CHAPTER 33

MEDICAL SCIENCES
MEDICAL BIOCHEMISTRY

Doctoral Theses

01. SINGH (Vijay Kumar)
Effect of Organochlorine Pesticides on Insulin Signaling.
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Abstract
(Verified)

Exposures to DDT and lindane are claimed to cause insulin resistant state and thereby, diabetes mellitus. The present study explored the biochemical basis of DDT- and lindane-induced insulin resistance. Low concentration of DDT and lindane treatment did not affect glucose uptake but, at high concentrations, the same caused hemolysis and thus, attenuated glucose uptake by blood cells. In wistar rats, sub-chronic exposures to DDT and lindane for 8 weeks induced oxidative stress (measured from serum malondialdehyde), pro-inflammatory state (assayed by serum TNF-α) and insulin resistance (measured from HOMA-IR) but did not affect pancreatic β-cell function (measured from HOMA-β) and blood glucose homeostasis (assessed from fasting plasma glucose). HOMA-IR correlated with serum malondialdehyde (MDA) and TNF-α. In L6 myotubes, total antioxidant level was decreased and MDA level was increased dose dependently on sub-toxic DDT and lindane treatment indicating an oxidative stress. TNF-α level in media was not changed on DDT and lindane treatment. IkBα and JNK expression and their phosphorylation was increased on sub-toxic DDT exposure. Lindane treatment phosphorylated IkBα, p38MAPK and JNK. These indicate activation of redox sensitive kinases (RSKs). HSP70 expression and HSP25 phosphorylation increased dose dependently on lindane treatment. But only HSP25 phosphorylation increased on DDT treatment. Tyrosine phosphorylation of insulin receptor did not change on DDT and lindane treatment. However, tyrosine phosphorylation of IRS-1 and serine phosphorylation of Akt were decreased on DDT and lindane treatment. Glucose uptake in myotubes was also decreased dose dependently on sub-toxic DDT and lindane treatment. We conclude that sub-toxic DDT and lindane exposures induce oxidative stress and pro-inflammatory state. That, in turn, activates RSKs and HSPs. Activated RSKs and HSPs interfere with insulin signaling and thus, attenuates insulin-induced glucose uptake in muscle cells explaining the biochemical basis of insulin resistance induced by organochlorine (e.g., DDT and lindane) exposures.

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