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CHRONIC ADMINISTRATION OF APOMORPHINE: EFFECTS ON STRIATAL TYROSINE HYDROXYLASE ACTIVITY K. Gale* (Spon: S. Schwartz) Georgetown Univ. Sch. of Med. and Dent., Wash., D.C. 20007

Apomorphine (APO) was administered to rats for 10 days via subcutaneous reservoirs (Goode, Br. J. Phcol. 41: 558, 1971) which were refilled daily. A total of 20 mg/kg/day APO was infused over a 12-16 hr period during which continuous stereotyped gnawing behavior was observed. On day 11 (at least 12 hrs after removal of APO) animals were sacrificed for assay of tyrosine hydroxylase (TH). In comparison to controls (saline infusion), rats receiving chronic APO showed: 1) a 30-50% reduction in Vmax of striatal TH; and, 2) a 2-3 fold increase in affinity (decrease in apparent Km from 0.9 mM to 0.3-0.4 mM) of striatal TH for pteridine cofactor. In rats receiving chronic haloperidol (Hal) (1 mg/kg i.p. x 2/day, for 10 days) no change in TH Vmax or Km for cofactor was found at 24 hrs after the last injection of Hal. Hal, chronically administered concurrently with APO, blocked the effect of chronic APO on striatal TH, indicating that dopamine receptor stimulation is involved in the APO-induced alterations of striatal TH. The reduction in TH Vmax after chronic APO is consistent with the concept of interneural negative feedback control of striatal TH activity. Furthermore, the similarity between the increase in affinity of striatal TH for cofactor which occurs after an acute injection of Hal, and that seen after removal of chronic APO, suggests that withdrawal of APO may activate striatal TH by causing a reduction in the feedback inhibition on dopaminergic neurons.

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DIFFERENTIATION OF THE STEREOTYPED AND DYSKINETIC BEHAVIORS INDUCED BY INTRASTRIATAL INJECTIONS OF DOPAMINE AND 3-METHOXYTYRAMINE. Jeanne M. Beno* and Leonor Rivera-Calimlim. Univ. of Rochester Medical School, Rochester, N.Y. 14642.

A comparative study was made of the behavioral phenomena induced by dopamine (DA) and its metabolite 3-methoxytyramine (3MT). Rats unilaterally implanted with stainless steel cannulae were pretreated with nialamide (75 mg/kg I.P.) and injected with from 6.25-100 µg of DA or 3MT. Both compounds produce dose-dependent responses with a mean latency of 8-10 min. The DA response was characterized by hyperactivity, contralateral circling, intense gnawing and "classic" stereotyped behavior. 3MT induced intense sniffing and dyskinetic behavior including mouthing, tongue protrusion, and involuntary limb movements. At latencies of 2-3 hr, dyskinetic behavior could be seen to develop in DA injected rats. Rarely, at similarly long latencies, 3MT could be shown to induce circling, hyperactivity, and stereotyped locomotion. The primary response to each drug was still ongoing at these times hence the behaviors are not mutually exclusive. Chlorpromazine (2-7 mg/kg I.P.) rapidly, and selectively inhibited the DA-specific behaviors, but only inhibited 3MT dyskinesias in cataleptic doses. It is suggested that DA and 3MT produce qualitatively different behavioral responses by acting at different receptors. Production of dyskinesias by DA may be contingent upon its metabolism to 3MT. Induction of hyperactivity and circling by 3MT may be the result of demethylation to DA. (Supported in part by NSF Fellowship No. SMI 77-22040.)

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NEUROLEPTIC-INDUCED DYSKINESIAS IN SQUIRREL MONKEYS AFTER REPEATED TREATMENT WITH HALOPERIDOL. J. M. Liebman* and R. Neale* (SPON: R. Robson). Research Dept., CIBA-GEIGY Corp., Summit, N. J. 07901

Tolerance to haloperidol-induced catalepsy in rats has been demonstrated by numerous investigators. In the present studies, adult male squirrel monkeys (Saimiri sciureus) were treated at weekly intervals with haloperidol (1.25 mg/kg p.o.). After eight weeks, catalepsy no longer followed treatment consistently; instead, a haloperidol-induced dyskinetic syndrome emerged in which the subjects manifested abnormal movement patterns, including rocking and writhing. Bouts of vigorous, although ataxic, locomotion were interspersed with periods of quiet during which abnormal postures, characterized by limb extension and apparent muscular tension, prevailed. Once these movement patterns had been established in response to haloperidol, they were readily elicited by chlorpromazine, thioridazine and sulpiride, but not by clozapine, non-neuroleptic agents, or the treatment vehicle. Baclofen antagonized the haloperidol-induced dyskinetic syndrome without alleviating other effects of haloperidol, such as extrapyramidal tremor or impairment of Sidman avoidance responding. These results indicate that tolerance to haloperidol may not result solely from a simple alteration in the number of dopamine receptors (Science 197: 596, 1977) but may also involve compensatory changes in the function of other neural systems involved in movement.

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TREATMENT OF TARDIVE DYSKINESIA WITH DIPHENHYDRAMINE. Richard F. Tislow and Arleen I. Skversky*. Northwest CMHC and Dept. of Psychiatry, Univ. of Pa., Philadelphia, Pa.

Tardive dyskinesia (T.D.) is one of the belated side effects in patients treated with neuroleptics. Customary anticholinergic agents do not prevent its occurrence. This work describes an effective treatment with diphenhydramine, 25 to 50 mgm once to four times a day. Observations were made since Oct. 1975 until present in 121 patients (65% females) ages 18-78 years. Eleven of these patients had T.D. Results: Of 121 patients, 11 (9.09%) had T.D. of varying degrees of severity at the onset of this study. Using our treatment approach we observed a gradual decline in severity and incidence of T.D. At present, 4/10 showed minimal, and 6/10 had no signs of T.D. In one patient there was no change. Significance: The treatment of patients with T.D. presents a therapeutic and ethical dilemma; how to maintain such patients in good mental health and at the same time to deal with T.D. The present work suggests an approach to this problem.

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LSD, TRICYCLIC ANTIDEPRESSANTS AND NEUROLEPTICS INHIBIT HISTAMINE STIMULATED ADENYLATE CYCLASE IN BRAIN. S. Maayani*, J.P. Green, and H. Weinstein. Pharmacology, Mount Sinai School of Medicine, City University of New York, New York 10029

Three different classes of psychotropic drugs blocked the histamine H_2-receptor linked to adenylate cyclase in homogenates of guinea pig hippocampus and cerebral cortex. D-LSD and 2-bromo-LSD were competitive inhibitors with pA_2 values of 5.95 and 7.16, respectively. The pA_2 value of cimetidine, the H_2-antagonist in clinical use, was 6.22. L-LSD did not block the H_2-receptor. Tricyclic antidepressant drugs also blocked the histamine stimulated adenylate cyclase in a competitive manner; they did not inhibit activation of adenylate cyclase by fluoride or GppNHp. The drugs and their pA_2 values were: amitriptyline (7.35), doxepin (6.8), chlorimipramine (6.7), imipramine (6.6), nortriptyline (6.1), desipramine (5.9), dibenzepine (5.8), protriptyline (5.7), iprindol (5.5). Phenothiazines, too, competitively blocked the histamine-stimulated adenylate cyclase. The drugs and their pA_2 values were chlorprothixene (7.2), chlorpromazine (6.7), thiethylperazine (6.6), α-fluphenthixol, (6.6) fluphenazine, (6.3) and β-fluphenthixol (5.5). The pA_2 values of six H_2-antagonists on histamine stimulated adenylate cyclase in brain were very similar to the pA_2 values for the pharmacological effects of histamine on the H_2-receptor in rat uterus and guinea pig atria. The same pA_2 values were obtained with dimaprit or histamine as agonist. (Supported by NIMH Grant MH 17489 and NIDA Grant DA 01875.)

2108 PHARMACOLOGY

EFFECTS OF LSD ON UNIT ACTIVITY AND EXTRACELLULAR POTASSIUM RESPONSES IN CAT CORTEX DURING VISUAL STIMULATION. A. Dray* B. Connors*, P.C. Fox*, M. Hilmy*, C. Moore* and G.G. Somjen. Department of Physiology, Duke University Medical Center, Durham, N.C. 27710

In doses up to 50 µg/kg i.v. LSD depressed the response to optical stimuli, and the unstimulated background firing of some neurons, but enhanced the activity of other neurons in the primary visual receiving area of cats. Larger doses were invariably depressant. To estimate average cell population behavior, transient elevations of extracellular potassium ($[K^+]_o$) were recorded with ion-selective microelectrodes. Such $[K^+]_o$ responses were selective for stimulus orientation and for direction of stimulus movement. 10 to 25 µg/kg doses of LSD caused a depression of $[K^+]_o$ transients, in 4 out 5 experiments and an enhancement in one experiment. The difference between the responses to preferred and to non-preferred stimuli decreased in 3 cases, and the preferred direction was reversed on one occasion. These changes may in part account for the distortion of visual perception produced by LSD. (Supported by PHS Grant DA 01458)