The 7th Biennial Meeting of the European Behavioral Pharmacology Society (EBPS’98), a Joint Meeting with the Behavioral Pharmacology Society Brno, Czech Republic, September 2–6, 1998

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The EBPS’98 Meeting took place over 4 days at the Interhotel Voroněž, Brno, Czech Republic, September 2–6, 1998. The meeting attracted an international audience of over 270 participants from 25 countries. A wide range of important topics was covered and discussed in three plenary lectures, nineteen symposia, one workshop, three free communication sessions, and three poster sessions with 131 poster presentations. Abstracts of all presentations are published in a supplement of the journal *Behavioural Pharmacology* (Vol. 9, Suppl. 1). This report covers only plenary lectures and some of the symposia presented at the meeting.

PLENARY LECTURES

The introductory plenary lecture by **E. Zvartau** (Pavlov Medical Univ., St. Petersburg, Russia) sketched out the historical outlines of behavioral pharmacology in Eastern Europe and covered data and information from the Czech Republic, Bulgaria, Hungary, Poland and Russia, from the “Pavlovian era” of the 1950s and early 1960s to the present time.

**R. Mechoulam** (Hebrew Univ., Jerusalem, Israel), in his plenary lecture, described recent knowledge about the isolation of endocannabinoids and anandamides and their activating effects at CB1 receptors inhibiting adenylyl cyclase and N-type voltage-dependent Ca\(^{2+}\) channels. The discovery of endocannabinoid analogs stable for hydrolysis and exhibiting prolonged activity opens the possibility of development of endocannabinoid-type drugs which might help in mapping as-yet unrecognized anandamidergic systems in the body.

**J. Leysen** (Janssen Research Foundation, Beerse, Belgium) discussed in her plenary lecture the relationship between *in vivo* receptor occupancy by antipsychotics and their be-
behavioral effects. Research results indicate that different behavioral effects emerge with different degrees of D2 receptor occupancy, and that with different compounds, markedly different degrees of receptor occupancy produce similar effects. A partial explanation is seen in full antagonistic vs. partial agonistic or inverse agonistic actions of different compounds. However, concomitant occupation of various neurotransmitter receptors, such as serotonin (5-HT), α-adrenergic, histamine H1, and M cholinergic receptors may also be of significance.

SYMPOSIA

Because of space limitations the following presentations were selected from the symposia program. The introductory symposium of the meeting was entitled Behavioral Pharmacology in the XXI Century.

G. Koob (Scripps Research Inst., La Jolla, CA, USA) pointed out that the future of drug abuse research must include the study of the molecular and cellular basis of neurochemical and neuroanatomical adaptations at different stages of addiction. However, the development of new behavioral models for investigation of system changes, which account for vulnerability to relapse and prolong abstinence, is also of particular importance.

K. Miczek (Tufts Univ., Boston, MA, USA) discussed how behavioral pharmacology methods describing behavioral reactions to repeated salient life events, such as social defeat stress and repeated drug action, can add to understanding of molecular mechanisms, including gene expression, and are capable of delineating the relevant neural sites of drug action.

J. Barrett (Wyeth-Ayerst Research, Princeton, NJ, USA) stressed that animal models of various psychiatric disorders are useful in providing insight into both the behavioral processes that affect drug action and neurochemical mechanisms through which drugs produce their effects. For the development of new, valid, mechanism-based animal models, the information gained from the use of genetically engineered transgenic animals and techniques such as gene expression and transcriptional profiling will play a crucial role.

Finally, T. Robbins (Univ. Cambridge, UK) described recent developments in cognitive neuropharmacology and neurochemistry, including the use of scanning techniques to investigate normal and pathological brain function and its relationship to behavior.

Speakers (L. Tecott, Univ. Cambridge, UK; C. Hayser, Scripps Research Inst., La Jolla, CA, USA; C. Borelli, I.G.M.C., Strasbourg, France; R. Gainetdinov, Duke Univ., Durham, NC, USA) at the symposium entitled Behavioral and Pharmacological Studies in Transgenic Animals demonstrated that a null mutation of 5-HTT receptors causes an obesity syndrome in mice, and this receptor subtype is a target for the appetite suppressant effect of dexfenfluramine. Mutant D2-/- animals have reduced locomotion and altered coordination of movements, and it was shown that D2 receptors are involved in mechanisms of reward by different drugs of abuse. Mice with a genetic deletion of the dopamine transporter (DAT) have 5-fold elevated extracellular levels of dopamine (DA) and 300-times slower clearance of the released DA and hypersensitive postsynaptic D1 and D2 DA receptors. This hyperdopaminergic phenotype of DAT knockout mice might be a model of neuronal adaptations to long-term psychostimulant abuse.
Speakers (C. Blaha, Macquarie Univ., Sydney, Australia; J. Druhan, Univ. PA, Philadelphia, PA, USA; B. Everitt, Univ. Cambridge, UK; L. Porrino, Bowman Gray School of Medicine, Winston-Salem, NC, USA) at the symposium entitled Neuropharmacology of Conditioned Craving: Responses to Psychomotor Stimulant Drug Cues presented results suggesting that the length of post-drug withdrawal may be important for increases in DA levels associated with conditioned stimuli that induce reinstatement of drug-seeking behavior. In the case of cocaine, excitatory amino acid receptors may play an important role in conditioned cue-elicited craving that promote relapse in recovering abusers. N-methyl-D-aspartate (NMDA) and (AMPA) kainate receptor-antagonist pretreatment prior to drug-environment pairings prevented conditioned hyperactivity and place-preference in rats. Lesions of the basolateral amygdala prevented the acquisition of cocaine-seeking behavior but did not impair cocaine self-administration, showing that the lesions did not change the primary rewarding effects of cocaine. Broader expanses of the orbitofrontal cortex and portions of the amygdala are activated following chronic cocaine self-administration, but not in the short term, which may underlie the progression that leads from early experiences with cocaine to addiction.

More detailed attention to the neurochemical and neuroanatomical defining characteristics of the nucleus accumbens (NAc) was paid by the speakers (P. Voorn, Vrije Univ., Amsterdam, The Netherlands; A. E. Kelley, Wisconsin Psychiatric Inst., Madison, WI, USA; G. Di Chiara, Univ. of Cagliari, Italy; J. Parkinson, Univ. Cambridge, UK) at the symposium Exploring Functions of the Nucleus Accumbens Core and Shell. NAc is divided into a core and shell on the basis of heterogeneous distributional patterns of a number of histochemical markers. There is evidence that specific input-output channels exist in both core and shell and different neurochemical environments differentially affect signal processing through these channels. NAc is best known for mediation of the reinforcing and rewarding properties of drugs of abuse. However, it also subserves behaviors linked to natural rewards, such as feeding, drinking, sex, exploration, and appetitive learning. Local infusion of a selective NMDA antagonist into the core, but not the shell, during the early stages of learning completely blocked acquisition of a bar-press response for food in hungry rats. Thus, the core, involving glutamate-linked mechanisms, is important for response-reinforcement learning. The shell is more linked to viscero-endocrine systems. Infusion of an AMPA antagonist or GABA agonist into the medial shell immediately elicited feeding. The effect was blocked by local inhibition of the lateral hypothalamus (LH), and selectively activated Fos expression in the LH. Phasic DA transmission in each compartment of the NAc might subserve separate roles in the acquisition and expression of motivated behavior. Using brain microdialysis in freely moving rats, it was shown that during a strong appetitive/anticipatory response phasic stimulation of DA transmission is present in the core but not in the shell.

In the symposium Role of Adenosine A2A Receptors in the Limbic System: Implications for the Treatment of Schizophrenia, the speakers (J. A. Ribeiro, Faculty of Medicine of Lisbon, Lisbon, Portugal; M. Morelli, Univ. Cagliari, Italy; S. Ferre, Karolinska Inst., Stockholm, Sweden; B. Baldo, Scripps Research Inst., La Jolla, CA USA) referred to adenosine’s contribution to the tuning of hippocampal excitability. This may be provided by the cross-talk between A1-inhibitory and A2A-excitatory adenosine receptors, and tonic A1 activation can be attenuated when A2A receptors are activated. A2A receptor agonists induce an increase in the c-fos-encoded protein Fos-like immunoreactivity (FLI), evaluation of which is used to study potential sites of action of drugs acting in the CNS.
The antipsychotic drug clozapine induced a pattern of FLI similar to that of A2A agonists, and the A2A-receptor antagonist 5-amino-7-(2-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-epsilon]-1,2,4-triazolo[1,5-c]pyrimidine (SCH 58261) antagonized the effect. This observation supports the concept that A2A receptors are involved in the mediation of antipsychotic effects. Moreover, specific antagonistic interactions exist between subtypes of adenosine and DA receptors in the basal ganglia, in particular between adenosine A2A and DA D2 receptors in the striopallidal GABAergic neurons, which originate in the ventral striatum. Since D2 receptors in this region are involved in the antipsychotic effects of neuroleptics, adenosine A2A agonists provide a potential new treatment for schizophrenia.

The speakers (R. Maldonado, INSERM 266, Paris, France; M. Papp, Krakow, Poland; N. Barden, Laval Univ., Quebec, Canada; H. Szechtman, McMaster Univ., Hamilton, Ontario, Canada) at the symposium Non-Monoaminergic Targets for Antidepressant Action, pointed to a possible involvement of opioid, glutaminergic, and glucocorticoid receptor systems and immune activation in the etiology of depressive disorders. In several animal models, the activation of the opioid system by administration of the enkephalin catabolism inhibitor N-[R(S)-2-benzyl-3(S)(2-amino-4-methylthio)butyl-dithio]-1-oxo-propyl-L-phenylalanine benzyl ester (RB101) or exogenous opioids produced antidepressant-like effects. These effects were influenced by co-administration of a CCK-B antagonist (3R-[+]-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H,4-benzodiaze-pin-3-yl]-N-[3-methylphenyl] urea, L-365,260) suggesting an interaction between endogenous CCK and opioids. In the chronic mild stress model (CMS) of depression, animals treated with ACPC, a partial agonist at strychnine-insensitive glycine sites acting as a functional NMDA antagonist, recovered faster than those treated with the antidepressant imipramine or NMDA antagonists (DL-[E]-2-amino-4-methyl-5-phosphono-3-pentanoic acid, CGP 37849), its R-enantiomer (CGP 40116), or dizocilpine (MK-801) which also showed antidepressant-like effects. Antidepressants stimulate glucocorticoid receptor (GR) gene expression and render the hypothalamic-pituitary-adrenocortical (HPA) axis more sensitive to glucocorticoid feedback, and thus, might be important for the reversion of alterations of the HPA system present in depressed patients. Studies with the MRL-lpr substrain of mice suggest that development of lupus-like disease leads to an autoimmunity-associated behavioral syndrome (AABS) with alterations in cognitive and emotional functions resembling those found in models of depression. The AABS symptoms may also be induced by administration of interleukin-6 (IL-6). On the other hand, immunosuppressant treatment with cyclophosphamide prevents some of AABS symptoms.

New Directions in the Pharmacological Manipulation of Ingestive Behavior was the title of the symposium whose speakers (D. Gehlert, Lilly Research Labs., Indianapolis, IN, USA; S. Rosenzweig-Lipson, Wyeth-Ayerst Research, Princeton, NJ, USA; P. Clifton, Univ. Sussex, Brighton, UK) presented recent results about the role of neuropeptide Y (NPY) and glucagon-like peptide-1 (GLP-1) in the regulation of food intake. Central administration of a 36-amino acid peptide, NPY, resulted in a dramatic increase in food consumption, and subchronic treatment in obesity. The feeding response appeared to be mediated by the Y1 and Y5 receptors from the at least six members of the G protein-coupled NPY receptor family. Treatment with selective nonpeptide Y1 antagonists produced a dose-dependent reduction in food consumption and body weight, and improvement in several endocrine parameters. Due to its glucose-dependent release of insulin GLP-1 (7-36)amide has been suggested as a treatment for diabetes mellitus and also as an endogenous food intake regulator. The GLP-1 (7-36)amide and exendin-4, both,
GLP-1 receptor agonists, suppressed food intake in rats. This effect was antagonized by pretreatment with the GLP-1 antagonist, exendin 9-39 amide. In mice lacking the GLP-1 receptor the decrease in food intake after GLP-1 (7-36)amide was not apparent. Infusion of GLP-1 (7-36)amide to humans enhanced rating of satiety and decreased ratings of hunger. CRF plays a major role in coordinating the endocrine, autonomic, and behavioral responses to stress, but there is also evidence supporting its primary role in obesity and ingestive behavior. The increase in endogenous synthesis and secretion of CRF in the hypothalamus induced by adrenalectomy reverses obesity. The anorexic effects of CRF appear to be mediated by CRF₂ receptors, while the endocrine and anxiogenic side effects are a consequence of CRF₁-receptor activation. Thus, CRF₂ receptor-agonists, and also CRF-binding protein inactivating CRF represent strategies for the treatment of obesity.