Introduction

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Drugs of abuse represent a wide array of chemical classes. Therefore, it is not surprising that the consequences of drug abuse are highly dependent upon the chemical in question and vary considerably across drug classes. During the past decade, understanding of the actions of these drugs at the molecular and cellular levels has increased dramatically, thereby providing insight into developing new strategies for the treatment of drug dependence. However, the interaction of a drug with a particular biochemical system is only one factor to be considered when evaluating the pathological impact of substance abuse. The route of administration, the pharmacokinetics of the drug, conversion to toxic metabolites, and interindividual responsive-ness are just a few factors. The objective of this monograph is to evaluate the current status of knowledge of metabolism, pharmacokinetics, and pharmacodynamics of drugs of abuse. The overall goal is to identify innovative approaches for the management and treatment of the adverse consequence produced by drugs of abuse.

One of the most important challenges of drug abuse research has been providing an explanation for why all individuals do not respond or react in a similar fashion to a drug. Metabolism plays a critical role in the pharmacological and toxicological consequences of drug exposure. It is well known that the rate of formation of active, inactive, or toxic metabo-lites varies among individuals. The past decade has been marked by the characterization of substrate specificity for a large number of P-450 enzymes and the development of biochemical tools for quantitation of these enzyme levels. These advances have allowed determination of the role of metabolic enzymes in susceptibility to drug dependence, metabolic tolerance, and variability in the toxic consequence of exposure.

The future holds great promise for utilizing a "fingerprint" of P-450 enzymes as genetic markers for predisposition to either enhanced or diminished drug dependence. It is also becoming increasingly clear that brain metabolism has a more prominent role than previously thought. Notable examples include opioid, amphetamine, nicotine, and cocaine metabolism by specific isozymes to varying degrees in different organs. Both synthetic and degradative enzymes for neurotransmitters and endogenous ligands, including the putative endogenous cannabinoid ligand anandamide, deserve attention. Future

efforts should be directed toward characterization of additional isozymes responsible for metabolism of drugs of abuse, understanding regulation of gene expressions resulting in polymorphism, understanding induction of enzymes, development of selective substrates and inhibitors, and development of kinetic models, to name a few. Selective enzyme inhibitors hold promise for ameliorating the toxicity produced by metabolism of some drugs and diminishing drug use of other agents which are converted to potent compounds. The development of animal models with selective enzymatic profiles could serve to assess risk and aid in development of potential therapeutic agents for treatment of drug abuse.

While there has always been concern that metabolic transformation of agents to reactive adducts could result in neurotoxicity, 1-methyl-4-phenyl-1,2,6-tetrahydropyridine (MPTP) provided dramatic evidence. There is direct evidence, as well as considerable indirect evidence, for formation of reactive adducts for neurotransmitters, including dopamine and serotonin, and for exogenous amines such as methamphetamine, phencyclidine, and nicotine. It is now well established that certain dose regimens of methamphetamines produce neurodegeneration of dopaminergic and serotonergic neurons in several species, an effect which could also occur in humans. Several lines of evidence suggest that methamphetamine itself is not directly responsible for this neuronal damage, but rather that it produces oxygen radicals which in turn oxidize the neurotransmitters serotonin and dopamine to toxic metabolites that destroy their respective neurons. At present, the mechanism by which methamphetamine produces its neuronal toxicity has not been fully explained and is worthy of pursuit. If aberrant metabolites of dopamine and serotonin are found to be responsible for methamphetamine-induced toxicity, it is essential that these agents be identified and the mechanisms for their formation and action at the neuron be elucidated.

There is speculation that long-term exposure to cyclic tertiary amines such as cocaine, phencyclidine, and phenothiazines may result in biochemical lesions through the formation of reactive metabolites. This premise is supported by the induction of a parkinsonian state by MPTP. Although the initial product of microsomal oxidation is an electrophilic endocyclic iminium intermediate which is thought to be the reactive species primarily responsible for neurotoxicity, there is now evidence that the iminium is in equilibrium with the endocyclic enamine and that the latter is transformed to reactive species. The presence of iminium- detoxifying enzymes in cytosolic and microsomal fractions suggests that rapid inactivation of the iminium

species averts toxicity by minimizing formation of the iminium. If the premise is correct, future efforts should be devoted to designing drugs which have a higher affinity for the iminium-detoxifying enzymes. Characterizing these enzymes and identifying the reactive species of both iminium-enamine equilibrium products will provide a better understanding of the mechanisms involved in the neurotoxicity of cyclic amines and the development of strategies for minimizing their occurrence. The localization of these enzymes and establishment of substrate specificity would be of considerable interest.

Metabolism also plays a critical role in the pharmacology of cocaine. The rapid hydrolysis of cocaine via two different pathways leads to its rapid inactivation/detoxification. This rapid metabolism has been a major determinant in the methods and modes of cocaine abuse. Identification and characterization of these hydrolytic enzymes would be useful in that selective induction of these enzymes offers a potential treatment strategy for dealing with cocaine overdose. It is conceivable that long-term elevation of the enzyme or enzymatic activity could be used in conjunction with maintenance therapy for cocaine addicts. Hydrolases or esterases are also responsible for the transesterfication of cocaine. The pharmacological effect of cocaine is prolonged and enhanced when cocaine is used in conjunction with ethanol. A carboxylesterase catalyzes an ethyl transeterification of cocaine to cocaethylene, which is biologically active. In addition, ethanol inhibits cocaine metabolism. The increased levels of cocaine and cocaethylene may contribute to the prolonged and enhanced effects of cocaine. Characterization of the responsible enzymes would be important for developing substrate specificity and other means for attenuating this process. An alternative approach to detoxification involves biocatalysts. Theoretically, these agents would be devoid of pharmacological properties themselves, a feature that is not always present in therapeutic compounds. In principle, the biocatalysts should work in an exponential fashion which would enable them to detoxify large quantities of the drug. While biocatalysts have tremendous potential, there are many unanswered questions. In addition, development of appropriate models for evaluating biocatalysts is essential.

It seems highly improbable that either in vitro model systems or computer simulations will be introduced in the near future that would give researchers the confidence to administer drugs to humans without prior testing in other animal species. Most likely animal models will continue to be used as predictors for pharmacokinetics and toxicity of drugs in humans. Improvements in allometric models, or the correlation of pharmacokinetics among different species, is to be encouraged. Also, hair has been identified

as an excellent repository for detection of abused drugs. While there is relatively little controversy regarding hair analysis for the purpose of establishing the occurrence of drug use, the reliability of monitoring the incidence of prior use is far less certain. It remains to be determined whether a pharmacokinetic model can be developed which has a high degree of predictability for temporal incorporation of drugs in hair.

The primary focus of the adverse consequences of drugs of abuse has been directed toward the central nervous system (CNS), with justification. These drugs are abused because of their actions on the brain, and they serve as important probes for exploring brain function as it relates to cognition, pain perception, pleasure, and so forth. Most of the adverse consequences of drug exposure emanate from the CNS, either through impairment during intoxication or long-term behavioral changes. Increasingly, attention is being directed to the adverse effects of drugs of abuse on the entire organism rather than merely the brain. The National Toxicology Program examines the pathological consequences of long-term exposure to any drug. An important aspect of this program is the attempt to establish the relevance of the animal results with human exposure.

The acquired immunodeficiency syndrome (AIDS) epidemic has served to increase awareness that the adverse consequences of drug abuse extend beyond the acute and chronic effects produced by these drugs on the brain. The immune system has received considerable attention because both opioid and cannabinoid receptors have been identified in spleen cells. Additionally, specific effects of several drug classes on immune function are now well documented. These studies not only provide important insights into the potential harm that drugs of abuse inflict on a compromised immune system; they provide opportunities to elucidate the mechanism of action these drugs.

Lastly, the mode by which individuals abuse drugs has become an increasingly important factor. When the primary mode of cocaine abuse switched from nasal insufflation to inhalation, a transformation in the abuse of cocaine occurred. The ease by which cocaine free base could be volatilized and inhaled, coupled with savvy marketing strategies of drug pushers, have made a lasting impact on the manner in which drugs are abused. Although methamphetamine has been smoked for many years in some cultures, the recent rise in heroin inhalation underscores this point. The question arises as to whether drugs are more addictive when inhaled. While this questions remains to be answered, it is clear that inhalation and smoking represent highly efficient means of abusing some drugs. There is now concern as to whether the pattern and frequency of use of other drugs might change as dramatically as that of cocaine if the route of

administration changes to volatilized and inhaled. Furthermore, establishing the pharmacokinetics of drugs after inhalation should serve to determine whether sensitivity is enhanced via inhalation.

There is a need for new strategies in providing direct evidence for the formation of reactive intermediates and the identification of adducts. Since the formation of adducts may be without adverse consequence, it is important to establish models for assessing the outcome, particularly with regard to qualitative and quantitative analysis of adduct formation, measurement of neuronal impairment, and pathological relevance. Current treatment approaches for dealing with life-threatening conditions arising from acute drug intoxication stress amelioration of symptomatic consequences. New therapies in the future may well include highly selective enzyme inhibitors, alterations in the activity of metabolic enzymes, use of biocatalysts, and so forth. Additionally, establishing pharmacogenetic polymorphism may well explain individual sensitivity and vulnerability to CNS-acting drugs. Adding new research tools is necessary for meaningful advances in the management of drug abuse treatment.

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