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 combating 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 $K_r$) 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 ‘come-back 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$_3$) 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 ($D_{2\text{short}}$ and $D_{2\text{long}}$), 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.

**DOPAMINERGIC PATHWAYS AND RECEPTOR PHYSIOLOGY**

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 contemporary 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 extra-pyramidal side-effects (and modest affinity for D2 receptors in vitro) had consistently low levels of D2 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 re-interpretation of the importance of D2 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-HT2) receptor subclass. Meltzer et al. (1989) proposed, on the basis of drug affinity data, that the ratio of 5-HT2A to D2 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 andquetiapine, shared a strikingly high degree of 5-HT2A receptor occupancy (>90%) over their entire dose range (Nordstrom et al., 1993a; Nyberg et al., 1993; Travis et al., 1998; Kapur et al., 1999; Jones et al., 2001). This is unsurprising given that olanzapine, risperidone andquetiapine were developed on the basis of their high 5-HT2A/D2 receptor affinity profiles. It appears from the results of further studies (particularly the failure of pure 5-HT2A antagonists to show striking therapeutic effects) that 5-HT2A 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 D2 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. (1993b) and later Kapur et al. (2000a) showed that symptom reduction and side-effect reduction could be fitted to a threshold model of striatal D2 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. (2000a) demonstrated that striatal D2 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% D2 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 D2/D1 receptor occupancy (38–87%).

Furthermore, individual responses to similar degrees of D2 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. (2000a) despite similar levels of D2 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 D2 receptors in schizophrenia were crucial to the genesis of the dopamine hypothesis. Increased striatal D2 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 D2 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 D2 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 [123I]-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 D2 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 D2 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 D2 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 andquetiapine) exhibit cortically selective D2 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; Xiberras 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 D₂ receptors exhibit this effect robustly across their whole dose range, whereas atypical drugs with higher affinity for the D₂ receptor (e.g., risperidone) display dose-dependent limbic selectivity (Xiberras 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 D₂ blockade is too much?**

The advent of antipsychotic drugs with very low affinity for dopamine D₂ receptors (most notably clozapine and quetiapine) begged the question whether D₂ receptor blockade was invariably required for antipsychotic efficacy. Imaging studies using PET reveal that striatal D₂ receptor occupancy by these drugs changes considerably over a 24 h period, even in steady state (Geifert et al., 1998; Kapur et al., 2000b). Consideration of the D₂ 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 D₂ receptor (driven, as these authors see it, by fast dissociation ‘off’ the receptor) clozapine and quetiapine exhibit transiently high D₂ 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 D₂ receptors, may antagonise the system in a manner that preserves physiologically responsive endogenous dopamine transmission across a wide dose range (Kapur et al., 2000b). 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 D₂ 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).

**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 D₂ affinity, by designing compounds selective for dopamine receptor subtypes found at greater densities in limbic or cortical regions (for example D₃ 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 therapies and future drug development. Novel agents with specific action at presynaptic D₃ 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 D₂/D₃ 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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