Focus on Clozapine: a new explanation for its atypical character

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Although atypical antipsychotics have become the treatment of choice for schizophrenia, there is no consensus on the mechanisms of action leading to the ‘atypical’ character of these medications. Atypical antipsychotics are often referred to as ‘novel’, even though the prototypical antipsychotic of this series, clozapine, has been introduced into clinics for decades. Clozapine was found effective in some of the animal models predicting an antipsychotic action, for instance blockade of apomorphine-induced climbing, but not on models such as blockade of apomorphine-induced stereotypies. The dissociation between the effects of clozapine, which contrasts with those of the classical antipsychotics like haloperidol that is equally effective on both models, did not draw particular attention initially, was not recognized as an indication for a potential atypical clinical profile and is still incompletely understood. Psychiatrists using clozapine in psychotic patients at the time of its introduction in clinics were not particularly impressed by its therapeutic efficacy and were daunted by the serious side-effects that led to the discontinuation of the drug. The interest in clozapine was rejuvenated in 1988 after the publication of a double-blind clinical study showing the efficacy of clozapine in psychotic patients refractory to typical antipsychotics, such as chlorpromazine (Kane et al., 1988). Due to its potentially harmful side-effects, neutropenia and agranulocytosis, the use of clozapine is now restricted to patients who do not respond to other antipsychotic medications, under strict monitoring of peripheral neutrophil counts.

There is no consensus on the definition of the term atypical antipsychotic. All psychiatrists agree that atypical antipsychotics elicit fewer extrapyramidal side-effects (EPS), which include Parkinson-like symptoms at the initiation of the treatment and tardive dyskinesia after long-term use, than typical antipsychotics. Indeed, lesser propensity to elicit EPS was noticed in all clinical trials with the more recent atypical antipsychotics olanzapine, risperidone or amisulpride. Importantly, the lower risk of side-effects attributed to atypical antipsychotics should be restricted to EPS, as weight gain and associated metabolic dysfunctions, such as diabetes and cardiovascular complications, are nowadays a serious concern with olanzapine, while amisulpride elicits hyperprolactinaemia. However, as far as efficacy is concerned, the data are more conflicting. The studies reporting on superior efficacy of atypical antipsychotics against positive symptoms of schizophrenia are confounded by the fact that comparator doses have often been excessive and controlling this factor eliminated such an advantage. Moreover, the advantage in efficacy is only seen in very large studies, suggesting that it is small, and is further compromised by a bias of recruitment of patients in these studies, which include a significant proportion of poorly responding patients. Regarding negative symptoms of schizophrenia, the alleged higher efficacy of atypical antipsychotics also seems modest, but has been documented in some studies. However, it is still not clear whether the superiority of clozapine on some dimensions represents a primary effect of the drug or an effect related to the absence of adverse effects.

Nevertheless, in recent meta-analyses, clozapine emerges above all antipsychotics in terms of effect size, followed by amisulpride and then olanzapine and...
risperidone (Davis and Chen, 2005; Geddes et al., 2000). It is thus of importance to understand the origin of the atypical nature of clozapine. The fact that both atypical and typical antipsychotics share the property to block dopamine D2/D3 receptors gave rise to the hypothesis that the peculiar feature of atypical antipsychotics is related to non-D2/D3 receptor activity. Among these, the serotonin 5-HT2 receptor has received much attention. The 5-HT2 hypothesis postulates that the unique feature of atypical antipsychotics is their greater affinity for 5-HT2 receptors rather than dopamine receptors. Indeed, clozapine, which has a higher serotonin/dopamine receptor affinity ratio in vitro than typical antipsychotics and the newer atypical antipsychotics olanzapine, risperidone and some others were designed to reproduce this feature. However, the higher 5-HT2/D2 or D3 receptor binding ratios of atypical antipsychotics is mainly reached by a lower affinity at D2/D3 receptors. Moreover, positron emission tomography studies indicate that atypical antipsychotics fully occupy 5-HT2 receptors at doses that do not produce any antipsychotic effect, whereas their clinical efficacy emerges at doses at which D2 receptor occupancy exceeds 65%, a value which is not different to that reached with typical antipsychotics (Kapur and Seeman, 2001). These data suggest that 5-HT2 receptor blockade is neither sufficient nor necessary in antipsychotic effects. It may, nevertheless, have a role in the protection against EPS, or/and in the generation of other side-effects.

The study by Marcus and colleagues (2005) in this issue offers a new, more plausible explanation for the atypical character of clozapine. In their elegant study, they combine an electrophysiological study with patch-clamp recordings and a behavioural study in rats, with which they shed a new light on dysfunctions in schizophrenia and suggest a novel, rapidly testable, approach to the treatment of this disorder. In their electrophysiological study, they show that application of clozapine, but not of raclopride, a typical D2/D3 antipsychotic, onto pyramidal neurons of the prefrontal cortex, facilitates evoked excitatory post-synaptic potentials and currents via a dopamine-mediated mechanism involving the dopamine D1 receptor. This result is particularly relevant for schizophrenia, because these neurons carry the main glutamatergic output of the prefrontal cortex and there is growing evidence implicating glutamate deficit in schizophrenia. Thus, blockade of glutamate neurotransmission by non-competitive antagonists at the N-methyl-D-aspartate (NMDA) receptor subtype, such as phencyclidine (PCP, ‘angel dust’), produces psychotic symptoms. Repeated exposures to the drug elicit auditory hallucinations, anxious labile or paranoid states and decreased frontal blood flow, so that PCP abuse is associated with a psychopathological and functional state similar to schizophrenia (Jentsch and Roth, 1999). Moreover, direct evidence for altered NMDA receptor function in schizophrenia has been recently reported (Emamian et al., 2004) and genetic linkage studies in schizophrenia now show that the most plausible susceptibility genes functionally interact with glutamate pathways (Harrison and Owen, 2003).

Remarkably, the effect of clozapine is reproduced by the combination of the typical antipsychotic raclopride and idazoxan, a selective α2 adrenoreceptor blocker. This is accounted for by the potent α2 receptor antagonist property of clozapine, which in this compound complements the D2/D3 receptor antagonism. This is an original and important finding, because the noradrenaline/dopamine interactions on glutamate neurotransmission have not been extensively documented.

Previous results by the same authors show that clozapine alone or the combination of α2 and D2/D3 receptor blockade enhances dopamine release in the medial prefrontal cortex (Hertel et al., 1999). Thus, the results provide a new explanation for the augmentation of antipsychotic activity by idazoxan (Litman et al., 1996). Moreover, the study suggests that blocking α2 receptors counteracts the detrimental D2 receptor-mediated suppression of NMDA function. It also places a major role on cortical noradrenaline, which, although in line with previous studies, was not previously recognized. Furthermore, it provides a novel hypothesis for the atypical character of clozapine based on its α2 receptor antagonism, which markedly departs from current hypotheses, notably the serotonin/dopamine interactions that were advocated in the mode of action of atypical antipsychotics. The next part of the study provides an original result showing that clozapine, or the combination of α2 and D2/D3 receptor blockade, but not individual α2 or D2/D3 receptor blockade, corrects working-memory deficits produced by acute NMDA receptor blockade. The last part is also remarkable and greatly strengthens the behavioural study, because it shows that at the doses of raclopride and idazoxan used in the behavioural experiments, the α2C and D2 receptors were occupied exactly to the same extent as by clozapine.

Hence, this study is particularly relevant for our understanding of the dysfunctions present in schizophrenia. The recognition that α2 receptor blockade plays a role in the atypical character of clozapine provides a new conceptual frame for clinical studies in schizophrenia with combined α2 and D2/D3 receptor
blockade. However, it seems that there is no unique feature of atypical antipsychotics as a class, since olanzapine, quietapine and amisulpride have low affinity at $a_2$ receptors. Amisulpride poses another confusing problem, because this compound is specific for $D_2/D_3$ receptors, without any significant affinity for non-dopamine receptors. Interestingly, it has almost equal affinities at $D_2$ and $D_3$ receptors, whereas almost all other antipsychotic drugs prefer $D_2$ receptors. A contribution of $D_3$ receptors to the atypical character of amisulpride is supported by the observation that blockade of the $D_3$ receptor is sufficient to enhance dopamine release in the medial prefrontal cortex (Lacroix et al., 2003).

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Statement of Interest
None.

References


Jentsch J, Roth R (1999). The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 20, 201–225.


