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Obesity Paradox: An Age-Dependent Cardioprotection against Persistent Organic Pollutant Exposure?

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Scope and background: The accumulation of persistent organic pollutants (POPs) emitted into the atmosphere contributes to the environmental pollution. Exposure to POPs such as 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a major cause of increased morbidity and mortality in populations being exposed. Indeed, these lipophilic chemicals resist to degradation leading to widespread global dispersion, bioaccumulation, and long-term release into the environment in various forms (e.g. vapor, sediment, water) [1-2]. Notably, POPs contaminate the food chain, which is considered the main source of human exposure. At the organism level, POPs are mainly accumulated in the adipose tissue, which acts as a storage compartment in the body [3-4] and may modulate the toxicity of organic pollutants on target organs such as the heart and the skeletal muscle[1-3]. By storing POPS, the adipose tissue can initially protect target organs from their harmful effects. However, adipose tissue is a dynamic tissue, which changes its properties and may display "remodelling" in the context of ageing process or obesity, thus affecting its storage capacity. Furthermore, adipose tissue may release POPs into the circulation, particularly in the event of weight loss [5-6]. One of the organic pollutants, TCDD, is known to activate the AhR pathway implicated in xenobiotic mechanism, which induces several target genes such as cytochrome P450 (CYP). In response, CYP-mediated substrate oxidation can generate highly reactive metabolites that induce oxidative stress and DNA/protein damage, thereby contributing to inflammation of the adipose tissue and to the aggravation of metabolic disorders [7].

Objective and methods: To assess the putative cardioprotective effect of adipose tissue against POPs wild-type mice (n=10/group) reproducing two conditions of vulnerability (obesity induced by a 16-week high-fat diet (HFD) and ageing [1, 5 and 14 months]) were first exposed to TCDD during one month (intraperitoneal injections of 4µg/kg of TCDD, twice per week). Then, using the same experimental design, we induced a fat mass reduction by either a switch diet (caloric restriction) or a lipectomy (surgical removal of the epididymal fat).

Preliminary Results: As compared with control diet groups, HFD protects young obese mice, but not in adults from the consequences of TCDD exposure as shown by the improved insulin resistance, decreased body weight and adipose tissue mass. Interestingly, TCDD blunts the HFD-and ageing-induced cardiac remodelling in obese young mice but not in adult ones, by decreasing the myofibroblasts activation, thus reducing the myocardial collagen deposition level and by decreasing the hypertrophy of the cardiomyocytes. These results are associated with a non-aggravation of cardiac function by TCDD in obese mice in both, young and adult mice. Circulating and tissue TCDD dosages are on-going as well as analyses in the old mice (14-month old).

Conclusion: These preliminary results suggest an obesity paradox leading to cardioprotection in TCDD-exposed young mice, blunting the noxious impact of POPs on the heart in an age-dependant manner.

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