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Pharmacology

BIOCHEMICAL ASPECTS OF "LSD-PSYCHOSIS." D. V. Siva Sankar (intr. by F. Cotui.) Creedmoor State Hospital, Jamaica 27, New York, N. Y.

We have carried out comparative investigations on the enzymatic and metabolic effects of the hallucinogenic drug, lysergic acid diethylamide (LSD) and its non-hallucinogenic bromo analog (BOL). The enzymatic studies were made using rat cerebral and cerebellar homogenates in a buffered Krebs Ringer bicarbonate medium. LSD enhanced the oxidation of glucose, succinate and citrate by the cerebral preparations, while it either depressed it or did not have marked effect on the cerebellar enzymatic activity. The effects of reserpine and serotonin were similar to those of LSD while the action of BOL was different. Further details and the effect on amine oxidase and amino acid decarboxylase activity will be presented. The metabolic effects of LSD and BOL were investigated using intact rats in metabolism cages. The most important effect of LSD (not shown by BOL) was the decrease in urinary urea and keto acid excretion. This may possibly involve oxidative metabolism as related to liver function. These studies show somatic involvement in an experimentally produced "psychosis." Studies have been made on the urinary excretion of phosphate, phenolics, amines, metabolites of tryptophan-3-C^{14}, etc. The results of these studies will be presented and discussed.

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ANTICONVULSANT PROPERTIES AND METABOLIC ASPECTS OF N-ALKYL SUBSTITUTED BENZILIC AMIDES. J. R. Albert* and J. H. Weikel, Jr., Dept. of Pharmacol., Mead Johnson & Co., Evansville, Ind.

The anticonvulsant activities of N-alkyl substituted benzilic amides (synthesized by Dr. F. A. Grunwald) were determined in mice by the maximal electroshock (M.E.S.) and subcutaneous metrazol tests. This series was most active against M.E.S. and had potent anti-metrazol activity as well. Benzilic amide itself was potent in both tests, but the dose producing neurological deficit was near the protective dose. N-alkyl substitutions of methyl, ethyl and isopropyl groups decreased M.E.S. potency in that order. Cyclohexyl, tert. butyl, sec. butyl and propyl derivatives were inactive. N-ethyl benzilic amide (NEBA) had optimal activity for both M.E.S. and metrazol tests. NEBA had mixed depressant and stimulant actions at high levels, whereas benzilic amide had a hypnotic action at high but non-lethal levels. An analytic test was developed to estimate total benzilic amides in biological fluids and tissues. A metabolite of NEBA, identified as benzilic amide by mixed melting point, infrared absorption spectra, and counter current distribution, was found in the urine. Mice given repeated daily administration of NEBA became tolerant to minimal electroshock seizure. The development of tolerance paralleled a decrease in benzilic amide brain content. Mice given repeated daily doses of benzilic amide did not show tolerance.

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Pharmacology

SELF-SELECTED BRAIN STIMULATION REWARD THRESHOLDS MODIFIED BY DRUGS. Larry Stein (intr. by J. Seifter.) Wyeth Institute for Medical Research, Philadelphia 1, Penna.

In self-stimulation experiments, animals with permanently implanted electrodes work to stimulate certain brain sites electrically just as animals will work to obtain conventional rewards like food. These self-stimulation procedures have been extended by allowing the animals to regulate the intensity as well as the rate of the stimulation, and arranging conditions so that the animal continuously self-selects his threshold for rewarding brain stimulation. After a few weeks of training, the performance is sufficiently stable to provide a dependable and precise baseline for the evaluation of drugs. With electrodes in the posterior hypothalamus and midbrain tegmentum of the rat, intraperitoneal injections of d - and dl - amphetamine (0.5 - 1 mg/kg), phenylethylamine (30 mg/kg), and methylenedioxyamphetamine (1.5 - 3 mg/kg) lowered the reward threshold. In the same sites, chlorpromazine (1.5 mg/kg), reserpine (0.6 - 1 mg/kg), serotonin (4 mg/kg, SC), and LSD-25 (0.01 mg/kg) increased the reward threshold or knocked out self-stimulation behavior altogether. Sodium pentobarbital (15 mg/kg) also stopped self-stimulation at the peak of its action but, in contrast to the other drugs, lowered the threshold before and after the peak effect.

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INTERACTION OF LYSERGIC ACID DIETHYLAMIDE (LSD) WITH POLYPEPTIDES WHICH STIMULATE SMOOTH MUSCLE. Carroll M. Smith* and Edward J. Walaszek, Dept. of Pharmacology, Univ. of Kansas Medical School, Kansas City, Kansas.

It has been reported (Krivoy, B. J. Pharm. 12: 361, 1957), that LSD in conc. of 1 mcg/ml and less potentiated the stimulating effect of the neurohumoral polypeptide substance P on the isolated guinea pig ileum. Under similar conditions histamine was not potentiated. It was speculated that this interaction may bear some relationship to the hallucinogenic action of LSD. We have confirmed the potentiation of substance P by LSD and have further shown a similar potentiation of bradykinin and substance A, two smooth muscle stimulating polypeptides which are devoid of central nervous system effects. LSD was added to the organ bath 2 minutes before the addition of the agonist. Potentiation was most clearly seen when the conc. of LSD was 0.03 to 0.1 mcg/ml. LSD in conc. higher than 0.1 mcg/ml consistently gave a marked stimulating effect of its own. All potentiations were easily reversed by washing the ileum with fresh Tyrode's solution. Other known hallucinogens were unable to potentiate the stimulating effect of substance P. It is concluded that this potentiation by LSD probably bears no relationship to its hallucinogenic properties and the mechanism of potentiation is probably due to the inhibitory effect of LSD on enzymes capable of inactivating polypeptides.

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EFFECTS OF PUFFER POISON ON NEUROMUSCULAR TRANSMISSION. J. H. Fleisher, P. J. Killos and C. S. Harrison (intr. by J. H. Wills.) U.S. Army Chemical Warfare Laboratories, Army Chemical Center, Md.

Injection of 50 microgms. of puffer poison (PP) in saline into the anterior chamber of the rabbit eye in vivo produced a prolonged mydriasis. Degeneration of post ganglionic adrenergic fibers to the eye prior to injection had no effect on the production of mydriasis with PP, suggesting no involvement of adrenergic pathways. Carbamylcholine (0.1 mg/kg.) injected subcutaneously into a rabbit showing mydriasis following intraocular injection of PP produced marked pupillary constriction indicating PP to have little or no effect on postsynaptic cholinergic receptors. Incubation of the isolated rat phrenic nerve-diaphragm preparation in solutions containing as little as 0.06 microgms. PP per ml. produces neuromuscular block accompanied by marked inhibition of acetylcholine (ACh) release. This concentration of PP has little or no effect on ACh formation by rat brain slices. It is concluded that the primary effect of PP on neuromuscular transmission is an inhibition of ACh release.

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EFFECTS OF THALIDOMIDE ON CENTRAL NERVOUS SYSTEM DRUGS. W. L. Kuhn* and E. F. Van Maanen, Dept. of Pharmacology, Scientific Division, The Wm. S. Merrell Co., Cincinnati, Ohio.

Clinical studies with thalidomide (α-[N-phthalimido]glutarimide) have shown that 100 mg given orally induces sleep in man. Experiments in animals revealed that, unlike the usual sedative and hypnotic drugs, thalidomide does not produce loss of righting reflexes. Symptoms of mild central nervous system depression were observed in mice and dogs with 30 mg/kg intraperitoneally, but loss of righting reflexes did not occur with doses of 4000 mg/kg in mice or 100 mg/kg in dogs. The most prominent effects of thalidomide occurred in combination with other centrally acting drugs. In mice 30-100 mg/kg prolonged sleeping time and reduced the HD_{50} (Hypnotic Dose-50) of hexobarbital and barbital, suggesting that thalidomide does not potentiate barbiturates by blocking metabolic pathways in the liver. Thalidomide had no anticonvulsant activity as judged by the maximal electroshock procedure; however, 100 mg/kg reduced the Anticonvulsant Dose-50's of diphenylhydantoin and phenobarbital in mice by ratios of 1.95 and 2.2, respectively. This dose had no effect on the LD_{50} of diphenylhydantoin and it increased the LD_{50} and HD_{50} of phenobarbital by a factor of only 1.2. Thalidomide did not block the conditioned avoidance response in rats; however, it potentiated this activity and the central nervous system depressant action of chlorpromazine.