

Analytical Psychopharmacology

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Overview

The overall research program of the department is: to apply current “state of the art” technology and to develop such technology where needed to study the pharmacokinetics and pharmacodynamics of psychotropic drugs (both of use and abuse); to develop novel techniques to explore the metabolism of new psychotropic compounds and enantiomers in an attempt to elucidate the true mode of action of these compounds and to develop new experimental paradigms to evaluate pharmacological challenge studies; to explore the basic molecular pharmacology of alcohol abuse and alcoholism with particular emphasis on the endocannabinoid system; to achieve the synergy needed for such studies at both the basic and clinical level extensive interdepartmental collaborations are necessary.

The methodology developed over the past decades is of value in clinical studies. Therefore in addition to the research program described above the laboratory serves as a core facility in two NIMH and one NIDA clinical research centers, a NIDA Medication Development Research Unit and several large multicenter clinical studies within the Institute. The laboratory continues extensive collaborations with many academic research centers within and outside of the USA.

Research Programs

We continue our long-established assay development program to explore the pharmacokinetics and pharmacodynamics of new psychotropic drugs and their metabolites and, where appropriate, their enantiomers. Extensive collaborations continue with academic groups involving drug addiction, suicide, schizophrenia, depression, obsessive compulsive disorder, anxiety, childhood psychiatric disorders and autism. Basic work involves investigations at the cellular and molecular level of the interaction of alcohol with the endocannabinoid signaling system, especially membrane-delimited signal transduction research. Faculty members in our department currently have extramural support for their research activities, including support from NIMH, NARSAD, NIAAA and private sector grants.

Current Clinical Research

New analytical methodology for the determination of therapeutic agents of interest in psychiatry continues to be the focus of Dr. Suckow’s work. During the past year, development of a highly specific and sensitive liquid chromatography/mass-spectrometry procedure for measuring plasma dihydroxidine, an experimental D₁ dopamine receptor agonist, has progressed to the validation level. Other procedures for measuring GABA receptor agonists baclofen and vigabatrin are presently under development. Several protocols requiring frequent assays for the typical (e.g., chlorpromazine, haloperidol, fluphenazine, perphenazine, etc.), and atypical (e.g., aripiprazole, risperidone, ziprasidone, clozapine, olanzapine, quetiapine) antipsychotics, are on-going.

Simultaneous identification and quantitation of D-serine and L-serine has recently been achieved and is currently in use in several multi-center clinical studies. In collaboration with Dr. Daniel Javitt at Nathan Kline Institute, single-dose pharmacokinetics of d-serine will be determined in subjects following several different oral doses of d-serine. Thereafter, the peak and trough levels will be monitored throughout the study. Other excitatory amino acids, e.g., glutamate, glycine, will also be assayed. The determination of plasma d-cycloserine has begun in studies involving autistic children.

Dr. Lo and staff of the Immunoassay group continue their efforts in psychoneuroendocrine research protocols collaborating with many clinical research centers. An assay was developed and validated during this year for spinal fluid CRH content and a large number of CSF samples analyzed. Plasma levels of prolactin, ACTH, cortisol, melatonin, 6-sulfatoxymelatonin, testosterone, dexamethasone, beta-methasone, corticosterone and growth hormone were completed using methodology previously validated in our laboratory. These assays involve human, primate and rodent research protocols.

Current Basic Research

Recent discovery of the endocannabinoid system (ECS) has led to a surge in investigations of its role in addiction. Dr. Hungund's group was the first to report modulation of the ECS in synaptosomal membranes of chronic alcohol exposed (alcohol-tolerant) mice. Since then they have established a role for the ECS in alcohol-dependence and voluntary alcohol consumption and demonstrated possible utility of drugs targeted against the ECS system in reducing alcohol tolerance/dependence and voluntary alcohol consumption. They have also shown that an altered ECS could contribute to depressive and suicidal behavior. These studies have been continued and extended to isolate and identify the molecular targets at the level of signaling systems downstream, which could provide additional tools to treat addiction-related problems associated with alcohol abuse and alcoholism. They are currently exploring the possible role played by the ECS in neurobehavioral deficits in the offspring of mothers drinking during pregnancy. Preliminary results seem to implicate a role for system in the Fetal alcohol syndrome

In an extension of the above studies Dr. Basavarajappa (supported by his NIAAA K01 –award has continued his work on experiments aimed at elucidating the cellular and molecular signaling mechanisms involving endocannabinoids and CB1 receptors, specifically in alcohol-induced suppression of synaptic neurotransmission and synaptic plasticity. These signaling processes may provide important clues as to how alcohol and similarly acting drugs affect memory processing. Although our recent studies have provided several lines of evidence suggesting that the CB1 receptors and their endogenous agonists play an important role in the pharmacological and behavioral effects of alcohol, including alcohol-drinking behavior, none have identified the underlying molecular mechanisms. During the last year we have obtained considerable preliminary data, which suggest that endocannabinoids play a critical role in alcohol action on synaptic neurotransmission processes. The findings from these current studies are likely to provide support linking the endocannabinoid-mediated retrograde signaling pathway with alcohol-induced impairment of synaptic neurotransmission. Furthermore, these studies may be helpful in elucidating the importance of the endocannabinoid system in synaptic plasticity and in memory impairment resulting from alcohol and drug abuse.