Main Submission

PPARγ ligands: Is timing the key to therapeutic vs. obesogenic effects?

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Obesity and several diseases associated with obesity have become epidemic in Western society, including type II diabetes, cardiovascular disease and hypertension. To prevent future cases and develop effective therapies for existing patients, researchers have worked to understand the etiology of obesity. The pervasive axiom has been that obesity is caused by prolonged imbalances between energy intake and output.[1] Simply put, obese individuals eat too much and do not exercise enough. However, recent evidence suggests that, like most diseases, the development of obesity may involve numerous genetic and environmental risk factors that interact in complex ways. At the cellular level, obese individuals have more, and much larger, adipocytes (fat cells) than the rest of the population. This basic biology is problematic for proponents of the energy-imbalance theory, because adipocyte number is established by early adulthood,[2] often before over eating habits and sedentary-lifestyles take effect. Therefore, obesity in adulthood may result from predisposing factors rather than recent lifestyle decisions.

Several theories have been postulated to explain obesity predisposition, including single nucleotide polymorphisms in multiple genes, viral infections, chronic stress and sleep reduction. More recently, a group of chemicals known as obesogens have emerged as factors that may contribute to a predisposition to obesity. Obesogen researchers believe that exposure to certain environmental chemicals can cause obesity by altering adipocyte tissue biology. Significantly, the effects of these chemicals are postulated to be independent of the classic modifiable risk factors: diet and exercise. At present, a PubMed search for "obesogens" only garners 19 papers; however, the significance of chemical exposures that drive obesity should not be understated. Obesogens, including diethylstilbestrol, bispehnol A, phthalates and organothins, alter normal lipid hemostasis by targeting nuclear receptors that govern adipocyte differentiation, resulting in the accumulation of lipids and adipogenesis.[3] The obesogen theory is especially intriguing, because one of the nuclear receptors targeted by these chemicals is the peroxisome proliferator-activated receptor (PPAR)γ, a receptor that confers a protective effect in multiple diseases.[4]

Drugs in the thiazolidinedione (TZD) class, which target PPARγ, have been used for years to treat obesity-associated diseases such as type II diabetes and atherosclerosis. TZDs enhance adipocyte differentiation, resulting in an increase in the proportion of smaller, mature adipocytes within adipose tissue. This is of significance, as larger, immature adipocytes produce more of the proinflammatory cytokines that, together with fatty acids, are thought to be responsible for the development of insulin resistance.[5]

Emerging evidence also suggests that TZDs may have a promising role in the treatment and management of several types of cancer, another disease for which obesity is a risk factor.[6] Specifically, PPARγ ligands have been shown to reduce tumour burden by decreasing cell proliferation and inducing differentiation, phenotypic changes that are desirable compared to the cytotoxic effects of most current chemotherapeutics. Indeed, the inclusion of PPARγ ligands in chemotherapy regimens has been shown to decrease the doses of traditional cytotoxic agents required for positive effects and, in some cases, has allowed cells to overcome resistance to them.[7]

Despite these successes in diabetes and cancer, PPARγ ligands are not without their pitfalls. Studies have shown that prolonged use of PPARγ activators leads to edema and weight gain,[8] which is consistent with the well-established notion that PPARγ activators are adipogenic.[9] The therapeutic versus harmful effects of PPARγ activation therefore need to be carefully assessed, given the potential for PPARγ ligands to reduce morbidity and mortality due

to cancer, diabetes and other diseases. This is especially important since hundreds of thousands of individuals worldwide use TZDs as front-line therapy for type II diabetes, not to mention the fact that PPARγ activators, such as some fatty acids, are present in foods.[4]

Further research should be performed to clarify the specific mechanisms by which obesogens activate PPARγ and whether the dose or age of exposure is most relevant to their effects. The obesogen theory, which states that adipogenic chemicals alter adipocyte numbers in adolescence, implies that exposures later in life are not as harmful. This means that there may be a critical time period in which PPARγ activators act as obesogens and exert harmful effects. This is significant, because if the obesogen theory holds true, PPARγ activating drugs should not be used to treat children and pregnant women. In this model, neonatal through pre-teen obesogen exposure could increase the number of an individual's adipocytes, making them susceptible to obesity throughout their lives. It would be unfortunate if it turns out definitively that PPARγ activation is harmful to young people, as prophylactic treatment with PPARγ activators has shown protective effects in a number of diseases, including malignant breast cancer.[10] Given the prevalence of obesogens in the environment, eliminating exposure does not seem possible. Therefore, a thorough understanding of how they exert harmful effects is critical to reducing obesogen-driven morbidity in our population.

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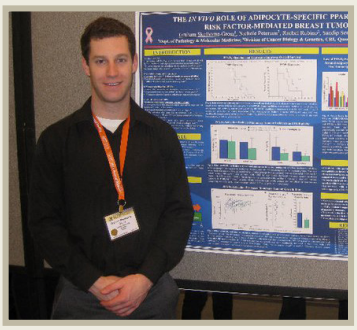

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