CROSS-SPECIES EXTRAPOLATION IN THE ASSESSMENT OF NEUROTOXICITY. David A. Eckerman. University of North Carolina, Chapel Hill, NC.

The use of animal data in the evaluation of potential adverse effects of neurotoxicants on human cognitive function will be reviewed. In particular, the effects of representative toxicants including metals, agents that impair primarily through cholinergic blockade, and selected solvents or agents which produce solvent-like effects, on measures of learning and memory will be contrasted across species to determine which of the various measures used for assessment in different species are generally selective to, and sensitive for, neurotoxic impairment. Of the various approaches used to determine cognitive impairment across species, their relative sensitivity to distinguish sensory, motor, and emotional/motivational effects from cognitive effects will be discussed. Both the predictive and construct validities of popular procedures to assess learning- and memory-impairing effects of toxicants will also be evaluated. Specific recommendations will be offered regarding animal measures that optimally assess risk of impairment of neurobehavioral function. Differences in strategies designed to screen for cognitive impairment, in contrast to studies designed to elucidate specific behavioral determinants of toxicant effects, will also be discussed. Attention will be placed on the need to screen exhaustively for behavioral toxicity and adequately characterize functional impairments. The use of a meta-analytic database approach in the assessment cognitive impairment will be described and advocated for the continuation of refinement of animal test methods and their functional interpretations. In addition, the ability to address those aspects of human cognition that have been difficult to model using animal testing will be discussed. This speaker will also serve as a discussant for the effects seen in the first three paper presentations.

SYMPOSIUM

Behavioral Factors in Drug Sensitization and Tolerance.
Chairs: *Christine A. Sannerud* and *Charles W. Schindler*, National Institute on Drug Abuse, Baltimore, MD.
Discussant: *James Smith*, Mercer University, Atlanta, GA.

CONDITIONED SENSITIZATION TO COCAINE: PHARMACOLOGICAL AND NEUROANATOMICAL SUBSTRATES. Susan R. B. Weiss,* Robert M. Post,* Dave Fontana,† and Agu Pert.* *NIMH, Bethesda, MD, and †Syntex Research, Palo Alto, CA.

We evaluated the effects of various pharmacological agents or brain lesions on a 2-day conditioned cocaine sensitization paradigm. Rats were treated with a high dose of cocaine on day 1 (40 mg/kg) or saline, and tested for their locomotor response to a low dose challenge of cocaine on day 2 (10 mg/kg). Previous studies have shown this paradigm to produce conditioned or context-dependent sensitization, that is, increased locomotor activity *only* in animals treated with the high dose of cocaine in the test environment. Dopamine antagonists (D_1, D_2, or mixed) block the development but not the expression of conditioned cocaine sensitization. Lesions of the nucleus accumbens or the amygdala also interfered with the development of cocaine sensitization, without blocking cocaine's activating effects on day 1. Overall, the data demonstrate the importance of dopamine systems, particularly in the nucleus accumbens and amygdala, for the development of conditioned sensitization to cocaine.

BEHAVIORAL AND PHARMACOLOGICAL FACTORS INFLUENCING ENHANCED SENSITIVITY TO OPIOID ANTAGONISTS. C. W. Schindler, J. L. Katz, R. J. Marley, T.-P. Su and S. R. Goldberg. NIDA Addiction Research Center, Baltimore, MD.

Previous research has indicated that there are two types of enhanced sensitivity observed following opioid antagonist treatment. The first type has been observed primarily in rodents, occurs following continuous infusions of the antagonist, disappears soon after the cessation of antagonist treatment, and is correlated with opioid receptor up-regulation. The second type has been observed primarily in primates, can occur with acute antagonist treatment, and is persistent. We have recently shown that this second type of enhanced sensitivity can also be observed in rodents. When rats were given naltrexone in a cumulative dosing manner once per week over a period of 8 weeks, enhanced sensitivity was observed to naltrexone's response rate suppressant effect as well as naltrexone-elicited salivation. This enhanced sensitivity persisted for at least 10 weeks without any naltrexone injections. Further, the enhanced sensitivity appeared to develop through conditioning processes. In pharmacological characterization studies, it was determined that while the opioid agonists morphine and ethylketocyclazocine partially antagonized the enhanced sensitivity, the nonopioid chlordiazepoxide did not. Further, only naloxone showed complete cross-sensitivity to naltrexone, while limited cross-sensitivity was observed for diprenorphine, MR 2266, and amphetamine. In studies of receptor binding, μ receptors were unchanged in sensitized animals, while κ and δ receptors were increased or decreased depending on the brain area studied. Finally, enhanced sensitivity to naltrexone was associated with an up-regulation in GABA receptor function. These studies demonstrate the relative complexity of opioid antagonist-induced enhanced sensitivity.

COMPENSATORY LEARNING IN ETHANOL TOLERANCE AND ITS SUBSEQUENT "HEDONIC" VALENCE. David V. Gauvin and Frank A. Holloway. University of Oklahoma Health Sciences Center, Oklahoma City, OK.

The presentation will focus on : a) the characteristics of learning factors in the development of tolerance to ethanol's (ETOH) disruptive effects on rat operant performance; b) the consequences of such tolerance development and of other historical factors, on ETOH's subsequent hedonic properties; and c) the limited aspects of behavioral sensitization to ETOH. In studies of rat operant performance, tolerance develops to both the biphasic effects of ETOH. The degree of tolerance developed: a) lasts for up to 6 months; b) relates to the learned adaptations to task-specific disruption of behavior during chronic regimens; c) is not dependent on environmental cues associated with the task; and d) is not present in control subjects. Tolerance development would appear to be an interaction between the direct and/or delayed effects of ETOH and the functional characteristics of the task. Tolerance may contribute to or facilitate ETOH consumption by reducing the "costs" of drinking. We have conducted two sets of studies to indirectly examine the issue by asking how tolerance development in the operant task might alter subsequent changes in ETOH's positive and/or negative hedonic properties as measured by ETOH place learning or conditioned ETOH taste aversion. Although a number of studies have demonstrated a

behavioral sensitization to ETOH's stimulant-like effects in mice, rat studies to date have shown no such sensitization. In fact, given the opportunity, rats will develop tolerance to the rate-increasing or stimulant effects of low dose ETOH treatments, whereas mice will not. Genetic and cross-species limitations have been proposed for this difference. In sum, during the process of tolerance development in the operant situation, rats apparently "actively" learn to compensate for the ETOH-related decrease in reinforcement delivery associated with performance disruptions under schedules of reinforcement sensitive to both the rate-increasing and rate-decreasing effects of ETOH. Additionally, this tolerance to ETOH's disruptive effects appears to subsequently reduce ETOH's usual negative hedonic valence, thereby enhancing its "net" reward properties.

BEHAVIORAL FACTORS INVOLVED IN CONTINGENT TOLERANCE TO BENZODIAZEPINES (BZ). Christine A. Sannerud. NIDA-Addiction Research Center, Baltimore, MD.

The present studies were conducted to evaluate the interactive role of behavioral variables with drug administration in the development of tolerance to benzodiazepine agonists. The first study evaluated the role of behavioral variables in the development of tolerance to the sedative effects of chlordiazepoxide (CDP) and the effect on sensitivity to acute administration of other BZ and non-BZ drugs. Rats received CDP either before (PRE) or after (POST) exposure to the daily experimental session. Large group differences were seen in the rate and degree of tolerance development to CDP. Group PRE showed 3- or 4-fold shifts to the right in the weekly CDP dose-response curves, 10-fold rightward shifts in the midazolam dose-response curves, slight sensitivity to flumazenil, 10-fold increased sensitivity to FG 7142, and cross-tolerance to pentobarbital. Group POST showed no tolerance to CDP, no change in flumazenil, but a 10-fold increased sensitivity to FG 7142. Several ongoing studies are further characterizing the specific behavioral contributions and are evaluating the biochemical correlates underlying CDP contingent tolerance. A second study evaluated the ability of behavioral variables to modify the development of tolerance to the discriminative stimulus (DS) effects of midazolam (MDZ). Rats were trained to discriminate MDZ from no drug in daily sessions consisting of multiple discrete 20-min trials. Tolerance developed to the DS effects of MDZ when it was given while training was suspended: at week 4 chronic MDZ produced 0.5–2 log-unit increases in the minimum discriminable dose of MDZ. In contrast, continued training during chronic MDZ produced no tolerance to MDZ's DS effects: at week 4 chronic MDZ the MDD of MDZ was not different than prechronic or either saline condition. Taken together these data demonstrate that chronic drug administration is necessary but insufficient to produce tolerance to a drug's effect. This emphasizes the need to evaluate interactions between behavioral variables and training contingencies to modify a drug's effects during chronic administration.

BEHAVIORAL PROCESSES IN OPIOID TOLERANCE. Ellen A. Walker and Alice M. Young. Wayne State University, Detroit, MI.

Tolerance to the behavioral effects of repeatedly administered opioids is regulated by both behavioral and pharmacological processes. This discussion will review ways in which behavioral processes can alter the development, progression, and maintenance of tolerance to the effects of opioids in a variety of behavioral paradigms. The discussion will emphasize the interactions of behavioral and pharmacological factors. Opioids exert prominent direct effects on operant behaviors, and sensitivity to such effects can diminish upon repeated drug administration. The development and magnitude of such tolerance can be modulated by a variety of behavioral influences, including prior behavioral conditions, ongoing differential reinforcement contingencies, and stimulus control processes. In addition to exerting direct effects on operant behaviors, opioids can function as discriminative or conditional stimuli, and tolerance to these functional effects can also be modulated by behavioral influences. Finally, opioids can alter reflexive behaviors, and tolerance to such effects can be modulated by behavioral processes, such as respondent conditioning, blocking, extinction, and sensory preconditioning. In each of these behavioral paradigms, the influences of behavioral processes on tolerance can, in turn, be modulated by pharmacological factors, such as agonist efficacy, maintenance dose and treatment regimen. Characterization of such multiple influences on tolerance development will require further study of both pharmacological and behavioral processes.

SYMPOSIUM

Relationship of Problem Severity to Treatment Outcome in Cocaine Dependence.

Chairs: *John Grabowski,* University of Texas Health Science Center, Houston, TX, and *Stephen T. Higgins,* University of Vermont, Burlington, VT.

Discussant: *George Bigelow,* The Johns Hopkins University School of Medicine, Baltimore, MD.

FLUOXETINE DOSE, VISIT FREQUENCY, AND SEVERITY IN COCAINE DEPENDENCE TREATMENT. John Grabowski, Ronith Elk, Howard Rhoades, Kathy Cowan, Joy Schmitz and Kimberly Kirby. University of Texas Health Science Center, Houston, TX.

The antidepressant fluoxetine is one of several medications studied for efficacy in treatment of cocaine dependence. Grabowski et al. (in preparation) describe no clear benefit of fluoxetine (retention or cocaine-free drug screens) in a double-blind study of cocaine-dependent patients. Grabowski et al. (in preparation) describe limited benefit of fluoxetine in a cocaine-using methadone-maintained opiate population, while Batki et al. (1990) reported clear benefit in an open study with a similar population. Reports of other pharmacological interventions have likewise been equivocal. There is a need to examine data from heterogeneous drug-using populations in medication trials to determine if differential effects emerge as a function of patient characteristics or treatment elements.

This double-blind placebo-controlled study examined the joint action of fluoxetine and clinic visit frequency in cocaine treatment (3 × 2). Intake reviewed major areas including drug history, medical status, psychiatric status, and social function. Patients were assigned to fluoxetine doses of 0 mg, 20 mg, or 40 mg and began a 2-week stabilization phase within 3 days. Medication effect was examined in the context of patients receiving either 2 or 5 take-home doses per week (clinic