standardized ischaemic H-shaped double-flap wounds were created on the back. After 14 days, relaxin-treated rats had a significantly smaller area of surface necrosis at the wound than controls. Relaxin is thought to have stimulated healing of the ischaemic wounds by increasing blood flow through vasodilation and angiogenesis. However, it had no effect on healing times for well-vascularized wounds.

Potential future clinical uses

Connetics believes that the vasodilatory and pro-angiogenic properties of relaxin could be used to treat conditions caused by constricted blood vessels, including peripheral arterial, cardiovascular and renal disease. There are currently few treatment options for the advanced stages of these diseases. In peripheral arterial disease, surgery is often necessary, resulting in approximately 179,000 revascularization surgeries and 68,000 amputations in the US each year. 'We are very optimistic about relaxin for peripheral vascular indications,' said Krisztina Zsebo, Executive Vice President of Research and Product Development at Connetics.

Enrollment will begin shortly for a Phase II clinical trial of 120–140 peripheral arterial disease patients who have recently undergone surgical revascularization of a lower extremity and who have at least one unhealed ischaemic or operative wound in that region. They will be treated for 16 weeks with continuous subcutaneous infusion of rhRlx at 10, 25 or 100 $\mu g\ kg^{-1}\ day^{-1}$, or placebo. The study will evaluate the time to complete wound healing, as well as a range of related parameters. As peripheral arterial disease is often accompanied by renal disease, the study will also evaluate the effect of rhRlx on renal function.

As well as working on a range of cardiovascular and renovascular indications, Connetics is also pursuing clinical development of relaxin for the treatment of infertility, and conducting ongoing trials in scleroderma.

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Jo Whelan

Startling new impetus for schizophrenia research

An abnormal reaction to prepulse inhibition (PPI) of the startle reflex (see Box 1 and Fig. 1) is common in schizophrenics. Tonmoy Sharma and colleagues (Institute of Psychiatry, London, UK) have now shown that the severity of this abnormal response can accurately distinguish between early-onset and adult-onset disease[1]. This new information could lead to a significant reduction in time necessary for the development of new antipsychotics.

'These two identifiable subtypes of schizophrenia are well known but until now, there has been no marker: patients have been categorized by medical history and, if a late diagnosis was made, the picture becomes very cloudy,' explains Sharma.

A complex disorder

Schizophrenia is a group of disorders, first recognised in the 1940s. Since then, progress in developing therapeutic strategies and in understanding the molecular basis of the disorder has been relatively slow compared with, for example, cognitive disorders such as

Box 1. Prepulse inhibition

Prepulse inhibition of the startle reflex is the reduction in a strong startle response in people subjected to a lesser stimulus before the main stimulus. In this study, the main stimulus was 40 ms of white noise at 115 dB – a click loud enough to elicit a blink response. The pre-pulse was 20 ms of white noise at 85 dB – not enough to elicit a blink response. The pre-pulse was presented 30, 60 and 120 ms before the main pulse response, or not at all. In normal subjects, the main stimulus alone elicits the blink response.

The pre-pulse inhibits their response to the main stimulus, making them less likely to blink. The inhibitory mechanisms activated by the prepulse are thought to reduce the impact of the pulse to prevent the brain from 'overload' of information. Reduced prepulse inhibition has been repeatedly demonstrated in schizophrenics, which fits the proposed deficiencies of information processing that are thought to underlie the disease.

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Alzheimer's disease. 'The science has been held back by the wrongly held belief that schizophrenia is a functional disorder: a "mental illness". It is now clear that the main factor underlying the disorder is a physical abnormality of many different parts of the brain, with corresponding disruption of cognitive function,' says Sharma.

Severe, early-onset disease typified by diagnosis at an early age (<19 years) is associated with a poor long-term outcome and such patients often respond poorly to anti-psychotic therapy. Key maturation events occur in the brain in the late teens to early 20s. Synaptic pruning affects cognitive function in the brain, making the individual capable of more complex abstract thought. If the brain has structural abnormalities, this process does not happen normally, and this is when the symptoms become apparent in patients with early-onset schizophrenia.

Sharma stresses that the brain abnormalities that underlie schizophrenia are difficult to detect and their distribution and severity cannot be easily correlated with clinical symptoms. 'Until recently, the only way to categorize patients was in terms of their symptoms; those with paranoid delusions, those with hallucinations, and so on. The problem is that individual patients exhibit a range of different symptoms over time, and can move from one category to another, and back again,' says Sharma. A shift in thinking away from this traditional view of schizophrenia towards the acceptance that it is a physical cognitive disorder will have profound implications for therapy and drug development.

Using PPI in the search for better drugs

Last year, Sharma and colleagues demonstrated that older-generation antipsychotics such as haloperidol do not correct defects in PPI abnormalities, whereas new-generation antipsychotics

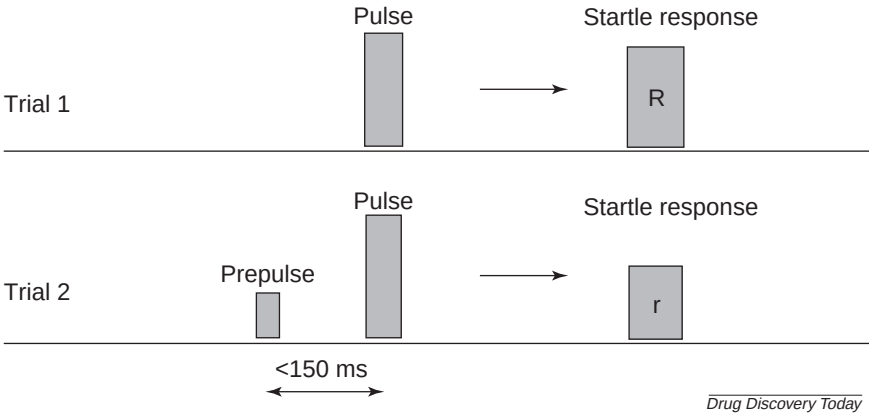

Figure 1. *In trial 1, a sound stimulus is applied without prepulse. The sound is loud enough to elicit the startle response. In trial 2, a prepulse (a sound stimulus not loud enough to startle) given milliseconds before the main pulse inhibits the level of startle response. In schizophrenics, prepulse inhibition is reduced but can be brought back to normal levels by antipsychotics that act as cognitive enhancers.*

such as clozapine do (Fig. 2)[2]. The exact mechanism of action of this effect is not yet fully established, but the workers suggest that it is caused either by the action of clozapine on prefrontal regions of the brain, or because the drug affects a broader range of neuroreceptors. In the future, more effort should focus on finding drugs that do inhibit the PPI response, particularly in early-onset patients. Such drugs increase cognitive function and, if therapy starts soon after diagnosis, could provide a better

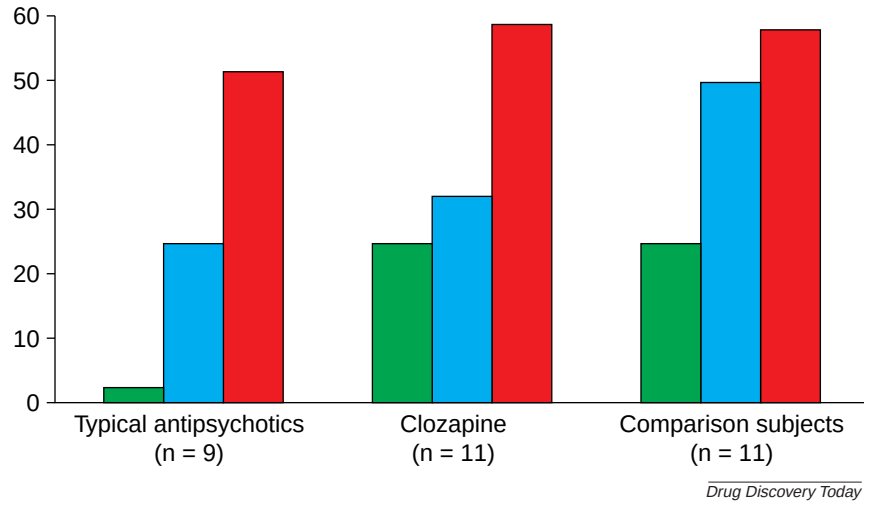

Figure 2. *The effect of typical antipsychotics and clozapine on normalizing prepulse inhibition (PPI) in schizophrenics. Mean PPI of the startle response by prepulse trials with 30 ms, 60 ms, and 120 ms prepulse-to-pulse intervals in patients treated with typical antipsychotics and clozapine, and comparison subjects. Clozapine is superior to typical antipsychotics, particularly at short prepulse intervals.*

long-term prognosis for early-onset schizophrenics.

The PPI test is used in animals as a standard indicator in the pharmaceutical industry when screening for drugs with antipsychotic potential. 'This study shows for the first time that the PPI test is a valid test in patients as well as animals. As PPI inhibition can screen for drugs that could be useful cognitive enhancers, this should reduce the amount of animal work necessary to demonstrate efficacy prior to Phase I clinical trials,' predicts Sharma. Rigorous safety tests will still need to be carried out but the direct link between animal and human results could reduce a typical drug development schedule by as much as two-and-a-half years.

Cognitive enhancement

The next step will be to identify more specific cognitive enhancement targets. Some pharmaceutical companies are already hot on the trail. Cortex Pharmaceuticals (Irvine, CA, USA) have carried out a small Phase I study using the Ampakine CX516, which stimulated improvements in performance on tests of verbal learning and memory, problem solving and attention and finger tapping in a small number of schizophrenic patients (for more detail, please see the next article; Ref. 3). The company is now partnered with Organon (Oss, The Netherlands) and is undertaking two larger Phase II studies, due to start later this year. Sharma welcomes this renewed interest in antipsychotics and also anticipates a fresh approach to the genetics of schizophrenia. 'I think that having a simple test that can distinguish early-onset patients will also help to accelerate research into this area,' he says.

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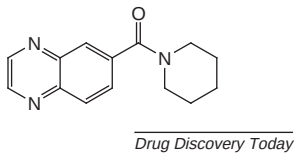
Kathryn Senior

Modulating AMPA receptors: key to mild cognitive impairment and memory?

A series of AMPA receptor modulating agents is entering clinical trials for the treatment of mild cognitive impairment (MCI) in a study funded by the Institute for the Study of Aging (New York, NY, USA). The lead compound in this series, CX516 (Fig. 1), has already been shown to enhance memory in rats and normal elderly volunteers, and is in Phase IIa clinical trials for Alzheimer's Disease (AD).



Drug Discovery Today

Figure 1. *The chemical structure of CX516.*

Mechanism of AMPA receptor modulators

Glutamate is the predominant neurotransmitter in the mammalian brain. Approximately 45% of glutamate receptors in the human brain respond to DL-α-hydroxyl-5-methyl-4-isoxaxolepropionic acid (AMPA) as an agonist, and are consequently designated AMPA-type receptors. They have been implicated in memory and other higher-order cognitive functions, such as thinking. Furthermore, AMPA receptors can potentiate the other main type of glutamate receptors, the *N*-methyl-D-aspartate (NMDA) receptors.

The hippocampus, which is the key brain area for memory development, is rich in glutamate receptors, and activation of these receptors leads to long term potentiation (LTP)[1]. Cortex Pharmaceuticals (Irvine, CA, USA) has developed a series of AMPA-receptor modulating agents, termed Ampakines, that enhance the signal caused by neurotransmitter release at AMPA receptors and have been shown to cross the blood–brain barrier. They act by slowing the kinetics of receptor opening, allowing more sodium ions to pass into the neurons, leading to an increase in neurotransmitter release. The response of AMPA receptors in tissue culture to an electrical stimulus is enhanced if an Ampakine is added before the stimulus is given[2]. If the receptors are frequently stimulated in a stable pattern, this enhancement is preserved for weeks or months[3]. Vince Simmon, President and CEO of Cortex Pharmaceuticals says, 'Measuring this electrophysiological response, which is LTP, is as near as we can get to measuring memory in cell culture.'

Preclinical studies

Ampakines have been shown to improve learning and memory in rats and mice. One early report[4] describes the enhancement of short- and medium-term

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