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