HYPERSENSITIVITY TO D-AMPHETAMINE YEARS AFTER EARLY SOCIAL ISOLATION William T McKinney, M D Professor of Psychiatry, University of Wisconsin School of Medicine, Clinical Sciences Center, 600 Highland Avenue, Madison, WI 53792, and Gary W Kraemer, Ph D Associate Scientist, Primate Laboratory, 22 North Charter Street, Madison, WI 53715

Following removal from a one month period of isolation during the second six months of life, rhesus monkeys exhibited a range of abnormal behaviors They were subsequently rehabilitated, using behavioral methods, and showed age appropriate social behaviors under baseline conditions However, the administration of low doses of d-amphetamine at 30–36 months of age precipitated bouts of severe aggression some of which could be terminated only by separating them into individual cages They also showed other behavioral effects plus a much higher elevation of cerebrospinal fluid norepinephrine in response to the amphetamine than control animals with no history of early isolation

THE BENZODIAZEPINE-GABA RECEPTOR SYSTEM AND SOCIAL ATTACHMENT Thomas R Insel Laboratory of Clinical Science, NIMH, Poolesville, MD 20837

Maternal-infant attachment in rodents provides a potentially useful model for testing hypotheses about human developmental psychobiology Recently, clinical researchers have linked childhood separation anxiety to adult anxiety disorders (Gittleman, 1985) To investigate one aspect of this link, we studied the role of the benzodiazepine-GABA receptor system in a rodent model of separation distress Infant rats, when isolated, emit ultasonic distress vocalizations These ultrasonic cries, inaudible to human observers, are a potent stimulus for eliciting maternal retrieval Diazepam, an anxiolytic benzodiazepine, was found to decrease, while pentylenetetrazol, a potent anxiogenic, was found to increase the number of these ultrasonic distress calls during a 2-minute isolation test The benzodiazepine receptor antagonist, RO-15-1788, which generally lacks intrinsic effects, also decreases the number of ultrasonic distress calls at relatively low doses (5 0 mg/kg) suggesting that the benzodiazepine receptor system may be involved in the physiologic mediation of these calls To further investigate this possibility, benzodiazepine receptors were labeled *in vivo* with ^{3}H-RO-15-1788 injected either during a quiet period with littermates or during a period of social isolation Results from autoradiographic studies of labeled brain sections suggest that certain subgroups of benzodiazepine receptors may be involved in the neural response to social separation

ALCOHOL AND AGGRESSION INTERACTIONS WITH GONADAL HORMONES AND BENZODIAZEPINES Klaus A Miczek Department of Psychology, Tufts University, Medford, MA 02155

Alcohol and benzodiazepines share a similar behavioral profile in preclinical tests For example, the effects of these drugs on attack and threat behavior as compared to those on defensive behavior are characterized by biphasic dose-effect curves, i e , low doses increase attacks and threats, whereas higher doses decrease these behaviors Tolerance develops to the aggression-suppressant effects of these drugs, and increases in aggression are seen during withdrawal from chronic exposure to these drugs That these drugs share common mechanisms of action for their behavioral effects, particularly those on aggression, is likely, since they potentiate each others pro- and anti-aggressive effects One current strategy focuses on the GABA-benzodiazepine receptor-chloride ion channel complex The benzodiazepine receptor antagonist Ro15-1788 blocks the increasing as well as decreasing effects of diazepam on aggression, but fails to show similar effects on alcohol's aggression-modulating effects The partial benzodiazepine antagonist Ro15-4513 blocks the sedative and motor impairing effects of ethanol to some extent, but does not block the aggression-decreasing effects of ethanol, Ro15-4513, similar to partial or full inverse agonists, has aggression-suppressing effects in itself, and leads to seizures in squirrel monkeys Another strategy examines gonadal steroids and their releasing hormones as potential mediators of the aggression-modulating effects of alcohol In mice, rats and squirrel monkeys that have high blood titers of testosterone, low doses of alcohol increase aggressive behavior toward intruders or toward members of the social group The aggression-heightening effect of alcohol is seen only when the dominant males in a social group are in the mating season, i e , when testosterone is elevated to more than 200 mg/dl in blood When subordinate monkeys receive SC testosterone injections to produce blood levels in exess of those seen in dominant monkeys, similar aggression-heightening effects of alcohol can be seen Castrated mice that are implanted SC with large testosterone pellets or receive testosterone implants into discrete subcortical structures show aggression-heightening effects of low to intermediate doses of alcohol and require twice as high alcohol doses to suppress aggressive behavior than intact mice The interaction of alcohol with androgen-sensitive sites in the CNS and with benzodiazepine receptors as potential mechanisms for the alcohol-aggression effects promises to provide clues for the neurobiological basis for these highly significant actions of alcohol

SYMPOSIUM

Risk Assessment Techniques in Behavioral Toxicology
Sunday August 30, 1987 • 11 00 a m –12 50 p m
Marriott Marquis Hotel • Gotham Room
Chair *Michael Gage,* U S Environment Protection Agency, Research Triangle Park, NC

PROVIDING DATA FOR RISK ASSESSMENT ACUTE BEHAVIORAL TOXICITY OF SOLVENTS Ronald W Wood, Ph D Research Associate Professor of Environmental Medicine, New York University Medical Center, New York, NY 10016

Reflecting upon the problems of risk extrapolation below the doses used experimentally, Dews called for a new approach to small risk estimation, namely the determination of an ED 10 for each replicate, the variation in this estimate, and the subsequent assumption of a normal distribution to estimate the dose which produces a 10^{-5} or 10^{-6} effect (Dews, 1980) Dews (1986) expanded upon this notion, and offered an example drawn from the work of his collaborators (Glowa *et al* , 1983) In proposing a similar method to generate allowable daily intakes, Crump (1984) advocated the