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Meeting Report

Novel drugs and products in neuroscience

Highlights from the International Brain Research Organisation (IBRO) World Congress of Neuroscience meeting

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CONTENTS

Abstract

The 7th International Brain Research Organisation (IBRO) World Congress of Neuroscience was held at the Melbourne Convention Centre in Melbourne, Australia, July 12-17, 2007. Many aspects of neuroscience were considered at this meeting. This report highlights the novel drugs discussed at the IBRO meeting including Na^+/Ca^{2+} exchange inhibitors, new drugs for the treatment of psychosis, anxiolytics, treatments for spinal cord injury, Huntington's disease, multiple sclerosis, drugs acting at allosteric sites and neuroprotective agents.

Introduction

The 7th IBRO World Congress of Neuroscience was held at the Melbourne Exhibition and Convention Centre, Australia, July 12-17, 2007. Many aspects of neuroscience were considered at this meeting. This report only highlights the novel drugs and products discussed at this meeting.

Is Na^+/Ca^{2+} exchanger family activity beneficial or detrimental during brain ischemia?

Ischemia in the brain leads to a massive Na^+ influx and K^+ efflux that causes permanent depolarization and toxic Ca^{2+} overload. Members of the Na^+/Ca^{2+} exchanger family (NCX) exchange Ca^{2+} for Na^+, and can operate in a forward or reverse mode. In the brain there are three different NCXs: NCX1, NCX2 and NCX3. Dr. L. Annunziato (Department of Neuroscience, University of Naples, Italy) has shown that inhibiting NCX1 or NCX3 with antisense oligodeoxynucleotides increases the extent of brain damage induced by permanent occlusion of the middle cerebral artery in rats (1). It seems likely that these oligodeoxynucleotides are blocking the NCX in the forward mode, as drugs that block the reverse mode have been shown to be beneficial in brain ischemia. Thus, drugs that increase the forward mode of the NCX may also be useful for the treatment of brain ischemia.

In rat hippocampal CA1 neurons, simulation of ischemic depolarizations led to high intracellular Ca^{2+}. Dr. L. Kiedrowski (The Psychiatric Institute, University of Illinois at Chicago, USA) has shown that **KB-R7943** (Fig. 1), which inhibits the reverse mode of the NCX, suppressed a fraction of this ischemic Na^+-dependent Ca^{2+} influx (2). Dr. Kiedrowski suggested that inhibition of Na^+-dependent Ca^{2+} influx with drugs such as KB-R7943 is likely to decrease ischemic brain damage.

SEA-0400 (Fig. 1) also inhibits the reverse mode of the NCX. Dr. T. Matsuda (Laboratory of Medicinal Pharmacology, Graduate School of Pharmaceutical Sciences, Osaka University, Japan) described the pharmacology of SEA-0400. SEA-0400 inhibits Na^+-dependent Ca^{2+} uptake into cultured neurons, astrocytes and microglia with an IC_{50} of 5-33 nM, making it a much more potent inhibitor than KB-R7943. SEA-0400 inhibits NCX1 and NCX2, but not NCX3, and inhibits the reverse mode. SEA-0400 reduces infarct volumes in the rat cerebral cortex and striatum after transient middle cerebral artery occlusion (3). SEA-0400 attenuated Ca^{2+} paradox injury in cultured astrocytes and protected against nitric oxide (NO)-induced cytotoxicity in cultured microglia and astrocytes. More recently, Dr. Matsuda has shown that SEA-0400 reduced ischemia-reperfusion injury in mice. Thus, drugs that inhibit the reverse phase of NCX have potential in the treatment of brain ischemia, *e.g.*, stroke.

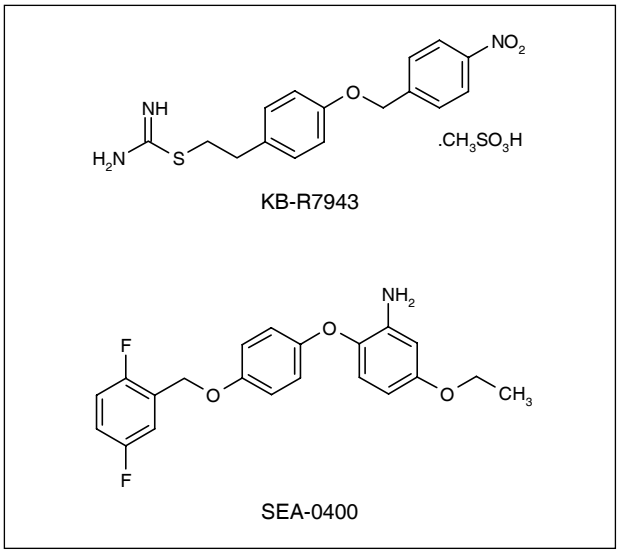

Fig. 1. Inhibitors of the reverse mode of NCX.

Psychosis

Dr. M. Shahid (Department of Pharmacology, Organon Laboratories, Ltd., Newhouse, Lanarkshire, UK) discussed dopamine/serotonin receptor-based treatments for psychotic disorders, *i.e.*, schizophrenia and the manic phase of manic depression. The atypical antipsychotic drugs were considered to be a major advance over the older antipsychotics until the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial were published. CATIE showed that 74% of subjects with chronic schizophrenia taking the study medications stopped taking their medications before 18 months, and this was usually due to lack of efficacy or intolerable side effects. The discontinuation rates were similar for the old antipsychotic agent perphenazine and the second-generation/atypical agents (olanzapine, quetiapine, risperidone) (4). This clearly indicates the need for newer, more effective and more tolerable antipsychotic drugs.

Ziprasidone and **aripiprazole** (Fig. 2) are partial agonists at dopamine D2 receptors that have recently been approved for the treatment of schizophrenia. **Bifeprunox** (Fig. 2) is another partial agonist at dopamine D2 receptors being developed for the treatment of psychosis. Dr. Shahid considers that one advantage that partial agonists at dopamine D2 receptors have over the other antipsychotics is a lesser ability to cause prolactinemia. However, ziprasidone was a late edition to the CATIE study, and did not show benefits over the other agents.

Several 5-HT subtypes facilitate dopamine release, but the 5-HT_{2C} receptor subtype, which has a high level of constitutive activity, inhibits tonic and evoked release of dopamine (5). Dr. Shahid suggested that selective 5-HT_{2C} agonists may be useful in the treatment of psychosis. **WAY-163909** (Fig. 3) is a selective 5-HT_{2C} agonist that decreases extracellular levels of dopamine in the nucleus accumbens without affecting the striatum. In animal models, WAY-163909 decreases apomorphine-induced activity without inducing catalepsy and reduces phencyclidine-induced locomotor activity without altering spontaneous activity. WAY-163909 reverses MK-801-disrupted prepulse inhibition of startle in mice. In conditioned avoidance response paradigms, WAY-163909 reduced avoidance responding (6). This suggested that 5-HT_{2C} agonists such as WAY-163909 have similar pharmacological profiles to the atypical antipsychotics.

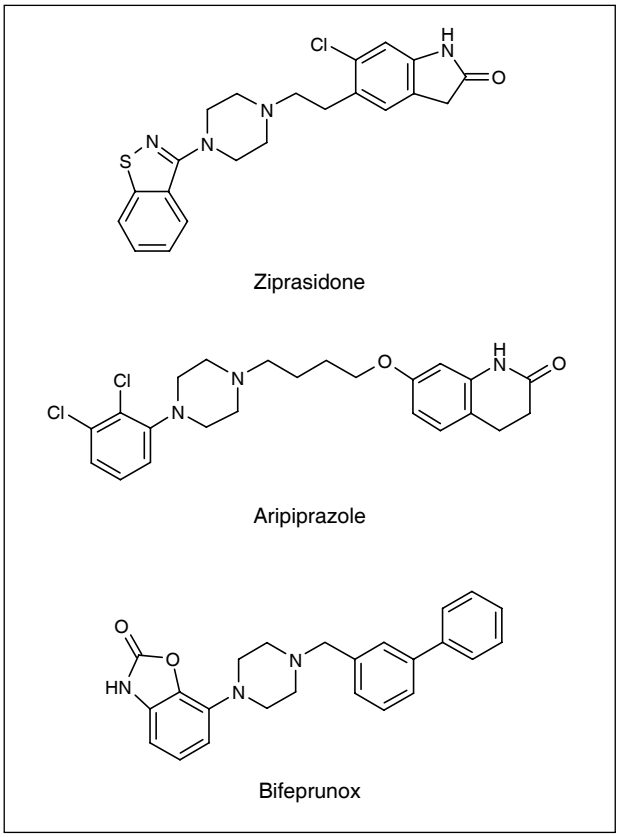

Fig. 2. Partial agonists at dopamine D_2 receptors.

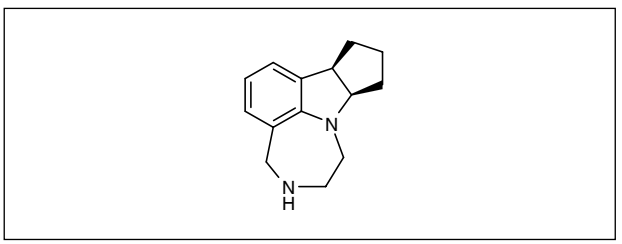

Fig. 3. Selective 5-HT_{2C} agonist WAY-163909.

The final group of drugs acting at dopamine/serotonin receptors mentioned by Dr. Shahid that may have clinical potential in psychosis are the 5-HT_6 antagonists. Two of these, **SB-271046** (Fig. 4) and **LY-483516** were in clinical development, and at least one other, **Ro-04-6790** (Fig. 4), was being developed for the treatment of psychosis. Although Dr. Shahid discussed some drugs with a single target as having potential in psychosis, he considers that drugs with multiple targets are more likely to be successful in psychosis.

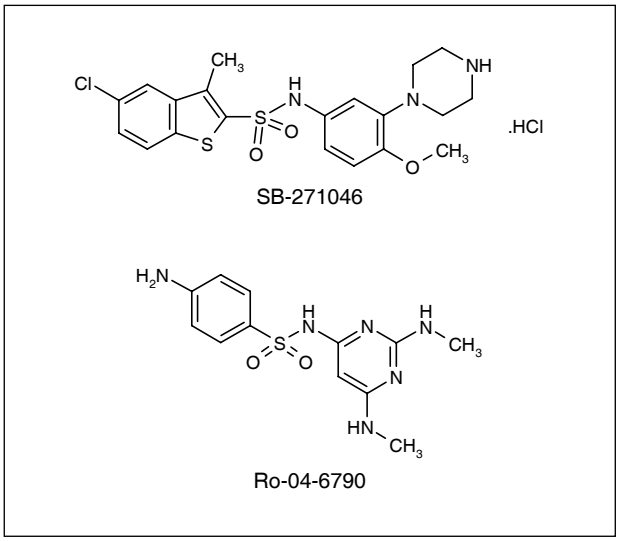

Fig. 4. 5-HT_6 antagonists.

Novel antipsychotic drugs were also discussed by Dr. F. Tarazi (Department of Psychiatry and Neuroscience Program, Harvard Medical School, Boston, Massachusetts, USA). Acadia Pharmaceuticals is developing **pimavanserin tartrate** (ACP-103; Fig. 5), a 5-HT_{2A} inverse agonist, as a co-therapy for the treatment of schizophrenia with either risperidone or haloperidol. NCT0036116 was a phase II clinical trial in subjects with schizophrenia, which showed that the efficacy of low-dose risperidone was increased by the addition of pimavanserin, whereas the side effects (especially weight gain) were reduced.

Reduced glutaminergic activity is a feature of schizophrenia. Ampakines (**CX-516**, **CX-717** and **Org-24448**; see Fig. 6) are AMPA receptor-positive modulators that act on an allosteric site of AMPA-type glutamate receptors to enhance neurotransmission and facilitate hippocampal long-term potentiation (LTP). CX-516 was studied for cognitive enhancement in schizophrenia in patients receiving clozapine, olanzapine or risperidone. Unfortunately, no cognitive benefits were observed with CX-516 (7). Drugs that directly stimulate AMPA-type glutamate receptors are also being evaluated clinically in schizophrenia. Dr. Tarazi reported that the mGluR_2/R_3 prodrug **LY-2140023** was superior to placebo in subjects with schizophrenia and had a better metabolic profile than olanzapine.

Dr. S. Dahl (Department of Pharmacology, University of Tromsø, Norway) discussed the glycine transporter as a target in schizophrenia. Inhibiting the glycine transporter-1 (GlyT-1) should, by increasing the levels of glycine, potentiate glutamatergic neurotransmission. An inhibitor of GlyT-1, **SSR-504734** (Fig. 7), was effective in animal models of schizophrenia. It normalized prepulse inhibition deficit in mice and reversed hypersensitivity to the locomotor effects of *d*-amphetamine (8).

The last group of drugs for schizophrenia discussed by Dr. Tarazi were the nicotinic acetylcholine agonists, including the partial α7 agonists **DMXB-A**, **MEM-3454** and **TC-1734** (ispronicline) (see Fig. 8). In subjects with schizophrenia being treated with antipsychotics, DMXB-A was shown to improve neurocognitive skills measured by the Assessment of Neuropsychological Status score (9). MEM-3454 is in phase I trials and TC-1734 has been shown to improve cognitive skills in healthy volunteers (10).

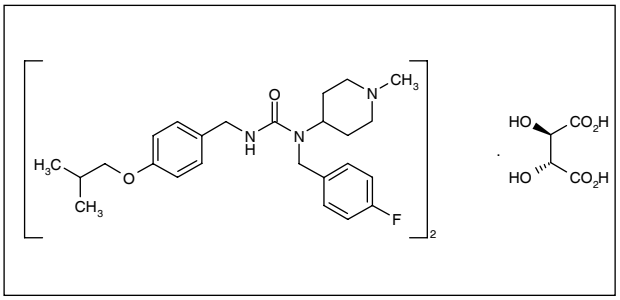

Fig. 5. 5-HT_{2A} inverse agonist pimavanserin.

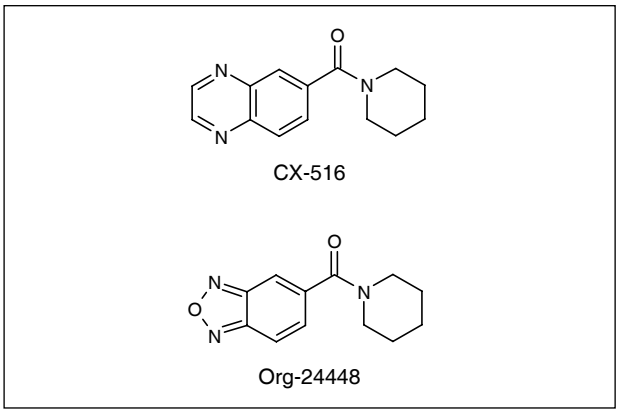

Fig. 6. Ampakines.

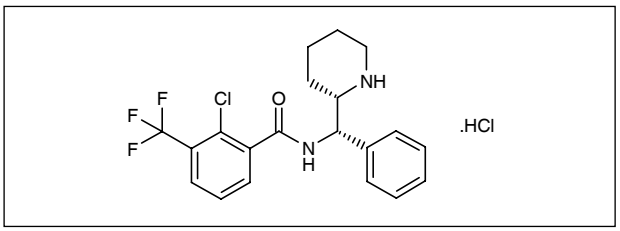

Fig. 7. Inhibitor of the glycine transporter-1 SSR-504734.

The P-glycoprotein transporter reduces the levels of olanzapine, risperidone and quetiapine in the brain. Dr. R. See (Department of Psychiatry/Neurosciences, Medical University of South Carolina, Charleston, South Carolina, USA) is developing inhibitors of the P-glycoprotein transporter in the hope that these will increase brain levels of these agents, and decrease any peripherally mediated side effects. Dr. See has shown that the P-glycoprotein inhibitor **PSC-833** (valspodar; Fig. 9) increases the penetration of risperidone into the brains of rats.

Anxiolytics

Anxiety disorders are becoming increasingly common, with around 20 million people in the United States

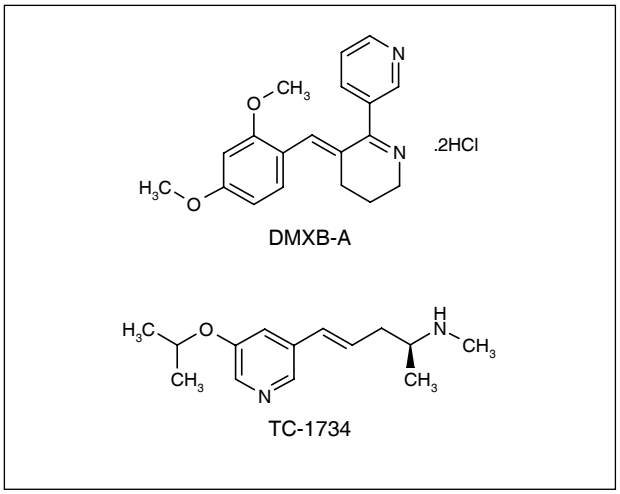

Fig. 8. Nicotinic acetylcholine partial $\alpha 7$ agonists.

suffering from some form of anxiety disorder. Whereas the 5-HT_6 receptor antagonists have therapeutic potential in psychosis (discussed previously), 5-HT_6 agonists have potential in the treatment of anxiety. **WAY-181187** and **WAY-208466** (Fig. 10) are selective 5-HT_6 receptor agonists with K_d values of 2.2 and 4.8 nM, respectively. WAY-181187 decreases cortical dopamine and 5-HT levels. In the rat schedule-induced polydipsia model of obsessive-compulsive disorder, oral administration of WAY-181187 decreased adjunctive drinking behavior (11). This suggests that WAY-181187 may be useful in anxiety disorders such as obsessive-compulsive disorder.

Dr. S. O'Connor (Bionomics, Ltd., Thebarton, Australia) is developing **BNC-210** as an anxiolytic agent. The exact mechanism underlying the anxiolytic effects of BNC-210 in rodents is unknown. BNC-210 inhibits the noradrenaline transporter (K_i = 6.3 μM), the NK_2 receptor (9.4 μM) and the adenosine A_3 receptor (13 μM). BNC-210 (0.01 mg/kg) was effective in the elevated plus maze model in rats and the marble-burying anxiety model in mice. Tolerance did not develop to the anxiolytic effect of BNC-210. Other animal testing showed that BNC-210 had no effect on locomotor activity, did not impair memory and was not an antidepressant. Although Dr. O'Connor would not reveal the structure of BNC-210, he said it belongs to a chemical class with a long history of safety in pharmaceutical use.

Spinal cord injury

At the spinal cord injury special interest forum, Dr. Michael Fehlings (Division of Cell and Molecular Biology, Toronto Western Hospital, Toronto, Ontario, Canada) briefed the audience on the current status of clinical trials in spinal cord injury. **Riluzole** is an Na^+ channel blocker that has already been approved for clinical use in the treatment of amyotrophic lateral sclerosis. Animal studies have shown that riluzole is neuroprotective in experimental spinal cord injury (12), and it is now in phase I/II trials in North America for spinal cord injury.

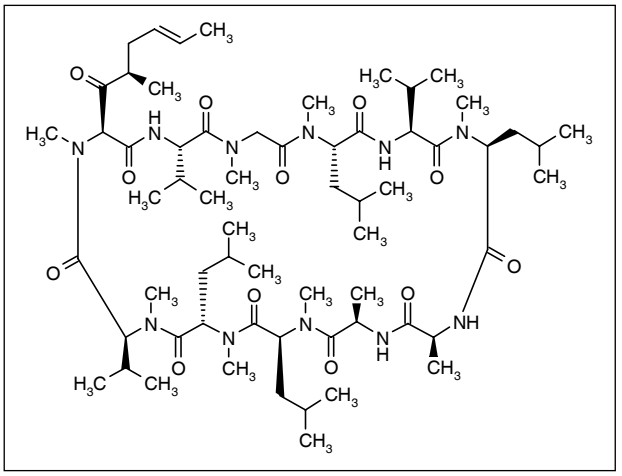

Fig. 9. P-glycoprotein inhibitor PSC-833

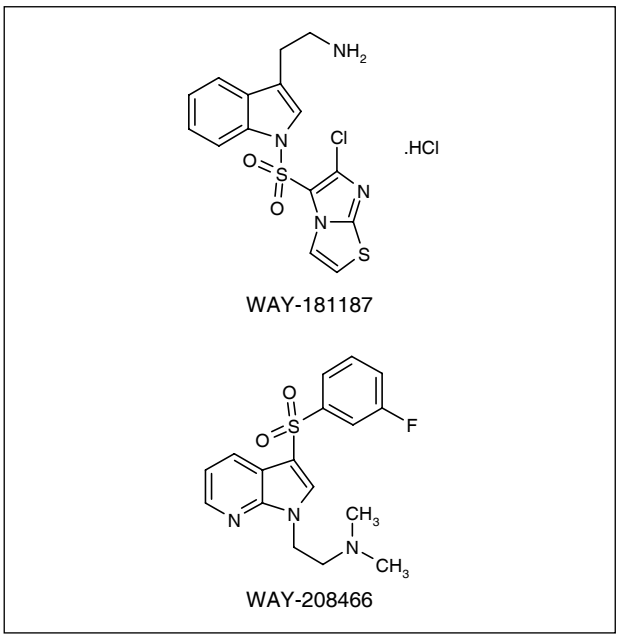

Fig. 10. Selective 5-HT_6 receptor agonists.

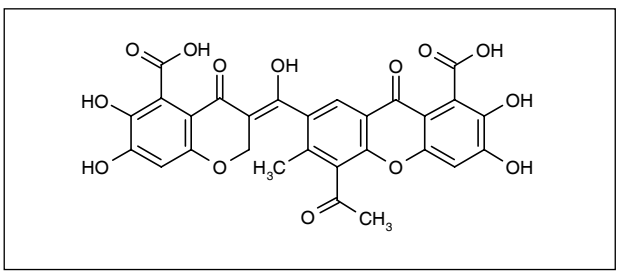

Fig. 11. The selective inhibitor of semaphorin 3A SM-216289.

Axons in the spinal cord show little ability to regenerate after injury, probably because regeneration is inhibited by axonal growth inhibitors. Semaphorin 3A is a major inhibitor of axonal regeneration. Dr. Okano (Keio University School of Medicine, Tokyo, Japan) has demon-

strated that **SM-216289** (Fig. 11) is a strong and selective inhibitor of semaphorin 3A. In rats with transected spinal cords, SM-216289 enhanced regeneration and/or preservation of injured axons, and caused a marked enhancement of functional recovery (13).

The activation of Rho blocks nerve regeneration. Consequently, Dr. Fehlings said that it is not surprising that agents that block Rho are being assessed in spinal cord injury. BioAxone Therapeutics has licensed **Cethrin** to Boston Life Sciences for phase II testing in spinal cord injury. Cethrin is a recombinant inhibitor of Rho that has been shown to be safe and well tolerated in a phase I/IIa trial in spinal cord injury. As this was a small open-label study with no control, it was not possible to demonstrate efficacy. However, encouragingly, some of the patients did recover sensory and/or motor function, and some converted from complete to incomplete injury. Novartis has a Rho antibody (**AT1355**) in phase I clinical trials for spinal cord injury.

Inhibition of Nogo-A stimulates axonal sprouting caudal to spinal cord injury. In adult macaque monkeys, antibodies to Nogo-A have been shown to enhance axonal sprouting, which parallels functional recovery (14). Thus, Nogo-A antibodies are undergoing further clinical development for use in spinal cord injury.

During the symposium on stem cells in the treatment of spinal cord injury, Dr. A. Mackay-Sim (National Adult Stem Cell Centre, Griffith University, Brisbane, Queensland, Australia) discussed the use of olfactory ensheathing cells. Animal studies have shown that these cells promote functional recovery after implantation into injured spinal cord. Olfactory ensheathing cells are accessible by biopsy of the olfactory mucosa in the nose and can be grown in large numbers *in vitro*. These cells have been shown to be safe when used in paraplegics with complete thoracic injuries occurring 6-32 months previously, but the study was too small, and is presently too short, to determine whether there were any functional improvements. Dr. P. Jendelova (Institute of Experimental Medicine, Prague, Czech Republic) has shown that autologous bone marrow cell implantation is also safe in subjects with acute and chronic spinal cord injury, but this clinical trial was also too small to determine efficacy.

Huntington's disease

Huntington's disease (HD) is an autosomal dominant genetic disease that results in progressive neuronal degeneration in the neostriatum and neocortex, with associated functional impairments in motor, cognitive and psychiatric domains. Dr. R. Barker (Cambridge Centre for Brain Repair, University of Cambridge, UK) discussed cell therapy in HD. Allotransplant of fetal striatal tissue in a few patients with mild to moderate HD has shown variable effects, but no clear benefit has been shown to date.

Dr. P. Patterson (California Institute of Technology, Pasadena, California, USA) is investigating the use of intrabodies (intracellularly expressed antibodies) as therapeutics for HD. **MW8** binds to the *C*-terminus of exon 1 in the huntingtin (htt) protein and reduces mutant htt-induced aggregation and toxicity in cell cultures and acute brain models of HD (15). **VL12.3**, another intracellular antibody against htt, also rescues toxicity in a neuronal model of HD (16). More recently, Dr. Patterson has produced intrabodies against the proline-rich domain of htt (**Happ1** and **3**), which reduce mutant htt-induced aggregation and toxicity in cell culture models.

Dr. B. Connor (Department of Pharmacology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand) is using adeno-associated viral (AAV) vectors to deliver gene-based therapeutics to the brain. In a rodent model, AAV1/2 vectors containing a promoter driving brain-derived neurotrophic factor (**AAV-BDNF**) or X-linked inhibitor of apoptosis (**AAV-XIAP**) were injected into the striatum of rats. Subsequently, quinolinic acid was administered to produce a rat model of HD. Both AAV-BDNF and AAV-XIAP attenuated ipsilateral forelimb use bias, and AAV-BDNF also prevented sensorimotor neglect development and reduced the loss of the striatum. These results suggest that AAV-BDNF may have potential for treating HD in its early stages.

Polyunsaturated fatty acids have a structural and functional role in neuronal membranes. **Eicosapentaenoic acid** reduced motor manifestations and death in a transgenic model of HD. Dr. A. Hannan (Howard Florey Institute, University of Melbourne, Australia) discussed clinical trials in HD with **ethyleicosapentaenoic acid** (ethyl-EPA). The first phase III clinical trial of ethyl-EPA did not show a benefit in HD (17). However, subgroup analysis showed that patients with < 45 CAG repeats did have improvements in total motor score 4. As a consequence, a further phase III trial of ethyl-EPA is being undertaken in patients with CAG repeat expansion of $\geq$ 36 (NCT00146211).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). About 70% of patients present with relapsing-remitting disease, which is characterized by acute exacerbations with full or partial remissions. At the MS workshop, Dr. J. King (Royal Melbourne Hospital, Parkville, Victoria, Australia) reviewed the present and future treatment of multiple sclerosis. **Natalizumab**, a humanized monoclonal antibody, binds to the $\alpha_4\beta_1$ integrins of leukocytes to reduce cell adhesion and migration (inflammation). In a phase II clinical trial, natalizumab was shown to reduce relapses in subjects with relapsing-remitting MS. One year after phase III clinical trials, natalizumab was approved by the U.S. FDA for use in relapsing-remitting MS, but was withdrawn after 3 months based on 2 reported cases of progressive multifocal leukoencephalopathy, a viral disease usually confined to people with immunodeficiency. Dr. King considers that the efficacy of natalizumab is much greater than the interferons. Due to the safety concerns, natalizumab is currently restricted to use

as monotherapy in subjects with MS who are inadequately controlled by oher immunomodulators.

In the overreactive immune response in MS, T-lymphocytes probably damage myelin. Interleukin-2 (IL-2) is required for the growth of T-cells. **Daclizumab** is a humanized monoclonal antibody to the IL-2α receptor of T-cells and has been used to prevent organ transplant rejection. In an open-label phase II trial in 10 subjects with MS with an incomplete response to interferon beta therapy, daclizumab was well tolerated, reduced new lesions and improved clinical outcomes (18). Double-blind trials are now indicated for daclizumab in subjects with MS.

Alemtuzumab is another humanized antibody that depletes T-cells. In a phase II trial comparing alemtuzumab to interferon beta-1a in subjects with MS, alemtuzumab was shown to reduce relapses and improve function. Unfortunately, the trial was stopped prematurely, as alemtuzumab caused immune thrombocytopenic purpura (low platelets) in 2 subjects, 1 of whom died. Alemtuzumab may go forward to phase III with precautions to prevent depletion of platelets.

Rituximab is a human-mouse chimeric monoclonal antibody to the B-cell CD20 antigen used to deplete B-cells. Rituximab is the first drug to target B-cells in MS. Although rituximab was shown to decrease lesions in MS, it has been associated with a high incidence of adverse effects, particularly infusion reactions, and the future development of rituximab for MS is uncertain.

Fingolimod (Fig. 12) is an agonist at sphringosine-1 phosphate receptors that reduces circulating T-lymphocytes. In a phase II proof-of-concept trial in subjects with relapsing-remitting MS, oral fingolimod was shown to reduce the number and volume of lesions and the relapse rate. Fingolimod decreased heart rate and blood pressure (19). Fingolimod is now being tested in a phase III clinical trial in comparison with interferon beta-1a.

Teriflunomide (Fig. 13) is a metabolite of **leflunomide** (Fig. 13) that has recently been shown to inhibit the interaction of T-cells with antigen-presenting cells to form immunological synapses, which are essential for immune responsiveness (20). In a phase II trial in subjects with relapsing-remitting MS, oral teriflunomide was shown to be well tolerated and to reduce lesions (21). Teriflunomide is presently being assessed in a phase III trial in subjects with MS.

Cladribine (Fig. 14) is a purine analogue that has lymphocytotoxic activity. In phase II trials for MS, cladribine has been shown to reduce lesions but has mixed results in decreasing neurological disability (22). Cladribine is presently being tested in combination with interferon beta-1a in subjects with MS.

Fumaric acid esters are useful in the treatment of psoriasis. Recently, fumaric acid esters have been tested in 10 subjects with relapsing-remitting MS and were shown to decrease the number and volume of lesions (23). Fumaric acid esters are presently in phase III trials for this indication.

Finally, Dr. King mentioned **interferon tau**. Interferon tau can be given orally and increases antiinflammatory cytokines. Interferon tau is currently in phase II clinical evaluation at several clinical centers for MS.

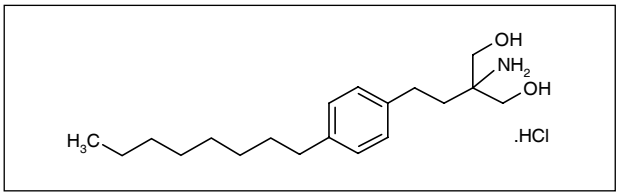

Fig. 12. Sphringosine-1 phosphate receptor agonist fingolimod hydrochloride.

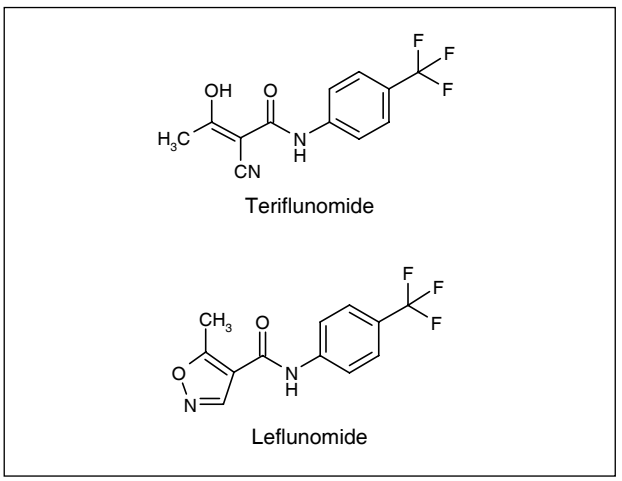

Fig. 13. Leflunomide and its metabolite teriflunomide.

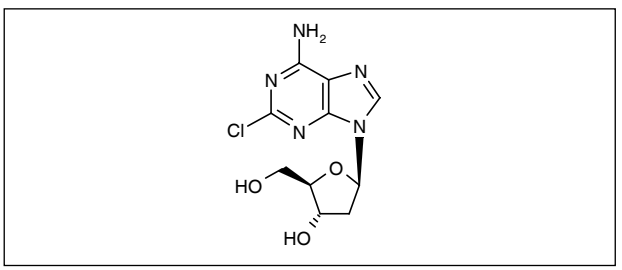

Fig. 14. Purine analogue cladribine.

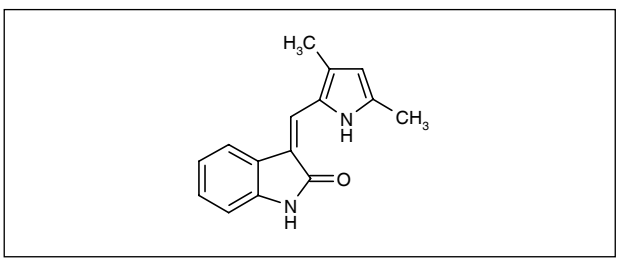

Fig. 15. KDR inhibitor semaxanib.

Semaxanib (Fig. 15), a KDR inhibitor being developed as an antiangiogenic drug, has recently been shown to have efficacy in the experimental autoimmune encephalomyelitis (EAE) model of MS (24). Dr. M. Gresle (Howard Florey Institute, University of Melbourne, Parkville, Australia) demonstrated that semaxanib

decreased IL-2 levels in the EAE model in transgenic mice. Also, semaxanib (50 mg i.p.) improved functional outcome and there was no reduction in oligodendrocytes in the lumbar spinal cord or optic nerve.

Drugs acting at allosteric sites

Endogenous ligands act at the orthosteric sites of their receptors, and most receptor-active drugs presently available also act at this orthosteric site. Allosteric ligands bind to sites on the receptors distinct from the orthosteric site, both to modulate the effect of the orthosteric ligand and the effects of the receptor in their own right. The first allosteric drug to be approved for clinical use was **cinacalcet**, which binds to the calcium-sensing receptor to increase its activation by extracellular calcium. Cinacalcet is used to treat secondary hyperparathyroidism in subjects with chronic kidney disease.

The discovery of subtype-selective muscarinic acetylcholine receptor agonists and antagonists has been hampered by the high degree of conservation of the acetylcholine binding site among the subtypes. This has hindered the development of selective M_1 receptor agonists, which may be useful in the treatment of the cognitive deficits associated with Alzheimer's disease and schizophrenia. Dr. C. Langmead (Psychiatry CEDD, GlaxoSmithKline, Harlow, UK) has shown that **AC-42** (Fig. 16) is an allosteric agonist at M_1 receptors (25). Subsequently, Dr. Langmead has carried out a pharmacological characterization of an analogue of AC-42, **77-LH-28-1**, which is also a selective M_1 receptor agonist. 77-LH-28-1 stimulates the M_1 receptor allosterically, and this leads to calcium mobilization and inositol phosphate accumulation. 77-LH-28-1 acted as a full agonist at rat hippocampal M_1 receptors to increase cell firing. 77-LH-28-1 is active after subcutaneous administration and stimulates the hippocampus after this route of administration.

Dr. A. Christopoulos (Drug Discovery Laboratory, Department of Pharmacology, Monash University, Clayton, Victoria, Australia) considers that allosteric agonists at the M_4 receptor may also be useful in the treatment of schizophrenia. In his laboratory, they have shown that **Win-51708** (Fig. 17) is an allosteric agonist at M_4 receptors (26). In the phencyclidine rat model of schizophrenia, the allosteric M_4 receptor agonist **LY-2033298** decreased locomotor activity, which provides further evidence that M_4 agonists may be useful in the treatment of psychosis.

Metabotropic glutamate (mGlu) receptors regulate synaptic transmission in numerous synapses and represent an important target in diseases of the brain. Dr. L. Prezeau (Institute of Functional Genomics, INSERM, Montpellier, France) discussed some drugs that act as allosteric modulators of these receptors. **Bay-36-7620** (Fig. 18) is an allosteric antagonist at $mGluR_1$ receptors that has been shown to have neuroprotective and anticonvulsant activity (27). In contrast, **Ro-01-6128** (Fig. 18) is an allosteric agonist at $mGluR_1$ receptors. As allosteric modulators, **MPEP** is an inverse agonist, **DFB** is a full agonist and **CPPHA** is an antagonist at $mGluR_5$ receptors. Agonists at $mGluR_5$ may have antipsychotic and cognition-enhancing activity.

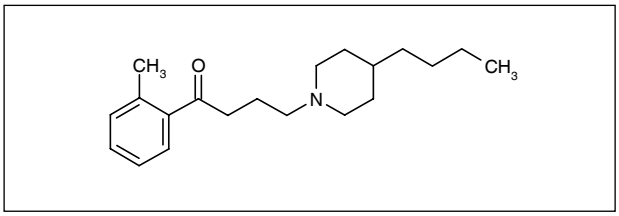

Fig. 16. Selective M_1 receptor allosteric agonist AC-42.

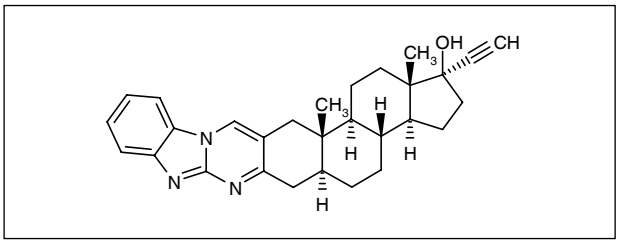

Fig. 17. Allosteric M_4 receptor agonist Win-51708.

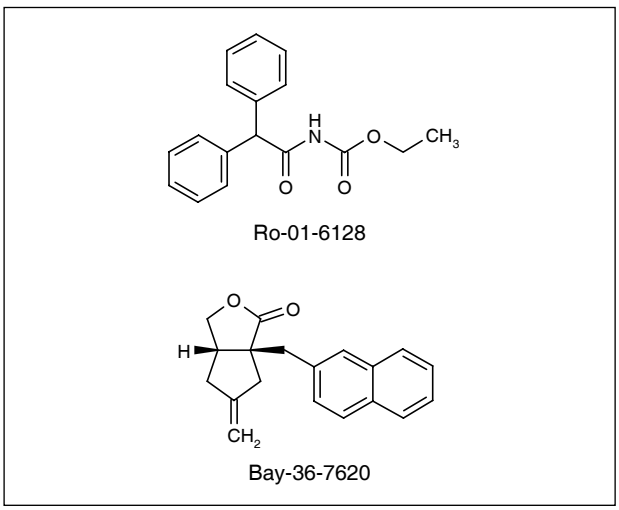

Fig. 18. Ro-01-6128, an allosteric agonist, and Bay-36-7620, an allosteric antagonist at $mGluR_1$ receptors.

Dr. J. Conn (VICB Program in Drug Discovery, Vanderbilt Medical Center, Nashville, Tennessee, USA) talked further about the potential for $mGluR_5$ agonists to treat the negative symptoms and cognitive disturbances associated with schizophrenia. Antagonists at $mGluR_5$ receptors were initially developed (*e.g.*, **SIB-1757**; Fig. 19) and shown to be anxiolytic in patients. **CDPPB** (Fig. 19) was one of the first allosteric agonists at $mGluR_5$ receptors developed. CDPPB penetrates the brain and reverses amphetamine-induced locomotor activity and amphetamine-induced deficits in prepulse inhibition in rats, which are models of psychosis (28). **ADX-47273** (Fig. 19) is another allosteric $mGluR_5$ potentiator that reverses amphetamine-induced deficits in prepulse inhibition. Dr. Conn subsequently developed more potent allosteric antagonists at $mGluR_5$ receptors, **VU-29** (Fig.

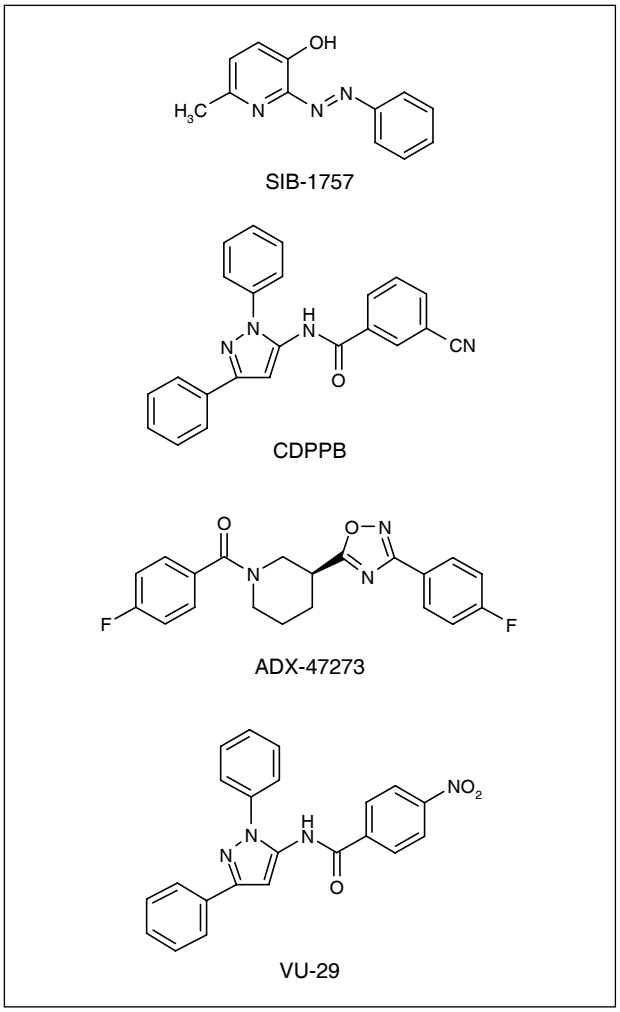

Fig. 19. Allosteric modulators of $mGluR_5$ receptors.

19) and **VU-75**, which has an EC_{50} of 3.3 nM. VU-29 potentiates LTP in the hippocampus, which suggests that it may improve memory.

The GABA system has been implicated as a target for alcohol abuse. The $GABA_B$ receptor allosteric agonist **CGP-7930** (Fig. 20) has been shown to reduce ethanol self-administration in alcohol-preferring rats (29).

Selected posters

Anticonvulsant

Stimulation of the trypsin receptor PAR2 is known to be cytoprotective. As PAR2 is widely distributed in the brain, stimulation of this receptor may also be neuroprotective. **SLIGRL** (Fig. 21) is a brain-accessible, nonproteolytic PAR2 agonist. Dr. R. Lohman (Department of Pharmacology, The University of Melbourne, Melbourne, Victoria, Australia) has shown that PAR2 was co-expressed with trypsin in the neurons of the rat hippocampus. In the amygdala electrical kindling model of epilepsy in rats, SLIGRP increased the afterdischarge

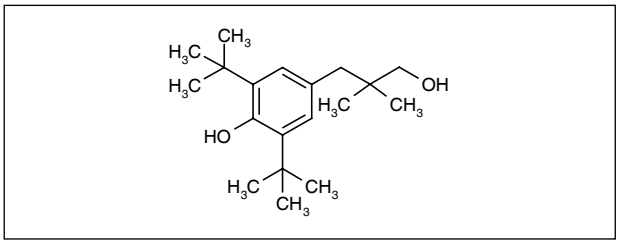

Fig. 20. $GABA_B$ receptor allosteric agonist CGP-7930.

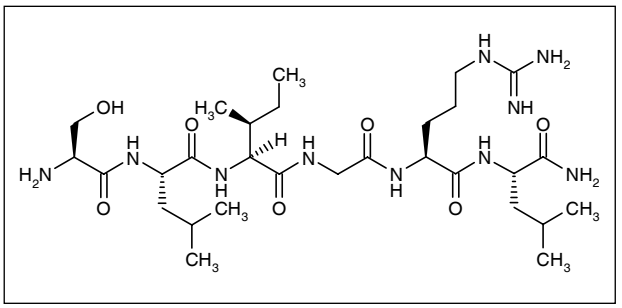

Fig. 21. PAR2 agonist SLIGRL.

threshold and reduced the number of seizures and their severity. This suggests that PAR2 agonists such as SLIGRL may be useful in the treatment of epilepsy.

Cerebrocast

Cerebrocast has therapeutic potential in the treatment of neuropathic pain and toxicity due to azidothymidine. Cerebrocrast is an atypical 1,4-dihydopyridine since it does not act as a calcium channel modulator. Rather, cerebrocast has been shown to be antiinflammatory and to regulate mitochondria. Dr. Rumaks (Department of Pharmacology, University of Latvia, Riga, Latvia) has shown that in the rat chronic constriction injury model of neuropathic pain, cerebrocrast (0.1 mg/kg i.p.) prevented mechanical hyperalgesia. In control rats, cerebrocast increased the pain threshold, indicating that it also has analgesic activity.

Azidothymidine is the most widely used treatment in HIV/AIDS but it has many side effects, which are probably mediated at the level of the mitochondria. Dr. J. Pupure (from the same group as Dr. Rumaks) has recently shown that azidothymidine increased the activity of the mitochondrial enzyme caspase-3 6-fold in mice brain tissue, suggesting apoptosis is taking place, and this response was reduced by cerebrocast. This suggests that cerebrocrast has therapeutic potential for reducing the toxicity of azidothymidine.

5-HT_6 receptor antagonists

At Suven Life Sciences (Hyderabad, India), Dr. R. Nirogi is developing the 5-HT_6 receptor antagonist **SUVN-507**. SUVN-507 has a K_i of 0.5 nM at 5-HT_6 receptors. *In vivo* brain dialysis showed that SUVN-507 (3 and 10 mg/kg) increased extracellular levels of acetylcholine

in the rat hippocampus and levels of glutamate in the frontal cortex. In the scopolamine rat model of Alzheimer's disease, SUVN-507 reversed the spatial and episodic memory deficits in the Morris water maze and the novel object recognition task. Dr. E. Mitchell (University of Washington, Seattle, Washington, USA) showed that a 5-HT_6 antagonist being developed by Roche, **Ro-4368554** (Fig. 22), was also able to improve memory in aged rats.

Specific antagonist of GPCR135

Relaxin-3 is the endogenous ligand for GPCR135. Dr. S. Sutton (Johnson & Johnson, Pharmaceutical Research & Development, San Diego, California, USA) has a chimeric peptide, R3/15, which is a specific agonist at GPCR135 and stimulates feeding behavior in rats. This effect can be blocked with a specific GPRC135 antagonist (details not disclosed). GPCR135 antagonists may have therapeutic potential in the treatment of obesity.

Antalarmin and ethanol administration

Corticotropin-releasing factor (CRF) is a neuropeptide involved in the anxiogenic response to stressors and may be involved in dysphoria-associated drug-seeking behavior. Dr. M. Cowen (Howard Florey Institute, University of Melbourne, Australia) has shown that central administration of the CRF_1 receptor antagonist **antalarmin** (Fig. 23) reduced ethanol self-administration in the alcohol-preferring rat.

Neuroprotective agents

Glutamate excitotoxicity and c-Jun activation are associated with neurological disorders such as cerebral ischemia, epilepsy, Parkinson's disease and Alzheimer's disease. Dr. A. Mead (Centre for Neuromuscular and Neurological Disorders, The University of Western Australia, Perth, Australia) has tested 19 peptides from a c-Jun yeast-2-hybrid screen for their efficacy in preventing cell death following glutamate excitotoxicity in primary cortical neuronal cultures and found 5 that were neuroprotective. Truncated versions of two of the neuropeptides, PYC36D-TAT and PYC38D-TAT, have also been shown to be neuroprotective.

At Neuren Pharmaceuticals (Auckland, New Zealand), Dr F. Sieg is developing neural regeneration proteins. One of these, **NNZ-4921**, is the *N*-terminus of calcium-dependent activator protein of secretion 2 (CADPS2). At 40 pg/kg/day i.p., NNZ-4921 prevented motor disorder caused by pyridoxine intoxication. Dr. W. Sun (Department of Anatomy, Korea University College of Medicine) is also developing neuroprotective neuropeptides. These are derived from thymosin β, which has a role in angiogenesis, cellular migration, wound healing and apoptosis. These peptides have been shown to suppress staurosporine-induced neuronal apoptosis *in vitro*.

Dr. M. Bickerdike, at Neuren Pharmaceuticals, is developing the novel diketopiperazine **NNZ-2591** as a neuroprotective agent. At 1-5 mg day i.p., NNZ-2591 was neuroprotective in a rat model of Parkinson's disease. GlaxoSmithKline is also developing an agent that has been shown to be neuroprotective in a rat model of Parkinson's disease. Dr. J. Aguirre (Department of Human Physiology and Pharmacology, School of Medicine, University of Malaga, Spain) has shown that this novel cyclooxygenase type 2 (COX-2) inhibitor reduces MPTP-induced injury of nigrostriatal dopamine neurons in the mouse.

Pyrimidines are involved in many biochemical processes and have the potential for therapeutic use, but they are poorly absorbed after oral administration. Dr. R. Garcia (Wellstat Therapeutics, Gaithersbury, Maryland, USA) is involved in the development of **PN-401** (triacetyluridine; Fig. 24), which allows for the oral delivery of high levels of uridine. In a transgenic mouse model of Alzheimer's disease, PN-401 decreased the degeneration of neurons and the plaque area in the hippocampus and cortex. PN-401 also decreased the degeneration of neurons in the piriform cortex and striatum in a mouse model of Huntington's disease. In a model of Parkinson's disease, PN-401 reduced mortality and increased striatum dopamine. Thus, PN-401 has potential in a range of neurodegenerative diseases.

Clioquinol (Fig. 25) is an 8-hydroxyquinoline that inhibits β-amyloid (Aβ) toxicity *in vitro*. Clioquinol has

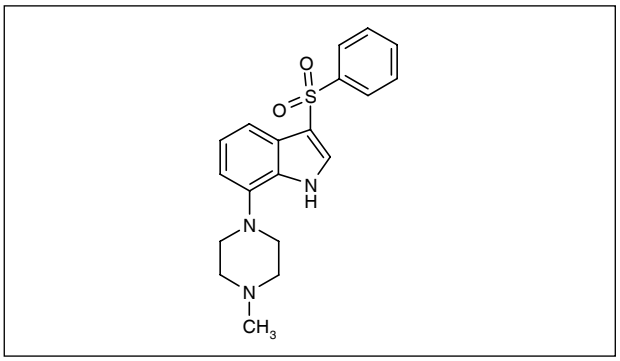

Fig. 22. 5-HT_6 antagonist Ro-4368554.

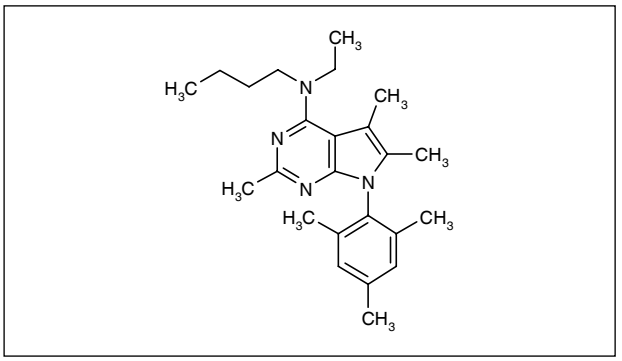

Fig. 23. CRF_1 receptor antagonist antalarmin.

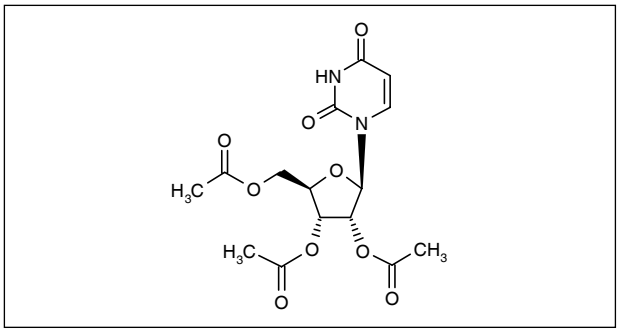

Fig. 24. PN-401.

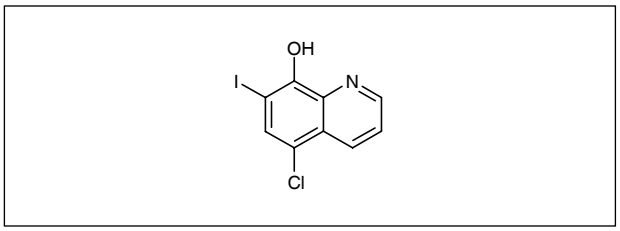

Fig. 25. Clioquinol, an 8-hydroxyquinoline.

been shown to slow cognitive decline in subjects with moderately severe Alzheimer's disease (30). **PBT-2** is a second-generation 8-hydroxyquinolone that is superior to clioquinol in preclinical tests. Dr. P. Adlard (The Mental Health Research Institute of Victoria, Australia) used *in vivo* tests to show that PBT-2 (30 mg/kg by oral gavage for 9 weeks) reduced Aβ burden by 50% in a transgenic mouse model of Alzheimer's disease. In the Morris water maze, PBT-2 improved cognition in mice over 5 days. Prana Biotechnology has started a phase II trial of PBT-2 in early-stage Alzheimer's disease.

In stroke, the angiotensin AT_2 receptor is upregulated. Dr. C. McCarthy (Department of Pharmacology, Monash University, Victoria, Australia) has shown that in spontaneously hypertensive rats, the AT_2 receptor agonist **CGP-42112** protects against stroke injury in the ET-1 model of stroke. CGP-42112 (1 ng/kg/min) reduced cortical infarct volume and motor deficits in the ledged beam test.

Sensorineural hearing loss results from damage to the sensory hair cells, and the degeneration of these cells is probably due to the loss of neurotrophin support. Exogenous application of neurotrophins to the deafened guinea pig cochlea prevents further degeneration. Neuroprotective cells containing neurotrophins transplanted into the cochlea have a similar effect. Dr. J. Andrews (University of Melbourne, Australia) is working with Living Cell Technologies (Auckland, New Zealand) to encapsulate these neuroprotective cells to improve the survival of the sensory nerves.

Neuropathic pain

α-Conotoxin Vc1.1 (ACV1) is a synthetic peptide deduced from the cDNA of the Australian marine cone snail *Conus victoriae*. ACV1 is a competitive nicotinic acetylcholine receptor (nAChR) antagonist. Dr. B. Livett (Department of Biochemistry and Molecular Biology, University of Melbourne, Victoria, Australia) has shown that in the streptozotocin-induced diabetic rat model of peripheral neuropathy, ACV1 (30 μg/kg s.c.) had an antiallodynic effect and reduced oxidative stress markers.

Antidepressants

A major drawback to using the selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression is that they can impair sexual function. At Wyeth, Dr. Sukoff Risso (Discovery Neurosciences Wyeth Research, Princeton, New Jersey, USA) is developing **WAY-426**, which in addition to being an SSRI is also a $5\text{-}HT_{1A}$ receptor antagonist. Oral treatment with WAY-426 (30 mg/kg) was effective in the olfactory bulb removal model of depression in the rat, without altering sexual function. Drugs that act solely as SSRIs impaired sexual function in the rat. Thus, drugs that combine SSRI and $5\text{-}HT_{1A}$ receptor antagonism, such as WAY-426, may be useful in the treatment of depression without disrupting sexual function.

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