Drugs of the Future 2010, 35(3): 251-260

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.3.1488758

MEETING REPORT

HIGHLIGHTS FROM THE 39TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE

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SUMMARY

The 39th Annual Meeting of the Society for Neuroscience (October 17-21, 2009) was hosted in the city of Chicago. Over 30,000 attendees from around the world gathered in the windy city to share and discuss the latest developments in neuroscience research. In this report, we focus on presentations relating to the development of neurological and psychopharmacological drugs, as well as those describing recent advances in the field of optogenetics, a promising research tool that holds the potential for identifying specific neuronal circuits that could be exploited for therapeutic purposes.

INTRODUCTION

The Society for Neuroscience is the world's largest organization of scientists and physicians devoted to further the understanding of the brain and nervous system. Its annual meeting can be considered one of the largest sources of news on emerging developments in this vast field. The 39th edition, held in Chicago, coincided with the 40-year anniversary of the Society for Neuroscience's inception. A central mission of the Society for Neuroscience is to facilitate the integration of neuroscience research directed at all levels of biological organization by encouraging translational research and the application of new scientific knowledge, in order to develop improved disease treatments and cures. Indeed, during the 2009 annual meeting, more than 30,000 attendees from around the world had the opportunity to choose from over 16,000 presentations showing the latest advances in brain and nervous system research, to learn, share, discuss and integrate neuroscience knowledge and future perspectives. In this report, we focus on presentations relating to therapeutic advances in the areas of neurology and psychopharmacology, as well as those pertaining to recent developments in the field of optogenetics, a promising research tool that holds the potential for identifying specific brain circuits involved in pathological conditions, and thus for improving therapies.

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HIGHLIGHTED PRESENTATIONS ON THERAPEUTICS

Neurological drugs

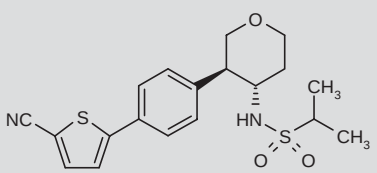
Nicotine was assessed in patients with amnesic mild cognitive impairment in a multicenter pilot study. Nonsmoking amnesic subjects with mild cognitive impairment (N = 74) were randomized to receive either transdermal nicotine (15 mg/day) or placebo for 6 months in the double-blind part of the trial, which was followed by an open-label part, during which a nicotine patch was applied for another 6 months. Cognitive assessments performed at baseline and on days 91 and 182 of the trial using the Cognitive Drug Research battery revealed significant improvements in delayed word recall accuracy, speed of memory and choice reaction time accuracy with nicotine treatment compared to the results obtained with placebo. Clinical Global Impression of Change (CGI-C) data indicated that a greater proportion of subjects administered nicotine (23%) exhibited an improvement compared to those receiving placebo (9%). A strong trend in favor of nicotine was noted in patient self-assessment of cognitive impairment and alertness. In addition, nicotine administration correlated with a significant reduction in systolic blood pressure compared with placebo. Nicotine therapy was well tolerated in this study population, with a similar incidence of adverse events in the nicotine and placebo groups. The study supports further clinical exploration of the putative beneficial effects of transdermal nicotine as symptomatic treatment for amnesic mild cognitive impairment (1).

The ability of the nicotinic acetylcholine receptor (nAChR) $\alpha_4\beta_2$ positive allosteric modulator **A-969933** (NS-9283) to enhance ineffective doses of nicotine, resulting in effects expected from higher nicotine doses in the central nervous system (CNS), was evaluated in a preclinical study. In male Sprague-Dawley rats, slow-wave electroencephalography (EEG) measurements of cortical activation revealed a significant and dose-dependent reduction of EEG slow-wave amplitude caused by nicotine alone at doses of 0.62 and 1.9 µmol/kg i.p.). Coadministration of A-969933 (1 or 3 µmol/kg) with a 0.62 µmol/kg i.p. dose of nicotine was found to induce a dose-related reduction in EEG amplitude that was significantly greater than

that seen with nicotine alone. A-969933 had no effect on EEG in the absence of nicotine. In the nicotine drug discrimination test, the combination of A-969933 (10 or 30 µmol/kg) with an inactive dose of nicotine resulted in a significant, dose-dependent increase in nicotine discrimination, similar to the effects seen with escalating doses of nicotine alone. A-969933 alone showed no effects on nicotine preference (nicotine lever choice) in nicotine-trained rats. In rats sensitized to nicotine (0.4 mg/kg) or vehicle administered 4 days/week s.c., A-969933 failed to alter locomotor activity either alone or in combination with nicotine, although the combination resulted in decreased locomotor activity at a dose of 10 µmol/kg A-969933. These results suggest that the EEG-stimulating effects of nicotine may be regulated partly by positive allosteric activation of nAChR $\alpha_4\beta_2$ receptors (2).

SUVN-623, a serotonin 5-HT_6 receptor antagonist, was evaluated in animal models of cognition. The 5-HT_6 receptor subtype is almost exclusively expressed in the CNS, predominantly in brain regions associated with cognition and behavior, and acts as a modulator of acetylcholine, glutamate and serotonin neurotransmission. As such, it represents a good target for the development of treatments targeting neurodegenerative and cognitive disorders, such as Alzheimer's disease. Pharmacokinetic profiling of SUVN-623 in rats (10 mg/kg p.o. or i.v.) and dogs (10 mg/kg p.o. or 3 mg/kg i.v.) revealed respective C_{max} values of 296 and 793 ng/mL and plasma half-lives of 2.17 and 11.28 h. The compound's bioavailability was 75% in rats and 53% in dogs. The brain penetration index following a 1 mg/kg/h infusion in rats was established at 3.81. The potential procognitive effects of SUVN-623 on spatial and episodic memory were assessed in the Morris water maze and the novel object recognition task in rats. In the Morris water maze paradigm, SUVN-623 (1 and 3 mg/kg p.o.) was observed to attenuate scopolamine-induced cognitive deficits by causing a significant decrease in the latency and path length to target. SUVN-623 administration at 3 and 10 mg/kg p.o. correlated with an increase in the exploration time towards a novel object compared to a familiar object in the test phase of the novel object recognition task. Additional evaluation of SUVN-623 as a potential therapeutic candidate for the treatment of cognitive deficits is supported by this study (3).

PF-4778574, a novel AMPA receptor potentiator under development by Pfizer for the treatment of schizophrenia and cognitive disorders, was evaluated in a series of in vivo assays. Neuropharmacokinetic analysis in Sprague-Dawley rats revealed respective C_{max} values of 105, 2.7 and 70.3 ng/mL in plasma, cerebrospinal fluid (CSF) and brain, with half-lives of 0.7, 1.3 and 0.8 h. In cognitive assessments, PF-4778574 was found to enhance glutamate signaling by overcoming an NMDA receptor antagonist-induced deficit in synaptic transmission in anesthetized rats. The compound also caused performance improvements in preclinical cognition models with or without NMDA receptor antagonism, such as the radial arm task in rats, the delayed matching-to-sample task in monkeys and the rat novel object recognition task. In safety evaluations, PF-4778574 administration at higher doses correlated with an elevation in cerebellar cyclic guanosine monophosphate (cGMP) levels prior to inducing a disruption in rotarod performance in mice or in movement-related tremor in nonhuman primates. The research team concluded that further investigation of the mechanism of action of PF-4778574 is expected to provide insight into its exposure separations between cognition enhancement and disruption of motor coordination (4).



PF-4778574

The novel α_7 receptor nAChR agonist **WYE-103914** was found to exhibit high affinity for rat α_7 nAChR expressed in GH4-C1 cells (K_i = 44 nM) and increased the intracellular calcium concentration (EC_{50} = 130 nM, E_{max} = 99%), as measured by the fluorescent imaging plate reader FLIPR. WYE-103914 displayed high selectivity (> 100-fold) for α_7 over α_1, α_3 and $\alpha_4\beta_2$ nAChRs and the 5-HT_3 receptor subtype. In a rat model of novel object recognition (48-h delay paradigm), the compound (1 mg/kg p.o.) caused a statistically significant increase in visual learning and memory retention, an effect which was counteracted by pretreatment with the selective α_7 nAChR antagonist methyllycaconitine (5 mg/kg i.p.). Pretreatment of rats in the novel object recognition model (1-h delay paradigm) with WYE-103914 prior to administration of the NMDA receptor antagonist MK-801 (median effective dose [MED] = 19 mg/kg p.o.) resulted in a reversal of the memory-disrupting effects of MK-801. In the mouse social odor recognition paradigm, WYE-103914 administration (3 mg/kg p.o.) immediately after training correlated with a statistically significant reversal of social odor recognition disruption induced by concurrent MK-801 treatment (5). In a separate study, WYE-103914 was also evaluated alone or in combination with antipsychotic drugs in rodent models relevant to schizophrenia. In preclinical models of antipsychotic activity, WYE-103914 failed to block apomorphine-induced climbing in mice and was unable to decrease conditioned avoidance responding in rats at doses of up to 54 mg/kg i.p. and 30 mg/kg i.p., respectively, unlike the atypical antipsychotic risperidone, which was found to block apomorphine-induced climbing at doses below those required to affect apomorphine-induced stereotypy. The antipsychotic effects of risperidone were not affected by coadministration of WYE-103914 at a dose of 10 mg/kg p.o. in the apomorphine-induced climbing test. However, risperidone was seen to produce a larger decrease in avoidance responding in the presence of WYE-103914 (3 mg/kg p.o.) than when it was administered alone. The cognition-enhancing effects of WYE-103914 (3 mg/kg p.o.) were preserved in the presence of impairing doses of risperidone (0.03-3 mg/kg i.p.) in the object recognition test in rats. These data support further evaluation of the concomitant administration of WYE-103914 and an antipsychotic agent for the treatment of cognitive dysfunction (6).

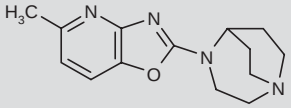
A design approach using the three-point pharmacophore model was employed by scientists at Oxygen Healthcare in an in vitro screen of potential histamine H_3 receptor antagonists. This approach led to the identification of **O2h 10/08**, a lead compound with high affinity

for the H_3 receptor (pK_i > 8.5). The H_3 receptor is known to regulate neurotransmission in the CNS and has been implicated in the regulation of cognitive and homeostatic functions. The identification of H_3 receptor antagonists is expected to provide potential treatment approaches for conditions such as attention deficit hyperactivity disorder, dementias associated with Alzheimer's disease (AD) and schizophrenia, sleep disorders, as well as metabolic imbalances leading to obesity. Evaluation of O2h 10/08 against a panel of six major cytochrome P450 (CYP) isozymes revealed no significant inhibition of any of the major CYP enzymes at a concentration > 1,000-fold higher than the K_i value for the H_3 receptor. The binding profile of O2h 10/08 showed great similarity to that of the antihistamine dimebolin hydrochloride (Dimebon™), which is currently in phase III clinical development for the treatment of AD. The study supports the future development of O2h 10/08 as an H_3 receptor antagonist for the treatment of cognitive disorders (7).

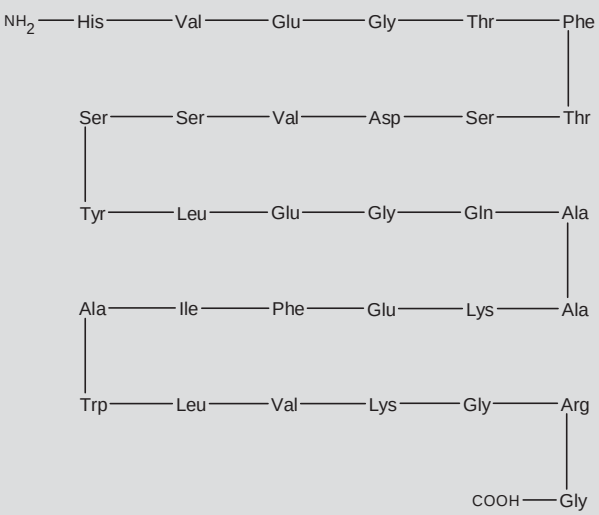
Scientists at Pfizer disclosed data on the discovery of **CP-810123**, a novel α_7 nAChR agonist, for the treatment of cognitive deficits in schizophrenia. CP-810123 demonstrated high affinity (α_7 K_i = 13.5 nM) and selectivity (K_i = 8970, 5370 and 269 nM, respectively, for $\alpha_4\beta_2$, $\alpha_3\beta_4$ and 5-HT_3 receptors) for the α_7 nAChR. In vivo characterization of the compound revealed good oral bioavailability (73% in rats) and brain penetration (brain/plasma ratio of 1.5). Ex vivo in rat hippocampal homogenates CP-810123 displayed an ED_{50} value of 0.34 mg/kg. In a rat model of amphetamine-induced auditory gating deficit, CP-810123 (0.3 and 1 mg/kg s.c.) caused a significant reversal of the effects of amphetamine (1 mg/kg i.v.). In the rat novel object recognition test, CP-810123 (0.32 and 1 mg/kg s.c.) reversed scopolamine-induced cognitive deficits. Based on encouraging preclinical data, CP-810123 has progressed to regulatory toxicology studies and clinical evaluation (8). The compound is currently in phase I clinical trials at Pfizer for the treatment of schizophrenia.

AMG-0683 is a novel potent β-secretase 1 (BACE1) inhibitor (BACE1 IC_{50} = 9.9 nM) designed to overcome the problems of rapid CYP-mediated metabolism and susceptibility to P-glycoprotein transport, which are commonly associated with BACE1 inhibitors and result in a reduction in oral bioavailability and duration of action. AMG-0683, unlike other BACE1 inhibitors, displayed favorable membrane permeability (17 × 10^{-6} cm/s) and a low efflux ratio (1.7). Acute oral administration of the compound to rats in the absence of P-glycoprotein or CYP3A4 inhibitors correlated with an ablation in β-amyloid (Aβ) levels in the brain and CSF of treated animals. The study supports the future development of AMG-0683 for the treatment of Aβ-associated conditions, such as AD (9).

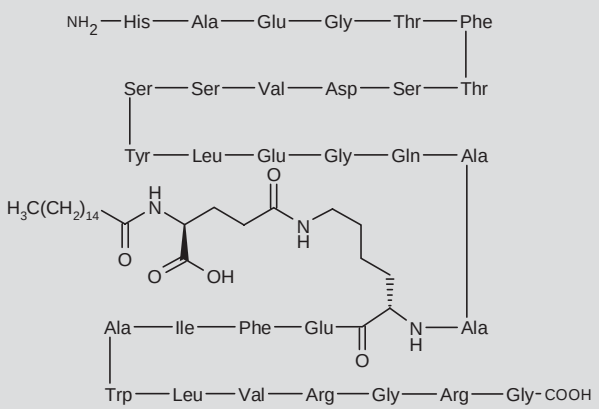
Glucagon-like peptide 1 (GLP-1) is an endogenous peptide that has been shown to possess neuroprotective properties. Novel GLP-1 analogues were recently evaluated for their ability to prevent neurodegeneration and cognitive decline by normalizing insulin signaling in the brains of mouse models of type 2 diabetes, which has been identified as a risk factor for AD. The GLP-1 analogues **(Val8)-GLP-1** and **liraglutide** (Victoza®) were assessed for their ability to cross the blood–brain barrier and potentially influence neuronal communication and synaptic plasticity in male C57BL/6 mice in a study conducted by U.K. scientists. Injection (i.p.) of 25 nmol/kg or 250 nmol/kg of (Val8)-GLP-1 or liraglutide resulted in significant increases in the levels of either peptide in the brains of injected mice at 30 min or 3 h postinjection, which indicated crossing of the blood–brain barrier (10). The effects of (Val8)-GLP-1 and liraglutide on neuronal communication were addressed in male Wistar rats injected with either compound at a dose of 15 nmol/5 µL i.c.v. Synaptic plasticity measurements performed via excitatory postsynaptic potential recordings in the CA1 region of the hippocampus via implanted electrodes revealed significant enhancement in long-term potentiation (LTP) caused by both liraglutide and (Val8)-GLP-1. The data demonstrate a facilitatory effect of GLP-1 analogues on LTP and suggest



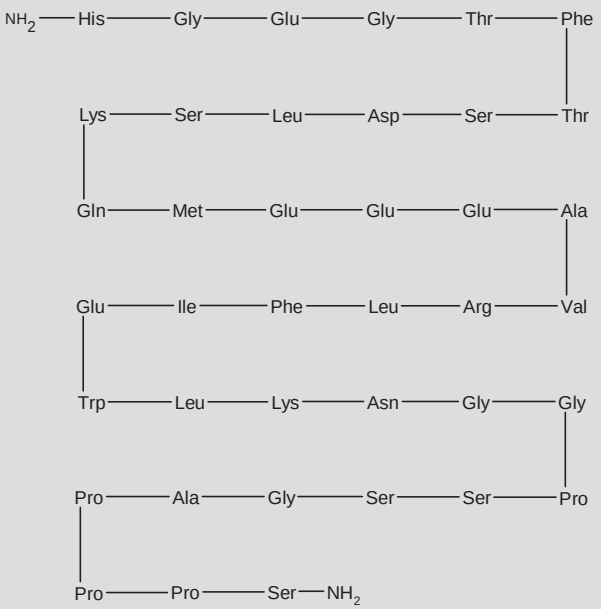
CP-810123



(Val8)-GLP-1



Liraglutide



Exenatide

that they may act to redeem the impairment of neuronal transmission manifested in conditions such as AD (11).

Treatment of *ob*/*ob* and *db*/*db* mice (models of mild and severe diabetes, respectively) with the GLP-1 analogues liraglutide and **exenatide** (Amylin™) at 25 nmol/kg administered i.p. as a single daily dose over a period of 8 weeks correlated with significant increases in stem cell proliferation in the granule cell layer of the dentate gyrus, as detected by 5-bromo-2-deoxyuridine (BrdU) incorporation (58% and 45% increases, respectively, in BrdU-positive cells in liraglutide-treated *ob*/*ob* and *db*/*db* mice). In exenatide-treated animals, BrdU-positive cell number increases of 65% and 85%, respectively, were seen in *ob/ob* and *db/db* mice. The increased proliferation of stem cells as a result of treatment with GLP-1 analogues may potentially lead to the replacement of the lost neurons and confer protection in neurodegenerative diseases (12).

Antisense oligonucleotide technology prevents the expression of proteins involved in disease processes and is therefore considered therapeutically beneficial to patients. Isis Pharmaceuticals has developed **ISIS-388241** and **ISIS-387898**, a human-specific and a pan-mouse/human huntingtin oligonucleotide, respectively, for the inhibition of huntingtin protein expression in Huntington's disease (HD). The pharmacodynamics and pharmacokinetics of these second-generation oligonucleotides in the CNS following continuous intracerebroventricular (i.c.v.) infusion or intrastriatal bolus injection were investigated in a recent study presented at the meeting. BACHD mice (a transgenic mouse model expressing human mutated *HTT* and exhibiting progressive motor deficits) infused with ISIS-387898 (75 µg/day i.c.v. for 2 weeks) displayed a sustained inhibition of both mouse and human huntingtin for a period of up to 91 days following treatment cessation. Single intrastriatal bolus administration of ISIS-387898 (50 µg/2 µL) to C57BL/6 mice resulted in a prolonged reduction of mouse *Htt* mRNA expression. ISIS-388241 i.c.v. infusion to BACHD mice at 50 µg/day for 2 weeks caused a prolonged inhibition of human, but not mouse, *HTT* mRNA expression. The tissue half-life for both oligonucleotides in mouse brain was calculated to be approximately 20 days and a concentration of > 20 µg/g was deemed sufficient to generate the desirable pharmacological profile (13).

The novel selective µ opioid receptor antagonist **ADL-5510** was assessed for its ability to modify levodopa-induced dyskinesia (LID) in an MPTP-lesioned macaque model of Parkinson's disease (PD). ADL-5510 (0.1, 1, 3 and 10 mg/kg p.o.) reduced LID, dystonia and chorea without interfering with the antiparkinsonian benefit of levodopa, unlike the nonselective opioid antagonist naltrexone (1, 3 or 10 mg/kg s.c.), which had no effect on LID. ADL-5510 demonstrated a U-shaped dose–response relationship for reducing LID, with the highest activity seen at 1 and 3 mg/kg, the lowest activity observed at 10 mg/kg and no activity at 0.1 mg/kg. The study results support the potential development of ADL-5510 as an adjunct to dopamine replacement therapy for the treatment of PD (14).

The effects of the novel adenosine A_{2A} receptor antagonist **K-056** (Kyowa Hakko Kirin) on the sleep–wake state, migraine and motor function in PD were evaluated in a series of preclinical models in a number of studies. Oral administration of K-056 to reserpine-induced cataleptic mice caused a reduction in catalepsy, with an ED_{50} value of 0.13 mg/kg. In mice and rats with haloperidol-induced catalepsy, the compound reduced catalepsy symptoms with an ED_{50} of 0.02 mg/kg. In MPTP-treated marmosets, K-056 displayed antiparkinsonian activity by improving motor disability score and locomotor depression at a dose range of 0.1-10 mg/kg, without inducing dyskinesia. Adjunct therapy of K-056 (1 mg/kg) with levodopa (up to 10 mg/kg) resulted in an increase in maximum antiparkinsonian activity induced by levodopa without affecting the maximum LID score in MPTP-treated marmosets (15). K-056 (0.3 and 1 mg/kg p.o.) and the wake-promoting agent modafinil (100 and 300 mg/kg p.o.) induced similar wake-promoting effects in rats. K-056 significantly prolonged sleep onset latency and increased total wake time, without affecting the circadian rhythm of the sleep–wake cycle, which suggested its potential use for the treatment of sleep disorders (16). K-056 was also found to be effective in rat models of acute and prophylactic migraine. Intraduodenal administration of the compound at 0.3 and 3 mg/kg significantly inhibited the increase in cerebral blood flow induced by electrical stimulation of the trigeminal nerve in the acute migraine model. A reduction in the number of repeated cycles of potassium chloride-induced cerebral hyperemia was seen following oral administration of K-056 (0.3 and 3 mg/kg) in the prophylactic migraine model (17).

A-1010002 is a humanized monoclonal antibody that targets the rat and human repulsive guidance molecule A, a neurite growth inhibitor, thus permitting neuroregeneration following spinal cord and brain injury. A-1010002 acts by functionally neutralizing the interaction between repulsive guidance molecule A and its receptor and coreceptors neogenin and bone morphogenetic proteins BMP-2 and BMP-4. The in vivo activity of A-1010002 was evaluated in a rat optic nerve crush model. Local application of A-1010002 at the crush

nerve site correlated with a significant increase in the number of regenerating growth-associated protein 43 (GAP-43)-positive fibers at 200, 400, 600 and 1200 µm distal to the crush site. Regeneration was not seen in animals treated with a control antibody. In the same paradigm, systemic administration of A-1010002, via i.v. or i.p. injection, resulted in the detection of GAP-43-positive fibers extending far beyond the crush site. This study provides the first in vivo evidence of long-distance neuronal regeneration by the local or systemic application of a repulsive guidance molecule A-neutralizing antibody following nerve injury (18).

JNJ-1930942, a positive allosteric modulator of the nAChR α_7 receptor, was found to increase the peak and net charge response to choline, acetylcholine and PNU-282987 in an electrophysiological assessment performed in the GH4C1 cell line. The compound acts mainly by altering the receptor desensitization characteristics, without having a major effect on activation/ deactivation kinetics or recovery from desensitization. In mouse hippocampal slices, JNJ-1930942 was seen to increase neurotransmission across the synapses in a concentration-dependent manner and induced long-term potentiation (LTP) of electrically evoked synaptic responses in the dentate gyrus. In vivo in DBA/2 mice, the compound was able to improve a genetically based auditory deficit, which suggests its potential use for the treatment of cognitive dysfunction (19).

Investigators at Cortex Pharmaceuticals have identified Ampakine compounds that are positive allosteric modulators of the AMPA-type glutamate receptor and may affect synaptic activity and have the potential to treat neurological diseases. The lead compound, **CX-1837**, was found to facilitate AMPA receptor function in HEK-293 cells expressing AMPA receptors, to potentiate glutamate-evoked Ca^{2+} signals in HEK-293 cells expressing various AMPA receptors, to potentiate responses at all AMPA receptor subunits tested (with enhanced potency at GluR1-flop- and GluR2-flip-containing receptors) and to facilitate evoked excitatory postsynaptic potentials in rat hippocampal slices. In anesthetized rats, CX-1837 1.0 mg/kg i.p. significantly facilitated LTP. The compound also facilitated pro-brain-derived neurotrophic factor synthesis in mice. Performance was improved in a rat cognition test and in an object working memory model in rhesus monkeys, and an excellent pharmacokinetic profile was measured in rats, with oral bioavailability of 100% and a $t_{1/2}$ of 2 h (20).

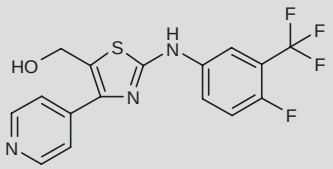
MSD-9 (MSDC-0160, Mitoglitazone™), a novel thiazolidinedione agonist of peroxisome proliferator activated receptor PPARγ, was tested for possible anti-amyloidogenic activity in mice. Male 5xFAD mice, which bear five familial mutations in the amyloid precursor protein (three mutations) and presenilin-1 (two mutations) and develop robust amyloid plaque pathology as early as 6 weeks postnatally, were given MSD-9 (100 or 300 parts per million in chow) and were subsequently analyzed for brain amyloid burden after 1 month. MSD-9 administration correlated with a 15% decrease in total soluble $A\beta_{1-42}$ levels in the hippocampus and may represent a novel target for therapeutic intervention for the treatment of neurological conditions associated with Aβ burden, such as AD (21).

In an effort to inhibit emesis induced by motion or toxins without inducing anxiety, Cenomed BioSciences researchers have developed a 5-HT_{1A} receptor agonist and tested it in short-hair domestic felines, a useful model for both emesis and anxiety. In these animals, **CM-2385** blocked chemical-induced emesis without producing anxiety and defensive/aggressive behavior. The agent also significantly increased the latency to emesis induced by cisplatin, decreased acute and delayed emesis due to cisplatin in cats, and dose-dependently and significantly inhibited emesis produced by cisplatin in shrews. CM-2385 also inhibited emesis due to motion in cats. The company is seeking partners to evaluate the compound in clinical trials (22).

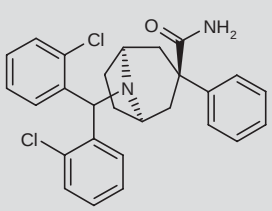
Psychopharmacologic drugs

Lu et al. presented a novel, orally active nociceptin opioid-like peptide (NOP) receptor agonist, **SCH-655842** (Schering-Plough), that displayed a cross-species anxiolytic-like profile. In the mouse Geller-Seifter test, SCH-655842 (30 mg/kg) exhibited anxiolytic activity, increasing the percentage of punished responding comparable to Ro-64-6198 and diazepam (3 mg/kg). The number of buried marbles was significantly reduced in mice following administration of SCH-655842 (30 mg/kg), similar to the benzodiazepine chlordiazepoxide (10 mg/kg). SCH-655842 caused reductions in locomotor activity, body temperature and rotarod performance in wild-type mice but not in NOP receptor knockout mice, which suggested that the anxiolytic-like effects of the compound are mediated by the NOP receptor. In rats, SCH-655842 (70-100 mg/kg) reduced rotarod performance but had no effect on locomotor activity, fixed-ratio responding or beam walking at doses as high as 100 mg/kg. In the rat conditioned lick suppression test, SCH-655842 exhibited anxiolytic activity at a dose range of 3-10 mg/kg. SCH-655842 (1-3 mg/kg) also demonstrated a dose-dependent reduction in separation-induced vocalizations in a guinea pig model of anxiety. The study supports additional preclinical assessment of SCH-655842 prior to evaluation in human anxiety disorder trials (23).

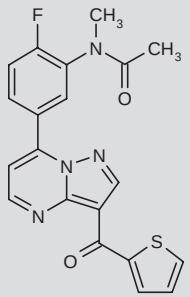
GF-015535-00, a member of the pyrazolopyrimidine class of compounds which act as selective modulators of the $GABA_A$ receptor



JNJ-1930942



SCH-655842



GF-015535-00

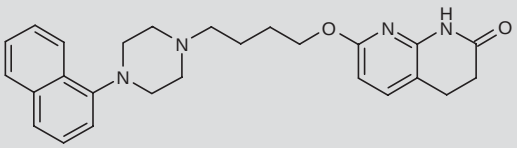
subunit α-1, was evaluated for its sedative, cognitive and sleep-inducing activity compared to indiplon, zaleplon and zolpidem in a recent in vivo study. Oral administration of GF-015535-00 to mice inhibited spontaneous motor activity in the open field with an ED_{50} value of 0.13 mg/kg compared to ED_{50} values of 0.2, 1.4 and 2.01 mg/kg, respectively, exhibited by indiplon, zaleplon and zolpidem. The MED of GF-015535-00 that was able to reduce the duration of wakefulness and increase that of non-rapid eye movement and/or rapid eye movement sleep, as measured by EEG, was estimated at 1.2 mg/kg. The respective MED values for indiplon, zaleplon and zolpidem in the induction of sleep were estimated at > 1.8, > 12.6 and 12 mg/kg. GF-015535-00 induced cognitive impairment in the two-way active avoidance paradigm with an MED of 10 mg/kg (similar to indiplon), which was 10-fold higher than the MED of zaleplon inducing cognitive impairment in the same mouse model. The study supports the potential therapeutic benefit of GF-015535-00 for the management of sleep-related disorders (24).

The histamine H_3 receptor antagonist **WAY-364416**, which has previously demonstrated in vivo procognitive activity, was evaluated as adjunct treatment for schizophrenia in a series of preclinical models. The combination of inactive doses of WAY-364416 (1 and 3 mg/kg p.o.) with subeffective doses of aripiprazole (0.54 mg/kg i.p.), olanzapine (0.54 mg/kg i.p.) and risperidone (0.1 mg/kg i.p.) resulted in potentiation of the effects of these atypical antipsychotics in the conditioned avoidance response test in Sprague-Dawley rats. An inactive dose of WAY-364416 (30 mg/kg i.p.) potentiated the antipsychotic efficacy of olanzapine (0.01-1 mg/kg i.p.), risperidone (0.003-0.3 mg/kg i.p.) and aripiprazole (0.01-1 mg/kg) in the apomorphine-induced climbing and stereotypy assay in CF-1 mice. Administration of WAY-364416 alone had no effect in either behavioral model. In the novel object recognition assay in Long Evans rats, WAY-364416 (3 mg/kg p.o.) significantly enhanced recognition memory administered either alone or in combination with olanzapine (0.54 mg/kg i.p.). In an extrapyramidal side effect liability model, WAY-364416 (30 mg/kg i.p.) did not potentiate aripiprazole-induced catalepsy in CF-1 mice. This study supports the potential therapeutic use of WAY-364416 in combination with current antipsychotics for the treatment of schizophrenia based on its ability to improve cognitive function and potentiate antipsychotic activity while maintaining an atypical antipsychotic profile (25).

CM-2395 is a novel multireceptor modulator under development as an antipsychotic agent for the treatment of schizophrenia. Investigation of the in vitro binding profile of the compound revealed full agonist activity for the 5-HT receptor (K_i = 14 nM), partial agonism at the dopamine D_{2s} receptor (K_i = 230 nM) and antagonism at the α_{1A}-adrenoceptor (K_i = 5 nM) (26). Evaluation of the efficacy and secondary pharmacology of CM-2395 in male C57BL/6 mice revealed similar effects to clozapine in attenuation of phencyclidine (PCP)-induced disruption of prepulse inhibition and hyperlocomotion. However, unlike clozapine, CM-2395 showed no cognition-disrupting effects. CM-2395 is expected to enter phase I clinical trials as a next-generation clozapine-type pharmacotherapy for the treatment of both the positive and negative symptoms of schizophrenia (27).

PF-00217830 is a dopamine D_2 and 5-HT_{1A} receptor partial agonist/5-HT_{2A} receptor antagonist which has entered phase II investigation as a treatment for schizophrenia. Recent presentations described potent binding affinities, with K_i values of 0.8, 0.2, 0.1, 3 and 11 nM, respectively, for D_2, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{1B} and 5-HT_{2C} receptors. In in vitro functional assays, PF-00217830 was a potent partial agonist at D_2 receptors (35% intrinsic activity [IA]), a potent 5-HT_{1A} partial agonist (26% IA), a potent 5-HT_{2A} antagonist (IC_{50} = 34 nM) and a moderate α_{1A}-adrenoceptor antagonist (IC_{50} = 131 nM) (28). In vivo, PF-00217830 demonstrated functional D_2 partial agonism similar to aripiprazole and was more potent than aripiprazole in inhibiting spontaneous locomotor activity (a measure of antipsychotic potential) in rats. Greater 5-HT_{2A} in vitro binding affinity appeared to result in more potent inhibition of DOI-induced head twitches in rats compared to aripiprazole. The inability to induce catalepsy in rats suggested a low liability for extrapyramidal motor side effects (29). Ex vivo binding studies in rats and nonhuman primates showed that PF-00217830 and aripiprazole dose-dependently occupied striatal D_2 receptors, and PF-00217830 was more effective than aripiprazole in occupying frontal cortex and hippocampal 5-HT_{2A} and 5-HT_{1A} receptors. PF-00217830 was also less effective than aripiprazole in occupying SERT binding sites in rat and nonhuman primate cortex (30).

Results from the preclinical evaluation of the potent and selective nicotinic $\alpha_4\beta_2$ receptor antagonist **SUVN-911** were also disclosed at the meeting. In vitro, SUVN-911 exhibited strong binding to the human recombinant $\alpha_4\beta_2$ receptor (K_i = 7.7 nM) and antagonized the epibatidine-induced calcium influx in recombinant CHO cells with a K_b value of 7.1 nM. In vivo, the compound displayed a favorable pharmacokinetic profile in rats, with high oral bioavailability (92%) and a terminal half-life of 4.19 h, and it also demonstrated good brain penetration, with a brain-to-plasma ratio of 3.8. Evaluation of SUVN-911 (10 and 30 mg/kg) in animal models of depression showed charac-

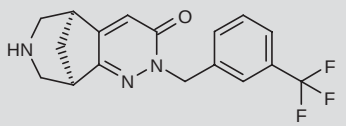


PF-00217830

teristic antidepressant properties in the mouse forced swim test (FST) and the differential reinforcement of low rates of responding (DRL-72s) assay. The compound caused a reduction in immobility time in the FST and increased the number of rewards and reward efficiency while decreasing the number of lever responses in the DRL-72s assay. SUVN-911 has been selected for further evaluation for the management of mood disorders (31).

The nAChR subunit α_6, unlike other nAChR subunits, exhibits an expression pattern which is largely restricted to catecholaminergic neurons, and is thought to play a role in the regulation of dopamine release. It may therefore represent a potential target for pharmaceutical intervention in disorders involving dopamine signaling. Scientists at Pfizer identified a series of small-molecule compounds that display high affinity for $\alpha_6/\alpha_4\beta_4$ chimeric nAChRs, as well as $\alpha_3\beta_4$ AChRs, with K_i values in the low nanomolar range. One such compound, **PF-4888086**, exhibited K_i values of 1.9 and 3.2 nM, respectively, for the $\alpha_6/\alpha_4\beta_4$ and $\alpha_3\beta_4$ nAChRs. In vitro application of PF-4888086 to rat hippocampal slices caused the release of [^{3}H]-norepinephrine with an EC_{50} value of 41 nM, which indicated functional activity at native nAChRs. In vivo in microdialysis studies, s.c. administration of PF-4888086 (1, 3.2 and 10 mg/kg) evoked sustained increases in dopamine and norepinephrine in the rat prefrontal cortex (32). In animal models predictive of antipsychotic activity, PF-4888086 was found to decrease both spontaneous and methamphetamine-stimulated locomotor activity and to increase the inherently low level of prepulse inhibition (PPI) in mice. In the conditioned avoidance response test in rats, PF-4888086 enhanced the activity of a subeffective dose of risperidone (0.1 mg/kg). Risperidone (at a low dose of 0.32 mg/kg) increased the potency of PF-4888086 in a C57BL/6J mouse model of PPI. In a mouse model of prefrontal cortical activity, PF-4888086 reversed mescaline-induced scratching, with a 50% inhibitory dose (ID_{50}) of 0.176 ng/kg s.c. This effect was counteracted by mecamylamine but not hexamethonium, which suggested the involvement of a centrally acting nicotinic mechanism. Collectively, these results support further evaluation of α_6 and α_3 nAChRs as potential targets for the development of antipsychotic drugs (33).

The highly selective estrogen ERβ agonist **KB-099520** displayed increased serotonergic activity and exhibited antidepressant effects in rodent behavioral models of depression in two studies. In vivo electrophysiological recordings from dorsal raphe nucleus neurons in anesthetized male SD rats revealed a significant increase in spontaneous firing activity of 5-HT neurons following treatment with KB-099520 (30 µmol/kg for 3 days) compared to citalopram (20 mg/kg for 3 days) or vehicle control. These effects of KB-099520 were seen at 24 h following the last dose and did not appear to be mediated by desensitization of the 5-HT_{1A} receptor. Acute administration of KB-099520 to C57BL/6 male and ovariectomized female mice induced the expression of tryptophan hydroxylase 1 (TPH1) mRNA, which is the rate-limiting enzyme for 5-HT synthesis, in the raphe nucleus in a dose-dependent manner and without increasing uterine weight in female mice at doses up to 800 µmol/kg p.o. or 180 µmol/kg s.c. Enhanced cell proliferation was seen in the dentate gyrus of male mice at 24 h following a single injection of KB-099520, as detected by an increase in the number of Ki-67-immunoreactive cells (34). Acute and subchronic moderate dosing of KB-099520 (at 30 and 10 mg/kg, respectively) to C57BL/6 mice resulted in a decrease in immobility time in the FST. Investigation of the antidepressant activity of KB-099520 compared to fluoxetine (10 mg/kg) in helpless H/Rouen mice (an animal model of endogenous depression) showed similar effects for both compounds in causing a decrease in the time spent immobile in the tail suspension test at 30 min following the first s.c. injection. Neither compound had an effect in control mice, which indicated the absence of undesirable depressant activity. The research team concluded that KB-099520 may represent a promising drug candidate for the treatment of depression (35).



PF-4888086

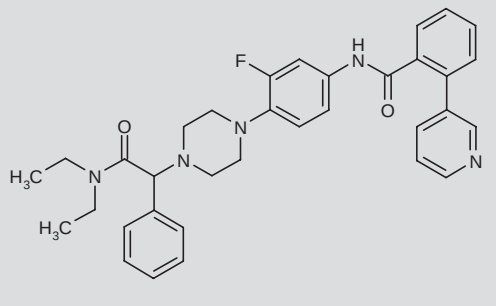
Results from the in vitro and in vivo pharmacological characterization of the monoamine reuptake inhibitor **SEP-230864** were disclosed by Sepracor scientists. Functional uptake studies performed in CHO cells expressing human recombinant transporters for serotonin (SERT), norepinephrine (NET) and dopamine (DAT) revealed the ability of SEP-230864 to block monoamine reuptake at SERT, NET and DAT with respective IC_{50} values of 1, 3 and 11 nM. A lower inhibitory potency was observed against rat recombinant SERT, NET and DAT (IC_{50} = 12, 62 and 85 nM, respectively). In vivo in the rat FST and the mouse tail suspension test, the MEDs of SEP-230864 were estimated at 30 and 10 mg/kg p.o., respectively. The compound displayed analgesic effects in the formalin flinch test and in a chronic constriction injury model, with an MED of 30 mg/kg p.o. In the rat prefrontal cortex, SEP-230864 (3, 10 and 30 mg/kg p.o.) caused a significant, dose-dependent increase in 5-HT and norepinephrine levels (by up to approximately 500% vs. baseline), and at a dose of 30 mg/kg p.o. the compound increased dopamine levels by approximately 200% versus baseline in the rat striatum. Ex vivo receptor occupancy studies in mouse brain using [^{3}H]-citalopram (for SERT), [^{3}H]-nisoxetine (for NET) and [^{3}H]-WIN-35428 (for DAT) revealed a 50% receptor occupancy (RO_{50}) for SEP-230864 of 3, 1 and > 30 mg/kg p.o., respectively. The study supports future evaluation of SEP-230864 for the treatment of neuropsychiatric disorders (36).

The novel amylin-mimetic peptide **PSN-0041** displayed enhanced pharmacological properties over native amylin and exhibited superiority over known antidepressants in a preclinical study. PSN-0041, identified during a screen of more than 200 amylin analogues using PsychoGenics' proprietary in vivo drug discovery technologies, was found to be more potent than amylin (1 mg/kg/day s.c. by 7-day infusion) at decreasing immobility in the FST in C57BL/6J mice at a dose of 0.03 mg/kg/day s.c. for 7 days. In the marble-burying test in mice PSN-0041 (3 mg/kg i.p.) significantly reduced the number of buried marbles compared to amylin (3 mg/kg i.p.), and its activity was sustained for up to 4 h. In rats PSN-0041 (0.05 and 1 mg/kg i.p.) displayed a longer duration of action than amylin (0.1 mg/kg i.p.) in the stress-induced hyperthermia test (up to 8 h). Sustained s.c. infusion

of amylin or PSN-0041 (at 10 μg/kg/day for 2 weeks) to rats fed a high-fat diet resulted in a decrease in body weight gain during the treatment period. PSN-0041 was more efficient than amylin in food intake and body weight reduction. Chronic administration of PSN-0041 (0.1, 0.3 or 1 mg/kg/day) by s.c. osmotic pump did not disrupt sexual behavior in rats, unlike the antidepressant paroxetine (10 mg/kg/day i.p.), which correlated with expected reductions in sexual behavior following administration for 7-14 days. The study supports further evaluation of the antidepressant effects of PSN-0041 (37).

JNJ-31020028 was presented as a novel small-molecule antagonist of the neuropeptide Y Y_2 receptor, and it was evaluated in vitro and in a variety of in vivo models. JNJ-31020028 inhibited the binding of [^{125}I]-PYY to human and rat Y_2 receptors in KAN-Ts cells and hippocampal cultures, with respective pIC_{50} values of 8.07 and 8.22. It also displayed selectivity (> 100-fold) over human Y_1, Y_4 and Y_5 receptors. In in vitro functional assays, JNJ-31020028 exhibited antagonist activity by inhibiting the PYY-stimulated calcium response in KAN-Ts cells expressing a chimeric G-protein (G_{qi5}), with a pK_b value of 8.04. In vivo, following s.c. administration to rats, JNJ-31020028 was observed to penetrate the brain and occupy Y_2 receptor binding sites in a dose-dependent manner. Systemic injection of the compound correlated with an increase in norepinephrine release, but had no effect on other neurotransmitters (i.e., serotonin and dopamine) in the hypothalamus and did not affect the release of norepinephrine in the cortex. The compound exhibited no anxiolytic activity in a number of rodent models of anxiety; however, it did cause a significant decrease in stress-induced corticosterone levels and normalized food intake in stress-induced anorexia. Results obtained in this study suggest a potential modulatory role for Y_2 receptors in specific situational conditions (38).

The small-molecule modulator of the AMPA receptor **EPAT** displayed positive allosteric modulating activity on both recombinant and native AMPA receptor function in preclinical studies. In vitro EPAT was found to potentiate glutamate-mediated calcium flux in HEK-293 cells expressing recombinant rat AMPA receptor subunits, with pEC_{50} values of 5.8, 5.5, 5.3 and 6.1, respectively, for GluR1i, GluR2i, GluR3i and GluR4i subunits. In HEK-293 cells expressing recombinant GluR1i and GluR2i subunits, EPAT was observed to act as an effective modulator of deactivation, as well as desensitization of AMPA, in an outside-out patch clamp recording with ultrafast perfusion assay. Whole-cell patch clamp recordings of native AMPA receptors in rat cultured cortical neurons revealed that coapplication of EPAT (1-100 μM) with glutamate (0.5 mM) led to a decrease in receptor desensitization, with a subsequent increase in steady-state current in a reversible and concentration-dependent manner. The study supports the potential use of EPAT for the evaluation of the therapeutic potential of glutamatergic enhancement for the treatment of psychiatric and neurological conditions (39). In vivo in chloral hydrate-anesthetized rats, EPAT (0.3 mg/kg i.p.) enhanced AMPA-evoked single neuron activity in the CA1 region of the hippocampus by 69% at 30-35 min postadministration. This activity was suppressed by 84% following administration of the AMPA antagonist NBQX, which indicated that the observed neuronal excitation was a consequence of AMPA receptor activation by EPAT (40).



JNJ-31020028

In a series of preclinical tests presented at the meeting, **BNC-210** displayed an anxiolytic profile, which would support its potential therapeutic benefit for the treatment of generalized anxiety with comorbid depression. BNC-210 (1, 10 and 100 mg/kg) significantly and dose-dependently reduced anxiety levels in prestressed rats in the elevated plus maze test. The compound also exhibited antidepressant activity in the rat FST following administration at 10, 20, 30 and 100 mg/kg at 1 h prior to exposure to the test. Chronic administration of BNC-210 (10, 30 and 100 mg/kg/day for 14 days) caused a half-log increase in antidepressant potency. The 30 mg/kg/day dose also correlated with a significant reduction in immobility time. After a 14-day dosing period, abrupt cessation of BNC-210 administration did not result in the incidence of adverse physical events (withdrawal signs), which are commonly observed with opioids, benzodiazepines or selective serotonin reuptake inhibitors (SSRIs). The safety and pharmacokinetics of BNC-210 are currently being evaluated in healthy volunteers in a phase I trial (41).

HIGHLIGHTED PRESENTATIONS ON OPTOGENETICS

Optogenetics is a relatively new technique that combines light and genetics to unravel brain mechanisms underlying physiopathological processes. This powerful tool allows specific neuronal networks to be switched on and off with remarkable precision using light stimuli. Interrogation of neural circuits can be conducted by directly probing the necessity and sufficiency of a defined circuit element within milliseconds, as well as cell type-specific optical perturbations, along with suitable readouts such as electrophysiology, measurements of optical circuit dynamics and behavioral studies in mammals. Specifically, this technique entails the delivery of genes encoding light-sensitive proteins (e.g., bacterial opsins) to deep mammalian brain structures in vivo.

Several abstracts showing the latest findings driven by optogenetic approaches were presented at the meeting. Dr. Covington (Mount Sinai School of Medicine) showed that in mice stimulation of medial prefrontal cortex cells (the brain region known for processing emotion) with laser light has antidepressant-like effects similar to those observed following infusion of histone deacetylase inhibitors, providing deeper understanding and suggesting potential therapies for sufferers who do not fully recover with antidepressant medication (42). Dr. Zhang (Stanford University) talked about the discovery and development of new engineered light-sensitive proteins with increased sensitivity to light from diverse ecological niches. It is

expected that these new opsins will further enhance the sensitivity and specificity of optogenetic techniques (43). Dr. Stuber (UCSF) presented data showing that the optogenetic-mediated stimulation of specific neural connections leads mice to behave as if they are addicted to drugs, an important step toward determining the brain pathways responsible for brain reward mechanisms (44). Finally, Dr. Häusser's research team at University College London has successfully used a novel light-sensitive construct to demonstrate that reactivation of complex memories may involve only a small fraction of brain cells (granule cells in the hippocampal dentate gyrus), a concept that was lacking direct experimental evidence so far (45).

DISCLOSURES

The authors state no conflicts of interest.

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