Current research and development of new treatments for schizophrenia

In this science article, Mark Ashton and Adam Todd examine the pathophysiology of schizophrenia, current treatments on the market and research into new treatments.

The World Health Organization estimates that there are 24 million people affected by schizophrenia worldwide, with many sufferers in the 15–35 years age range. The disorder is complex and individuals exhibit a range of symptoms, both positive and negative. Positive symptoms include delusions, hallucinations (often auditory), irrational thought patterns, which are often accompanied by the idea that an external agency has interfered with those thoughts, and abnormal behaviour, which is occasionally aggressive.

The negative symptoms include social withdrawal and a flattening of emotional response. In addition to the positive and negative symptoms, there is also often more general cognitive dysfunction, including depression, anxiety and memory impairment.1

Pathophysiology

Although the exact cause of schizophrenia is unknown, it is known to involve a combination of genetic and environmental factors, which result in changes in a number of brain structures and in the chemistry and physiology of the brain. A number of in vivo studies using various neuroimaging techniques have reported that the whole brain and grey matter volume is reduced in individuals with schizophrenia. Areas that appear to be susceptible to this reduction include the hippocampus, amygdala, the superior temporal gyrus, the prefrontal cortex, the thalamus, the anterior cingulate and the superior temporal gyri, the prefrontal cortex, include the hippocampus, amygdala, the thalamus, the anterior cingulate and the corpus callosum.2

The leading theory to account for the pathophysiology of schizophrenia involves an excess of the neurotransmitter dopamine and, although direct evidence for the role of dopamine is sparse, there is a large body of indirect evidence from a number of sources. The three main dopaminergic pathways are the nigrostriatal pathway (important for motor control), the mesolimbic/mesocortical pathways (involved in emotion and drug-induced reward mechanisms) and the tuberohypophyseal neurons, which run from the hypothalamus to the pituitary gland. The effects of dopamine are mediated by interaction with a group of dopamine receptors, D1–D5. These G-protein-coupled receptors are divided into two groups, the D1 family (made up of D1 and D5) and the D2 family (made up of D2, D3 and D4). An excess of dopamine is thought to occur either through excess production (presynaptic dopamine overactivity) or through postsynaptic dopamine overactivity mediated either by increased D2 receptor density or increased postreceptor action.

A weakness of the theory, as originally formulated, was that it only provided an explanation for one set of symptoms, namely the positive symptoms.3 However, later versions of the dopamine theory were able to account for both sets of symptoms. For example, it has been suggested that schizophrenia is the result of an imbalance between excessive stimulation of D2 receptors in subcortical regions and an under-activation of D1 receptors in cortical regions — the over-stimulation resulting in the positive symptoms, while the deficient stimulation of the cortical D1 receptors leads to the negative symptoms.3

An alternative description of the underlying neurochemical basis of schizophrenia suggests the involvement of a hypofunctional glutamate system, particularly decreased neurotransmission at the N-methyl-D-aspartate (NMDA) glutamate receptor.4 Glutamate, an excitatory neurotransmitter, operates via two families of receptors — metabotropic receptors (mGlu1–mGlu8) and ionotropic receptors (including the kinate, 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl]propanoic acid and NMDA subtypes).5 Various pieces of evidence exist that lend support to this hypothesis, but particularly striking is the observation that administration of ketamine (NMDA receptor antagonist) can induce symptoms in healthy volunteers that resemble some of the positive and negative symptoms of the condition.

It is, however, worth noting that, due to the reciprocal interactions between the dopaminergic and the glutamatergic systems, many of the effects could still be the result of changes in the dopaminergic systems.

Another neurotransmitter that has been implicated in the pathophysiology of schizophrenia is the inhibitory transmitter γ-aminobutyric acid (GABA). GABA is widely used in the brain and spinal cord and exerts its effects by acting on a family of ionotropic receptors (GABAa, GABAb and GABAc), whereby it is involved in the modulation of anxiety, muscle tension, epileptogenic activity and memory functions. Numerous postmortem studies of schizophrenic patients have...
5-HT3 is a ligand-gated cation receptor. There are many antipsychotic drugs currently on the market available to treat schizophrenia, some of which have been available for many years. Generally speaking, there are two broad classes of antipsychotics available: conventional antipsychotics and atypical antipsychotics. Conventional antipsychotics are thought to act by targeting D2 receptors in the brain and interfering with dopaminergic neurotransmission. Examples of conventional antipsychotic drugs include chlorpromazine, prochlorperazine, haloperidol and trifluoperazine. Unfortunately, although blockade of D2 receptors in the brain can help treat symptoms associated with schizophrenia, it may also cause extrapyramidal symptoms, something that can be troublesome for patients. Extrapyramidal symptoms consist of parkinsonian symptoms (eg, tremor), dystonia, dyskinesia, akathisia (restlessness) and tardive dyskinesia (involuntary movements of the face, tongue and jaw). These symptoms can be difficult to predict because they are often dependent on a number of things, such as dose, drug and patient factors. Some of the symptoms may stop on cessation of therapy, but other symptoms, such as tardive dyskinesia, may be irreversible.

Atypical antipsychotics include aripiprazole, olanzapine and quetiapine. They are often better tolerated than the conventional antipsychotic agents. They are generally associated with lower incidence of extrapyramidal symptoms and, as a result, are a welcome alternative to conventional agents.

Clozapine, another atypical antipsychotic, is also used in the treatment of schizophrenia, but only in patients unresponsive to, or intolerant of, conventional antipsychotic drugs because it has been associated with agranulocytosis.

Current research

Dopaminergic Agents

Cariprazine Cariprazine is a novel atypical antipsychotic that is currently under development by Gedeon Richter Ltd, Forest Laboratories Inc and Mitsubishi Tanabe Pharma Corp. It differs from all the current second generation antipsychotics, which, with the exception of amisulpride, bind to D2 and 5-HT2A receptors. Cariprazine exhibits partial agonism at D2, D3 and 5-HT1A receptors and antagonism at 5-HT7 receptors, with animal data suggesting that the levels of activity at D2 and D3 receptors are low, while the agonist activity at 5-HT1A is high. The hope with cariprazine is that it will provide an effective way of mitigating some of the cognitive deficit that is often associated with schizophrenia in addition to providing an antipsychotic benefit.

Lurasidone Lurasidone is an atypical antipsychotic that was granted approval at the end of 2010 by the US Food and Drug Administration for the treatment of schizophrenia. It has a high affinity for the D2, 5-HT2A and 5-HT7 receptors, where it acts as an antagonist, while it acts as a partial agonist at the 5-HT1A receptor. Lurasidone appears to be well tolerated and associated with few of the side effects that are observed with many other members of this class.

Glutamate agents

A potential new class of treatments for schizophrenia that operate via a novel mechanism appear to be emerging and a number of pharmaceutical companies have active development programmes in this area. Eli Lilly’s LY2140023 appears to be the most advanced candidate in this class, with recruitment to a phase III trial under way. LY2140023 is a prodrug of the orthosteric agonist (LY-404039), which operates at the metabotropic glutamate receptor 2/3 (mGluR2/3) and is active as long as it is bound to the receptor. Along with other mGluR agents, the precise mechanism by which they operate is still unclear, although these agents may be exerting their effects by modulation of the dopaminergic system because it has previously been demonstrated that mGluR2/3 agonists inhibit dopamine release. An important feature of LY2140023 was that there was no weight gain, which is normally associated with olanzapine. In fact, many patients who received LY2140023 actually observed modest weight loss.

Adjunct therapies

Rasagiline Rasagiline (selective monoamine oxidase inhibitor-B) is currently licensed for the treatment of Parkinson’s disease where it is used to treat cognitive deficit. A current trial is examining the possibility of using rasagiline as an adjunct therapy to treat the cognitive impairment and negative symptoms associated with schizophrenia and is due to report in 2011.

Ralphexine Ralphexine, a selective oestrogen receptor modulator, is being investigated as an adjunct therapy for use in the treatment of schizophrenia in postmenopausal women. Ralphexine is known to modulate the effects of oestrogen in the central nervous system, thereby improving emotional symptoms, memory and information processing. A larger trial, following on from an earlier smaller study, is expected to report this year.

Bexarotene A phase III trial involving the synthetic retinoid bexarotene is currently under way to evaluate its usefulness as an adjunct therapy for use with standard antipsychotic treatment. The study is a follow-up to a previous successful pilot programme.

Conclusion

Over the years a great deal of progress has been made in the management of schizophrenia. The introduction of atypical antipsychotics has proved successful since they are generally associated with fewer extrapyramidal side effects than the conventional agents. It would also appear that the pharmaceutical industry still considers this disease as an attractive target for drug design and there are, indeed, many novel agents in early development. For this progress to continue, it is vital research into developing new agents is maintained.

References


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