2786 *Pharmacology*

CENTRAL MUSCLE RELAXANT PROPERTIES OF SOME MONO-AND DI-HALO-2-AMINOBENZOXAZOLES. Adolph P. Roszkowski, Elaine D. Kacmarik* and Louise Jacobs*. McNeil Laboratories, Inc., Fort Washington, Pa.

Although numerous studies relating to the central muscle relaxant properties of 2-amino-5-chlorobenzoxazole (zoxazolamine) have appeared, other halo-substituted analogues in this series have not previously been examined extensively and will be the subject of this report. The dose of zoxazolamine which produces a 50% loss of righting ability (PD_{50}) is 81 mg/kg in mice, intraperitoneally (i.p.) and 415 mg/kg orally (p.o.). The 6-Cl or 5- or 6-Br substituted analogues were found to be approximately in this same potency range. They were more potent and displayed a greater margin between paralytic and lethal dose levels than did the 5-F or -I substituted agents. The 5-Cl,6-Br analogue was also in this potency range, but the 5-Br,6-Cl analogue was decidedly less active in the mouse with PD_{50}'s of 350 mg/kg, i.p. and 740 mg/kg, p.o. Surprisingly, this agent was found to be remarkably active in the rat in that the oral PD_{50} was 59 mg/kg or only 1/12 of the mouse p.o. PD_{50} and 1/6 of the mouse i.p. PD_{50}. Likewise, preliminary studies indicate that the 5,6-dichloro analogue is only moderately potent in both mice and rats i.p., but very potent p.o. A complete summary of the structure-activity relationships in this series will be presented.

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EFFECTS OF LSD ON EVOKED POTENTIALS AND BEHAVIOR IN THE CONSCIOUS CAT. Arthur S. Schwartz*. (spon: E. Eidelberg). CNRC, St. Elizabeths Hospital, Washington, D. C.

The effect of low (10-35 μg/kg) and high (1 mg/kg) doses of LSD on amplitude of visual and auditory evoked responses and the gross sensory responsivity of conscious cats was assessed. Responses were compared to the mean pre-injection amplitude, and then pooled for each particular structure and dose level to be compared to the mean amplitude of the response after saline injection. The results for low LSD doses showed increased variability of response amplitude in all areas monitored (auditory and visual cortices, lateral geniculate body and cochlear nucleus), and a slight increase in amplitude of geniculate responses only. Behaviorally, auditory and visual responsiveness increased slightly. After high LSD doses, cortical responses were enhanced, while subcortical responses were depressed. Behaviorally, auditory responsivity markedly increased while visual responsivity was depressed. Lack of agreement between aspects of the behavioral and electrophysiological data may reflect (a) a differential function of cortical versus subcortical centers of the two sensory systems, or (b) the fact that evoked potential amplitude in the above areas bears little or no relation to the differential behavioral effects of LSD, and that other response parameters or other neural areas are involved.

2788 *Physiology*

EFFECT OF LSD-25 ON THE WALKING ACTIVITY AND PATTERN IN THE GOAT. Werner P. Koella, Roger F. Beaulieu* and John R. Bergen Worcester Fndn. for Exp. Biol., Shrewsbury, Mass.

The influence of two different doses of LSD-25 (15 and 7.5 μg/kg body weight iv.) on the goat was investigated in a modified open field test. In the larger dose and, to a lesser degree, in the smaller dose the drug increased the walking activity, measured as total walking distance per time unit. Under the influence of this psychotomimetic the animals developed pronounced walking stereotype patterns manifested by "squaring" (i.e., walking along the wall of the experimental room) or by other forms such as small rectangles, circles, figure eights, or L's. Any of these patterns was found to be specific for a particular goat; every animal reacted with the very same pattern each time LSD was administered. These effects usually appeared within 5 to 10 minutes after the administration of the drug and abated within 60 minutes thereafter. With repeated injections at intervals of 1 to 3 days, tolerance to the drug developed. Female goats were found to be more sensitive to the drug than male animals. (Supported by a grant from NIH.)

2789 *Pharmacology*

SOME AUTONOMIC PROPERTIES OF AMIMETHYLINE, A NEW ANTIDEPRESSANT. Clement A. Stone, Curt C. Porter and Vernon G. Vernier. Merck Institute for Therapeutic Research, West Point, Penna.

Amimethyline (5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene hydrochloride), possesses a number of interesting autonomic properties. The agent proved to be a potent antagonist of phenethylamine pressor responses, while potentiating those induced by norepinephrine in the anesthetized, ganglion-blocked dog. The new agent was the most active of the several antidepressants (amitriptyline, imipramine and their nor analogs) studied. Extension of this finding to other norepinephrine releasing agents demonstrated that the catecholamine depleting effects of guanethidine, metaraminol, α-methyl-m-tyrosine, 6-hydroxydopamine and tyramine on the hearts of mice were prevented by prior administration of amimethyline. Again this agent proved to be the most active of the several antidepressants examined. Amimethyline slightly inhibited the depleting effect of tetrabenazine on brain catecholamines in mice, although it completely antagonized its sedative action. Amimethyline, and several other antidepressants were also found to be capable of preventing the adrenergic neuron blocking action of guanethidine and bretylium on the cat nictitating membrane. The relationship of these several peripheral actions to central antidepressant actions of the compounds studied remains unknown.

2790 *Nutrition*

INTERACTION OF ANTIDEPRESSANTS WITH AMPHETAMINE, COCAINE, α-METHYL-METATYROSINE, AND TETRABENAZINE. Carl L. Scheckel* (spon: S. H. Rubin). Hoffmann-La Roche Inc., Nutley, N. J.

Imipramine-like antidepressants were compared with a variety of other compounds using rats conditioned to respond in a continuous avoidance procedure (RS 40", SS 20"). The minimum effective doses that increased rate of avoidance responding (stimulation) were determined for each compound in three tests: 1) amphetamine potentiation, 2) cocaine potentiation, and 3) stimulation in combination with an inactive dose (0.2 mg/kg, s.c.) of tetrabenazine (TBZ). Desmethylimipramine, desmethylamitriptyline, amitriptyline, and imipramine (in decreasing order of potency measured in the TBZ-stimulation test) were active in all three tests. Atropine, scopolamine, trihexyphenidyl, promethazine, and iproniazid potentiated amphetamine and cocaine, but did not stimulate with TBZ. Chlorpromazine, promazine, azacyclonol, methylphenidate, and phenindamine were inactive in all three tests. The imipramine-induced stimulation of amphetamine, cocaine, and TBZ was blocked by 16 hr. pretreatment with α-methyl-metatyrosine (α-MMT, 500 mg/kg, i.p.). Pretreatment with α-MMT attenuated, but did not block atropine potentiation of amphetamine. Since α-MMT selectively depletes brain norepinephrine (NE), the absence of imipramine-induced stimulation in the α-MMT pretreated rat indicates that brain NE is involved in the activity of imipramine.

2791 *Pharmacology*

PSYCHOPHARMACOLOGY OF IMIPRAMINE AND DESIMIPRAMINE; Heninger, G.* & DiMascio, A. (sponsor - Friend, Dale) Mass Mental Health Center, Boston, Mass.

Desimipramine has been shown to be one of the primary metabolites of imipramine, an agent used in psychiatry as an antidepressant agent. Preliminary clinical trials have shown that desimipramine also has antidepressant properties. This study was intended as a parametric investigation of the effects of these two agents when administered to normal male subjects. The study was done double-blind and with a placebo control. The two drugs were tested at 50, 100 and 200 mg. doses. Drug actions were recorded pre-drug, and 2, 4 and 8 hours after the oral administration of one of the doses of the drugs, on a battery of tests that included physiologic, psychomotor, cognitive functioning and affect state measurements. Desimipramine produced only minor tachycardia. In contrast, imipramine produced marked hypnotic effects as evidenced by a slowing or impairment of almost all functions examined and, in a subjective feeling of diminution of mental and physical energy. The procedure allowed for a comparison of the magnitude of drug effects, the dose-response curves, and potency. On the basis of the comparison of drug actions, conclusions are drawn relative to their chemical structure - behavioral effect relationships, as well as to their implications for usage in clinical psychiatry. (NIMH-My-2726)