The Murine Brain Slice as a Model for Investigation of Environmental Toxin Involvement in the Etiology of Parkinson's Disease

by

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(Abstract)

Epidemiological and analytical studies have suggested that environmental exposure to neurotoxic insecticides may exist as a factor in the etiology of Parkinson's Disease (PD). This study has focused on two insecticides, dieldrin and heptachlor epoxide, members of the cyclodiene class of The cyclodienes are environmentally persistent, and brain insecticides. residues of these compounds are correlated with the occurrence of PD. Cyclodiene mode of action has been attributed to two mechanisms: 1) facilitation of neurotransmitter release (with specificity for release of dopamine) and 2) antagonism of the inhibitory neurotransmitter, GABA. In order to assess the relative contributions of these two mechanisms leading to toxicity, eletrophysiological studies were undertaken in murine striatal slices. Extracellular recordings of spontaneous nerve discharge were used to compare the effects of the cyclodienes and the prototypical GABA antagonist, picrotoxinin, upon striatal neurons. At low micromolar concentrations of cyclodiene, depression of firing, consistent with dopamine release and not GABA antagonism, was seen. Alternatively, application of the prototypical GABA antagonist, picrotoxinin, produced excitation in slices. Additionally, the inhibitory action of dieldrin was blocked by a dopamine receptor (D_1)

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antagonist, fluphenazine, verifying that cyclodiene-released dopamine was responsible for the observed depression of striatal neurons. These results suggest that the ability of these cyclodienes to evoke neurotransmitter release may significantly contribute to the neurotoxicity of these cyclodienes *in vivo*. In light of this data, the neurotoxic potential of the cyclodiene insecticides must be reassessed, particularly within the scope of PD.

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