Role of Lindane in Membranes. Effects on Membrane Fluidity and Activity of Membrane-Bound Proteins

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The influence of lindane (gamma-hexachlorocyclohexane) on fluidity of plasma membranes from rat renal cortical tubules has been investigated. Preincubation with lindane increased membrane fluidity. This effect was accompanied by (i) a decrease in the transport of glucose with regard to the controls and (ii) an inhibition of the $\beta$-adrenergic stimulatory activity upon cyclic AMP accumulation. However, a significant decrease of the membrane fluidity was found when rats were injected with lindane for 12 days. The injection of lindane exerted the opposite effect on the membrane proteins, the glucose transporter and the $\beta$-adrenergic receptor, enhancing the glucose uptake and increasing the isoproterenol-stimulated cyclic AMP accumulation. A possible explanation of the difference could involve a resistance to membrane disordering by lindane through a regulatory mechanism that would balance the activity of many lindane-sensitive proteins in insecticide-injected rats.

KEY WORDS: lindane; membrane fluidity; adenylate cyclase; glucose transport.

INTRODUCTION

Lindane, the gamma isomer of hexachlorocyclohexane, is an important organo-chlorine insecticide extensively used in developing countries as a household, agricultural and gardening pesticide and in human and veterinary medicine as an ectoparasiticide to treat lice and scabies infestation (1, 2). Lindane gains entry into the body system as a food toxicant, by inhalation into lungs or by diffusion through the skin (3, 4). Even though lindane is rapidly metabolized in the body and most of the metabolites are excreted in water-soluble form (5, 6), this insecticide is accumulated in the adipose tissue and in the membrane lipid bilayer of the cells (7).

The adverse health effects of lindane have been studied extensively. The

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principal responses of acute exposure to lindane in animals appear to be neurological and behavioral alterations (8, 9), although changes in hepatic and kidney functions have also been documented in chronic exposure (10). Lindane incorporates in membrane lipid moieties and this effect perturbs membrane permeability (7). In this way, previous in vitro toxicity studies from our group with lindane have demonstrated that this toxicant increased the membrane fluidity in a way that is clearly dose-dependent (11, 12). Therefore, many cellular events in which membranes are involved would be affected by lindane. In this regard, lindane interacts with (a) the modulation of calcium levels (13–15); (b) the inositol phospholipid turnover (16–19); (c) the γ-aminobutyric acid (GABA)-activated chloride channels (20–22); (d) the stimulatory activity of several agonists on cyclic AMP accumulation (23–27); and (e) the glucose transport (18, 28). However, the changes in membrane fluidity induced by lindane, when the toxicity studies were carried out in vitro, were different from the changes induced when the insecticide was injected subcutaneously in chronic toxicity studies (12), suggesting a resistance to membrane disordering by lindane through a regulatory mechanism that would balance the membrane lipid composition (12, 29).

These features prompted us to study the possibility that renal adaptation to lindane intoxication could affect the activity of membrane-bound proteins. For this purpose we tested in isolated renal cortical tubules the effect of lindane treatment on: (i) β-adrenergic stimulation of cyclic AMP accumulation and (ii) glucose uptake.

MATERIALS AND METHODS

Chemicals

Diphenylhexatriene (DPH) was obtained from Sigma (St. Louis, MO, U.S.A.); dimethylsulphoxide (DMSO) from Merck (Darmstad, Germany); lindane (99%) from Chem. Service (West Chester, PA, U.S.A.) and 3-O-methyl-D-(U-14C)glucose (357 mCi/mmol) from Du Pont (Boston, Mass, U.S.A.). All other chemicals were of analytical grade.

Animals and Treatment

Male Wistar rats aged 75–80 days were separated into two groups of six rats each. The animals from one of the groups were injected subcutaneously with 1 mg/100 g body weight of lindane dissolved in sesame oil (10 mg/ml) at the same time every day for 12 days. The animals from the other group (control rats) were injected at the same times with sesame oil without lindane. The animals were killed by decapitation. The kidneys were removed and the medulla was carefully dissected out. Miniprisms of the resultant chips of kidney cortex were made by use of a McIlwain tissue chopper. The miniprisms were pooled in 30 ml of ice-cold Hank's solution-Hepes buffer, pH 7.4 containing 6 mM glucose (α-buffer) and washed three times.