Effects of non-dioxin-like polychlorinated biphenyl congeners (PCB 101, PCB 153 and PCB 180) alone or mixed on mature adipocytes 3T3L1: induction of leptin resistance

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Polychlorinated biphenyls (PCBs) are widely pollutants in the environment and together with dioxins and furans form the group of Persistent Organic Pollutants (POPs). PCB 101, 153 and 180 belong to a group of seven congeners, named "PCBs target" which are considered by the International Scientific Community, as indicators of the degree of contamination by PCBs.

It is also known that these compounds promote the phenomenon of bioaccumulation in adipose tissue of animals and man. This observation is consistent with the idea that PCBs may be involved in the development and progression of endocrine-metabolic diseases (obesity, diabetes, increased risk of cardiovascular diseases, metabolic syndrome) and interfere with the normal function of the endocrine tissue fat. Adipose tissue plays a pivotal role not only in the storage and mobilization of substances with high metabolic energy, but play an important role in the regulation of energy homeostasis through the secretion of specific hormones, such as leptin. The hyperleptinemia characterizes the vast majority of obese individuals and many studies show that this hormone plays an atherogenic role contributing to insulin resistance by altering endothelial function, promoting platelet aggregation and arterial thrombosis (1).

Here, we reported experiments conducted on mature adipocytes treated with PCB 101, 153 and 180 associated two by two, or all three together, where we observed an increase in the expression of leptin gene in particular when PCBs are combined, and a concomitant reduction of activity of its receptor. This reduction of Ob-Rb in adipocytes, associated with high synthesis of the hormone, supports the occurrence of an insensitivity to the hormone correlated to leptin-resistance of adipose tissue, a typical metabolic alteration of obesity. To confirm this hypothesis, we investigated how PCB 101, 153 and 180 affect the expression of important proteins involved in the signaling of leptin receptor. In particular, the phosphatase PTP1B, a negative regulator of leptin signaling, results induced by the association of the PCB 153 with the 180 or of all PCB, supporting the hypothesis that these congeners can act with synergistic mechanism. Subsequently, we evaluated whether these pollutants affect the intracellular signal transduction pathways of Ob-Rb receptor JAK/STAT. Indeed, PCBs in combination (PCB 153+180 and all three together) induced a decrease in the phosphorylation of STAT3 with a significant reduction in the ratio pSTAT3/STAT3 in adipocytes. Subsequently, it was highlighted the ability of these pollutants to modulate the expression of adiponectin and cytokines, such as IL-6 and TNF-α.

The data obtained are interesting, since the PCB concentrations used *in vitro* are comparable to levels of exposure in humans, and strongly support the hypothesis that these substances may interfere with the pathway related to the development of obesity and related diseases.

(1) Beltowski J. Atherosclerosis. 2006;18:47-60.