SYMPOSIUM

Neurobehavioral Toxicology of Learning and Memory: Environmental Determinants of Effects.

Chair: *John R. Glowa*, Inter-Institute Unit on Behavior, National Institutes of Health, Bethesda, MD.

Discussant: *Peter B. Dews*, Harvard Medical School, Cambridge, MA.

THE NATURE OF LEAD-INDUCED LEARNING IMPAIRMENTS AND NEUROTRANSMITTER SYSTEM INVOLVEMENT. D. A. Cory-Slechta. University of Rochester School of Medicine, Rochester, NY.

Despite considerable evidence documenting the deleterious effects of even very low levels of lead (Pb) exposure on cognitive functions in humans and experimental animals, little is as yet understood about the selectivity of these effects, the nature of the underlying error patterns, or the behavioral mechanisms involved. Moreover, neurotransmitter system alterations are certainly proved by Pb exposure, but the respective contribution of these effects to learning deficits have not been clearly delineated. Using a multiple schedule of repeated acquisition (RA) and performance (P) of response sequences, we have found that Pb exposure indeed produces selective learning impairments as indicated by decrements in accuracy on the RA but not the P component of the schedule. Analysis of error patterns, however, showed a performance basis for the Pb-induced decline in RA accuracy comprised of a perseverance on the P sequence during RA components. Perseverance also occurred on a single lever, a response pattern never reinforced by the schedule. Based on the nature of these error patterns and suggestions in the literature of attentional deficits resulting from Pb exposure, the possibility that the deficits in stimulus control served as the behavioral mechanisms of these effects of Pb was explored. A 5-s tone was added to each transition between the RA and P components of the schedule. The intervention had little effect on RA accuracy levels, however, suggesting that the behavioral mechanism(s) of these effects lie elsewhere. Attempts to begin to explore the involvement of neurotransmitter systems in these effects have relied on a) comparisons of error patterns on the RA component produced by Pb to those found with cholinergic glutamatergic antagonists; b) comparisons of acute dose-effect curves in control vs. Pb-treated rats administered dopaminergic or glutamatergic compounds; and c) comparisons of generalization curves of control and Pb-treated rats trained to discriminate dopaminergic, cholinergic, or glutamatergic compounds from saline using standard drug discrimination paradigms. Results to date suggest dopaminergic supersensitivity and/or NMDA receptor complex subsensitivity may be involved in Pb-induced learning deficits.

COLD-INDUCED CHANGES IN BEHAVIOR: RELATION TO ALTERATIONS IN CATECHOLAMINES. John R. Thomas, Stephen T. Ahlers, David Shurtleff and John Schrot. Naval Medical Research Institute, Bethesda, MD.

Exposure to ambient cold temperatures affects a variety of behavioral functions, possibly through stress-related mechanisms. One sensitive behavioral effect of exposure to cold stress, which does not occasion hypothermia, is an impairment of performance on a delayed matching-to-sample task in humans and rats. During cold exposure matching accuracy is decreased when the delay intervals between the sample and test stimuli are long, while accuracy at short intervals is usually unaffected. Another salient feature observed when subjects perform under delayed matching-to-sample schedules in the cold is that response latencies to the sample and test stimuli are considerably shorter. Subsequent experiments have examined the effects of cold stress on the temporal characteristics of responding maintained under differential reinforcement-of-low-rate schedules. The results of these studies indicate that exposure to the cold shifts the relative distribution of interresponse times to the left, that is, shorter values. Our studies have also examined how the effects of cold stress may result from disruption of catecholamine neurotransmission. Specifically, these studies show that exposure to cold stress results in excess release and subsequent depletion of norepinephrine and possibly dopamine. Recent findings from our laboratory indicate that administration of the catecholamine precursor tyrosine reduces cold-induced impairment of matching accuracy in both humans and rats. Tyrosine administration also decreases cold-induced impairment of responding maintained under differential reinforcement-of-low-rate schedules. These data suggest that the disruption of matching accuracy and the alterations in temporally controlled performances under the differential reinforcement-of-low-rate schedules as a result of cold stress share a common underlying mechanism, depletion of central catecholamines. Additional research, directed at exploring the possible role of neuropeptide-Y and corticotropin-releasing factor in the modulation of cold-induced performance impairments and central catecholamine release, will be discussed.

NEUROBEHAVIORAL TOXICOLOGY OF CHOLINESTERASE-INHIBITING PESTICIDES. Robert C. MacPhail. U.S. Environmental Protection Agency, Research Triangle Park, NC, and University of North Carolina, Chapel Hill, NC.

Cholinesterase inhibitors have been used extensively as insecticides both in this country and worldwide. The two major classes of cholinesterase inhibitors are the carbamates and organophosphates. Many of the behavioral and neuropharmacological effects of these pesticides are similar to those of drugs used either clinically or experimentally. Accidental (acute) exposure of humans has produced many effects, via actions on the central and/or peripheral nervous system, that are similar to those seen in laboratory animals. Much less is known, however, about potential long-term effects produced by acute exposures. Repeated exposures of laboratory animals to cholinesterase inhibitors have frequently been reported to result in tolerance to the effects seen after acute exposure. Given the importance of cholinergic neurotransmission in learning, memory, and a number of other nervous system functions, questions remain regarding the role of exposure duration. This presentation will review recent data on the effects of acute and repeated exposures of laboratory rats to a number of carbamates and organophosphates. A variety of paradigms have been used to assess these effects, including those that have been designed to assess spatial memory and schedule-controlled performances. The presentation will also address possible sites of action of cholinesterase inhibitors, and the roles that measures of learning, memory, and performance can play in assessing the neurobehavioral toxicology of these compounds.