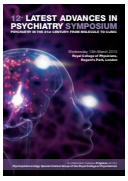
Is dopamine still the key to treating schizophrenia?



Current antipsychotics are useful in treating schizophrenia but do not offer a complete solution to managing the illness. Recent research suggests that modifying targets upstream of dopamine receptor blockade may hold the key to an improved psychopharmacological approach, explained Dr Oliver Howes, Honorary Consultant Psychiatrist at the South London and Maudsley NHS Foundation Trust, speaking at a satellite symposium organised by Roche at the 12th Latest Advances in Psychiatry meeting in London in March. Steve Titmarsh reports.

Treatment for schizophrenia has moved far from the 'state of the art' in the 18th Century when patients were kept in asylums where the wealthy could pay to go and observe the 'inmates', remarked Dr Howes. In the 19th and early 20th Century lobotomy, insulin coma and artificial hibernation found favour. These were, of course, quite risky treatments without great benefit. Then, in 1951/52, chlorpromazine arrived and with it a revolution in treatment. Initially, the drug was given alongside hibernation therapy, which chlorpromazine was thought to enhance. But soon it became clear that chlorpromazine alone was a superior treatment.

Haloperidol was subsequently developed in 1958 and used in patients in 1959, followed by clozapine, also used in patients in 1959. The 1960s and 70s saw an 'explosion' in the development of compounds largely based on the pharmacology of chlorpromazine and haloperidol. When dopamine receptors were discovered, they were initially called 'neuroleptic' receptors.

Clozapine's efficacy was so pronounced that researchers tried to replicate its pharmacology in the development of newer drugs. That led to the development of second- and third-generation antipsychotics.

Dopamine holds sway

However, the newer antipsychotics still predominantly act via blockade of dopamine D_2 receptors. It was thought that some of the second-generation drugs acted via the serotonin 5-HT_{2A} receptor. But at sub-clinical doses, drugs such as olanzapine and risperidone show almost 100 per cent blockade of $5HT_{2A}$ receptors, whereas clinical efficacy is seen only at doses where around 70-90 per cent of D_2 receptor blockade occurs.[1] Also, amisulpride, another second-generation drug, is highly selective for D_2 receptors with very little occupancy of $5HT_{2A}$ receptors. So $5HT_{2A}$ receptor activity does not seem to explain the efficacy of newer drugs.

In terms of efficacy, none of the second-generation antipsychotics appear to be significantly superior to clozapine,[2] again suggesting that $5HT_{2A}$ receptor activity is not the complete answer to treating symptoms of schizophrenia.

Partial relief of disease burden

Andrews *et al.* calculated that current treatments for schizophrenia provide relief from around 13 per cent of disease burden. Even with optimal treatment, they estimated that this would increase to around only 20 per cent.[3]

Many people with schizophrenia do not manage to integrate back into society, by finding employment for example: something that may be considered a real-world outcome. This is demonstrated by the fact that employment rates among people with schizophrenia are low in the UK at around 15 per cent.[4] This may be partly because although current treatments target positive symptoms there are less obvious benefits when it comes to negative symptoms and cognitive deficits, which are stronger predictors of functional recovery than the psychotic symptoms.

Attempts to understand the pathophysiology of schizophrenia better include PET scan studies in healthy volunteers who have taken an antipsychotic,[5] which show that metabolism, particularly in the frontal lobes, falls with increasing dopamine receptor blockade. Similarly, reaction time (as a proxy measure of cognitive function) increases as dopamine blockade increases. So although antipsychotic drugs target psychotic symptoms they may have unwanted effects on cognitive and other functions that are important in recovery.

There is therefore a substantial unmet need among patients with schizophrenia, which may be addressed by seeking new targets for antipsychotic drugs. To

achieve this, we need to know much more about the biology of the illness, Dr Howes explained. So far, there have been some significant advances in the field.[6] For example, the dopamine system in people with prodromal symptoms shows an increased capacity for striatal synthesis of dopamine. These same people show a further increase in dopamine production when they develop psychosis.[7] Research thus suggests that there may be an abnormality upstream of the dopamine receptor. Clues are emerging that increased glutamatergic activity in the hippocampus may be driving overactivity in the dopamine system, which then leads to psychosis.[8]

Something else that must be borne in mind is that around 27 per cent of patients with a diagnosis of schizophrenia do not respond to pharmacological intervention.[9] To some extent, this probably reflects the variability of the illness. These refractory patients do not seem to have an abnormality in their dopamine system but they have been shown to exhibit elevated glutamate levels, particularly in relation to negative symptom severity.[10]

New neurotransmitter targets

In conclusion, Dr Howes said that although current antipsychotics, which largely act via the D_2 receptor system, are useful in treating psychotic symptoms they are less effective in alleviating the negative and cognitive symptoms, which seem to be important in achieving recovery from schizophrenia. Work examining the biology and pathophysiology of the illness seems to suggest there may be benefits from modifying targets upstream (*ie* presynaptically where synthesis and release of dopamine occurs) of postsynaptic dopamine receptors, in order to address an abnormality that may be leading to the changes in the postsynaptic dopamine system thought to result in many of the symptoms seen in people with schizophrenia. Glutamate has emerged as one such target: only time will tell whether the theory is borne out in practice.

References

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