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MEETING REPORT

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SUMMARY

The Society for Neuroscience hosted its 41st annual meeting in Washington, DC, and welcomed over 30,000 attendees. On the opening day of the conference, the poster sessions displayed a wide range of research in the neuroscience area, including work on animal models used for anxiety disorders, factors involved in neural plasticity, dependence and addiction, and also research in the behavioral pharmacology of addiction. Symposia sessions outlined research endeavors into animal models of shank mutations related to autism, the role of diet and exercise in promoting metabolic homeostasis, and the role of planar cell polarity (PCP) genes in the nervous system. This report highlights some of the research discussed.

Key words: Anxiety – Drug addiction – Multiple sclerosis – Epilepsy – Alzheimer's disease

PART I

ONO-2952 emerges as a potential treatment for stress-related disorders

The analysis of ONO-2952, a translocator protein (TSPO) antagonist, its selectivity for TSPO and brain steroid genesis in stress-loaded rats was presented by Seishi Katsumata of Ono Pharmaceutical. Initially, inhibition constants of ONO-2952 in various membrane functions were evaluated. In rat whole brain, human glioma Hs 683 and histiocytic lymphoma U-937 cell lines, ONO-2952 had K_i values of 0.33, 9.30 and 1.46 nmol/L, respectively, whereas it demonstrated K_i values of 551, 601 and 652 nmol/L, respectively, for human melatonin MT_2, progesterone receptor isoform B and α_{2C}-adrenoceptors. When administered into the hippocampus of rats exposed to restraint stress, ONO-2952 was found to inhibit pregnenolone production. Before stress induction, the rats had 3 ng/g tissue of pregnenolone, which increased to 5.5 ng/g tissue in the control group and 4 ng/g tissue with ONO-2952. The compound also conditioned fear stress-induced freezing behavior in rats. ONO-2952 (1 mg/kg p.o.) displayed similar efficacy to diazepam (3 mg). In the stress-loaded rat, a 3-mg dose of ONO-3952 had a plasma concentration of approximately 118 ng/mL and TSPO occupancy was approximately 94.5 and 95.1, respectively, in the cerebral cortex and hippocampus.

Further preclinical data for ONO-2952 were presented by K. Mitsui (Ono Pharmaceutical) regarding its ability to inhibit stress-induced defecation in rats. Restraint stress-induced norepinephrine (NE) release in the amygdala was investigated using intracerebral microdialysis and high-performance liquid chromatography (HPLC). It was also evaluated whether reverse microdialysis perfusion with the TSPO-selective agonist CB-34 into the amygdala would block the inhibitory effects of ONO-2952 in rats exposed to water avoidance stress. A 3-mg dose of ONO-2952 produced a significant ($P < 0.001$) decrease in restraint stress-induced NE release in the amygdala. When treated with ONO-2952, NE release was 210% greater than baseline levels during stress compared with 450% for control compound. A 1-mg oral dose of ONO-2952 significantly reduced water avoidance stress-induced NE release compared with control. When comparing water avoidance stress-induced defecation in rats, observations with ONO-2952 were again significantly ($P < 0.01$) different from control. When treated with control, rats produced on average nine feces during stress but only five feces when treated with ONO-2952 (1 mg). When coperfused with CB-34 into the amygdala, the inhibitory effects of ONO-2952 were attenuated in a concentration-dependent manner. Based on these results, it was concluded that ONO-2952 may have the potential to treat stress-related disorders. At this time, a phase I study in patients with irritable bowel syndrome is under way. The results of this study are expected early this year, at which time a second phase I study would commence.

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AT-1001 shows promise in a range of drug addiction models

Matt Costello of the University of California, Irvine presented data on AT-1001, an $\alpha3\beta2$ nicotinic acetylcholine receptor (nAChR) antagonist being developed in collaboration with Astraea Therapeutics and SRI international. AT-1001 (3 mg/kg) was evaluated in a rat model of nicotine addiction and was found to produce a marked reduction in nicotine self-administration compared with control. Motivation to take nicotine was decreased in the rats assessed and this did not affect responses to food. The blocking effect of AT-1001 was found to be more potent than a standard dose of mecamylamine (3 mg/kg). Although potent, the blocking effect of AT-1001 was not long-lasting. The AT-1001-reinforced response on day 1 demonstrated no effect by day 2. As rat data are more predictive of human behavior than data from mice, it was suggested that $\alpha3\beta4$ nAChRs could be targeted as tobacco dependence therapeutics.

Taline Khroyan and Lawrence Toll (SRI International) revealed preclinical data for AT-1001 from a study in cocaine dependence. AT-1001 is one of seven nAChR antagonists in development. AT-1001 was found not to induce conditioned place preference (CPP) in mice, an indicator that AT-1001 would not be abused if used by humans. At higher doses, AT-1001 reduced global activity. At a dose of 5 mg/kg it prevented cocaine-induced CPP, and behavioral sensitization from cocaine at doses up to 30 mg/kg. This effect was not repeated with CPP induced by morphine use, but higher doses of AT-1001 did prevent morphine-induced hyperactivity and reverse morphine-induced sensitization. These data indicated that AT-1001 and similar compounds could be effective for the treatment of cocaine addiction. Toxicology studies were planned.

PART II

Preclinical evaluation of a chemokine CX_3CR1 receptor inhibitor for relapsing–remitting multiple sclerosis

Anna Wollberg (AstraZeneca) presented new data on AZD-8797, a small-molecule inhibitor of the CX_3CR1 receptor (also known as the fractalkine receptor) that has demonstrated selectivity for this receptor versus a panel of other chemokine receptors and approximately 65 non-related receptors. The drug blocked human, rat and mouse CX_3CR1 receptors with binding constants of 10, 29 and 46 nM, respectively. Fractalkine-induced actin polymerization was reduced by AZD-8797 in primary monocytes from humans (IC_{50} = 80 nM) and rats (IC_{50} = 550 nM). The potential impact of AZD-8797 on the prevention and treatment of relapsing–remitting multiple sclerosis was assessed in female dark Agouti rats with experimental autoimmune encephalitis (EAE) induced by myelin oligodendrocyte glycoprotein. This model mimics several features of human multiple sclerosis, in particular the relapsing–remitting disease course, demyelination and axonal degeneration. Administration of AZD-8797 (6.8-78 μmol/kg/day s.c. via osmotic minipumps) from the onset of disease symptoms resulted in plasma concentration-dependent efficacy, as assessed by mean clinical scores. The IC_{50} value for AZD-8797 was approximately 2 μM. Administration of AZD-8797 (32 and 64 μmol/kg/day s.c. via osmotic minipump from days 17 to 45 post-EAE induction) after the first relapse in disease symptoms was associated with dose-dependent improvements in mean clinical scores (P = 0.023 and < 0.001 for the respective doses compared with vehicle). In addition, the frequency of relapses was ameliorated by AZD-8797 (P = 0.015 and < 0.0001 for the respective doses compared with vehicle). Immunohistochemical analysis of the spinal cord demonstrated that AZD-8797 reduced axonal damage and macrophage activation, as assessed using anti-PGP9.5 and anti-ED-1 antibodies, respectively. AZD-8797 also reduced inflammation (hematoxylin staining) and demyelination (Luxol fast blue/Pas staining). Oral or subcutaneous administration of AZD-8797 to rats produced minimal central nervous system (CNS) drug exposure, and it was postulated that AZD-8797 exerts its therapeutic effect by reducing the migration of CX_3CR1-expressing cells into the CNS.

NSI-15370, a positive modulator of neuronal voltage-gated potassium channels

Positive modulators of voltage-gated potassium K_V7 channels, for example, the anticonvulsant retigabine (Potiga™), have been used for the treatment of refractory partial-onset epilepsy and pain disorders. Studies to characterize the pharmacological profile of a novel positive modulator of K_V7 channels, NSI-15370, were discussed by Helle Erichsen (NeuroSearch). The synthesis of NSI-15370 resulted in an 84% yield of the hydrochloride salt, although it may also be produced as the free base. In vitro absorption, distribution, metabolism and excretion (ADME) and toxicology profiling demonstrated that NSI-15370 is 98-99% protein-bound and is a substrate for the cytochrome P450 isozymes 1A2, 2C19 and 3A4. NSI-15370 (1 μM at 1 hour) displayed stabilities of 68%, 32%, 6% and 33%, respectively, in human, mini-pig, rat and mouse microsomes. Using a fluorescent imaging plate reader assay and cloned channels, NSI-15370 was demonstrated to be a more potent inhibitor of all neuronal K_V7 channel subtypes ($K_V7.2$-7.5) relative to retigabine; for example, the EC_{50} value for NSI-15370 against $K_V7.2$ + 7.3 channel subunits was 0.13 μM versus 1.3 μM for retigabine. Patch clamp electrophysiology revealed that activation of K_V7 channels occurred at lower concentrations of NSI-15370 than retigabine. With regard to selectivity toward other ion channels, NSI-15370 (10 μM) exhibited 34% inhibition of hERG channel activity in HEK-293 cells, and activation of $GABA_A$ receptor subtypes in *Xenopus laevis* oocytes was not observed at concentrations of up to 30 μM. In dorsal root ganglion neurons, NSI-15370 inhibited voltage-gated sodium, calcium and potassium channels by 30%, 30% and 60%, respectively. Further in vitro characterization in acute rat brain slices demonstrated that NSI-15370 inhibited action potential firing in hippocampal CA1 pyramidal neurons. In mouse models of seizures induced by either electrical (6 Hz) or chemical (pentylenetetrazol) stimulation, as well as in a rat model of amygdala kindling, NSI-15370 (1-100 mg/kg) produced dose-dependent anticonvulsant activity. NSI-15370 was also tested in mice with hyperactivity induced by treatment with dizocilpine or chlordiazepoxide plus D-amphetamine. In both models, NSI-15370 reduced hyperactivity at dose levels that had minimal effects on normal behavior. These data indicated that, in addition to anticonvulsant properties, NSI-15370 was associated with antipsychotic and antimanic effects.

The novel, non-stimulant small-molecule monoamine uptake inhibitor EB-1020

The in vitro and in vivo features of EB-1020, a monoamine uptake inhibitor with greater effects on norepinephrine than dopamine uptake, were detailed by Frank Bymaster (Euthymics Bioscience). In vitro, EB-1020 inhibited norepinephrine, dopamine and serotonin

uptake with IC_{50} values of 6, 38 and 83 nM, respectively, compared with respective values of 1.9, 1600 and 750 nM for atomoxetine (Strattera®), 1400, 570 and 1900 nM for bupropion, and 170, 360 and 27,000 nM for methylphenidate (Ritalin®), a mild CNS stimulant approved for the treatment of attention deficit hyperactivity disorder (ADHD). Using a microdialysis technique, it was demonstrated that EB-1020 (10 mg/kg) administered intraperitoneally (i.p.) enhanced extracellular concentrations of norepinephrine, dopamine and serotonin in rat prefrontal cortex, with the greatest increase observed in norepinephrine levels. Dopamine levels in rat striatum were also increased by EB-1020 treatment. Because depression is often associated with ADHD, the effects of EB-1020 (10-40 mg/kg p.o.) were evaluated in a tail suspension test in mice. EB-1020 dose-dependently reduced immobility at a dose of 20 mg/kg, producing reductions from 30 minutes to 4 hours post-administration ($P < 0.05$ compared with vehicle control). To assess the potential for abuse of EB-1020, induction of locomotor hyperactivity or stereotypical behaviors was determined in comparison with D-amphetamine. At a dose of 30 mg/kg, EB-1020 was approximately 25% as active as D-amphetamine, and within the therapeutically active dose range of 3-10 mg/kg, EB-1020 was not associated with hyperactivity or stereotypic behavior. The potential efficacy of EB-1020 was evaluated in juvenile rats with hyperactivity caused by 6-hydroxydopamine forebrain lesions, a validated model of ADHD. EB-1020 (1, 3 and 10 mg/kg i.p.) displayed dose-dependent inhibition of locomotor activity. Reduced locomotor activity was observed from 5 to 20 and 35 to 90 minutes with the dose of 10 mg/kg ($P < 0.05$ compared with vehicle). Furthermore, in the same animal model, doses of 1-10 mg/kg of EB-1020 produced a level of efficacy that was equal to that of methylphenidate.

NKTR-192, an opioid analgesic with slow brain uptake and low abuse liability

Stephen Harrison (Nektar Therapeutics) presented data on the orally active μ opioid receptor agonist NKTR-192. Receptor binding and functional assays demonstrated that NKTR-192 binds selectively to human μ opioid receptors, with maximal inhibition of forskolin-induced cAMP formation in intact CHO cells. In a mouse acetic acid-induced writhing model, writhing responses were attenuated by NKTR-192 with an ED_{50} value of 13 mg/kg compared with 4 mg/kg for the approved opiate painkiller oxycodone. Using the same model, pretreatment of mice with an opioid receptor antagonist (20 mg/kg of naloxone methiodide or 3 mg/kg of naloxone) reversed the analgesic effects of NKTR-192 (100 mg/kg p.o.); these data indicated that NKTR-192 modulates both peripheral and central signaling pathways. In rats with inflammatory pain induced by intraplantar injection of complete Freund's adjuvant into the hind paw, NKTR-192 (300 mg/kg p.o.) increased the paw compression threshold at 45, 90 and 120 minutes post-dose ($P < 0.001$ versus baseline). In situ brain perfusion indicated that the rate of brain uptake of NKTR-192, a factor that is considered to be related to the abuse liability of opioid-targeted drugs, was lower than that of fentanyl, oxycodone and hydrocodone, suggesting that NKTR-192 has lower abuse potential than these three drugs. These data were in accordance with self-administration studies in cocaine-trained rats; intravenous NKTR-192 was associated with a lower response rate than intravenous oxycodone. Rat rotarod experiments suggested that administration of therapeutic doses of NKTR-192 (1-300 mg/kg p.o.) did not result in CNS side effects such as sedation.

PART III

Up-and-coming neuroprotective agents

Preclinical data relating to BB-3 (Angion Biomedica), a synthetic hepatocyte growth factor mimetic, were presented by R.E. Chaparro from Duke University. The ability of BB-3 to improve outcome after either permanent or temporary middle cerebral artery occlusion (pMCAO and tMCAO, respectively) was assessed using several rat models. In the pMCAO experiment, a daily dose of 3 mg/kg i.p. of BB-3 was found to improve rat neurological function. On a 48-point neurological scale, rats treated with vehicle scored an average of 13, while those receiving BB-3 had an average of 10. No physiological changes (i.e., infarct size) were observed in either group. In the tMCAO experiment, a daily dose of 6 mg/kg of BB-3 produced both physiological and neurological improvement. The average infarct volume size was 190 and 120 mm^3, respectively, with vehicle- and BB-3-treated rats; neurological scores were 12 and 7, respectively. BB-3 treatment also increased synaptophysin immunoreactivity over time. In both experimental conditions, a treatment delay of 6 hours was observed, but after 28 days a better outcome was seen in the BB-3-treated groups. No increases in brain temperature, systemic physiology or other possible factors that could produce a neuroprotective effect were seen; therefore, the positive effects were deemed to be due to BB-3 treatment. Dr. Chaparro's group began another preclinical study evaluating the efficacy of BB-3 in male and female rats subjected to tMCAO. Preliminary analyses from this study indicated that BB-3 has similar efficacy in both sexes.

Lili Zhang of Merck presented data on SCH-900229 (presumed to be GSI-1), a presenilin-1 (PS-1)-selective γ-secretase inhibitor, covering the safety profile of the compound and its performance in several models of Alzheimer's disease (AD). SCH-900229 had a membrane β-amyloid (Aβ) IC_{50} value of 1.3 nM and a cell Notch Aβ IC_{50} value of 46 nM. It showed no cytochrome P450 or pregnane X receptor issues. The compound displayed high selectivity for reconstituted PS-1 and PS-2 γ-secretase complexes in vitro, and was non-selective for amyloid precursor protein and Notch processing. In a rodent efficacy model, SCH-900229 had an acute dose–response in both rats and TgCRND8 mice. SCH-900229 had EC_{50} values of 0.03 and 0.06 μM and ED_{50} values of 0.5 and 0.4 mg/kg, respectively, against plasma and cortical Aβ. In rats, SCH-900229 had EC_{50} values of 0.04, 0.09 and 0.02 and ED_{50} values of 1.10, 0.30 and 3.70 mg/kg, respectively, against plasma, cerebrospinal fluid (CSF) and cortical Aβ. SCH-900229 appeared to have similar potency in the different compartments of the brain and very low plasma exposure was needed for a meaningful reduction in Aβ. In a 5-day study in TgCRND8 mice, oral SCH-900229 up to 100 mg/kg did not cause gastrointestinal (GI) toxicity, but Aβ reduction was still substantial. There was also no indication of thymus atrophy in treated mice, which suggests that there was no Notch inhibition. A toxicity study in dogs showed no evidence of thymus atrophy; however, SCH-900229 caused GI toxicity. At SCH-900229 doses that produced significant Aβ reduction, the compound was well tolerated in dogs.

The peripheral safety of KMX-010

Heath Crosby from Oklahoma State University outlined his team's work on a preclinical study of KMX-010, a glutaminase inhibitor. The aim of the study was to assess the effect of KMX-010, a compound

that has its action intracellularly, on the cell viability of rat skin fibroblast cells, in peripheral non-neuronal cells, and also the effect on the mitochondria of these cells. The cells were incubated with KMX-010, ranging in concentrations from 0.0002 to 500 μM for 6 hours, after which annexin levels were measured; annexin is an early apoptotic biomarker and would give an indication of changes in cell viability. No significant effect on annexin was observed and flow cytometry data identified no evidence of apoptosis (0% identified) in fibroblasts or in mitochondria. In rat fibroblasts, the EC_{50} of KMX-010 was found to be 232 μM, but this was not of concern, as the therapeutic concentration of KMX-010 was only 2 μM. These data suggested that KMX-010 had no effect on skin fibroblast cell viability, apoptosis or mitochondrial health over a large range of concentrations. Cell viability in peripheral cells would not be an issue. The next area investigated was the phases of the cell cycle. Incubated cells were allowed to reach log phase growth and each phase was observed for any irregularities compared to untreated cells. Cell phases G_1 and G_2 were completely unaffected by incubation, but a minor effect was seen during the S phase. This was seen as an artefact, as the cells were again behaving normally after 48 hours. The group planned to run safety and pharmacokinetic studies in other animal models, and were anticipating a small business innovation research grant in the near future.

Could PH-084 address a range of convulsive indications?

The evaluation of PH-084, a neuroactive oxazolidinone, for anticonvulsant activity in vitro was described by Samuel Kombian from Kuwait University. PH-084's influence on excitatory postsynaptic currents (EPSCs), action potentials and seizures, induced by both chemical and electrical means, was investigated. PH-084 was found to decrease excitatory synaptic transmission in the nucleus accumbens and hippocampus. This effect was concentration-dependent. A PH-084 concentration of 10 μM was found to reduce EPSC by 25.4%. Also, at 10 μM, PH-084 depressed isolated NMDA receptor-mediated synaptic responses by an average of 50%. In the hippocampus, action potential firing was suppressed by 10 μM levels of PH-084, with action potentials becoming 42.2% less frequent. The same concentration of PH-084 depressed magnesium-induced multiple spiking and spontaneous bursting. Population spikes were reduced by 47.5%. Interestingly, a high concentration of PH-084 did not cease the development of spikes and spontaneous bursts caused by zero magnesium, nor did pretreatment of hippocampal slices with PH-084. PH-084 also failed to influence stimulus train-induced bursts caused by high-frequency electrical stimulation of excitatory afferents. The group concluded that while PH-084 had potential as an anticonvulsant therapy for seizures with a chemical cause, it would not be suitable for seizures caused by electrical imbalances or as a treatment for epilepsy.

PART IV

Optimization of AC Immune's small-molecule inhibitors of $A\beta_{1-42}$ aggregation for AD

Data on a series of racemic compounds that inhibit the aggregation of $A\beta_{1-42}$ were disclosed by a representative of the Swiss-based biopharmaceutical company AC Immune during the 2010 SFN meeting. At this year's meeting, Andreas Muhs from the company discussed further optimization of this program; specifically, characterization of the individual enantiomers of one of these small molecules. The enantiomers, referred to as compound 1 and compound 2, were separated by chiral HPLC. In an in vitro thioflavin T (ThT) assay to assess the capacity of the two compounds to block $A\beta_{1-42}$ aggregation, compound 2 displayed greater potency than compound 1. The inhibitory effect of compound 2 on $A\beta_{1-42}$ aggregation was subsequently verified by density separation and oligomer-specific ELISA. Administration of compound 2 (2 mg/kg i.v. or 10 mg/kg p.o.) to rodents revealed that levels of brain exposure to the enantiomer were good and not significantly different from those achieved with the racemic compound. The potential therapeutic efficacy of compound 2 (10 mg/kg p.o. for 4 weeks) was investigated in transgenic mice expressing amyloid precursor protein, a model of amyloid pathology in AD. Immunohistochemistry using the Aβ-specific antibody 6E10 demonstrated that compound 2 reduced levels of Aβ in both the cortex and hippocampus ($P < 0.05$ and 0.06 compared with vehicle). Short-term memory was enhanced by compound 2 relative to vehicle, as assessed by duration ($P < 0.01$) and frequency ($P < 0.05$) in a space object recognition test. Assessment in the Morris water maze revealed that compound 2 treatment was associated with a trend towards improvement in the learning phase of the test. Dr. Muhs stated that ongoing toxicology studies of compound 2 were generally promising; however, this compound (10 μM) displayed a small interaction with the hERG channel. In addition, it was revealed that compound 1 had a greater interaction with the hERG channel than compound 2. Telemetry in dogs was being used to further assess the cardiac safety of compound 2.

SUN-13837: a small molecule with bFGF-like neuroprotective properties for SCI

Shinya Ueno (Asubio Pharmaceuticals) summarized the biochemical effects of SUN-13837 (1 mg/kg for 10 days) in rats with spinal cord injury (SCI); SUN-13837 was administered from 90 minutes post-injury and animals were sacrificed 24 hours after the last dose. Compared with vehicle, SUN-13837 led to an increase in spinal cord levels of the neuroprotective compounds nicotinamide ($P = 0.009$), flavin adenine dinucleotide ($P = 0.028$) and *S*-adenosylhomocysteine ($P = 0.036$). Furthermore, levels of the neurotoxic factors heme ($P = 0.02$), isovalerylcarnitine ($P = 0.09$), hydroxyisovalerylcarnitine ($P = 0.08$) and 3,4-hydroxyphenyl acetate ($P = 0.007$) were reduced by treatment with SUN-13837 relative to vehicle. SUN-13837 also modulated neurotransmitter levels, with a 1.09- and a 1.20-fold increase in glutamate levels in the spinal cord and CSF, respectively. Changes in GABA levels could not be measured in the CSF, possibly because of rapid neurotransmitter degradation, but a 1.12-fold increase was detected in GABA levels in spinal cord tissue. The neuroprotective and neurotoxic factors that were identified in this study may be of use as biomarkers of the therapeutic response to SUN-13837 in acute SCI.

Functional recovery was assessed by Shiro Imagama (Nagoya University) using the Basso-Beattie-Bresnahan scale following administration of either SUN-13837 (1 mg/kg i.v. once daily for 10 days) or vehicle to rats with SCI at 90 minutes or 12 hours post-injury. The therapeutic time window of SUN-13837 was considered to be 12 hours because motor function was enhanced by treatment at either

time point. However, when administered at 90 minutes post-injury, the benefit of SUN-13837 was evident at 1-2 weeks ($P < 0.01$) and sustained until the end of the study at week 8 ($P < 0.05$); in contrast, improvement in motor function was only observed from week 5 onwards ($P < 0.01$) when the drug was administered at 12 hours post-injury. Evaluation of the molecular correlates of SUN-13837 treatment revealed that in rat cortical neurons, SUN-13837 and basic fibroblast growth factor (bFGF) augmented tyrosine phosphorylation of fibroblast growth factor receptor 1 (FGFR-1). While exposure to bFGF was associated with cell proliferation, as indicated by upregulation of cyclin D1 and downregulation of p27Kip1, SUN-13837 did cause cell proliferation or affect these markers.

Preclinical studies reveal molecular target of Sonexa's ST-101

ST-101 (Sonexa Therapeutics) is currently being evaluated in a phase II clinical trial in patients with essential tremor, and a phase II trial of the drug in patients with AD has been completed. Y. Yamamoto from Tohoku University presented preclinical data on molecular changes related to the procognitive effects of ST-101. Previous experiments demonstrated that depressive behavior in olfactory bulbectomized (OBX) mice was ameliorated by chronic treatment with ST-101 (0.5-1 mg/kg), and this effect correlated with neurogenesis in the dentate gyrus. In the present study, acute administration of ST-101 (1 mg/kg i.p.) produced a 50% increase in ACh release in the hippocampus of OBX mice, as assessed using microdialysis. Acute administration of ST-101 to OBX mice demonstrated that memory-related behaviors were improved, but hyperlocomotion and depressive behavior were not altered. At 1 hour post-ST-101 treatment, levels of calcium/calmodulin-dependent protein kinase II (CaMK-II) autophosphorylation, which are normally substantially reduced in the hippocampus of OBX mice, were elevated. In addition, ST-101 stimulated protein kinase C (PKC) and extracellular signal-regulated kinase (ERK) signaling in the hippocampal CA1 region of OBX mice. Because CaMK-II activity is associated with ACh release, it was concluded that the improved memory of ST-101-treated OBX mice, and of patients with AD treated with drug, was primarily mediated by enhanced ACh release and CaMK-II activation.

DISCLOSURES

The authors state no conflicts of interest.

The website for this meeting can be found at http://www.sfn.org/AM2011.