
Alexander Scriabine

Department of Pharmacology, Yale University Medical School, New Haven, CT, USA

The 28th annual meeting of the Society for Neuroscience was held from November 7 through 12, 1998 in Los Angeles, CA. The meeting was attended by over 24,000 participants. It consisted of 12 symposia, 14 special lectures, 117 slide sessions (10 to 15 presentations each) and ~14,000 posters. This report summarizes only those posters that were devoted to new drugs affecting the central nervous system (CNS).

ANTIDEMENTIA DRUGS

M. Yamazaki et al. (Fujisawa Pharm. Co, Tsukuba, Ibaraki, Japan) presented four posters on their new antidementia drug, FK 960 (N-[41-piperazinyl]-p-fluorobenzamide monohydrate). FK 960, at 0.1 to 10 mg/kg i.p., ameliorated memory deficits in scopolamine-treated rats and in animals with nucleus basalis lesions. It restored memory in old rats, in which physostigmine was ineffective. It also antagonized scopolamine effects in Rhesus monkeys. Its mechanism of action appears to involve stimulation of somatostatinergic neurotransmission. In the mossy fiber-CA3 pathway of guinea pig hippocampal slices, FK 960 augmented the development of long-term potentiation (LTP) after tetanus. In old rats, FK 960 increased the density of axosomatic synapses in the pyramidal cell layer of hippocampal CA3 region and the density of symmetrical synapses in the stratum pyramidalis.

P. Teismann and B. Ferger (Univ. Marburg, Germany) described microdialysis experiments in rats with KA-672 HCl (7-methoxy-6-[3-4-(methoxyphenyl)piperazin-1-yl]propoxy]-3,4-dimethyl-2H-1-benzopyran-2-one hydrochloride). This drug was reported to modulate dopaminergic and serotonergic neurotransmission. At 0.1 to 1.0 mg/kg i.p. KA-672 was found to increase serotonin turnover in the striatum of rats. DOPAC levels in dialysate were significantly increased. The authors suggested that KA-672 could be useful in the treatment of patients with Alzheimer’s disease.

E. Menzaghi et al. (SIBIA Neurosciences, Inc., La Jolla, CA in cooperation with scientists from Med. Coll. of Georgia and Thomas Jefferson Univ., Philadelphia, PA) presented two posters on SIB-1553A (Fig. 1), a subtype-selective (for β2 subtype) nicotinic agonist. SIB-1553A was previously shown to stimulate the release of acetylcholine, do-
pamine, and norepinephrine in the hippocampus and parietal cortex of rats. The drug was now shown to be more effective than nicotine in reversing deficits in working and reference memory and more effective than donepezil in improving memory in scopolamine treated mice, aging mice and Rhesus monkeys. In MPTP-treated monkey, SB-1553A improved performance in short delay trials indicating preferential effect on attentional function.

R. L. Papke et al. (Univ. Florida Coll. Med., Gainsville, FL, in cooperation with scientists from R. J. Reynolds Tobacco Co., Winston-Salem, NC) reported that RJR 2403 ([E]-metanicotine monofumarate) is, as a nicotinic agonist, selective for $\alpha_4\beta_2$ subtype of human nicotinic receptors. This selectivity suggests less propensity for side effects. Nicotine is not subtype selective. Reynolds Tobacco Co. is developing two other nicotine analogs, RJ-1734 and RJ 2557, that affect preferentially nicotinic receptors in the central (as compared to peripheral) nervous system.

T. Nishizaki et al. (Kobe Univ. School of Med., Kobe, Japan) demonstrated that nefiracetam, a known nootropic agent, acts as a nicotinic agonist. It facilitates synaptic transmission at presynaptic neuronal nicotinic receptors ($\alpha_4\beta_2$ and $\alpha_7$) in rat hippocampal slices. The authors attributed the cognition-activating action of nefiracetam to its nicotinic agonist effect.

M. S. Glasky et al. (NeoTherapeutics, Inc., Irvine, CA; McMaster Univ., Hamilton, Ont., Univ. Saskatchewan, SK, Canada; Univ. Chieti, Italy; and Davidson Coll., NC) presented 6 posters on AIT-082 (4-[(3-(1,6-dihydro-6-oxo-9-purin-9-yl)-1-oxopropyl)amino]benzoic acid). In cultured neurons and astrocytes AIT-082, at concentrations $\geq 100 \mu M$, increased intracellular concentrations of cAMP and stimulated the synthesis of neurotrophic factors including NGF, TGF$_{\beta}$, and S100$. In vivo$, in rats AIT-082 protected $\gamma$-aminobutyric acid (GABA) neurons in the caudate nucleus from $N$-methyl-D-aspartate (NMDA)-induced death. AIT-082 is thought to modulate NGF mRNA levels. In mouse hippocampal neurons, AIT-082 1 $\mu M$ promoted neurite recovery after glutamate-induced damage; it increased axonal length and branching. It improved working memory in young mice, as well as in aging mice with mild memory deficits and antagonized amnesia produced by L-NAME, MK-801 or scopolamine. In the denervated ventral dentate gyrus of rats with unilateral entorhinal cortex lesions, AIT-082 promoted cholinergic sprouting.

J. A. Kozlowski et al. (Schering-Plough Res. Inst., Kenilworth, NJ) reported the discovery of SCH-57790 (4-cyclohexyl-$\alpha$-4-{4-methoxyphenyl}sulfinylphenyl-1-piperazineacetoniitrile), a selective antagonist at $M_2$ receptors. The stereochemistry of sulfur had a strong influence on the receptor selectivity. The (S) sulfoxide isomer had a $K_\text{i} = 3 \text{nM}$ for $M_2$ receptors and 40-fold selectivity for $M_2$ vs. $M_1$ receptors. At 3 to 100 mg/kg p.o. SCH-57790 increased acetylcholine (ACh) release from the striatum for $> 3 \text{ h}$. At doses as low as 0.1 mg/kg p.o. the brain concentrations of the drug exceeded 10 ng/g tissue in 30 min. SCH 57790 antagonized inhibition of adenyl cyclase by oxotremorine. It enhanced memory in juvenile rats at doses as low as 0.01 mg/kg p.o.

**NEUROPROTECTIVE DRUGS**

X.-C. M. Lu et al. (Guilford Pharmaceuticals Inc., Baltimore, MD) reported that $N$-acetyl-aspartyl glutamate (NAAG), at 1 or 2 (but not 4) $\mu M$ by intracerebral injection
at 15 min before occlusion of middle cerebral artery (MCAO), reduced infarct size in rats. These findings suggest that inhibition of carboxypeptidase G2 may be neuroprotective by virtue of increasing brain levels of NAAG and may represent a new approach to the therapy of stroke.

**J. A. Monn et al.** (Eli Lilly and Co., Indianapolis and Greenfield, IN; Windelsham, Surrey, UK, in collaboration with scientists from Univ. Glasgow and Univ. Bristol, UK) presented eight posters on the neuroprotective activity of LY 379268 (1R,4R,5S,6R-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate). LY 379268 is a highly selective group-II mGlu-receptor agonist. Its $K_i$ for binding to mGlu$_2$-receptor subtype was 16 nM. It protected rat cortical cells in culture from NMDA- or kainate-induced neurotoxicity and reduced lactate dehydrogenase (LDH) release. It enhanced the responses of rat spinal neurons in vivo to NMDA or AMPA. At 0.1 to 10 mg/kg i.v., LY 379268 elevated glucose metabolism in auditory regions, superficial gray layer of the superior colliculus, and the molecular layer of hippocampus. At 3 to 30 mg/kg i.v., LY 379268 antagonized kainate-induced limbic seizures in rats. In gerbils subjected to the occlusion of both common carotid arteries, LY 379268 10 mg/kg i.p. given at 30, 60, or 120 min after occlusion reduced brain damage. At 3 mg/kg i.p. it reduced the development of carrageenan-induced hyperalgesia and had analgesic activity in the formalin test in rats.

According to **V. Bruno et al.** (I. M. N. Neuromed., Pozzilli, Italy; Lilly Res. Centre, Windlesham, UK, and Univ. Catania, Italy) group-I metabotropic receptor antagonists LY 367385 ([+]2-methyl-4-carboxyphenylglycine)and LY 367366 ([+]α-thioxantylmethyl-4-carboxyphenylglycine) had neuroprotective activity in various in vitro and in vivo models. LY 367385 is a selective mGlu1a antagonist, while LY 367366 is an antagonist also at mGlu$_4$ receptors. As a neuroprotective agent, LY 367385 is more effective than LY 367366. The authors suggested that mGlu1 receptors mediate excitotoxicity.

**Y. Rong et al.** (Univ. Southern CA, Los Angeles, CA, and Eukarion Inc., Bedford, MA) reported that EUK-134 (a salen manganese complex), a synthetic SOD/catalase mimic, at 10 mg/kg s.c., antagonized the neurotoxic effects of kainate on the limbic structures of rats. The authors concluded that neurotoxic effects of kainate are partially mediated by oxygen radicals.

**K. Shin-ya et al.** (Univ. Tokyo, Japan) described the neuroprotective effect of kaitocephalin (Fig. 1), a fungal metabolite. It protected rat hippocampal neurons in culture from NMDA-induced neurotoxicity with an EC$_{50}$ of 12 µM and blocked AMPA- but not kainate-induced Ca$^{2+}$ influx. It binds to NMDA receptors with a $K_i$ value of 8.4 nM.

**J. B. Phillips et al.** (Walter Reed Army Res. Inst., Washington, DC, and Proscript, Inc., Cambridge, MA) found that a novel proteasome inhibitor, PS-519, at 0.1 or 0.3 mg/kg i.v. given after occlusion, reduced infarct volume and improved neurological function in rats subjected to middle cerebral artery occlusion and reperfusion. The authors speculated that inhibition of the proteasome-ubiquitin pathway leads to inhibition of the transcription factor NF-kB and reaction to the injury. The chemical nature of PS-519 was not disclosed.

**C.-H. Park et al.** (Seoul Nat. Univ., Korea) reported neuroprotective effects of dehydroevodiamine HCl (DHED, Fig. 1), isolated from *Evodia rutaecarpa*. At 6.25 mg/kg i.p. once a day for 7 d, DHED reduced neuronal injury in rats with unilateral electrolytic entorhinal lesions or MCAO-induced infarcts. It also reversed cognitive impairment in a passive-avoidance test. DHED was previously reported to have anticholinesterase and anti-amnesic effects.
Y. Kagamihi et al. (ONO Pharmaceutical Co., Osaka, Japan) described in three posters the neuroprotective effects of ONO-2506, an astrocyte modulating agent. In 4-vessel occlusion (4-VO) and MCAO rat models of neuronal injury, ONO-2506 reduced injury and suppressed S-100 protein-induced astroglial activation. It also suppressed the expression of cyclooxygenase-2 (COX-2) and inducible NO synthase (iNOS) in the ischemic region. The expression of specific glutamate transporter (GLT-1) was reduced in focal ischemia; this reduction was antagonized by ONO-2506. The chemical nature of ONO-2506 was not disclosed.
J. W. B. Marshall et al. (Univ. Cambridge, UK, and Astra-Arcus, USA and Sweden) reported functional beneficial effects with clomethiazole (Fig. 1, ZENDRA) in a primate model of stroke (common marmosets with MCAO). Clomethiazole was administered as a bolus (40 mg/kg i.p.) followed by a slow infusion of the drug through an osmotic mini-pump for 1 d (~70 mg) to six animals, six others served as controls. In another study, clomethiazole reduced functional disability and brain damage.

M. Farooque et al. (Uppsala Univ., Sweden) found that clomethiazole (Fig. 1) 150 mg/kg i.p. had a neuroprotective effect in rats subjected to spinal cord compression injury. The first favorable results with clomethiazole in patients with stroke were recently reported (Wahlgren NG. Stroke 1998;29:287).

D. B. DeFranco et al. (Univ. Pittsburgh, PA) discovered that geldanamycin (GA; benzoquinoid ansamycin) prevents glutamate-induced neurotoxicity in the HT22 mouse hippocampal cell line and improved neurological outcome in rats subjected to asphyxia-induced cardiac arrest. GA binds to and disrupts the activity of heat-shock protein, hsp90. The authors suggested that GA works by disrupting the signaling pathway in neuronal cells that utilize hsp90 in apoptosis.

J. R. Dave et al. (Walter Reed Army Research Inst, Washington, DC, and Roche Biosciences, Palo Alto, CA) reported that a lipophilic use-dependent Na+ channel blocker, RS-100642 (Fig. 1), had neuroprotective activity in hypoxia/hypoglycemia-induced injury of primary rat cerebellar neurons (EC50 = 61 μM). It was even more potent against veratridine-induced neuronal injury (EC50 = 6 μM), but ineffective against glutamate-induced neuronal damage.

H.-C. Kim et al. (Kangwon National Univ., Chunchon, Korea) reported that aspalatone (APT; acetylsalicylic acid maltol ester; 3-[2-methyl-4-pyronyl]-2-acetoxybenzoate) 24 mg/kg p.o. twice a day for 2 d, protected rats from kainate-induced convulsions and death, while aspirin, 15 mg/kg p.o. twice a day for 2 d, enhanced kainate neurotoxicity. Both drugs given together had no effect. APT had antiplatelet and antithrombotic activities with minimal gastrointestinal side effects. The authors attributed the neuroprotective effect of APT to salicylmantol, a metabolite of APT, that is likely to act as an antioxidant.

S. Lautar et al. (Guilford Pharmaceuticals, Inc., Johns Hopkins Univ. School of Medicine, Baltimore, MD, and Uniform. Service Univ., Bethesda, MD) reported that GPI 6150, an inhibitor of poly(ADP-ribose)polymerase (PARP), reduced infarct volume in rat transient middle cerebral artery occlusion model. The accumulation of poly(ADP-ribose) in the ischemic region was also reduced by the drug. The authors suggested that PARP activation contributes to the neural damage during stroke.

C. G. Parsons et al. (Merz & Co., Frankfurt/Main, Germany) reported at the pharmacology of MRZ 2/579 (1-amino-1,3,3,5,5-pentamethyl-cyclohexane), a non-competitive NMDA antagonist. The kinetics and potency of MRZ 2/579 in blocking the NMDA-induced current in hippocampal rat embryonic neurons were similar to those of memantine; the peak IC50 was 1.2 μM. The binding sites of the two drugs at the NMDA receptor are likely to differ: memantine, but not MRZ 2/579, binds to an extracellular binding site. Either of the two drugs blocks voltage-dependent Ca2+ channels at very high concentrations (1 mM). Like memantine, MRZ 2/579 has a promising therapeutic profile in animal models of stroke, epilepsy, chronic pain, and alcohol or morphine dependence. In another poster from the same laboratory, Frankiewicz and Parsons compared the pharmacological properties of memantine and dizocilpine (MK-801). Memantine, but not dizocilpine, re-
stored LTP impaired by low Mg\(^{2+}\). In chronic degenerative diseases memantine is likely to be beneficial, while dizocilpine can be expected to have negative effects only.

**K. Othani et al.** (Sumitomo Pharmaceutical Co., Osaka, Japan) studied pharmacological properties of SM-18400 ([S]-9-chloro-5-\{p-aminomethyl-o-{carboxymethoxy}phenyl-carbamoylmethyl\}-6,7-dihydro-1H,5H-pyrind[1,2,3-de]quinazoline]-2,3-dione hydrochloride trihydrate), an NMDA-glycine site antagonist. The binding K\(_d\) to rat cortical or hippocampal membranes was 0.43 nM. SM-1800 inhibited the NMDA receptor-mediated polysynaptic reflex in the isolated spinal cord of neonatal rats with an IC\(_{50}\) of 2.2 nM and NMDA-mediated increase in Ca\(^{2+}\) in cultured primary rat cortical neurons with IC\(_{50}\) of 33 nM. These effects were antagonized by D-serine or glycine. SM-1800 could be of therapeutic value in the treatment of brain ischemia.

**T. H. Iohansen et al.** (NeuroSearch A/S, Glostrup, Denmark) presented SPD 502 (8-methyl-5-\{4-{N,N-dimethysulfamoyl}phenyl\}-6,7,8,9-tetrahydro-1H-pyrrolo[3,2h]isoquinoline-2,3-dione-3-O-\{4-hydroxybutyric acid-2-yl\}oxime), a novel competitive AMPA-receptor antagonist. It inhibited AMPA-binding with an IC\(_{50}\) of 43 nM, but had no affinity for kainate or glycine binding sites. In cultured mouse cortical neurons SPD 502 inhibited AMPA with an IC\(_{50}\) of 0.14 \(\mu\)M. *In vivo*, SPD 502, by microiontophoretic administration to rat hippocampus, inhibited AMPA-induced single neuron spike activity. SPD 502 is expected to have neuroprotective activity.

According to **W. Maruyama et al.** (Natl. Inst. Longevity Sci., Obu, Japan; Inst. Appl. Biochem., Gifu, Japan, and Natl. Parkinson’s Found., Haifa, Israel), rasagiline, at 10 nM, protected human dopaminergic neuroblastoma cells (SH-SY5Y) from peroxynitrite-induced apoptosis. Rasagiline was effective only if added 20 min before (but not after, or simultaneously with) peroxynitrite donor, SIN-1. The mechanism of protection is under further investigation.

### COGNITION-ACTIVATING AGENTS

**P. Lestage et al.** (Servier Research Inst., Croissy-sur-Seine, France) described in three posters cognitive-activating effects of S 18986-1, a positive modulator of AMPA-type glutamate receptors. At 30 to 300 \(\mu\)M S 18986-1 enhanced AMPA-induced norepinephrine release in rat hippocampal slices. In rats, in object recognition task, S 18986-1 0.3 to 30 mg/kg i.p. reduced scopolamine-induced amnesia and at 0.1 to 10 mg/kg p.o. prolonged memory retention in young rats. It had no significant effect on forebrain ischemia in rats subjected to 4-vessel occlusion. The drug had no neurotoxic effects either *in vitro* at concentrations \(\leq 100 \mu\)M or *in vivo* by chronic administration to rats at 30 mg/kg/d i.p. for 14 d.

**C. Siwak et al.** (Univ. Toronto, Canada, and Vetoquinol Research Center, Lure, France) reported that adrafinil at 20 mg/kg/d for 14 d increased locomotion and exploratory behavior and accelerated acquisition of learning tasks in dogs. The effects were attributed to central adrenergic activation induced by adrafinil or its metabolite modafinil.

**E. Hori et al.** (Toyama Univ., Japan) found that NC-1900, (an arginine vasopressin derivative) normalized place-learning deficits in rats with CA1 hippocampal lesions.
NC-1900 was previously reported to enhance memory in behavioral avoidance tests, to inhibit the Cl⁻ current and to enhance neuronal activity in vitro.

According to A. M. Marighetto et al. (Univ. de Bordeaux, and Inst. Servier, Courbevoie, France) S 17092 (Fig. 1), an inhibitor of prolyl peptidase, at 10 mg/kg p.o., has in aging mice a selective cognitive enhancing effect in radial maze. The drug was previously reported to enhance memory in rodents in various other tests.

H. Sauer et al. (Guilford Pharmaceuticals, Baltimore, MD) reported that the FKBP ligand, GPI 1046 at 10 mg/kg/d for 3 w enhanced spatial memory performance in mice with age-related spatial memory impairment.

**ANTICONVULSANTS**

C. Rundfeldt and R. Netzer (Asta Medica R & D, Radebeul, Germany) reported previously that retigabine (D 23129; Fig. 2) has an anticonvulsant activity, probably due to its K⁺ channel-opening activity. The drug is currently in phase II clinical evaluation as an anticonvulsant agent. Further electrophysiological studies with this compound indicated that it is likely to open a previously unknown K⁺ channel.

A. U. R. Asghar and A. E. King (Univ. Leeds, Leeds, UK) studied the pharmacology of AR-R12495AA (Fig. 2), a major metabolite of remacemide, an anticonvulsant drug. They found that at 30 mg/kg i.p. AR-R12495AA has an antiinflammatory and analgesic effects in rats.

F. S. Menniti et al., J. T. Lazzaro, A. H. Ganong, and P. A. Seymour et al. (Pfizer Inc., Groton, CT) presented CP-465,022 (Fig. 2), a novel inhibitor of the AMPA subtype of the ionotropic glutamate receptor. At nanomolar concentrations it inhibited AMPA receptor-mediated ⁴⁵Ca²⁺ uptake in primary cultures of rat neurons. In rat cortical neurons, CP-465,022 blocked kainate-induced responses with an IC₅₀ of 30 nM. In vivo, CP-465,022 pentylenetetrazole-induced seizures in rats with an ID₅₀ of 1 mg/kg s.c. and AMPA-induced seizures in mice with an ID₅₀ of 1.5 mg/kg s.c.

**ANTIDEPRESSANTS**

O. Curet et al. (Synthelabo, Rueil-Malmaison, France) described a third-generation reversible and mixed monoamine oxidase (MAO)-A/B inhibitor, SL 65.0477 (Fig. 2). In rat brain homogenates, SL 65.047 inhibited MAO-A with an IC₅₀ of 4.2 nM and MAO-B with an IC₅₀ of 9.1 nM. In the rat brain, the drug inhibited MAO-A ex vivo with an ED₅₀ of 0.34 and MAO-B with an ED₅₀ of 0.29 mg/kg p.o. At 2 mg/kg p.o. in vivo, SL 65.0477 increased tissue levels of monoamines and decreased their deaminated metabolites in the frontal cortex and striatum; it increased the extracellular levels of dopamine (DA) 3-MT and decreased DOPAC, HVA, and 5-HIAA levels in the striatum of freely moving guinea pigs. N. Sontag et al. from the same laboratory presented data on a reversible MAO-B inhibitor, SL 34.0026-00 (Fig. 2), a tetrazoloxadiazole derivative, which selectively inhibited rat brain MAO-B with an IC₅₀ of 4.2 nM. Its ex vivo ED₅₀ for inhibition of the reversible inhibition of the same enzyme was 0.4 mg/kg p.o. At 5 mg/kg p.o., the drug...
depressed DOPAC levels in guinea pig striatum by 42% without affecting monoamines or other metabolites. SL 34.0026-00 is expected to be useful in the treatment of patients with Parkinson’s disease.

M. Spedding et al. (I. R. I. Servier Labs., Neuilly sur Seine, France) reported that the atypical antidepressant, tianeptine (Fig. 2), 10 to 50 μM, increased the amplitude of evoked population spike potentials in hippocampal slices of rats. It had no effect on ion channels. Direct modulation of hippocampal activity is likely to be responsible for its reported beneficial effects in memory models.

L. E. Rueter and P. Blier (McGill Univ., Montreal, Canada) and S. E. Gilbert Evans (Univ. Toronto, Canada) studied the pharmacological effects of the serotonin (5-HT\textsubscript{1A})-receptor agonist and 5-HT\textsubscript{2A}-receptor antagonist, flibanserin (Boehringer-Ingelheim,
At 3 to 30 mg/kg i.p., it antagonized amphetamine withdrawal-induced hypolocomotion. Flibanserin was found to increase the tonic activation of postsynaptic 5-HT$_{1A}$ receptors in limbic regions without attenuating 5-HT neuronal firing. It is suspected that flibanserin will be an antidepressant with a rapid onset of action.

C. E. Wallsten et al. (Astra Arcus AB, Sodertalje, Sweden) and S. Hjorth (Goteborg Univ., Sweden) described behavioral and microdialysis studies with NAS-181 (R-[+]-2-[3-morpholinomethyl-2H-chromen-8-yl]oxyethylmorpholine methanesulfonate), a 5-HT$_{1B}$-receptor antagonist, at doses ranging from 0.1 to 3.0 mg/kg, reduced ultrasound of rat pups separated from their dams, increased the incidence of wet dog shakes, and increased the prepulse inhibition of the startle response. In rats trained on DRL-72 schedule NAS-181 increased the number of pellets consumed and decreased the response rate. In microdialysis experiments, NAS-181 increased the efflux of 5-HT from the ventral hippocampus of rats. The authors suggested that NAS-181 may have an antidepressant activity.

ANTIPSYCHOTICS

D. J. Wustrow et al. (Parke-Davis Division of Warner-Lambert, Ann Arbor, MI) found that 4-substituted aryl piperazines have high affinity and good selectivity for dopamine$_4$ (D$_4$) receptors. They identified PD 172760 (7-[4-chloro-phenyl-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one) as the most promising candidate. Its $K_i$ for D$_4$ receptor was 4.3 nM. It was 100-fold more selective for D$_4$ than D$_2$ receptors. Its oral bioavailability was 55% and half-life 12.4 h; its brain to plasma concentration ratio was 11.5. It elevated DOPA levels in hippocampus, but not in striatum. In a second poster by L. M. Georgie et al., from the same institution, reported the results of studies in D$_4$-receptor knock-out mice in which PD 172760 had no effect on hippocampal DOPA.

ANALGESICS

O. Pozzi et al. (SmithKline Beecham Labs., Milan, Italy, and Univ. Milan, Italy) reported on the antihyperalgesic activity of a new non-peptidic delta opioid-receptor agonist, SB 235863. It was more potent than morphine in carrageenan-induced hyperalgesia in rat paw ($ED_{50} = 0.08$ mg/kg p.o.). It was less potent than morphine in abdominal constriction and tail flick tests. It caused no tolerance or withdrawal symptoms and had no effect on gastrointestinal motility or respiration. According to a second poster by S. Bingham et al. (SmithKline Beecham Labs., Harlow, Essex, UK) SB 235863 at 30 mg/kg s.c. or 100 mg/kg p.o. blocked thermal hyperalgesia in a rat model of established neuropathic pain.

K. Taniguchi et al. (Pfizer, Inc., Taiichi, Japan) evaluated CP-101,606 (Fig. 3), an antagonist of the NR2B subunit of the NMDA receptor, in carrageenan-induced hyperalgesia in rats. At 30 mg/kg s.c., the drug suppressed mechanical hyperalgesia at 0.5 or 2.5 h after carrageenan. It antagonized capsaicin or phorbol ester (PMA)-induced nociception with $ED_{50}$s of 7.5 and 5.7 mg/kg s.c., respectively. At 60 mg/kg, CP-101,606 caused no incoordination in the rotarod test.
P. Curzon et al., A. O. Koren et al., A. L. Nickel et al. (Abbott Labs., Abbott Park, IL, and National Inst. on Drug Abuse, Baltimore, MD) reported antinociceptive properties of A-85380 (3-[2\{S\}-azetidinylmethoxy]pyridine), a nicotinic agonist. It has subnanomolar affinity for nicotinic acetylcholine receptors (nAchRs) and has antinociceptive activity in rodent models of acute and persistent pain. Its antinociceptive action appears to be mediated through $\alpha_4\beta_2$ containing subtypes of nAchRs.
ANXIOLYTICS

B. Scatton et al. (Synthélabo Research, Bagneux, France) presented two posters on the antidepressant and anxiolytic effects of SL 88.0338-08 (4-[3,4-dihydro-5,8-dimethoxy-2(1H)-isoquinolinyl](methyl)-1-[3-ethoxybenzoyl]piperidine), an inverse agonist at 5-HT1A receptors. It had high affinity ($K_i = 2.6$ nM) and selectivity ($> 100$ fold) for 5-HT1A receptors. It blocked presynaptic effects of 8-OH-DOPAT (inhibition of dorsal raphe firing, reduction of brain 5-HTP levels, hypothermia in mice). It also potentiated 5-HTP-induced head twitches in mice. At 10 to 100 nM, SL 88.0338-08 antagonized 8-OH-DOPAT-induced inhibition of forskolin-stimulated cAMP production in rat hippocampus. It had anxiolytic activities in the punished drinking test and rat elevated plus-maze.

L. Cervo et al. (Mario Negri Inst., Milan, Italy, and Servier Labs., Courbevoie, France) reported that alnespirone (S20499; Fig. 3) 0.5 mg/kg s.c. selectively increased the rate of punished responses in rats. At 1 mg/kg s.c., the drug increased the rate of punished operant responses and reduced the rate of unpunished responding. Alnespirone was previously reported to have anxiolytic activity in many different models. The drug is likely to have anxiolytic activity in humans at doses having no effect on motor behavior.

R. A. McArthur et al. (Pharmacia & Upjohn, Nerviano, Italy, and Lund, Sweden) described the anxiolytic effects of 7-CI-kynurenine. The drug reduced the duration of ultrasound vocalization in rat pups separated from dams. It was effective at 275 mg/kg s.c.; at this dose, the drug produced no psychomotor side effects.

K. Kasamo et al. (Nihon Univ. School of Medicine, Tokyo, Japan) studied MKC-242 (5-[3-{([2S]-1,4-benzodioxan-2-ylmethyl)amino}propoxy]-1,3-benzodioxole HCl), a 5-HT1A agonist, for its ability to suppress spontaneous firing in the dorsal hippocampal CA1 pyramidal neurons in awake and unrestrained rats. At 0.1 to 6.0 mg/kg s.c., MKC-242 reduced firing activity; this effect was antagonized by WAY-100635, a 5-HT1A antagonist. The results supported the potential usefulness of MKC-242 in the treatment of anxiety.

M. Funada and C. Hara (Daiichi Univ., School of Pharmacy, Fukuoka, Japan) studied the effects of MKC-242 on stress-induced elevation of 5-HT levels in the amygdala of rats. At 5 mg/kg p.o., MKC-242 suppressed 5-HT release caused by psychological stress, induced by the communication box method. The authors suggested that MKC-242 may have anxiolytic or antidepressant activities.

S. Chaki et al. (Taisho Pharmaceutical Co. Ohmiya, Saitama, Japan) described two antagonists of corticotropin releasing-factor receptors (CRF1): CRA 1000 and 1001 (Fig. 3). Both compounds inhibited binding of CRF to rat cortical membranes with an $IC_{50}$s of 21 and 22 nM, respectively. CRF binding to membranes of rat pituitary cells with the expressed CRF1 (but not CRF2) receptors was also inhibited by either drug. CRF-induced ACTH secretion was inhibited by either drug in a dose-dependent manner. The authors suggested potential usefulness of CRA 1000 and CRA 1001 in the treatment of anxiety and/or depression.
ANTIPARKINSONIAN DRUGS

A. Howell et al. (Astra Arcus USA, Rochester, NY) discussed the antiparkinsonian potential of opioid delta-receptor antagonists. They studied tonazosine and its metabolite, SNC-80, in rats with unilateral 6-OH DOPA-induced forebrain lesions and rats pretreated with reserpine. Tonazosine caused only ipsilateral rotation, whereas SNC-80 caused initially ipsilateral and subsequently contralateral rotation. In reserpine-pretreated animals, tonazosine augmented the efficacy of L-DOPA.

G. Atringa et al. (Free Univ. Amsterdam, The Netherlands) evaluated SKF 83959, a D₁ antagonist in vitro, for antiparkinsonian activity in MPTP-treated monkeys. It had mild antiparkinsonian effects, but induced dystonia and dyskinesia.

DRUGS FOR OBSESSIVE-COMPULSIVE DISORDERS

G. D. Bartoszyk et al. (CNS Research, Merck KG, Darmstadt, Germany, and Lipha Research Center, Lyon, France) presented EMD 86006 (Fig. 3), a DA-receptor antagonist and a candidate for the treatment of patients with obsessive compulsive and spectrum disorders. It inhibited 5-HT uptake in mice in vitro and in vivo (ID₅₀ = 2.4 mg/kg p.o.) and antagonized p-chloroamphetamine-induced depletion of 5-HT in the hypothalamus of mice. It binds to human D₂ receptors with an IC₅₀ of 12 nM and to D₃ and D₄ receptors with an IC₅₀ of 3 nM. At 3 mg/kg p.o., this drug stimulated DOPA accumulation in rat striatum. EMD 86006 antagonized apomorphine-induced behavior in mice (ED₅₀ = 5 to 7 mg/kg p.o.).