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COMMENTARY

Optimisation of anti-psychotic therapeutics: a balancing act?

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Schizophrenia is a complex and debilitating disorder. Although effective therapeutic strategies are available, these are not without problems and are not universally efficacious. In this issue of the *British Journal of Pharmacology*, a trio of papers describe the characterisation of a potential, novel anti-psychotic medication, F15063. This compound combines antagonism of dopamine D_2-like receptors with agonism at 5-HT_{1A} receptors. Based on *in vitro* and *in vivo* profiles, the authors suggest that this compound approaches the 'optimal balance' for activity at these receptor systems.
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Abbreviations: DISC1, disrupted in schizophrenia 1; PDE4B, phosphodiesterase 4B

Schizophrenia is a complex and debilitating disorder, affecting roughly equal numbers of men and women. The economic cost of schizophrenia is substantial. In a recently published study, the overall cost in 2002 of schizophrenia in the US was estimated to be $62.7 billion (Wu *et al.*, 2005). Importantly, however, these figures do nothing to represent the human cost of this mind disorder.

Through genetic linkage analyses and studies of polymorphisms, a growing number of potential candidate genes for disease susceptibility have emerged. These include, but are not restricted to, neuregulin 1 (Hall *et al.*, 2006), dysbindin (Straub *et al.*, 2002), DISC1 and PDE4B (Millar *et al.*, 2005). For those interested, a recent review on the neurobiology of schizophrenia details a number of gene candidates in addition to those listed above (Ross *et al.*, 2006). Undoubtedly, increased knowledge regarding the genetic basis of schizophrenia and related psychotic disorders should allow for refinement of therapeutic targeting strategies in the future. Meanwhile, there are a number of anti-psychotic medications either currently available or under clinical trial.

Almost unfailingly, a key feature of anti-psychotic medication is the poor long-term compliance, typically owing to lack of efficacy or deleterious side effects (see Lieberman *et al.*, 2005). In this context, the National Institutes of Mental Health recently funded a Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, comparing olanzapine, quietapine, risperidone, ziprasidone and perphenazine. The duration of successful treatment was longest for the olanzapine group, yet 64% of olanzapine-treated patients had discontinued treatment within 18 months, with weight gain being a major issue (Lieberman *et al.*, 2005). Most notable, however, was that the remaining newer generation of atypical anti-psychotics appeared no more efficacious than perphenazine (Rosenheck *et al.*, 2006). This finding, combined with high discontinuation rates, clearly highlights the need for improved therapeutics to combat the symptoms of schizophrenia.

In this regard, a group of scientists from the Pierre Fabre research laboratories have developed a novel candidate molecule, namely F15063. A trio of papers in this issue of the *British Journal of Pharmacology* provide a thorough *in vitro* and *in vivo* characterisation of this compound (Depoortère *et al.*, 2007a, b; Newman-Tancredi *et al.*, 2007). In brief, F15063 acts primarily as an antagonist at dopamine D_2-like receptors with agonist activity at 5-HT_{1A} receptors and is devoid of affinity at a range of receptors implicated in adverse effects of anti-psychotics (e.g., sedation, weight gain; see paper I). Partial agonist activity at 5-HT_{1D} and dopamine D_4 receptors was noted, although these actions were far less pronounced compared with D_2-like and 5-HT_{1A} receptor activity. From an *in vivo* perspective, F15063 displayed an atypical anti-psychotic profile in tests of hyperdopaminergic activity, yet was devoid of cataleptogenic activity (at least for 5 days of repeated treatment). In addition, F15063 was able to overcome partially a PCP-induced social interaction deficit that could be antagonized

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by WAY100,635 (5-HT_{1A} receptor antagonist); overcome a scopolamine-induced amnesia during social recognition that was sensitive to L745870 (dopamine D_4 receptor antagonist) while having no disruptive effect on basal pre-pulse inhibition of the startle reflex. Collectively, these findings would predict efficacy against positive symptoms of schizophrenia with a relative absence of extra-pyramidal side-effects (Depoortère *et al*., 2007a). In addition, results in the third paper (Depoortère *et al*., 2007b) would suggest that F15063 also has properties that would be beneficial to target negative symptoms and cognitive deficits of schizophrenia. Clearly, the acid test of activity in humans remains to be answered.

The combination of dopamine D_2-like receptor antagonism and 5-HT_{1A} receptor agonism in one molecule is not confined to F15063. Indeed, other compounds sharing this pharmacology are currently undergoing clinical trials, for example bifeprunox. Moreover, clozapine, ziprasidone and aripiprazole, anti-psychotic agents already in clinical use, also possess these actions. The quiet enthusiasm surrounding F15063 is not therefore based on a novel pharmacology (although many of the other compounds mentioned have a more complex pharmacology than F15063), but rather on the relative balance between dopamine D_2-like receptor antagonism and 5-HT_{1A} receptor agonism. The lack of side-effect profile so far examined would suggest that the degree of 5-HT_{1A} receptor agonism is neither too low (which could result in residual catalepsy) nor too high (which could result in loss of anti-psychotic activity). Partial agonist activity at dopamine D_4 receptors may also have beneficial consequences. Undeniably, time will tell if F15063 and closely related molecules have a part to play in the balancing act of successful drug treatment of schizophrenia.

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