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.

REFERENCES

1 Kumari, V. *et al.* (2000) Prepulse inhibition of the startle response in men with schizophrenia. *Arch. Gen. Psychiatry* 57, 609–614

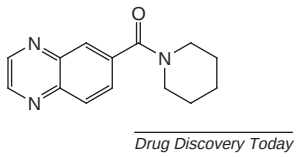
2 Kumari, V. *et al.* (1999) Normalization of information processing deficits in schizophrenia with clozapine. *Am. J. Psychiatry* 156, 1046–1051

3 Sansom, C. (2000) Modulating AMPA receptors: key to mild cognitive impairment and memory? *Drug Discovery Today* 5, 441–442

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

 1359-6446/00/$ – see front matter ©2000 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(00)01563-4

memory in rats by the lead compound, CX516 [Fig. 1; 1-(1,3-benzodioxol-5-yl-carbonyl)piperidine]. In the short-term memory test, trained male rats were initially allowed to retrieve rewards from four arms of an eight-arm maze with the other arms blocked. Four hours later the rats were released into the same maze, with all arms unblocked, and the number of 'incorrect' entries measured. Medium-term memory was tested using a two-odour discrimination task in which mature male rats were rewarded for selecting the 'correct' odour four days after initial training. In each case, rats that had been injected with CX516 before the initial training session performed significantly better than controls.

In another example, similar rats were injected with CX516 or vehicle on alternate days[5]. Their performance in a delayed nonmatch-to-sample (DNMS) test was shown to increase over a period of 32 days. Control rats that received only vehicle showed no improvement throughout the trial. Interestingly, the improvement in the experimental group continued on the days when they only received vehicle.

Human studies

The term 'age-associated memory impairment' covers a spectrum of conditions, ranging from normal memory decline to dementia. CX516 has been shown to improve recall of nonsense syllables in a double-blind trial in normal elderly volunteers[6]. Volunteers were aged 65–76 years and were tested in groups of ten (six placebo and four drug) over a period of three months. On average, volunteers taking the highest concentration of drug (900 mg) recalled over twice as many nonsense syllables after 5 min as those receiving placebo.

The upcoming trial of CX516, funded by the Institute of Aging, focuses on a group intermediate between these volunteers and AD patients: individuals with MCI. Patients diagnosed with MCI perform worse in memory tests than normal individuals of similar ages and educational levels, but are otherwise cognitively normal[7]. Although MCI has many possible causes, approximately 15% of patients with this condition develop AD every year.

Ronald C. Peterson, a neurologist at the Mayo Clinic (Rochester, MN, USA) and a key researcher in this field, says 'If we could cut this number [of MCI patients progressing to AD] in half using medications, there would be positive implications for quality of life.' The US government is already funding an evaluation of Vitamin E and Pfizer's Aricept (which is already licensed for mild to moderate AD) in slowing the progression of MCI patients to dementia.

Simmon is optimistic about the prospects for Ampakines for this group of individuals: 'We believe that it will be possible to improve memory in patients with MCI, rather than just slowing its decline.' More potent and specific AMPA modulating agents in this series, which are still in preclinical development, could be even more promising as treatments for this and other memory disorders.

REFERENCES

1 Arai, A. and Lynch, G. (1992) Factors regulating the magnitude of long-term potentiation induced by theta pattern stimulation. *Brain Res.* 598, 173–184

2 Staubli, U. *et al.* (1994) Facilitation of glutamate receptors enhances memory. *Proc. Natl. Acad. Sci. U. S. A.* 91, 777–781

3 Staubli, U. *et al.* (1994) Centrally active modulators of glutamate receptors facilitate the induction of long-term potentiation *in vivo*. *Proc. Natl. Acad. Sci. U. S. A.* 91, 11158–11162

4 Staubli, U. *et al.* (1994) Facilitation of glutamate receptors enhances memory. *Proc. Natl. Acad. Sci. U. S. A.* 91, 777–781

5 Hampson, R.E. *et al.* (1998) Facilitative effects of the Ampakine CX516 on short-term memory in rats: enhancement of delayed nonmatch-to-sample performance. *J. Neurosci.* 18, 2740–2747

6 Lynch, G. *et al.* (1997) Evidence that a positive modulator of AMPA-type glutamate receptors improves delayed recall in aged humans. *Exp. Neurol.* 145, 89–92

7 Petersen, R.C. *et al.* (1999) Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol.* 56, 303–308

Clare Sansom

News in brief

More reasons not to eat those chips!

Recent research at the Case Western Reserve University School of Medicine and University Hospitals of Cleveland (Cleveland, OH, USA) indicated that eating a high-fat diet in early and mid-adulthood might increase the probability of developing Alzheimer's disease in later life. This work, reported at the recent *World Alzheimer Congress 2000*, showed that the risk is increased in individuals with the ApoE-e4 allele marker, which is known to be linked to the development of Alzheimer's disease.

Researchers retrospectively analyzed foods consumed by 304 individuals (~70 years of age): 72 had Alzheimer's, 232 were healthy. Individuals with the ApoE-e4 allele who ate a higher-fat diet increased the risk of developing Alzheimer's by seven-fold, relative to those who did not possess this marker and ate a lower-fat diet.

It was found that 40–59 year-olds with the ApoE-e4 allele consuming high-fat diets (40% calories from fat) had a 29-fold increased risk of developing

1359-6446/00/$ – see front matter ©2000 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(00)01567-1