666

A ROLE FOR DOPAMINE IN THE STIMULANT EFFECTS OF AMPHETAMINE ON LOCUS COERULEUS SELF-STIMULATION. B.R. Cooper*, G. Ervin* and G.R. Breese. Biol. Sci. Res. Ctr., UNC Sch. of Med., Chapel Hill, N.C. 27514

Rats were implanted with bipolar stimulating electrodes aimed at either the locus coeruleus (LC) or substantia nigra (SN) and trained to self-stimulate using current intensities which maintained moderate to high rates of responding. These animals were then used to examine the importance of newly synthesized norepinephrine (NE) or dopamine (DA) for the central stimulant effects of d-amphetamine. Following a 24 hr. pretreatment with reserpine (2.5 mg/kg) to eliminate stores of amines, rats were given either 25 mg/kg L-α-methyltyrosine to block catecholamine synthesis or 50 mg/kg of the dopamine-β-hydroxylase inhibitor U-14,624, to block NE synthesis. When 1 mg/kg d-amphetamine was given 1 hr. after these synthesis inhibitors, vehicle and U-14,624-treated rats from the LC and SN groups displayed a marked increase in responding to d-amphetamine. Rats given α-MT did not respond after the d-amphetamine treatment. Results suggest that DA neural systems are implicated in the effects of d-amphetamine on self-stimulation even when electrodes are placed in the LC which contains NE cell bodies. (Supported by USPHS Grants MH-16522, HD-03110 and HD-24585.)

667

EFFECT OF SUBACUTE AND CHRONIC REM AND TOTAL SLEEP DEPRIVATION ON STRIATAL DOPAMINE AND ACETYLCHOLINE IN THE RAT. P.K. Ghosh,* P.D. Hrdina and G.M. Ling, Dept. of Pharmacology, Univ. of Ottawa, Ottawa, Ontario.

Changes in conc. of striatal dopamine (DA) and acetylcholine (ACh) in rats chronically (10 days) deprived of REM sleep were compared with those obtained after subacute (4 days) deprivation. Animals placed on small (7 cm diameter) islands surrounded by water were completely deprived of REM sleep but able to obtain some slow-wave sleep. Conc. of striatal DA was significantly increased after subacute and chronic REM sleep deprivation by 73 and 133%, respectively when compared to controls. Levels of ACh in the striatum were significantly enhanced (by 28%) after chronic, but moderately decreased (by 10%) after subacute deprivation of REM sleep. The locomotor activity (tested daily for 1 hr) was significantly higher in REM sleep-deprived animals. Upon termination of the subacute deprivation procedure the rats were agitated and aggressive; in contrast, after prolonged REM sleep deprivation they appeared apathetic, exhausted and responded less to external stimuli. Our data indicate that REM and total sleep deprivation result in marked alterations of both cholinergic and dopaminergic mechanisms in the rat striatum. In addition, behavioural as well as neurochemical differences appear to exist between the subacute and chronic sleep deprivation. (OMHF #356).

668

DOPAMINE AGONIST INDUCED DISORIENTATION IN A RAT SWIMMING TASK Karen Gale* and Akira Horita. Univ. of WA., Seattle, WA. 98195

Rats were trained to swim to a ladder in order to climb out of a tub filled with water (30°C). Time from placement in water (facing away from ladder at a distance of 20") to grasping of ladder with forepaws was recorded. Baseline scores averaging 2.5 sec were obtained from trained rats, who consistently swam directly to the ladder. Under the influence of d-amphetamine (AM) or apomorphine (APO) (4 or 5 mg/kg) the swimming became random and apparently nondirected; swimming ability per se was not impaired however, and the rats reached the ladder by chance after 10-60 sec. The AM and APO-induced disorientation was blocked by pretreatment with haloperidol or pimozide (0.25 mg/kg) at doses which did not completely block APO-induced stereotyped gnawing. A variety of compounds including scopolamine, phenoxybenzamine, clonidine, chlordiazepoxide, LSD, and 5-hydroxytryptophan, did not significantly affect the behavior of the rats in this task. However, scopolamine pretreatment (0.5-1.0 mg/kg) reduced the minimal effective dose of APO by 50-80%. The disorientation effect thus seems to be specific to stimulation of a dopaminergic system and subject to marked potentiation by cholinergic antagonism. In order to determine the nature of the disorientation, rats were also tested in water mazes of differing degrees of complexity and with various discriminative cues.

669

EVIDENCE FOR THE INVOLVEMENT OF DOPAMINERGIC MECHANISMS IN THE E.C.C. SYNDROME. Sabit Gabay, Philip J. Langlais* and Ping C. Huang*. Biochem. Res. Lab., VA Hosp., Brockton, Ma 02401 and Harvard Sch. Dent. Med., Boston, Ma 02115

Following daily injections of 3,3'-iminodipropionitrile (IDPN), 30 mg/100 gm body wt for seven days, rats display a permanent abnormal behavior characterized by excitation, choreiform head and neck movements and circling, the "E.C.C. Syndrome" (Gabay, Recent Advs. Biol. Psychiat., Vol. VIII, p. 73, 1966). Abnormal striatal dopamine metabolism has been suggested in the production of similar hyperkinetic motor activity. The levels of dopamine (DA), norepinephrine (NE), serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in the striatum were measured. While a decrease in both the 5-HT and 5-HIAA levels were observed, DA levels remained unchanged. Hyperkinesia has been observed with normal striatal dopamine levels. Administration of d-amphetamine (2.0 mg/kg) greatly potentiated the hyperkinesia, particularly the rotational movements. Chlorpromazine (1.0 mg/kg) and haloperidol (0.1 mg/kg), dopamine receptor blockers, were able to greatly reduce both the amphetamine potentiated, and the spontaneous rotations. These findings suggest the possibility that dopaminergic mechanisms play a role in the hyperkinesia of the E.C.C. Syndrome. (Supported by VA Research Program: 01/3012.1/69-05).

670

DIFFERENTIAL INCREASE OF BEHAVIORAL AND EXTRAPYRAMIDAL STIMULATING ACTIONS OF NEUROLEPTICS BY α-METHYLTYROSINE PRETREATMENT IN RATS. Barry Dubinsky*, J. K. Karpowicz*, Karey Sledge* and Roger C. Robichaud* (SPON: B. Dubnick). Warner-Lambert Res. Inst., Morris Plains, N.J. 07950.

Clinically, the antipsychotic action of phenothiazines may be potentiated by combining these agents with α-methyltyrosine methylester hydrochloride (AMT), an inhibitor of tyrosine hydroxylase. The aim of the present study was to determine the degree of enhancement of the behavioral (Sidman avoidance in nonlesioned Long-Evans rats) and the extrapyramidal stimulating (EPS) effects (in unilaterally caudate-lesioned rats) of chlorpromazine (CPZ) and haloperidol (HP) by AMT-pretreatment, at a dose (50 mg/kg, i.p.) having no behavioral or EPS effects. Compared with saline-pretreated subjects, AMT augmented the behavioral effect of 1 mg/kg, i.p. of CPZ (86 vs 47 percent avoidance, respectively) and 0.1 mg/kg, i.p. of HP (81 vs 54 percent avoidance, respectively). Enhancement was relative to the dose of each neuroleptic. ED_{50} values (95% C.L.) for EPS after CPZ were similar [3.7 (2.6 to 4.8) and 3.4 (2.6 to 4.3) mg/kg, i.p., respectively] but differed ($p<0.05$) after HP [1.0 (0.8 to 1.4) vs 0.4 (0.3 to 0.6) mg/kg, i.p., respectively] in saline- and AMT-pretreated subjects. Thus, it may be possible to experimentally dissociate desirable from undesirable actions of neuroleptics.

671

PSYCHOPHARMACOLOGIC CHARACTERIZATION OF THE ALARM PHEROMONE IN THE FATHEAD MINNOW. Lanna L. Ruddy* and David H. Baeder. Univ. of Mo.-Kansas City, Mo., Kansas City, Mo. 64110

Schreckstoff is a substance released upon injury to the epidermis of Ostariophysian fish. The released substance produces fleeing behavior in conspecifics (the Schreckreaktion). Behavioral and chemical analysis of Schreckstoff in Pimephales promelas was undertaken. Since Schreckstoff is released only upon injury to the skin, it was hypothesized that the active component of Schreckstoff is a histamine or histamine-analogue. The autacoids histamine, 5-HT, and bradykinin and the substance 48/80 were examined for their ability to produce a Schreckreaktion-like response. The histamine and the 48/80 produced responses topographically identical to those produced by Schreckstoff. The response to Schreckstoff, to histamine, and to 48/80 was blocked by pretreatment with antihistamine. All substances tested were olfactorially mediated; the use of narial plugging blocked the response to Schreckstoff, to the autacoids, and to 48/80. Chromatographic data showed histamine, histidine, and 5-HT to be present in the Schreckstoff extract-solution with histamine present in far greater amounts than any other identified substance. It was concluded that the active component of Schreckstoff is histamine or closely related analogue.