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Learning and Memory Enhancement by Neuropeptides
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As detailed in the first annual letter report for July 1, 1986-June 30, 1987, the major purpose of this work, is to study mechanisms responsible for the toxic effects of the organometal neurotoxin trimethyltin (TMT) on learning, in order to develop strategies for prevention or alleviation of toxicity. Trialkyltins are used as stabilizers for plastics, or as biocides for control of fungus, barnacles, bacteria and insects. As well as being an environmental anti-fouling toxicant of specific interest to the Navy, these compounds may also be of interest as a model treatments for study of learning/memory dysfunction resulting from exposure to other toxicants (e.g. other heavy metals, organic solvents), or arising from disease states. We study learning in an autoshaping task, in which rats learn to touch a lever to obtain food. During the past six months, two papers have been published:

Cohen, C.A., Messing, R.B. and Sparber, S.B. Selective learning impairment of delayed reinforcement autoshaped behavior caused by low doses of trimethyltin. Psychopharmacology (1987) 93: 301-307.

Sparber, S.B., Cohen, C.A. and Messing, R.B. Reversal of a trimethyltin-induced learning deficit by desglycinamide-8-arginine vasopressin. Life Sciences (1988) 42: 171-177.

In addition, another paper has been submitted for publication:

Gerbec, E.N., Messing, R.B. and Sparber, S.B. Parallel changes in operant behavioral adaptation and hippocampal corticosterone binding in rats treated with trimethyltin. Submitted to Brain Research.

Also being prepared for publication is a study showing that rats treated with TMT or a mixed ganglioside preparation (which was administered to determine a possible therapeutic effect in TMT-treated animals) have decreased concentrations of hippocampal glucocorticoid receptors, which may be related to cognitive impairments. This work was presented at the Xth International Congress of Pharmacology in August. Interestingly, TMT-treated rats have elevated levels of glial fibrillary acidic protein (GFAP), an indication of the cytotoxicity produced by this compound. Rats treated with gangliosides, which induce a cognitive impairment but no cell death, have normal levels of GFAP, but still exhibit the decrease in corticosteroid binding. Thus, this decrease is probably independent of hippocampal cell death, and may be a down regulation. In future work we wish to examine the effects of manipulations of the pituitary adrenal axis on TMT toxicity as measured behaviorally, biochemically and histologically.

We have also done some work with the opiate antagonist naloxone, a substance which has memory-enhancing properties in many assays, but have found that this substance actually impairs acquisition of autoshaped behavior, whether given before or after training sessions. A manuscript describing this work is in preparation, and an abstract was presented at the Neuroscience meeting in New Orleans (Society for Neuroscience Abstracts, [1987] 13: 634).

During the last year, work in our laboratory has also demonstrated that autoshaping is highly dependent upon the deprivation state of the animal: more food deprived rats learn faster. This is not simply a generalized behavioral activitation produced by food

deprivation, since more food deprived rats also show better learning of latent inhibition. It appears that deprivation state also influences the performance of rats exposed to TMT, similarly to its effect in normal animals. This is consistent with the capacity for a vasopressin analog to attenuate the learning deficit in rats treated with TMT, and indicates that the learning impairment is not absolute, but rather may be amenable to various palliative treatments. A manuscript describing this work is also in preparation. Our present research plans include studies investigating interactions between deprivation levels and effects of drugs and toxicants.

We have also been investigating an associative (cognitive) deficit caused by the high dose of TMT in our behavioral assays. It appears that although they may be hyperreactive to the lever, these animals do not behave similarly to normal animals during intertrial or reinforcement delay intervals. Normal animals spend more time near the lever during intertrial intervals, and more time near the trough during reinforcement delays. Rats given the high dose of TMT do not spend as much time as would be expected near the food trough during reinforcement delays. This work will be presented at the European Winter Conference on Brain Research, Tignes, France, March 6-12, 1988. In future work, we hope to find a biochemical correlate for these animals, and initial studies will be on glutamate receptors.

Other work in progress is concerned with two issues:

1. We have found that 6.0 mg/kg of TMT induces a decrease in hippocampal corticosterone receptors (see above). However, a higher dose (7.5 mg/kg) does not induce as large a decrease (in parallel with behavioral data showing that these animals make more lever touches in our autoshaping task) (see above). When rats given 6.0 mg/kg of TMT are required to respond in an operant fixed ratio paradigm in which the ratio requirement (number of responses necessary to obtain a food pellet) is doubled each day (progressive fixed ratio task), rats given 6.0 mg/kg make fewer responses than controls as the ratio requirement increases, while rats given 7.5 mg/kg of TMT make more responses than controls. Thus, rats given 6.0 mg/kg of TMT appear to provide a convenient preparation with which to investigate the functioning of hippocampal steroid receptors.
2. We are investigating the neurotoxic effects of tributyltin, a compound that is commonly found in fungicides and anti-fouling agents.

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