Drugs of the Future 2009, 34(1): 79-91

CCC: 0377-8282/2009

HIGHLIGHTS FROM THE 38TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE

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ABSTRACT

Over 31,000 attendees from around the world gathered last year at the 38th Annual Meeting of the Society for Neuroscience held in Washington, D.C., on November 15-19, 2008. The meeting provided an unparalleled forum for scientists to exchange the latest advances in the field of neurosciences. Here, we summarize featured lectures and presentations, especially those referring to new drug discoveries and biomarkers for the detection and treatment of neurological disorders.

HIGHLIGHTS OF SPECIAL LECTURES AND SYMPOSIA

Epigenetics in neurological disorders

The term epigenetics has been described as a type of molecular and cellular memory that results in stable changes in gene expression caused by mechanisms that do not alter the underlying DNA sequence. Known epigenetic modifications include DNA methylation, histone modification and chromatin remodeling, among others, which are carried out by different types of enzymes: histone deacetylases (HDACs) and histone acetyltransferases (HATs), as well as methyltransferases and demethylases. For instance, histone H3 acetylation confers chromatin a relaxed state that favors gene transcription, while its methylation can either promote or suppress gene transcription. DNA methylation occurs around or in gene promoters and is generally associated with transcriptional suppression. Epigenetic mechanisms have been involved in the pathogenesis of brain disorders, including fragile X syndrome, Rett's syndrome, Huntington's disease, schizophrenia and bipolar disorder (1). Dr. Yasui from the University of California at Davis, U.S.A., discussed the role of epigenetic gene regulation by methyl-CpG-binding protein 2 (MeCP2) and its implications for Rett's syndrome and autism spectrum disorders. Rett's syndrome is a pervasive neurodevelopmental disorder with childhood onset that almost exclusively affects females. Patients with Rett's syndrome are severely disabled due to profound cognitive and motor deficits. The disorder is caused by mutations in the X-linked gene encoding MeCP2, a member of a family of DNA-binding proteins that preferentially binds to methylated CpG dinucleotides (2). Historically, MeCP2 has been regarded as a transcriptional silencer, as it binds to CpG-methylated promoters and recruits HDACs and other factors involved in transcriptional repression to nearby genes. Nevertheless, recent investigations conducted at Dr. Yasui's lab have shown that MeCP2 may be more close to a broad-range epigenetic modulator rather than a proximal silencer of gene expression. Using a custom high-density oligonucleotide microarray designed for chromatin immunoprecipitation (ChIP) on chip analysis, scientists discovered that most MeCP2 binding sites are outside of genes (59%) and that only 6% are in CpG-rich regions, and thus promoter methylation appears not to be correlated with MeCP2 binding. Also, 63% of MeCP2-bound promoters are associated with active genes and only 6% are highly methylated, therefore challenging the classic view of MeCP2 as a gene repressor. These findings may have consequences for the understanding of Rett's syndrome, as well as for the design of new therapies (3).

The epigenetic mechanisms of drug addiction were reviewed by Dr. Renthal, The University of Texas Southwestern Medical Center, Dallas, TX, U.S.A. In his lecture, Dr. Renthal explained how epigenetic mechanisms may regulate the induction and maintenance of drug addiction. Drug use induces changes in gene expression in major structures of the brain reward circuit, such as the ventral tegmental area (VTA), the nucleus accumbens and the prefrontal cortex, which are thought to be mediated by epigenetic mechanisms (4). Dr. Renthal's research attempts to identify novel target genes involved in cocaine addiction by looking at changes in histone H3 and H4 acetylation after chronic cocaine using a genome-wide approach (ChIP-chip). Chronic cocaine use is known to increase histone H3 or H4 acetylation (but rarely both histones at the same gene). Dr. Renthal reported that chronic cocaine induces hyperacetylation at histone H3 of sirtuin *SIRT1* and *SIRT2* genes and this is correlated with upregulated expression of both genes. Sirtuins are NAD-dependent HDACs that play a role in mechanisms of aging and calorie restriction. Manipulation of sirtuin activity has been shown to regulate cocaine reward and self-administration behavior. Thus, using

the conditioned place preference protocol, mice found cocaine more or less rewarding, depending on whether they received resveratrol or sirtinol, a sirtuin activator and inhibitor, respectively. Similarly, blockade of sirtuin activity by sirtinol reduces cocaine self-administration. These results suggest promising avenues for the development of therapies for the treatment of cocaine addiction via genetic manipulation of sirtuins.

Evidence has emerged that blockade of HDAC activity by HDAC inhibitors in models of Huntington's disease (HD), experimental autoimmune encephalitis (EAE) and focal brain ischemia suggests their potential as neuroprotective agents for the treatment of neurodegenerative diseases and stroke, according to Dr. Langley from the Weill Medical College of Cornell University, New York, U.S.A. Further investigation of the neuroprotective mechanisms of HDAC inhibitors using in vitro models of oxidative stress-induced neuronal cell death has shown that protection may be associated with transcriptional upregulation of the tumor suppressor protein p21, a known cell cycle inhibitor. In vivo, loss of p21 increases neuronal damage in mice exposed to transient focal brain ischemia, hence indicating an endogenous role for p21 in neuroprotection. However, loss of p21 in neurons exposed to oxidative stress does not abrogate HDAC inhibitor protection of oxidative stress-induced cell death. In fact, it appears that HDAC inhibitors attenuate the MAPK/ERK pathway, which induces cell cycle arrest following glutathione depletion (5). Now it remains to be elucidated which HDAC isoforms are the best targets for neuroprotection. Recent work by Kozikowski et al. described potent HD6-selective inhibitors that do not induce histone acetylation and protect neurons from oxidative stress without causing toxic effects, suggesting that HD6 may be a suitable target (6).

Inherited neuronal ion channelopathies: new windows on complex diseases

The talk by Dr. Meisler from the University of Michigan, U.S.A., revolved around the complexity of sodium ion channelopathies. While gain-of-function missense mutations in the brain type I sodium channel $Na_v1.1$ are a primary cause of generalized epilepsy with febrile seizures plus (GEFS+), loss-of-function mutations in $Na_v1.1$ channels cause severe myoclonic epilepsy of infancy (SMEI, or Dravet syndrome; see article this issue), an intractable childhood epilepsy. The *SCN1A* gene encodes the alpha 1 subunit of the $Na_v1.1$ channel, which is essential for the initiation and propagation of action potentials in neurons. GEFS+ is a mild dominantly inherited epilepsy characterized by febrile seizures in childhood progressing to generalized epilepsy in adults. In contrast to GEFS+, SMEI is sporadic (de novo mutations), featuring a very early onset between 6 and 24 months and progressive seizures that eventually lead to ataxia. *SCN1A* mutations in GEFS+ encompass missense mutations that may lead to gain and loss of gene function and truncations that result in loss of function or haploinsufficiency. On the other hand, almost all mutations found in SMEI are point mutations that in 50% of cases lead to protein truncation and in the other 50% to amino acid substitutions (missense). However, functional studies using heterologous expression systems have failed to determine which missense mutations correlate with either a milder (GEFS+) or a more severe disease phenotype (SMEI) (7). Dr. Meisler went on to describe another previously unrecognized genetic disorder associated with *SCN1A* gene mutations. Vaccine encephalopathy, a disorder related to pertussis vaccination featuring refractory seizures and intellectual deficits, could be in fact genetically determined by de novo mutations (8). Familial hemiplegic migraine type 3 (FHM3) is another autosomal dominant disorder linked to *SCN1A* mutations and characterized by severe migraine with aura and hemiparesis (9). Mutations in other sodium channel genes have been shown to contribute to human disease, such as mutations in *SCN2A*, which have been identified in milder childhood forms of epilepsy (7, 10). An interesting case is that of the *SCN8A* gene. While mutations in *SCN8A* are known to cause congenital tremor in mice, no correlation with essential tremor in humans could be found (11).

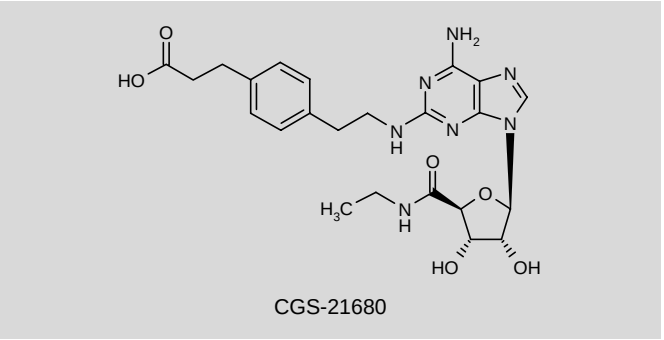
Dr. Dib-Hajj from Yale University, U.S.A., discussed the role of the $Na_v1.7$ sodium channel as a potentially promising drug target in inherited pain disorders. The $Na_v1.7$ sodium channel is encoded by the *SCN9A* gene and preferentially expressed in nociceptive dorsal root ganglion (DRG) neurons and sympathetic ganglion neurons in the peripheral nervous system. They are thought to contribute to repetitive firing, which probably translates into the amplification of weak threshold stimuli. Mutations associated with $Na_v1.7$ may give rise to two different pain disorders: inherited erythromelalgia and paroxysmal extreme pain disorder (PEPD), also known as familial rectal pain. *SCN9A* gene mutations have also been linked with a rare disorder causing congenital indifference to pain. Primary or idiopathic erythromelalgia is an autosomal dominant inherited disorder characterized by episodes of burning pain in feet, legs and hands, together with elevated skin temperature and redness. Typically, treatment consists in cooling down the affected areas, as patients are refractory to pain medications. However, recent findings at Dr. Dib-Hajj's lab suggest that newly identified *SCN9A* mutations may render some patients responsive to treatment with carbamazepine (12) and mexiletine (13), most likely because mutations somehow alter the electrophysiological properties of the $Na_v1.7$ channel. PEPD is an autosomal dominant inherited disorder characterized by sudden attacks of pain that increase in intensity upon recurrence. They usually affect genital, ocular and submaxillary areas and are accompanied by skin flushing. Interestingly, patch-clamp analysis of a mutation causing PEPD (A1632E substitution) showed that it slows channel deactivation and hyperpolarizes the voltage at which activation occurs, two changes that have also been observed in $Na_v1.7$ mutations causing inherited erythromelalgia. Also, mutant A1632E $Na_v1.7$ channels increased the firing frequency of DRGs and trigeminal ganglion neurons in response to suprathreshold stimuli, suggesting that this mutation may cause these neurons to be hyperexcitable in vivo (14).

Gain-of-function calcium channel mutations in inherited migraine was the topic of Dr. Pietrobon from the University of Padova, Italy. Familial hemiplegic migraine is a rare autosomal dominant subtype of migraine with aura. Three types of FHM have been described: FHM1 and FHM3 caused by mutations in the genes *CACNA1A* and *SCNA1A* encoding the alpha 1 subunits of the neuronal voltage-gated calcium channel $Ca_v2.1$ (conducting P/Q-type calcium currents) and the sodium channel $Na_v1.1$, respectively, and FHM2, caused by mutations in *ATP1A2*, the gene encoding the alpha 2 subunit of the sodium/potassium ATPase. Typically, FHM1 patients may show hemiparesis with visual, sensory and language disturbances, followed by headaches (typical attacks) or severe coma with prolonged hemiplegia (atypical attacks). Studies by Dr. Pietrobon's

group using knock-in mice carrying the FHM1 R192Q mutation that induces $Ca_v2.1$ gain-of-function, showed increasing $Ca_v2.1$-mediated neurotransmitter release from cortical neurons and facilitation of induction and propagation of cortical spreading depression (CSD), the phenomenon underlying migraine aura that may initiate migraine attacks. CSD consists of a sustained depolarization that progresses throughout the cortex, with intense spike activity followed by depression. Moreover, CSD correlates with the severity of the clinical phenotype of severe FHM1. Knock-in mice also exhibited increased glutamate release at synapses of cortical pyramidal cells, which suggests that facilitation of CSD in vivo could shift the finely tuned balance between excitation and inhibition towards excitation. This hypothesis has been at least partially confirmed by the finding that inhibitory neurotransmission remains unaltered in FHM1 R192Q knock-in mice (unpublished data).

Motor plasticity in spinal cord and brainstem: implications for spinal cord injury, ALS and sleep apnea

At his lab at the University of Wisconsin, U.S.A., Dr. Mitchell's work focuses on the mechanisms of neuroplasticity present in the respiratory motor control system and the implications that this form of plasticity may have in severe neurological disorders, including spinal cord injury (SCI), motor neuron disease and obstructive sleep apnea. Studies from Dr. Mitchell's lab concerning the respiratory motor control system have resulted in a model of compensatory plasticity called phrenic long-term facilitation (pLTF), which is triggered by acute, intermittent hypoxia and results in increased respiratory output. Moreover, pLTF induction appears to require spinal 5-HT receptor activation, which stimulates the synthesis of brain-derived neurotrophic factor (BDNF), which, via an interaction with Trk-B tyrosine kinase receptors, is needed for pLTF maintenance. Interestingly, this form of neuroplasticity could be used for the treatment of respiratory diseases characterized by a lack of ventilatory control (obstructive sleep apnea), and also for other disorders involving motor neuron dysfunction. Studies have shown that lateral cervical hemisection, which interrupts descending ipsilateral bulbospinal respiratory pathways that project to phrenic motor neurons, causes the activation of previously silent contralateral pathways and activation of phrenic motor neurons, hence inducing the recovery of the paralyzed hemidiaphragm. This is called the crossed phrenic phenomenon (15). Furthermore, Dr. Mitchell's investigations demonstrated that intermittent hypoxia could enhance crossed spinal synaptic pathways by increasing serotonergic innervation in the phrenic motor nucleus and hence improve respiratory function (16). Additionally, daily acute intermittent hypoxia has been seen to increase cervical spinal BDNF levels, and in rats with cervical hemisection exposure to daily acute intermittent hypoxia led to improved nonrespiratory motor behavior, observed by enhanced performance in the horizontal ladder task (unpublished data). Similarly, in patients with incomplete SCI, ankle plantar flexion augmented following acute intermittent hypoxia (unpublished data). Thus, intermittent hypoxia appears to be an attractive therapeutic strategy, although it is not devoid of adverse effects, which is why other alternatives are being pursued. Cervical adenosine A_{2A} receptor activation by systemic administration of the A_{2A} agonist **CGS-21680** causes transactivation of Trk-B receptors and elicits spinal pLTF, resulting in improved ventilatory capacity in rats (17). These promising results indicate the potential of this approach to ameliorate respiratory function in SCI patients. But could this work in motor neuron diseases such as amyotrophic lateral sclerosis (ALS)? In human ALS, most patients develop severe respiratory insufficiency, which eventually leads to death by ventilatory failure. Dr. Mitchell's observations in this field are still preliminary, but it appears that in the end-stage rat model of ALS (*SOD*^{693A}), which displays major respiratory motor neuron cell death, animals display an enhanced capacity to increase ventilation (tidal volume is increased) and elevated BDNF expression in phrenic motor neurons. Thus, these animals show a form of compensatory spinal neuroplasticity mechanisms that overcome severe respiratory motor neuron degeneration and preserve respiratory function, even at late stages of the disease.



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BIOMARKERS

Neurodegenerative disorders

A study led by Italian researchers has found reduced levels of transforming growth factor-β1 (TGF-β1) in the brain and serum of presymptomatic and symptomatic HD patients. TGF-β1 is thought to be neuroprotective. The decrease in TGF-β1 levels in presymptomatic subjects also correlated with reduced brain glucose metabolism and loss of white matter volume. These findings were corroborated in HD mouse models. In addition, wild-type mice showed increased TGF-β1 concentrations in the striatum compared to presymptomatic and symptomatic mice. These results point towards a defective production of TGF-β1 in the HD brain, which may contribute to neuronal death (18).

Researchers at King's College, London, U.K., have developed a novel in silico approach to discover candidate biomarkers of Alzheimer's disease (AD). This method comprises the automated analysis of whole-brain atrophy on magnetic resonance imaging (MRI) scans, which scientists have named SIENA (Structural Image Evaluation, using Normalization, of Atrophy) and which estimates the percentage brain volume change between two time points. In parallel, they developed an intelligence network of public domain information consisting of assertions linking AD, AD tissue, proteins and processes, from which C-reactive protein (CRP) was selected as a potential AD biomarker. The study included data from patients with AD and mild cognitive impairment (MCI), as well as from healthy controls. The rate of whole-brain atrophy was significantly greater in AD patients than in controls and MCI subjects. Strikingly, the percentage brain volume change in AD was strongly correlated with plasma

CRP levels, although these were not significantly different from those found in MCI subjects and controls (19).

Studies conducted at the University of Florida, U.S.A., have reported novel blood and cerebrospinal fluid (CSF) biomarkers of central nervous system (CNS) injury. Using a highly sensitive enzyme-linked immunosorbent assay (ELISA) they have reported the detection of the phosphorylated axonal form of the major neurofilament subunit NF-H (pNF-H) in the blood of animals with brain and spinal cord injuries, which correlates with the degree of axonal injury or degeneration. pNF-H has been detected in the blood in several transgenic mouse models of ALS and the mouse EAE model, and correlates with disease severity. Interestingly, pNF-H blood levels can be detected before symptom onset and, in the EAE model, they are dramatically reduced by pharmacological treatment, which provides a useful surrogate to monitor treatment efficacy. In human patients with aneurysmal subarachnoid hemorrhage, pNF-H has been detected in blood, as well as in CSF, with a good detection level. Both blood and CSF pNF-H levels have been found to be strongly predictive of patient outcome (20).

Protein levels of the cysteine protease inhibitor cystatin C appear to be reduced in the CSF of ALS patients, according to previous studies by researchers at the University of Pittsburgh, U.S.A., who have now evaluated the potential of cystatin C as a diagnostic and prognostic biomarker in both CSF and plasma. ALS patients displayed lower cystatin C levels in both CSF and plasma than controls, which strongly correlated with measures of disease progression. This correlation persisted during transient functional improvements observed in some patients. These results suggest the usefulness of cystatin C as a surrogate marker in ALS (21).

HDAC inhibitors have been proposed to be clinically beneficial for the treatment of Friedreich's ataxia (FRDA), an autosomal recessive disease caused by mutations in the *frataxin* (*FXN*) gene (intronic repeat expansion), which are associated with hypoacetylation of histones surrounding the gene. In attempt to identify an adequate biochemical surrogate of HDAC inhibitor action, researchers at Repligen have analyzed peripheral blood mononuclear cells (PBMCs) isolated from patients, expansion carriers and normal donors and extracted RNA samples before and after incubation with the HDAC inhibitor RGFA8. Treatment induced a dose-dependent increase in frataxin mRNA and protein in FRDA patient cells. In addition, FRDA cells also showed a distinct gene expression profile, with 1,283 differentially expressed genes compared to normal subjects. After HDACi treatment, 204 genes specifically changed in FRDA cells, of which 60% showed a trend towards normalization and 11% were completely normalized. These findings encourage further development of both nucleic acid- and protein-based biomarkers to monitor HDAC inhibitor treatment evaluation in FRDA (22).

Neuropsychiatric disorders

Researchers at Yale University, U.S.A., have discovered that lithium induces differential peripheral blood gene expression in patients with bipolar disorder, which may allow to distinguish responders from nonresponders. Using microarrays to measure gene expression levels in whole blood before and every 2 weeks during an 8-week treatment period with lithium, scientists identified a set of 127 genes that changed differentially in lithium responders and nonresponders after initiation of treatment. Many of these genes were identified to be regulated by the proto-oncogene c-Myc (23).

Addiction

Alterations in membrane phospholipid metabolism, high-energy phosphate metabolism and phosphorylated proteins may correlate with cognitive impairment in chronic alcoholism, according to researchers at the University of Pittsburgh, U.S.A. Increased phosphocreatine (PCr) levels were detected in right prefrontal cortex and left superior temporal cortex of chronic alcoholic subjects, which may be due to reduced synaptic activity in these regions. Reduced short nuclear magnetic resonance correlation time phosphomonoesters in left prefrontal and superior temporal cortex were also observed and may be consistent with reduced membrane phospholipid repair in those regions. These metabolite changes were positively correlated with Block Design (BD) Test scores, a sensitive measure of cognitive impairment in chronic alcoholics (24).

Preclinical biomarkers

Using the 6-hydroxydopamine (6-OHDA) model of parkinsonism in rats, researchers at the University of Grenoble have investigated the proteomic profiles of serum samples and striatum in order to identify specific biomarkers to evaluate Parkinson's disease progression. Proteomic analysis allowed the identification of four proteins weighing 3115, 3696, 5505 and 5497 Da, which significantly varied 5 weeks after 6-OHDA lesioning in all rats. Compared to the normal side, the lesioned striatum showed a specific profile, with three proteins weighing 4590, 16,064 and 16,221 Da that varied significantly. Thus, it appears that 6-OHDA lesions cause specific changes in protein expression in the striatum. Further investigation is ongoing to purify and identify the putative proteins specific for striatal degeneration (25).

NOVEL THERAPIES

Drugs for pain

PPC-5692, a new blocker of the acid-sensing ion channel 1a (ASIC1a), which plays an important role in conveying pain sensory pathways, has demonstrated analgesic efficacy in models of tonic nociceptive and inflammatory pain. PPC-5692 suppressed paw licking behavior in the formalin-induced model of nociceptive pain with an ED_{50} of 30 µmol/kg. It dose-dependently (10-100 µmol/kg s.c.) reduced thermal and mechanical hyperalgesia, as well as inflammation, in the acute carrageenan-induced rat inflammatory pain model. In rats with chronic osteoarthritis, PPC-5692 (100 mg/kg s.c.) attenuated thermal hyperalgesia and mechanical allodynia at 1.5 h after administration. Normal nociception was not affected by **PPC-5692** treatment (26). PainCeptor has also developed a novel series of low-molecular-weight nerve growth factor (NGF) antagonists, which prevent the interaction with Trk-A tyrosine kinase receptors, hence reducing pain in several models. **PPC-778** binds NGF and dose-dependently blocks its association with the Trk-A/p75 receptor complex (IC_{50} = 320 nM). NGF-dependent signaling, i.e., ERK-1 and ERK-2 phosphorylation, was also disrupted in a dose-dependent manner. This compound was also effective in models of

tonic pain (formalin-induced nociception, ED_{50} ≈ 10 mg/kg), acute inflammatory pain (reduction of carrageenan-induced thermal and mechanical hyperalgesia), capsaicin-induced pain and neuropathic pain (spinal nerve ligation and spinal nerve injury, around 50% reversal at 10 mg/kg s.c. in both models) (27).

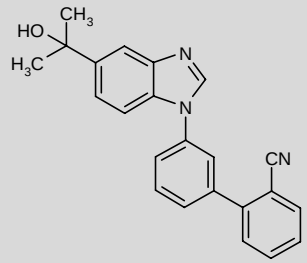
Researchers at Cara Therapeutics presented the pharmacological profile of a novel peripherally acting dual cannabinoid CB_1/CB_2 receptor agonist referred to as **CR-08**. CR-08 showed agonist activity at human and rat CB_1 (EC_{50} = 25 and 79 nM, respectively) and CB_2 receptors (EC_{50} = 4 and 7 nM, respectively) in cAMP functional assays, and no activity at a broad range of other pain targets. CR-08 showed efficacy in models of visceral, inflammatory and neuropathic pain. It attenuated acetic acid-induced writhing behavior in mice (ED_{50} = 7 mg/kg s.c.), suppressed hind paw edema in response to carrageenan injection in rats with greater efficacy than ibuprofen (relative ED_{50} = 5.3 mg/kg s.c.) and reversed tactile hypersensitivity in the spinal nerve ligation (Chung) model in rats (ED_{50} = 3.8 mg/kg p.o.). No central nervous system adverse effects were detected at doses up to 100 mg/kg p.o. CR-08 analogues are currently under development for inflammatory and neuropathic pain (28).

NeuroSearch scientists have developed **NS-11394**, a positive modulator of $GABA_A$ receptors. NS-11394 displayed high affinity for human $GABA_A$ α1-, α2-, α3- and α5-containing receptors (K_i = 0.4, 0.8, 0.5 and 0.1 nM, respectively). When given at 3 mg/kg, NS-11394 showed good oral bioavailability (82%) and high drug exposure. In vivo anxiolytic efficacy of NS-11394 was evidenced in rat models of anxiety (conditioned emotional response test, rat rotarod test in the presence of ethanol, cue fear conditioning) (29). Furthermore, NS-11394 (3-30 mg/kg) attenuated flinching in the rat formalin test and reduced mechanical allodynia in rats subjected to chronic nerve constriction. It was also active in models of inflammatory pain, as it completely reversed hind paw weight-bearing deficits following complete Freund's adjuvant injection. A spinal site of action was confirmed in hemisected spinal cords in vitro, where NS-11394 decreased spinal nociceptive reflexes and C-fiber-mediated windup. Antinociceptive doses were 20- to 40-fold lower than those inducing sedative or ataxic side effects (30).

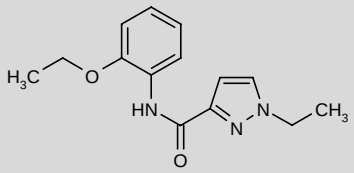
Research at Adolor has led to the development of a novel series of NGF Trk-A antagonists that have shown potential benefit in models of pain. Screening studies identified **ADC-01007293**, which bound to NGF Trk-A receptors (K_i = 25 μM) and blocked NGF-stimulated ERK phosphorylation (IC_{50} = 3.0 μM). Further research led to the identification of a more potent analogue, namely **ADC-02390946** (K_i = 17 μM, IC_{50} = 0.59 μM), which demonstrated significant antiallodynic activity in the spinal nerve ligation model in rats when given at 60 mg/kg 1 week after surgery (31).

Johnson & Johnson researchers reported the development of a novel δ opioid receptor agonist, **JNJ-20788560,** potentially useful in treating inflammatory hyperalgesia without causing adverse effects associated with activation of μ opioid receptors. JNJ-20788560 bound to δ opioid receptors (K_i = 2.0 nM) in rat brain membranes, was active in [^{35}S]-GTPγS functional assays (EC_{50} = 5.6 nM) and was 600-fold selective over the μ opioid receptor. It dose-dependently reversed inflammatory hyperalgesia in different models, including complete Freund's adjuvant-induced inflammation (ED_{50} = 13.5 mg/kg p.o.). Unlike morphine, JNJ-20788560 caused limited slowing of gastrointestinal motility, with only an 11% reduction at the highest dose (100 mg/kg p.o.), and it did not alter respiratory function in a blood gas study (pCO_2, pO_2 and pH) at doses ranging from 3 to 100 mg/kg p.o. No withdrawal effects were observed in mice or rats (32). The compound has been claimed in the patent literature (WO 2005003131).

Researchers at Alkermes have characterized a novel peripherally acting opioid antagonist in an attempt to provide an approach to avoid constipation in patients treated with opioid agonists, without affecting analgesia. **RDC-1036** was compared to methylnaltrexone (MNTX) in a test of gut motility in mice. Oral doses of RDC-1036 of 10 mg/kg resulted in greater suppression of morphine's inhibitory effect on prostaglandin-induced diarrhea than MNTX. In addition,



NS-11394



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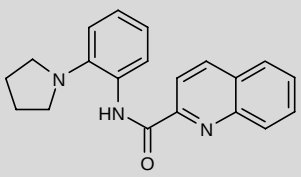

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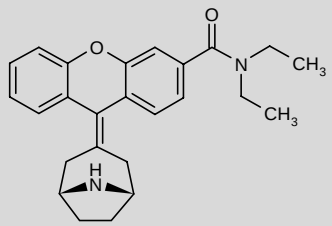


JNJ-20788560

RDC-1036 treatment was associated with a rapid onset and a longer duration of action (up to 4 h) than MNTX. The ability of RDC-1036 to block morphine's analgesic effects was evaluated in the hot plate and tail flick tests. While at 30 mg/kg p.o. RDC-1036 slightly reduced morphine-induced antinociception in the hot plate test, at 10 mg/kg (the minimum effective dose [MED] in the prostaglandin assay) it had no effect in the tail flick test (33).

Drugs for neurodegenerative disorders

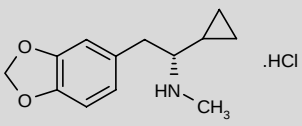
EnVivo scientists have reported on a novel HDAC inhibitor for the treatment of CNS disorders via epigenetic regulation of abnormal gene function, the underlying cause of several neurological and psychiatric conditions. **EVP-0334** inhibited HDAC activity in mouse cortical neurons and human astrocytes with an IC_{50} ranging from 0.3 to 1 µM. When tested in vivo, EVP-0334 caused increased acetylation of histones 2A, 3 and 4 in mouse brain (MED = 10 mg/kg). No genetic toxicity has been observed and 14-day treatment at doses exceeding the MED by more than 10-fold has not been associated with remarkable adverse effects or histopathological findings. Oral bioavailability was demonstrated in mice (37%) and dogs (45%) (34). EVP-0334 treatment resulted in significantly better mouse performance in the novel object recognition assay at both 1.5 and 24 h after administration and at doses known to increase histone acetylation in the striatum. Acquisition of learning in the mouse Morris water maze was also improved. These results support the ability of EVP-0334 to enhance both short- and long-term memory and that it may be potentially beneficial in treating cognitive deficits associated with neurological and psychiatric disorders (35).

SKA-PD-01 is a novel monoamine oxidase B (MAO-B) inhibitor developed by SK Life Science that preferentially inhibited MAO-B (IC_{50} = 0.011 µM) over MAO-A (IC_{50} = about 100 µM). In vivo it attenuated haloperidol-induced catalepsy and reserpine-induced akinesia at 20 mg/kg i.p. This compound also showed antiparkinsonian activity in the MPTP- and 6-OHDA-induced Parkinson's disease models. In MPTP-treated mice, treatment with SKA-PD-01 (20 mg/kg i.p.) improved motor abnormalities, increased dopamine concentrations in the striatum and protected from neuronal cell loss in the substantia nigra. SKA-PD-01 also showed a good pharmacokinetic and safety profile and potential activity in pain, anxiety, depression and epilepsy models (36).

Scientists at Atuka in collaboration with Canadian and Australian researchers have reported on **UWA-0121**, a novel molecule with dopaminergic and serotonergic activity, which may be useful for reducing the "wearing-off" and L-DOPA-induced dyskinesia in advanced Parkinson's disease. Following 45 days of twice-daily L-DOPA monotherapy (12.5 mg/kg p.o.), coadministration of L-DOPA (15 mg/kg s.c.) and UWA-0121 (1, 3 and 10 mg/kg s.c.) increased L-DOPA activity by 12%, 28% and 39%, respectively, hence reducing the "wearing-off" effect and dyskinesia induced by prolonged L-DOPA administration in the MPTP model of Parkinson's disease in marmosets (37).

Trap-101 is a new antagonist of the opioid-like receptor NOP (ORL1) developed by Tocris Bioscience for the treatment of Parkinson's disease. In 6-OHDA hemiparkinsonian rats, Trap-101 (10 and 30 mg/kg i.p.) dose-dependently improved akinesia and bradykinesia and reduced immobility time in the bar test, increased the number of steps in the drag test and increased performance in the rotarod test. These effects could be enhanced with the addition of subthreshold doses of L-DOPA (0.1 mg/kg). Behavioral effects of Trap-101 were associated with decreased glutamate and elevated GABA levels in the lesioned substantia nigra and reduced GABA release in the ipsilateral ventromedial thalamus. Similarly, these neurochemical changes were more pronounced with L-DOPA coadministration (38).

Dopamine depletion occurring in Parkinson's disease has been shown to selectively affect long-term potentiation (LTP), a cellular memory correlate, and to modify glutamate NMDA receptor composition in the postsynaptic density. Italian researchers have recently demonstrated how **Tat-2A**, a cell-permeable peptide that interferes with NMDA receptor trafficking by targeting the NR2 receptor subunit may be a novel approach to treat early stages of Parkinson's disease. Systemic administration of Tat2A to rats with partial dopaminergic denervation for 5 days significantly improved motor performance compared to sham-operated rats, an effect that was associated with long-lasting LTP recovery in hippocampal slices of treated rats and with a reduction in NR2A subunit interaction with striatal postsynaptic proteins (PSD-95) (39).



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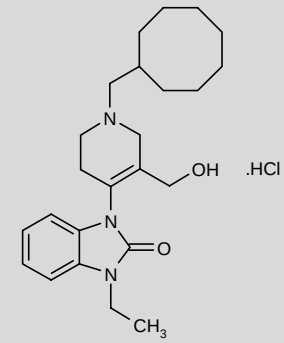
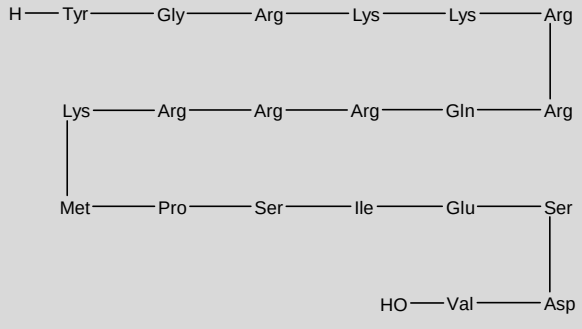


Trap-101



Tat-2A

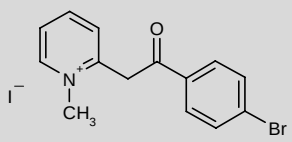
Disruption of the association between β-amyloid ($A\beta_{42}$) and α7 nicotinic acetylcholine receptors (α7 nAChRs) has been proposed to reduce neurodegeneration in AD. **S-24795**, discovered by Servier and the CUNY Medical School in New York, U.S.A., is a novel selective α7 nAChR partial agonist that reduced the interaction between $A\beta_{42}$ and α7 nAChRs in vitro, accompanied by a marked blockade of $A\beta_{42}$-induced tau hyperphosphorylation and intraneuronal $A\beta_{42}$ accumulation in cortical slices. Two-week treatment with S-24795 (0.3-1 mg/kg i.p.) in mice also prevented the $A\beta_{42}$/α7 nAChR association and $A\beta_{42}$ brain accumulation. Interestingly, S-24795 also suppressed the inhibition of α7 nAChR and NMDA receptor channel activity induced by $A\beta_{42}$, hence indicating that this could be a novel approach to attenuate Aβ-mediated synaptic dysfunction, as well as amyloid plaque and neurofibrillary tangle pathology in AD (40).

Researchers at the University of Kansas and the University of Minnesota, U.S.A., have identified **TH-237A** as a novel compound with potential utility in treating AD. In vitro TH-237A concentration-dependently protected primary cortical neurons against Aβ toxicity (EC_{50} approx. 5 nM) by preserving neuritic dystrophy and the integrity of the cytoskeleton. Administration of TH-237A (10 mg/kg daily for 12 weeks) to tau-mutant mice markedly reduced the amount of insoluble phosphorylated tau in the brain and spinal cord of treated animals. TH-237A treatment enhanced similar neuroprotective effects associated with dietary restriction (41).

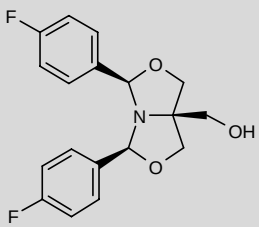
Keryx Biopharmaceuticals has reported first-in-human results for the orally available NGF enhancer **KRX-0501** (KP-544). The study compared the pharmacokinetics of both the free base (FB) and the monohydrochloride (HCl) forms of KRX-0501 in healthy volunteers (N = 6), who in the first part of the study received single doses of 15 mg KRX-0501 FB and 16.6 mg KRX-0501 HCl separated by at least a week. The second part of the study included 18 subjects who received active drug or placebo under fed or fasted conditions. In the first part, drug exposure and absorption time were similar in fasted volunteers following administration of either the FB or the HCl forms. In the second part of the study, drug plasma levels were higher after administration of the HCl than the FB, and food was found not to relevantly influence drug exposure. Ratios of mean values (HCl/FB) for all parameters (AUC, C_{max}, t_{max}) were comparable for both the fasted and the fed states, indicating that both forms of KRX-0501 are suitable for further clinical development (42). KRX-0501 is being developed for AD, HD and neuropathic pain.

D3 is a novel $A\beta_{42}$-binding peptide that was shown to reduce plaque burden in a mouse model of AD. Hippocampal infusion of D3 (9 µg/day) for 1 month to mice expressing APP (amyloid precursor protein) and PS1 (presenilin) mutations resulted in a significant reduction in Aβ load, which was associated with a decreased amount of inflammation markers near the remaining plaques compared to control animals. Aβ plaque reduction by D3 also improved cognitive performance in AD double transgenic mice in behavioral tests (water and Barnes maze). These results support further the development of D3 as a potential treatment for AD (43, 44).

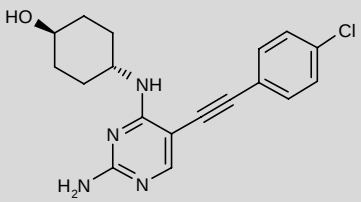
CHEC-7 is a new seven-amino-acid peptide that inhibits secreted phospholipase A_2 ($sPLA_2$) activity, developed by scientists at the Drexel University College of Medicine, that has recently shown benefit in a rat model of multiple sclerosis. Inhibition of $sPLA_2$ has been associated with neuronal survival and antiinflammatory effects. In this study, daily oral (1.5 mg/kg) or s.c. (0.1-1.5 mg/kg) treatment with CHEC-7 following induction of EAE resulted in a significant reduction in disease severity. Interestingly, oral delivery completely prevented disease in half of the animal population (45). CHEC-7 has been reported in the patent literature (US 2008249027).



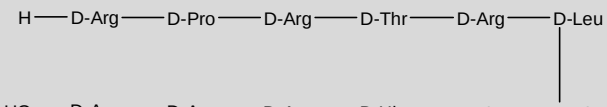
S-24795



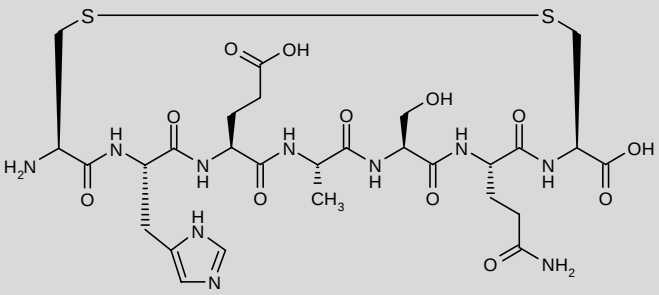
TH-237A



KRX-0501



D3



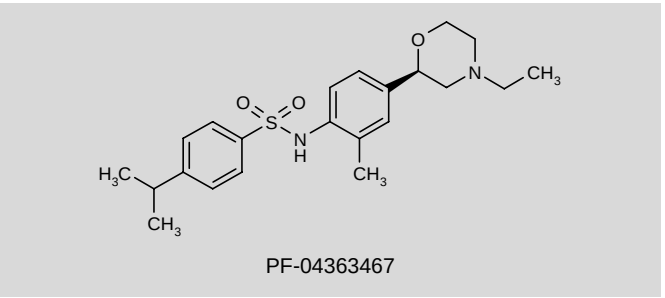
CHEC-7

Psychopharmacologic drugs

Researchers at Newron have identified a novel sodium channel blocker, **NW-3381**, that may be beneficial for the treatment of neuropsychiatric disorders. In vitro NW-3381 inhibited veratridine-evoked sodium (IC_{50} = 10 μM) and calcium (IC_{50} = 6 μM) influx due to prolonged depolarization and protected rat cortical neurons from veratridine-induced cell death (IC_{50} = 9 μM) (46). NW-3381 (3-10 μM) reduced repetitive firing in rat cortical neurons, displaying around 10-fold greater potency than lamotrigine. NW-3381 demonstrated a good cardiac safety profile in vitro with only weak inhibitory activity at $Na_v1.5$, L-type calcium and hERG potassium currents (47). NW-3381 was tested in seizure models in mice. In the maximal electroshock test (MES), NW-3381 was active after i.p. and oral administration (ED_{50} = 4.6 and 8.9 mg/kg, respectively). It was also more effective at 20 mg/kg p.o. than lamotrigine 30 mg/kg i.p. and completely protected mice from kainic acid-induced status epilepticus. Generalized seizures were also prevented by NW-3381 at 20 mg/kg i.p., while lamotrigine worsened seizure severity at 15 and 30 mg/kg i.p. Moreover, NW-3381 (5-10 mg/kg i.p. b.i.d.) was also effective in the amphetamine/chlordiazepoxide-induced hyperactivity test, a model of mania, and prevented phencyclidine (PCP)-induced cognitive dysfunction in mice (10 mg/kg i.p.) (48).

Researchers at Abbott have developed **A-964324**, a highly selective 5-HT_6 receptor antagonist. It showed high affinity for human 5-HT_6 receptors (K_i = 0.5 nM) and functional antagonism in cAMP assays (K_b = 3.04 nM). A-964324 (10 mg/kg i.p.) caused significant release of acetylcholine in rat medial prefrontal cortex, which is considered a neural correlate of procognitive effects. At 1-3 mg/kg i.p. it significantly and dose-dependently improved performance in the social recognition task. Using a model of cognitive flexibility in which animals should adapt to new rules for accessing food, A-964324 (3 mg/kg i.p.) significantly decreased the number of trials to criterion during strategy shifting. The number of regressive errors was also reduced, suggesting an enhanced ability to maintain a new strategy. A-964324 may be useful for the treatment of AD or cognitive deficits associated with schizophrenia (49).

SAR-110894 is a new histamine H_3 receptor antagonist from sanofi-aventis that may improve cognitive function and negative symptoms associated with schizophrenia or AD. In vitro binding studies showed high affinity and selectivity for human and rat H_3 receptors (K_i = 0.06 and 0.48 nM, respectively). Potent antagonism and/or inverse agonism at the human H_3 receptor was demonstrated in functional studies (IC_{50} = 0.065 nM). SAR-110894 (30 mg/kg p.o.) significantly increased histamine and acetylcholine levels in rat prefrontal cortex and hypothalamus. It improved cognitive performance, including long-term episodic memory in the visual object recognition task in mice, an effect specifically mediated by the H_3 receptor (50). SAR-110894 (0.1-10 mg/kg p.o.) also showed procognitive properties in different models of long- and short-term episodic memory (object recognition task), working memory (Y-maze task) and in a model of treatment-induced selective attention deficit (51). SAR-110894's antipsychotic and procognitive potential was assessed in two latent inhibition models. The compound reversed attentional perseveration induced by neonatal inhibition of the nitric oxide system, which mimics the neurodevelopmental aspect of schizophrenia at the adult stage. However, it did not suppress abnormally persistent latent inhibition induced by MK-801 administration, hence matching the profile of atypical antipsychotics (52).



PF-04363467

Studies showing that dopamine D_3 receptor activation may be neuroprotective in dopaminergic neurons have prompted Pfizer researchers to develop new D_3 agonist and antagonist pharmacological tools for studying Parkinson's disease and schizophrenia. The D_3 antagonist **PF-04363467** bound with high affinity for human D_3 receptors (K_i = 1.6 nM) compared to D_2 receptors (K_i = 318 nM) and showed 9-fold selectivity for activation of D_3 over D_2 receptors. In vivo, it potently suppressed the binding of a selective D_3 ligand to rat brain membranes (IC_{50} = 0.1 mg/kg). PF-04363467 blocked the protective effect of the D_2/D_3 receptor agonists pramiprexole and PF-833766 (affinity for human D_3 receptors of 0.48 nM) on MPTP-induced striatal dopamine depletion (53). PF-04363467 has been claimed in the patent literature (WO 2008026046).

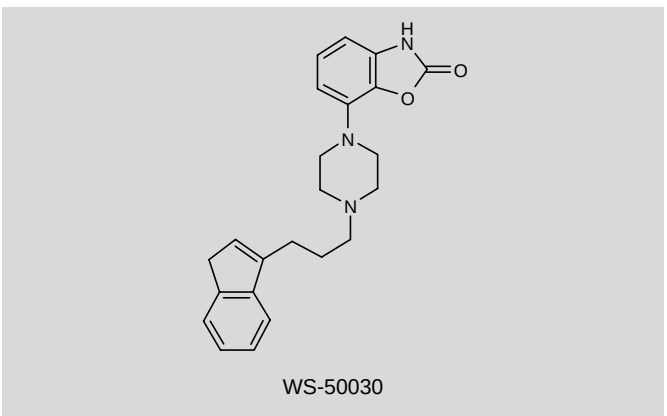
Increased vasopressin expression by abnormal activation of the hypothalamic–pituitary–adrenal (HPA) axis has been associated with depression and anxiety. Research at Abbott has led to the development of novel antagonists of the vasopressin V_{1B} receptor. **ABT-436** and **ABT-558** exhibited high affinity for human V_{1B} receptors (K_i = 0.3 and 0.29 nM, respectively) compared to V_{1A}, V_2 or the human oxytocin (OT) receptor. Both ABT-436 and ABT-558 also inhibited arginine–vasopressin (AVP)-induced calcium release from human V_{1B} receptors expressed in CHO cells (K_b = 0.6 and 0.1 nM, respectively). No major inhibitory activity against cytochrome P450 CYP450 enzymes was detected (54). When given to NMRI mice treated with AVP, oral **ABT-558** (20 mg/kg) significantly reduced plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone to 50% of controls. ABT-558 (10-100 mg/kg p.o.) also decreased ACTH levels induced by restraint stress to 60% of controls, and ABT-436 displayed similar activity. These results suggest the ability of these two molecules to normalize excessive AVP-induced HPA activation (55). The anxiolytic activity of these compounds was tested in the forced swim test, where both drugs decreased immobility time at doses of 10 mg/kg i.p., and they increased the number of punished responses in the Vogel conflict test (10 and 30 mg/kg i.p.). Also, chronic treatment with ABT-436 (3 mg/kg i.p.) reduced hyperactivity in the olfactory bulbectomized rodent model of depression (56).

Cenomed BioSciences' potential clinical candidate for schizophrenia **CM-2303** is a compound with combined activity as a potent 5-HT_1 receptor agonist (EC_{50} = 27 nM), dopamine D_2 receptor partial agonist (EC_{50} = 450 nM) and D_3 receptor full agonist (EC_{50} = 420 nM), as shown in functional cAMP studies (57). CM-2303 was able to dose-dependently reverse PCP-induced hyperlocomotion and pre-

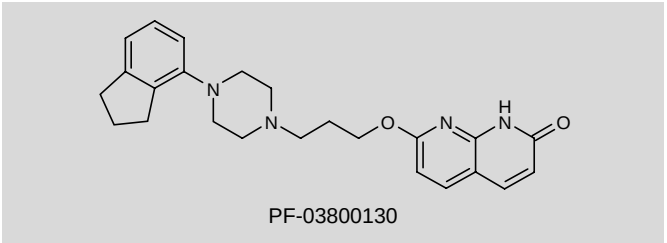
pulse inhibition deficits following s.c. administration (0.3-3 mg/kg), while being associated with low cataleptogenic potential. Additionally, CM-2303 did not affect cognition, as shown in learning and memory tests. Good oral availability was seen in rats after administration of 10 mg/kg. Cenomed plans to conduct preclinical safety studies in order to file an IND with the FDA, with a view to starting phase I evaluation in the second half of 2009 (58).

CM-2236 is a potent 5-HT_{1A} receptor agonist (EC_{50} = 43 nM) with additional potent agonist activity at α_{1A}-adrenoceptors (EC_{50} = 17 nM) that crosses the blood–brain barrier and has shown efficacy in three animal models relevant to posttraumatic stress disorder treatment. It markedly reversed PCP-induced prepulse inhibition deficits in a dose-dependent manner at 1-10 mg/kg s.c. In the open field test, 10-day treatment with CM-2236 significantly protected mice from developing a severe posttraumatic response to contextual fear. These results were correlated with increased neurite outgrowth in vitro (59).

Wyeth and Solvay have reported **WS-50030**, which showed partial agonist activity at human D_2 receptors (EC_{50} = 0.38 nM) and inhibited serotonin uptake in functional studies (IC_{50} = 56.4 nM). In vivo, it was able to block apomorphine-induced stereotyped and climbing behavior in mice with respective ID_{50} values of 0.50 and 1.02 mg/kg i.p., while being associated with minimal cataleptogenic potential at 0.3-10 mg/kg i.p. (60). WS-50030 attenuated bulbectomy-induced hyperactivity after chronic treatment (3-5.6 mg/kg i.p.), indicating antidepressant activity. Rat microdialysis studies revealed an increase in 5-HT in the medial prefrontal cortex following chronic WS-50030 treatment, confirming its serotonin reuptake-inhibitory activity. Together, these results support further investigation of WS-50030 as a novel antipsychotic with potential benefit in the treatment of resistant depression or schizophrenia-related negative symptoms (61). This compound has been described previously in patent literature (WO 2006061377).



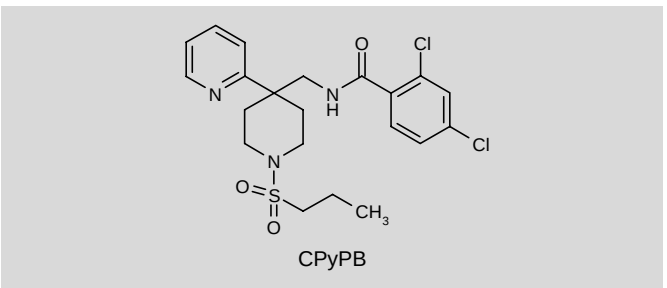
WS-50030



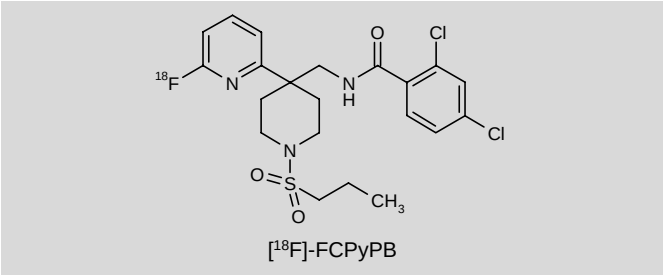
PF-03800130

Pfizer scientists reported on **PF-03800130**, a novel compound that has shown potent binding affinity (K_i = 6 nM) and activity as a partial agonist at human dopamine D_2 receptors (21%) comparable to the prototypical D_2 partial agonist antipsychotic aripiprazole. In addition, PF-03800130 demonstrated high affinity for the serotonin transporter (SERT) (K_i = 9.4 nM) and functional inhibition of serotonin reuptake (62). Receptor occupancy measurements in rats showed similar receptor occupancy for D_2 receptors and SERT. The projected human D_2 EC_{85} of PF-03800130 was 225-342 ng/ml (63). In vivo studies demonstrated dose-dependent inhibition of spontaneous locomotor activity at an MED of 3 mg/kg p.o., similar to aripiprazole, suggesting potential efficacy against the manic symptoms of schizophrenia. Moreover, the antidepressant potential of PF-03800130 was demonstrated by a significant increase in wheel rotations in the forced swim test (MED = 3 mg/kg i.p.), whereas aripiprazole showed no activity. PF-03800130 also showed a low potential for inducing extrapyramidal effects, as catalepsy was induced at 30 times the MED for locomotor activity inhibition (64). PF-03800138 exhibited an acceptable adverse effect profile regarding the induction of hyperglycemia associated with D_2-interacting antipsychotics (65). This compound has been described previously in the patent literature (WO 2005019215).

Blockade of the glycine transporter (GlyT1) has emerged as a new strategy for the treatment of schizophrenia. A new compound from Merck & Co., **CPyPB**, behaved as a potent and selective GlyT1 inhibitor by suppressing glycine uptake by human and rat GlyT1 with IC_{50} values of 4.4 and 5.2 nM, respectively, showing no affinity for human GlyT2 receptors or taurine transporters (IC_{50} > 10 mM). Good brain penetration was demonstrated using [^{3}H]-CPyPB as a radioligand, with high binding levels in the cerebellum and brainstem of rhesus monkeys. In in vivo microdialysis experiments, CPyPB (10 mg/kg i.v.) was found to significantly increase extracellular glycine levels in rat prefrontal cortex and reversed PCP-induced dopamine efflux. In behavioral experiments in mice, prepulse inhibition was significantly increased by CPyPB (10 and 30 mg/kg s.c.), indicating its potential utility in schizophrenia (66). A related compound, **[^{18}F]-**



CPyPB



[^{18}F]-FCPyPB

FCPyPB, is in phase I investigation at Merck & Co. as a radiopharmaceutical for brain imaging.

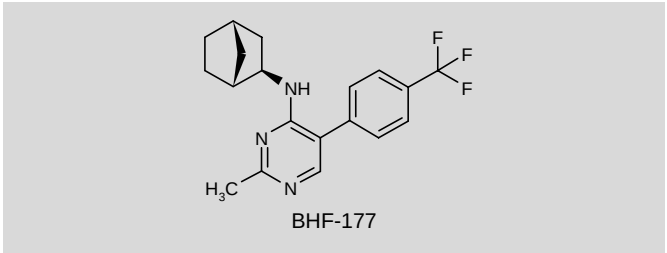
APD-916 is a novel histamine H_3 receptor antagonist developed by Arena in preclinical studies for its potential use as a wakefulness promoter. It showed high binding affinity at H_3 receptors across three different species (K_i = 1.2, 4.2 and 3.8 nM, respectively, at rat, human and dog receptors), and high selectivity (> 1,000-fold) over other targets, including other histamine receptors. The compound behaved as a potent inverse agonist at the recombinant human receptor in [^{35}S]-GTPγS binding assays (IC_{50} = 0.7 nM). Good oral bioavailability, rapid absorption, short half-life and high brain penetration were demonstrated in rats. At an MED of 0.3 mg/kg p.o., APD-916 increased wakefulness without affecting locomotor activity. Wake-promoting effects were sustained for up to 5 days of treatment and were more intense during the rodent's subjective night. In narcoleptic Dobermans, APD-916 markedly decreased the number and duration of food-induced cataleptic attacks for up to 24 h (67).

Novartis's **BHF-177** is a novel positive modulator of $GABA_B$ receptors, which have emerged as promising targets in the treatment of anxiety and addiction disorders. BHF-177 was found to potentiate $GABA_B$ responses at native and recombinant receptors. This compound also showed oral bioavailability and brain penetration. At oral doses of 100 mg/kg, BHF-177 did not impair mouse motor coordination in the rotarod test, in contrast to baclofen. Anxiolytic effects were detected at doses of 20 and 30 mg/kg p.o. in the stress-induced hypothermia test in mice. Further confirmation of BHF-177's anxiolytic activity is needed using other models not dependent on body temperature, as it induced hypothermia at doses of 40 mg/kg and above. In contrast to previous $GABA_B$ receptor positive modulators, BHF-177 was not genotoxic (68).

Treatment of spinal cord injury

Using proprietary zinc finger protein (ZFP) technology, Sangamo researchers have developed **AdV-ZFP-VEGF**, an adenovirus that generates a zinc finger transcription factor that promotes endogenous vascular endothelial growth factor VEGF-A expression, which has shown therapeutic potential following SCI. When administered to rats 1 day after spinal cord damage, AdV-ZFP-VEGF increased angiogenesis, reduced axonal degradation and decreased apoptosis in the spinal cords of injured animals. Thus, delayed treatment with AdV-ZFP-VEGF may be beneficial for the treatment of SCI (69).

Phospholipid degradation by phospholipases has been shown to contribute to secondary SCI. Researchers at the University of Louisville, U.S.A., have evaluated the effects of a novel small molecule with $sPLA_2$-inhibitory activity, **S-3319**. In adult oligodendrocyte precursor cultures, S-3319 protected against cytotoxicity and morphological changes induced by injury insults that upregulate $sPLA_2$-IIA expression. When given to mice before severe SCI, i.p. administration of S-3319 resulted in a significant 9.4% increase in the proportion of spared white matter and decreased lesion volume. Inhibition of $sPLA_2$-IIA was also associated with a 36% decrease in inflammatory cells, a 135% increase in oligodendrocyte number within the lesion and axonal growth. Treated animals recovered spontaneous bladder voiding and voluntary locomotion up to 9 weeks after injury, in contrast to vehicle-treated controls (70).

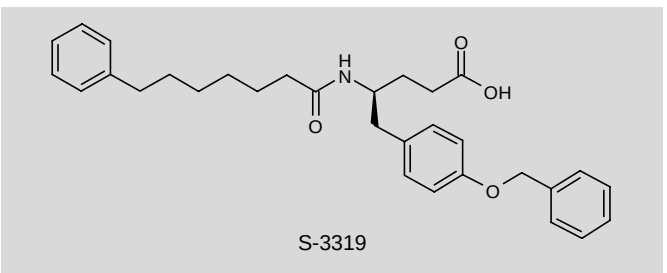


BHF-177

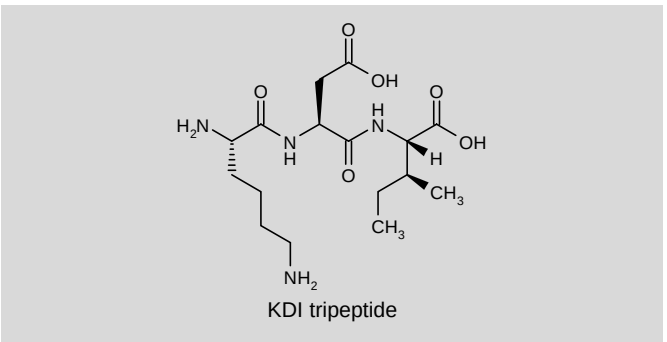
Scientists at the University of Helsinki, Finland, have discovered that a soluble domain of the γ1-chain of laminin-1 is able to promote spinal cord regeneration following SCI. This tripeptide (Lys-Asp-Ile), also named **KDI tripeptide**, which is also a potent inhibitor of AMPA glutamate receptors and oxidative stress, has recently shown efficacy in animal models of ALS. Intranasal daily application of the KDI tripeptide to transgenic mice overexpressing a mutated human *SOD1* gene (*g93a*), when animals already exhibit some degree of motor deterioration, was associated with prolonged life span up to 211 days of age (*g93a*-bearing mice usually die by day 110). Motor performance and spinal cord histology (motor neuron number, expression of neurofilament proteins, glial fibrillary acidic protein and laminins) of treated mice were comparable to normal littermates, whereas ALS animals showed profound spinal cord degeneration (71). KDI tripeptide has been claimed in the patent literature (US 2008249021).

Treatment of poisoning, drug abuse & dependency

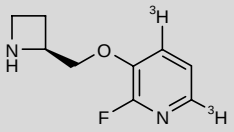
NMDA receptor antagonists are known tools to prevent ethanol withdrawal-related neurotoxicity. However, complete receptor blockade may have other undesired adverse effects. Therefore, researchers at the University of Kentucky, U.S.A., have developed compounds that modulate rather than block NMDA receptors, mimicking endogenous polyamines. **JR-220** is an iminoguanidine derivative that blocks polyamine binding to the NMDA receptor and



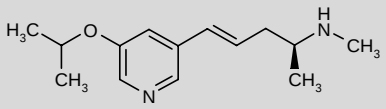
S-3319



KDI tripeptide



[^{3}H]-2-Fluoro-A-85380



Ispronicline

blocked ethanol withdrawal-induced cell death in hippocampal slices in vitro (72). Moreover, JR-220 treatment (15 mg/kg s.c.) given to rat pups (postnatal days 1-7) exposed to ethanol (6 g/kg/day) resulted in improved performance in the water maze test, indicating the ability of JR-220 to prevent ethanol-induced impairment in spatial memory (73). The effects of JR-220 were also assessed in a "drinking in the dark" paradigm in which C57Bl/6J mice were given daily access to 20% v/v ethanol for 4 h early in the dark phase of the light/dark cycle over 4 weeks (5 days on, 2 days off). After 4 weeks of conditioning, treatment with JR-220 20 mg/kg i.p. greatly reduced ethanol consumption compared to saline administration (74).

Diagnostic agents

Researchers at AstraZeneca have reported on the pharmacological profile of the radioligand **[^{3}H]-2-fluoro-A-85380** and the agonist AZD-3480 (**ispronicline**) at neuronal nicotinic receptors. In vitro binding studies using rat brain tissue resulted in K_d and B_{max} values of 37 pM and 172 fmol/mg, respectively, for [^{3}H]-2-fluoro-A-85380. Binding was blocked by AZD-3480 with a K_i of 1.5 nM. Following i.v administration, [^{3}H]-2-fluoro-A-85380 (0.68 nmol/kg) was found to preferentially localize in rat thalamus, as well as prefrontal cortex, striatum and cerebellum. Pretreatment with AZD-3480 (18.88 mg/kg p.o.) blocked the binding of [^{3}H]-2-fluoro-A-85380 in rat brain and labeling of the radioligand in rat brain regions, as shown in autoradiography studies. AZD-3480 generated dose-dependent receptor occupation with [^{3}H]-2-fluoro-A-85380 (75).

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