Toxicology 322 (2014) 1–13

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Review

A review on the molecular mechanisms involved in insulin resistance induced by organophosphorus pesticides

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ARTICLE INFO

Article history:
Received 16 April 2014
Received in revised form 23 April 2014
Accepted 24 April 2014
Available online 5 May 2014

Keywords:
Organophosphorus
Insulin resistance
Glucotoxicity
Lipotoxicity
Inflammation
Oxidative stress

ABSTRACT

There is increasing evidence reporting that organophosphorus pesticides (OPs) impair glucose homeostasis and cause insulin resistance and type 2 diabetes. Insulin resistance is a complex metabolic disorder that defies explanation by a single etiological pathway. Formation of advanced glycation end products, accumulation of lipid metabolites, activation of inflammatory pathways and oxidative stress have all been implicated in the pathogenesis of insulin resistance. Ultimately, these molecular processes activate a series of stress pathways involving a family of serine kinases, which in turn have a negative effect on insulin signaling. Experimental and clinical data suggest an association between these molecular mechanisms and OPs compounds. It was first reported that OPs induce hyperglycemia. Then a concomitant increase of blood glucose and insulin was pointed out. For some years only, we have begun to understand that OPs promote insulin resistance and increase the risk of type 2 diabetes. Overall, this review outlines various mechanisms that lead to the development of insulin resistance by OPs exposure.

Contents

Abbreviations: AGEs, advanced glycosylation end products; AKT, protein kinase B; AP1, activator protein 1; aPKC, atypical protein kinase C; CAT, catalase; CRP, c-reactive protein; DAG, diacylglycerol; FFAs, free fatty acids; G6Pase, glucose-6-phosphatase; GP, glycogen phosphorylase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; HK, hexokinase; HOMA-IR, homeostasis model assessment of insulin resistance; IKKβ, inhibitor kB kinase β; IL-1β, interleukin-1β; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; IR, insulin receptor; IRS-1, insulin receptor substrate-1; JNK, c-Jun N-terminal kinase; LDL, low density lipoprotein; MDA, malondialdéhyde; mTOR, mammalian Target of Rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nucleor factor kappa B; NO, nitric oxide; OPs, organophosphorus pesticides; PDX-1, pancreatic-duodenal homeobox-1; PEPCK, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase; PI3-K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PTB, phosphotyrosine binding domain; PTP1B, tyrosine-protein phosphatase non-receptor type 1B; ROS, reactive oxygen species; SOD, superoxide dismutase; TAT, tyrosine aminotransferase; TNF-α, tumor necrosis factor-α; VLDL, very low density lipoprotein.

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http://dx.doi.org/10.1016/j.tox.2014.04.009
0300-483X/

1. Introduction

The progressive changes in lifestyle promoting pollution and including continuous exposure to xenobiotics lead to an epidemic progression of metabolic and endocrine diseases (Everett and Matheson, 2010). The uncontrolled use of pesticides against enemies (insects, pests, parasites, rodents) is considered as the essential policy for modern agriculture. Pesticides helped to improve crop yields by preventing, controlling and eradicating the spread of highly lethal parasitic diseases. Actually, the most used pesticides in the world are organophosphorus (OPs) and carbamates (Costa, 2006). The widespread use of OPs pesticides constitutes an important factor of metabolic diseases such as type 2 diabetes (Saldana et al., 2007; Montgomery et al., 2008).

International epidemiological data reporting the prevalence of type 2 diabetes showed significant disparities between countries and ethnic groups. By cons, they uniformly reflect a significant increase in the prevalence of type 2 diabetes in industrialized or developing countries. Thus, the number of type 2 diabetics in the world would increase from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004). Type 2 diabetes results from interactions between genetic susceptibility, environmental factors and lifestyle choices. Our understanding of diabetes has remained rudimentary, for the most part being limited to the impact of physical inactivity or unhealthy dietary choices (Bhatnagar, 2009).

However, at the cellular and molecular levels, type 2 diabetes results from a disruption of the mechanisms controlling the capture, storage and use of glucose leading to hyperglycemia that announces an insulin resistance. It is now well known that insulin resistance may be induced or accelerated by environmental factors. Thus, factors related to lifestyle are now considered as a major determinant of the genesis of insulin resistance and hyperglycemia (Lee et al., 2007). Insulin resistance is defined as the inability of insulin to exert its physiological effects at a given concentration of the main targets: the skeleton muscle, liver and adipose tissue. Although, the end result of insulin resistance is a defect of glucose utilization by insulin target tissues, leading to diabetes. Insulin resistance is frequently associated with complex metabolic disorder and precedes the onset of type 2 diabetes (Tabák et al., 2009). The pathogenesis of common insulin resistance is not yet clarified, alteration in glucose metabolism or insulin signaling pathways, abnormal lipid metabolism and inflammation are considered as key mechanisms (Samuel and Shulman, 2012). Following nutrient consumption, insulin promotes carbohydrate uptake at key storage sites and prompts the conversion of carbohydrate and protein to lipids. Insulin, via the activation of protein kinase B (AKT), has two main functions. First, insulin inhibits the glucose synthesis and β-oxidation; secondly, it leads to the storage of glucose as glycogen and lipid via lipogenesis (Cho et al., 2001).

Insulin resistance state is developed when insulin is unable to accomplish its metabolic effects. When insulin resistance begins to occur, pancreatic β cells compensate by increasing basal insulin secretion. Since insulin secretion is less effective, type 2 diabetes is definitively established. Insulin resistance accelerates hepatic glucose production during postprandial phase causing hyperglycemia, while lipogenesis remain strongly activated by increasing acyl-CoA level, a natural inhibitor of β-oxidation. The main molecular mechanisms of insulin resistance are the alterations of insulin signaling, glucotoxicity, lipotoxicity, inflammation and oxidative stress. The aim of this review was to evaluate the molecular mechanisms of insulin resistance induced by OPs pesticides. First we aimed to explain several mechanisms proposed in the pathogenesis of insulin resistance. Further, the review discusses the OPs pesticides action on the molecular disruptions leading to insulin resistance and type 2 diabetes, based on the clinical and experimental evidences.

2. Molecular mechanisms of insulin resistance

2.1. The role of IRS in insulin resistance

IRS proteins contain many sites of phosphorylation in tyrosine and serine residues (White, 2002). Insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), by the insulin receptor (IR), results in intracellular transduction of the insulin signal, whereas serine phosphorylation, by serine kinases, modulates the function of tyrosine-phosphorylated IRS-1 in negative manner (Gual et al., 2005). Elevated serine phosphorylation inhibits the insulin signaling by downregulating IRS-1 protein levels (Shah et al., 2004) and inhibiting the interaction between IRS-1 and its downstream partner, the phosphatidylinositol 3-kinase (PI3-K) (Langlais et al., 2011).

Under normal condition, insulin stimulates tyrosine phosphorylation of IRS-1, followed by serine phosphorylation to inhibit insulin signaling (Gual et al., 2005). This mechanism is a kind of negative feedback of insulin on its own signaling pathways, to maintain normal glucose level. Further, insulin, via IR, is able to induce the phosphorylation of several sites very orderly and controlled in time, allowing a very precise control during insulin action (Yi et al., 2007; Boura-Halfon and Zick, 2009). This mechanism of phosphorylation on serine residues in response to insulin is very complex since it can have positive or negative effects or both on insulin signaling (Gual et al., 2005). Nowadays, it is well understood that insulin initially stimulates IRS-1 phosphorylation by insulin receptor in positive sites (Paz et al., 1999; Gual et al., 2005; Boura-Halfon and Zick, 2009). Phosphorylation of positive sites could prevent the phosphorylation of inhibitor sites (Luo et al., 2007; Weigert et al., 2008) and thus allow optimum signal transmission. Serine residues having an inhibitory effect are phosphorylated later and allow to stop insulin signal (Boura-Halfon and Zick, 2009). Therefore, under physiological conditions, the overall phosphorylation of IRS-1 on serine residues induced by insulin results from a very controlled balance between phosphorylation sites having a positive effect and sites having a negative effect.

Inhibitors sites are phosphorylated in response to insulin by the atypical protein kinase C (aPKC), the p70S6 kinase and mammalian Target of Rapamycin (mTOR) (Boura-Halfon and Zick, 2009). In physiopathological conditions the inhibitor sites are phosphorylated in response to several factors involved in insulin resistance such as inflammatory cytokines, fatty acids and reactive oxygen