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