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On the biochemical and molecular mechanisms by which malathion induces dysfunction in pancreatic islets *in vivo* and *in vitro*

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ABSTRACT

Recent studies showed that organophosphorus pesticides can increase incidence of metabolic disorders and diabetes. Considering the importance of pancreas in regulating blood glucose, the effect of malathion on essential elements of glucose-stimulated insulin secretion (GSIS) in *in vitro* and *in vivo* conditions were evaluated.

After dividing of rats into control and treatment groups, oral glucose tolerance test (OGTT) was examined and then kinetic of glucose as well as pancreatic response to raise blood glucose were evaluated. After isolation of islets from pancreas, its function as well as oxidative stress markers and essential elements of GSIS were examined.

Malathion at dose of 400 mg/kg impaired GTT and increased $AUC_{0-180\ min}$ ($P = 0.047$) and $T_{1/2\beta}$ of glucose ($P = 0.0016$), and reduced insulin response ($P = 0.005$) 30 min after oral administering of glucose. In addition to impaired glucose tolerance, there were significant increases in lipid peroxidation ($P < 0.001$), carbonyl groups ($P = 0.007$) and 8-deoxyguanosine ($P = 0.011$) as the biomarkers of reactive oxygen species (ROS)-mediated damage to lipid, protein and DNA, respectively in islets. In static condition, a remarkable decrease was observed in ratio of insulin release/mM glucose ($P < 0.001$) and a dramatic increase was seen in ROS formation at all glucose levels. Malathion only reduced ATP/ADP ratio in stimulating concentrations of glucose. Despite the dramatic reduction of glucokinase (GCK) mRNA expression ($P = 0.004$), the expression of glucose transporter 2 (GLUT2) ($P = 0.01$) was increased significantly.

Conclusion: Dysfunction of glucose metabolism and impairment of insulin secretion are associated with a depletion of energy and induction of oxidative stress following acute exposure to malathion.

1. Introduction

Malathion is one of the largest selling and useful organophosphorus (OPs) insecticides in the world. The main mechanism of action of this insecticide, like other OPs, is the inhibition of acetylcholinesterase (AChE) activity in the target tissues. There are numerous evidences that most of people have been exposed to OP pesticides in their workplaces, homes or through trace contaminants in food. Epidemiological studies in occupationally-exposed cases and also animal experiments have confirmed the role of OPs in impairment of glucose homostasis and induction of diabetes [1–4]. On the basis of an epidemiologic study done for the period of 1993–2003 in the US, prevalence of diabetes among OP applicators was mentioned [2]. This capability of OPs was already confirmed in animal models [1]. The change in critical enzymes activity in the metabolic pathways such as glycolysis, glycogenesis, glycogenolysis and gluconeogenesis, adrenal gland, and induction of oxidative stress in liver, muscle and pancreas were found responsible for this disturbing effect of OPs on glucose hemostasis [1].

Pancreas has a critical role in glucose hemostasis by insulin and glucagon secretion. Although OPs appear to be one of the leading causes of pancreatic dysfunction, the involved mechanisms have not been known fully elucidated yet. It has been shown that incubation of isolated islets of rat with different doses of malathion, diminishes secretion of insulin in the presence of basal (2.8 mM) or stimulating (16.7 mM) concentrations of glucose [3]. Change in activity of glutamate dehydrogenase (GDH) and glucokinase (GCK) enzymes have been reported as the mechanisms for glucose and insulin dysregulation by OPs [5,6]. Formation of free radicals in making the imbalance between oxidant and antioxidants of the

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