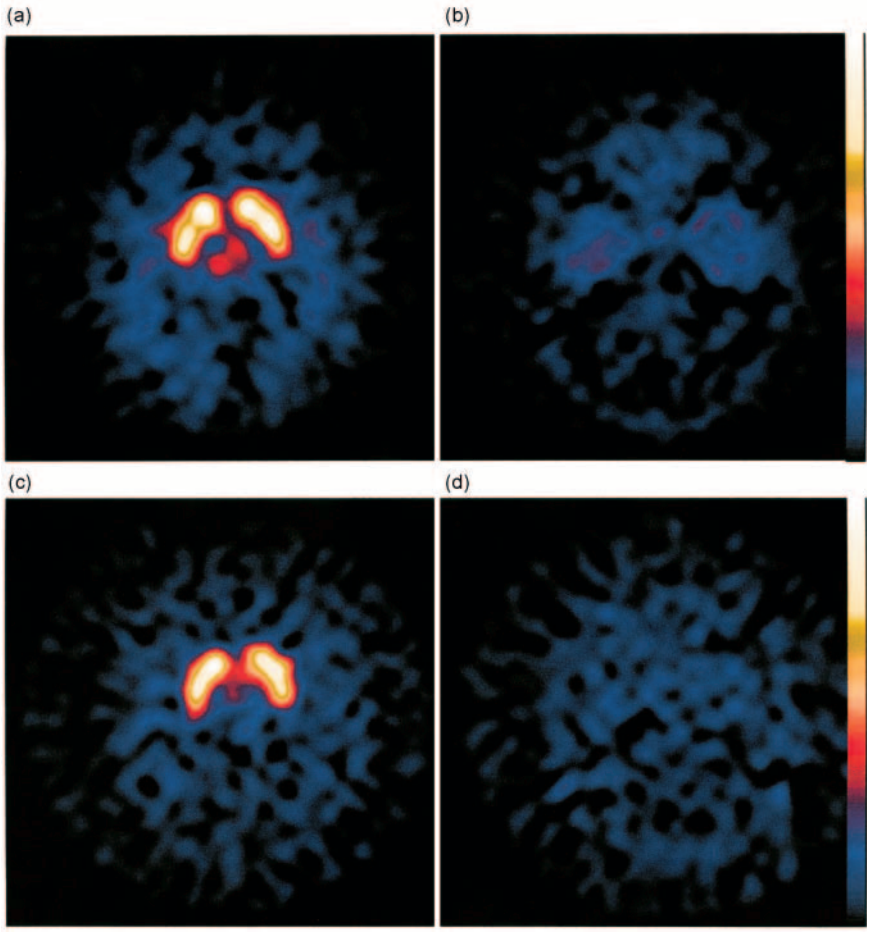

Fig. 1 Preferentially high occupancy of dopamine D_2/D_3 receptors in the thalamus and temporal cortex by risperidone in a patient treated with risperidone (dose <4 mg) compared with a healthy volunteer (see Bressan *et al*, 2003). (a, b) Normal volunteer: (a) striatum and thalamus, (b) temporal cortex and cerebellum. (c, d) Patient treated with risperidone: (c) striatum and thalamus, (d) temporal cortex and cerebellum.

TO AFFINITY. . . AND BEYOND! 'SMART' ANTIPSYCHOTIC DRUGS

The above suggests that a reasonable goal for effective, less-toxic treatment of schizophrenia is the regionally sensitive stabilisation of dopamine function, and not the 'blunderbuss' dopaminergic paralysis induced by classical antipsychotic drugs. This selective targeting could come about by exploiting behaviour intrinsic to compounds with low D_2 affinity, by designing compounds selective for dopamine receptor subtypes found at greater densities in limbic or cortical regions (for example D_3 receptors), or by modulating dopamine release through action at alternative systems (novel candidates include serotonin, sigma and glutamate receptor sites). Such ideas are certainly relevant to current therapeutics and future drug development. Novel agents with specific action at presynaptic D_3 autoreceptors controlling central dopamine release may offer more physiological modulation of dopamine than conventional antagonists (Reavill *et al*, 2000; Strange, 2001). It is apparent that as the neurochemical pathology of schizophrenia is not fully understood, and as many patients are only partially responsive or are insensitive to dopaminergic antagonism, many non-dopaminergic sites (especially those mediated by glutamate and serotonin) remain potent targets for future drug discovery. The availability of high- and low-affinity D_2/D_3 receptor antagonist antipsychotic drugs offers clinicians much choice, and the above data provide a rational evidence base for prescribing,

tailored as far as possible to individual patient responses.

DECLARATION OF INTEREST

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