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RÉSUMÉS OF RESEARCH PROJECTS IN PSYCHOPHARMACOLOGY

As in previous years, we are publishing again résumés of projects supported by the Psychopharmacology Research Branch, NIMH. The purpose is to inform the scientific community about ongoing studies in the field.

All résumés are prepared under contract. Before publication each résumé is sent to the principal investigator for approval. Amendments by the investigator are included in the printed version.

In this issue, we are presenting résumés on Preclinical Psychopharmacology in the areas of Drug Development (Chemical Synthesis, Isolation, and Characterization) and Mechanism of Action Studies (Physiological, Biochemical, Pharmacological, and Toxicological) and (Behavioral). Résumés in the above categories that were not returned by the investigators before going to press will appear in the next issue.

The summaries are only intended to give a brief description of the investigators' work and in no way attempt to represent the total scientific scope and implication of these projects.

Synthesis of Compounds Related to Lysergic Acid

Investigator: John C. Craig
University of California
San Francisco, California

Purpose: Understanding the mode of action and chemical makeup of compounds related to lysergic acid diethylamide (LSD) could lead to the development of new substances useful in the treatment of mental illness and migraine. With this goal in mind, the investigator is synthesizing compounds that are structurally related to lysergic acid, one of the main components of LSD. The pharmacological activity of these new compounds is examined to identify their structure-action relationship and to compare their effects with those of LSD.

Subjects: The subject matter consists of chemical substances related molecularly to lysergic acid. Experimental animals, including guinea pigs and rabbits, are used in tests of pharmacological activity.

Method: The methodological rationale of this investigation is that by retaining or omitting certain features of the lysergic acid molecule, it is possible to accumulate information regarding the requirements for pharmacological activity and thereby to associate particular structural and stereochemical moieties of the molecule with observed pharmacological responses. Beginning with relatively simple substances, the investigator builds up the desired molecular structures by selection of intermediates and reaction conditions. The spatial arrangements of the atoms in these products are then determined by means of modern instrumental techniques. Pharmacological studies are conducted both *in vitro* and *in vivo* to evaluate the effects of selected analogues on tone and rhythm of the uterus, contractions of the ileum, and vascular phenomena.

Results: Recently, the investigator completed initial pharmacological studies of the oxytocic activity of several of the more than 100 compounds synthesized during the course of this research project. The most active compounds were ergonovine, used as the standard for causing ileal contractions, norepinephrine, used as the standard for reversing ergonovine-induced contractions, and diethylamide derivatives, which are simplified LSD analogues lacking the pyrrole portion. The maximal sustained ileal contraction caused by ergonovine could be either completely or significantly reversed by approximately the same dose of either norephinephrine or the synthetic diethylamide analogues.

Other studies indicated that among LSD-type derivatives without the indole nucleus, those com-

pounds with an ester function possess oxytocic activity; while those with an amide function may be capable of reversing ergot-induced contractions. Since in contrast to the natural ergot alkaloids, the dihydroalkaloids—ergocristine, ergokryptine, and ergocornine—caused a reduction in tone and rhythm of the rabbit uterus and were also capable of inhibiting the uterotonic action of ergotamine or ergometrine on the isolated organ, the possibility exists that the synthetic diethylamide derivatives mimic the dihydroalkaloids while the ester derivatives mimic the natural alkaloids in their activities.

Extrapyramidal Dyskinesias and Brain Amine Metabolism

Investigator: Oleh Hornykiewicz
Clarke Institute of Psychiatry
Toronto, Canada

Purpose: This study attempts to define changes in brain amine metabolism of animals made dyskinetic by L-DOPA or chronic administration of neuroleptics. The investigator hopes to shed light on the neurochemistry of dyskinesia, a side effect of drugs used to treat certain clinical states, including schizophrenia and Parkinson's disease.

Subjects: Rhesus monkeys are used in these studies.

Method: The investigator extracts and separates L-DOPA, 3-0-methyl-DOPA, dopamine, and norepinephrine and its metabolites by a combination of the Dowex ion exchange method and alumina oxide extraction procedures. Serotonin, 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) are isolated by a modified organic solvent (butanol) extraction procedure. The methodology includes fluorometric determination of all of these compounds and radioisotope assay of L-DOPA decarboxylase, L-glutamic acid decarboxylase, and L-tyrosine hydroxylase activities.

Results: Intravenous administration of a single high dose of L-DOPA produced large, but regionally different, increases in dopamine and homovanillic acid concentrations throughout the brain as well as an elevation of the 5-HIAA concentration in most areas. A parallelism between the accumulation of dopamine formed from the administered L-DOPA and the regional distribution of L-DOPA decarboxylase was observed. Tentative evidence was obtained that the globus pallidus represents a key dopaminergic brain area. Chronic oral administration of L-DOPA only slightly affected the concentration and/or metabolism of brain amines. Chronic treatment with high oral doses of chlorpromazine resulted in persistent dyskinesias in one of two animals tested. The drug seemed to decrease utilization of serotonin in several important brain zones, especially limbic areas. Concomitantly, chlorpromazine may have increased serotonin turnover in the hypothalamus. These changes were not evident in the animal that did not develop persistent dyskinesias. The dopamine metabolism in the striatum of both animals was affected to approximately the same degree.

Toxicity of Psychotropic Drugs on Aminergic Neurons

Investigator: Rita Levi-Montalcini
Washington University
St. Louis, Missouri

Purpose: The investigator is assessing the effects of pharmacological agents on peripheral and central neurons containing catecholamines and indoleamines. She is particularly interested in the role played by these neurons in the regulation of homeostasis and behavior. Results of this study may help to establish dosage guidelines within which drugs widely used in the clinic can be administered without danger of irreversible neurotoxic lesions.

Subjects: Rats are used in the experiments.

Method: The approach is interdisciplinary, involving morphological, biochemical, pharmacological, and behavioral techniques. The investigator analyzes the effects of lesions induced in immature sympathetic neurons by adrenolytic agents; evaluates the degree of functional impairment induced by different types of chemical sympathectomy; and determines the dose levels at which permanent toxic effects are produced in nervous tissue. She is conducting similar studies in the central nervous system, evaluating the possible interactions of Nerve Growth Factor (NGF) and adrenergic blocking agents and exploring the possibility of inducing cytotoxic effects in tumor cells of sympathetic origin.