**Nutraceuticals molecular targets (III) Targeting protein receptors with polyphenols as new anti-obesity therapies**

In the previous column we proposed the use of a global scientific approach to elucidate the beneficial effects of plant polyphenols and other dietary compounds on human health. This approach is based on the identification of the metabolites derived from food components that are responsible for the health effects and the associated metabolic markers: i) the elucidation of their protein targets and concomitant metabolic pathways; ii) in silico techniques to screen for millions of compounds against the known molecular targets and finding for new candidates; iii) appropriate cellular and animal models to verify the mechanism of action and toxicity; v) human trials to demonstrate the beneficial effects associated to specific compounds. The transition of this global strategy occurs from the scientific field to the industry, and therefore the consumer, will take a few years. In the meantime, we will review some proteins or metabolic processes that have been recently proposed as putative targets in the alleviation of metabolic syndrome and obesity-related pathologies such as type 2 diabetes mellitus (T2DM).

The search for drugs with hypolipidemic effects started in the mid-1950s with the discovery of compounds with cholesterol-lowering properties. Despite their potential lipid-lowering activity, some of these drugs have exhibited worrisome side effects, such as hepatotoxicity and a risk of myopathy. Currently, these drugs are still widely prescribed both in USA and Europe (2). Looking at their chemical structure that bear a bi-phenyl moiety, one might think that plant polyphenols could also be candidates to reach similar molecular targets than those interacting with fibrates. In a group of these compounds, flavonoids are of particular interest, either mainly that showed hypolipidemic and hypoglycemic effects in diabetic mice model (3). The combination of the phenyl ether moiety with the thiazolidinedione structure lead to the discovery of glitazones. Again, phenyl moieties, such as those found in many plant polyphenols, seems to be a structural coincidence. Ciglitazone was the first developed glitazone in 1981 by Sankyo Co in 1988 (4).

**Glitazones or thiazolidinediones (TZDs)** are agonists (ligands or activators) of the peroxisome-proliferator-activated receptor γ (PPARγ), a nuclear receptor that is a key player in various biological processes such as glucose and lipid homeostasis. In 1994, the role of PPARγ as a major adipogenic transcription factor was discovered and one year later, PPARγ was suggested to mediate the antidiabetic action of a novel group of drugs called azothiapane. TZD are mostly expressed in adipose tissue, but it also appears in other tissues such as pancreatic beta cells and vascular endothelium. Lipid binding at PPARγ regulates transcription of several target genes that regulate fatty acid metabolism, glucose uptake, adipocyte differentiation, inflammation and intracellular lipolysis. Among the various actions of glitazones are promoting lipogenesis in adipose tissue, which results in reduced serum free fatty acid concentrations, reduced hepatic fat content and increased hepatic and peripheral insulin sensitivity (5). Basically, activation of PPARγ improves lipid management at different tissues and increases fatty acid storage. Indeed, PPARγ promotes adipocyte differentiation; stimulates fatty acid storage in adipocytes via the activation of several genes, such as lipoprotein lipase, fatty acid transport protein, C/EBPα, and acyl-CoA synthetase; and decreases free fatty acid secretion, resulting in enhanced adipocyte insulin signaling. All these effects can explain the body weight gain induced by TZD administration, a major drawback in the use of these drugs in the treatment of T2DM. Despite the efficacy of TZDs to reduce TZD, glitazones remain to be a controversial class of drugs. These drugs display undesirable metabolic side effects, such as fluid retention, body weight gain induced by TZD administration, a major drawback in the use of these drugs in the treatment of T2DM.

In the development of new synthetic PPARγ agonists, we must consider plant polyphenols as a potential source to discover lead compounds. These compounds may not be as potent as PPARγ agonists but may behave as fine or mild regulators of PPARγ by improving lipid management and glucose sensitivity and lacking the side effects of glitazones. New generation “selective PPARγ modulators” must be designed to induce specific changes in PPARγ conformation, resulting in the differential activation of genes activated by PPARγ, leading to a set of specific biological effects (6). Another concern may appear then, will the consumer and the industry be prepared for labelling products in such a way: “contains polyphenols with lipid lowering/glucone reduction effects through PPARγ modulation”? It is clear that both legislative and regulatory panels still have much work to be done.

**REFERENCES**


