Behavioral Pharmacology III

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DIFFERENTIAL IMPAIRMENT BY DRUGS OF DELAYED MATCHING PERFORMANCE IN FRONTAL AND NORMAL MONKEYS. S. D. Glick* and M. E. Jarvik. Albert Einstein Col. of Med., Bronx, N.Y., 10461.

Eight monkeys were trained to perform in a delayed matching test under five testing conditions: simultaneous, 0, 2, 8, and 32 sec. Dorsolateral frontal cortical ablations were performed bilaterally on four of the monkeys. When test performance of the frontal monkeys recovered to preoperative levels, a series of drugs was administered to both normal and frontal monkeys. Scopolamine, d-amphetamine and LSD induced severe accuracy impairments of the normal monkeys, whereas physostigmine, mecamylamine, chlorpromazine and alpha-methyl-dopa induced small accuracy impairments of the normal monkeys and chlordiazepoxide, pentobarbital and imipramine induced little or no change in the performance of the normal monkeys. All impairments occurred equally on all testing conditions indicating that no drug had a specific influence on short term retention. The frontal monkeys were insensitive to impairment of accuracy by d-amphetamine, chlorpromazine and alpha-methyl-dopa but were as sensitive as the normal monkeys to all of the other drugs. These results indicate that frontal cortical lesions have a selective influence on adrenergic mechanisms involved in matching behavior. (Supported in part by USPHS MH01225 and a Postdoctoral Fellowship from NIH 5T5 GM1674.)

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LEARNING IN THE ANESTHETIZED RAT. Barry D. Berger*(SPON: M.I. Gluckman). Wyeth Laboratories, Philadelphia, Penna. 19010

Rats were trained to drink milk in a test chamber and then were injected after different intervals (0 to 24 hr) with scopolamine methyl nitrate (1 mg/kg, i.p.) or saline. Seven days later, the latency of milk drinking was retested. Rats that had been given methyl scopolamine within 2 hr after original training drank more slowly or refused to drink on the test trial. These and other results indicate that the rats had learned to associate the milk with noxious effects of the drug. To test whether such associative learning can occur under anesthesia, rats were anesthetized with pentobarbital (35 mg/kg) or Dial-Urethane (0.6 ml/kg) immediately after milk-drinking training and then injected either 15 min or 2 hr later with methyl scopolamine. Anesthesia in durations of up to 10 hr did not affect the learning of the aversion and even intensified it when the interval between milk intake and scopolamine was prolonged. The anesthetics by themselves produced some aversion to the milk, but much less than in combination with methyl scopolamine. One explanation is that the milk-scopolamine association forms after the anesthesia has worn off, but it must be assumed that traces of both milk and drug can persist for 10 hr in the anesthetized rat. An alternative explanation is that certain types of learning (perhaps those not requiring the action of higher brain centers) can occur under anesthesia.

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Modification of Conditioned Behavior by Prior Experience: Effects of Pentobarbital. R.G.Wiley* (SPON: H.J.Burford). Northwestern University Medical School, Chicago, Ill. 60611

Previous experience with strong foot shock (prior aversive stimulation: PAS) can modify the subsequent conditional behavior of rats. This report describes attempts to attenuate PAS influence by pretreatment of rats with pentobarbital.

Food deprived animals were taught to press levers for food rewards on a continuous reinforcement schedule. After lever pressing rates (LPR) had stabilized, a mild paw shock (MPS) was coupled to each lever press along with food reward.

Saline control animals not given PAS showed a small and transient decrease in LPR when the MPS was added to the reinforcement complex. Animals given saline prior to PAS showed a profound and prolonged decrease in LPR during MPS trials. Animals receiving Na pentobarbital (25 mg./kg.,i.p.) 10 mins. before PAS showed significantly less disruption of LPR during MPS period. Giving the same dose of pentobarbital subcutaneously 20 mins. before PAS or i.p. immediately after PAS did not significantly alter subsequent disruptive effects of PAS on LPR during MPS trials.

Thus, it appears that the effects of PAS on subsequent conditioned behavior are not significantly modified by a nonspecific central depressant in less than severely neurotoxic doses. (Supported by USPHS, NIH Grant 2-TO1-GM-00162-11 and the Helen Brinton Fund).

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BEHAVIORAL AND NEUROCHEMICAL EFFECTS OF ARECOLINE IN RATS. Ram M. Bhatre*, S.N. Dutta and S.N.Pradhan. Howard Univ. Col. of Med., Washington, D. C. 20001.

In a previous study (Pradhan & Roth, Psychopharmacologia, 12, 358, 1968) several anticholinergic agents were shown to affect certain spontaneous as well as reinforced operant behavior in rats. This and many other reports indicate that central cholinergic mechanism plays a role in modulation and modification of behavior in man and animals. In this study, the effects of arecoline and its methiodide sale were investigated on several behavioral schedules in rats, and attempts were made to correlate the behavioral responses with brain (cortex, diencephalon and brain-stem) acetylcholine content. Arecoline (0.25-4 mg/kg, i.p.) usually decreased the responses, especially at high doses, in several behavioral situations including spontaneous motor activity, fixed-ratio (water and food), fixed-interval (food) reinforcement, differential reinforcement of low rates and shock avoidance. Arecoline methiodide tested on some of these schedules showed insignificant effects. Arecoline-induced depression of spontaneous motor activity could be antagonized by scopolamine, but not by methylscopolamine and mecamylamine. The acetylcholine content of the brain (esp. cortex and diencephalon) was increased following injection of arecoline. Thus a central cholinergic mechanism appears to be involved in the behavioral effects of arecoline. (Supported by U.S.P.H.S. Grant No. UI00472).

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A COMPUTER CONTROLLED SYSTEM FOR BEHAVIORAL STUDY IN INHALATION PHARMACOLOGY. T. O. T. TS'O*, B. K. J. Leong*, and Maynard B. Chenoweth. The Dow Chemical Company, Midland, Michigan 48640

A Foreground/Background computer system using PDP-8/i was developed for complex control and recording in psychopharmacological studies. The Foreground system handles 6 rat behavioral boxes, 11 independent input bits and 10 independent output bits per box. The Background facility makes the computer available for writing programs via teletype, analysis of data, paper tape data output, and/or Calcomp plotter. For inhalation study, each animal is exposed to the drug vapor while its behavior is monitored inside the box which serves as an air tight dynamic exposure chamber also. The drug vapor and compressed air are metered at desired proportions into a reservoir, drawn into each box and finally exhausted with a pump via a common buffer system. The pharmacological properties of methoxyflurane and halothane were studied under a compound schedule (duration 40 minutes) made up of alternate 5 minute intervals of FR-10 and CRF plus shock schedules with food pellets as reinforcement. The drugs were given at sub-anesthetic doses. The vapor concentration in each box was monitored at regular intervals with an infrared spectrophotometer.

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PHARMACOLOGICAL MODIFICATION OF PSYCHOMOTOR STIMULANT SELF-ADMINISTRATION IN THE RHESUS MONKEY. Marvin C. Wilson* and C. R. Schuster. Univ. of Michigan, Ann Arbor, Mich. 48104.

Rhesus monkeys, when allowed daily limited access (4 hour) to psychomotor stimulants (e.g., cocaine, methylphenidate, phenmetrazine, and pipradrol), self-administer the same total amount (±10%) of these drugs daily, regardless of unit dosage (mg/kg/injection) employed. Attempts were made to alter the reinforcing property of the psychomotor stimulants by pretreating the subjects with other agents such as pentobarbital, morphine, chlorpromazine (CPZ), phenmetrazine, and D-amphetamine.

Morphine and pentobarbital produced no changes in drug intake until large dosages were used which produced severe incapacitation. CPZ, however, produced large increments in psychomotor stimulant intake over a wide range of doses. Phenmetrazine and D-amphetamine pretreatment produced a dose-related depression in psychomotor stimulant self-administration. These results suggest that the reinforcing effects of psychomotor stimulants are mediated by their interaction with central adrenergic mechanisms. (Supported by NIMH grant 5R-10MH-12084.)