

DITHIOCARBAMATE PESTICIDE EXPOSURES, ALDEHYDE DEHYDROGENASE INHIBITION, AND RISK OF PARKINSON'S DISEASE

Beate Ritz, *UCLA, USA*

Shannon L. Rhodes, *UCLA, USA*

Arthur G. Fitzmaurice, *UCLA, USA*

Myles Cockburn, *USC, USA*

Jeff M. Bronstein, *UCLA, USA*

Background and Aims: Chronic exposure to pesticides has been associated with increased risk of sporadic PD in humans. A hallmark of PD is the selective degeneration of dopaminergic neurons in the substantia nigra. Several studies have suggested that 3,4-dihydroxyphenyl-acetaldehyde (DOPAL), the MAO-B product of dopamine metabolism, is toxic to dopaminergic neurons. We hypothesized that exposure to certain pesticides can potentiate this toxicity by inhibiting aldehyde dehydrogenase (ALDH) which would otherwise oxidize DOPAL to the less toxic DOPAC. Furthermore, human genetic variability in ALDH might influence susceptibility to PD in the presence of pesticide exposure.

Methods: To investigate this hypothesis we used both biochemical and epidemiologic approaches. Spectrophotometrically we determined the ALDH inhibiting activity of 30 pesticides in mitochondrial preparations containing rat hepatic ALDH and exposed primary neuronal cultures to these pesticides to determine the loss of dopaminergic neurons. In parallel, we performed genotyping of the ALDH2 gene on DNA samples from a case-control study of 363 incident PD patients and 427 population controls recruited in a region of California with extensive commercial agriculture. A geographical-information systems computer model we developed was used to assess each subject's exposure to commercial pesticides for the years 1974-1999, using state-mandated pesticide use reports, land use maps, and residential/occupational addresses.

Results: Age, gender, and smoking adjusted odds ratios of PD were estimated in logistic regression models including average lifetime exposure to specific pesticides, ALDH2 clade, and an interaction term. We found 50-200% increases in PD risk associated with exposure to fungicides identified in our biochemical screens (e.g. thiram, mancozeb, maneb) and observed a suggestive interaction between the ALDH2 clade and pesticide exposures.

Conclusions: Our results suggest that certain pesticides can impact ALDH function and may lead to increased PD risk. Furthermore, genetic variability in the ALDH2 gene appears to potentiate this effect.