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The role of the pancreatic endocannabinoid system in glucose metabolism

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The endogenous cannabinoid system participates in the regulation of energy homeostasis, and this fact led to the identification of a new group of therapeutic agents for complicated obesity and diabetes. Cannabinoid receptor antagonists are now realities in clinical practice. The use of such antagonists for reducing body weight gain, lowering cholesterol and improving glucose homeostasis is based on the ability of the endocannabinoids to coordinately regulate energy homeostasis by interacting with central and peripheral targets, including adipose tissue, muscle, liver and endocrine pancreas. In this review we will analyse the presence of this system in the main cell types of the islets of Langerhans, as well as the physiological relevance of the endocannabinoids and parent acylethanolamides in hormone secretion and glucose homeostasis. We will also analyse the impact that these findings may have in clinical practice and the potential outcome of new therapeutic strategies for modulating glucose homeostasis and insulin/glucagon secretion.

The endocannabinoid system: a new approach for treating type-2 diabetes

Glucose is a small polar monosaccharide with an outstanding role as cellular fuel. Its physiological importance can be exemplified by its being an absolute nutritional requirement of neurons. In its

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absence they die. Thus, an adequate homeostatic control of blood levels of glucose is vital. This is achieved mainly through the coordinated action of two key hormones, insulin and glucagon, that are synthesized and released into the bloodstream by the beta and alpha cells, respectively, that are immersed within the pancreatic islet of Langerhans. Insulin promotes glucose uptake in the liver, adipose tissue and muscle, whereas glucagon has opposite actions, mobilizing hepatic glucose (stored as glycogen) and promoting the release of free fatty acids from adipose tissue that finally reach the liver to enter the β-oxidation pathway producing ketoacids.

Some events can lead to a dysfunction of proper glucose homeostasis, causing increased glucose levels (hyperglycaemia). Islets autoimmunity (type 1) and obesity-related (type 2) insulin resistance are the two main events that trigger diabetes mellitus, the pathological entity that arises from hyperglycaemia. Diabetes mellitus has been classically divided in these two types of pathological conditions. In type-1 diabetes (T1D) beta cells are attacked by the immune system in a T-lymphocyte-mediated fashion, resulting in an immune infiltration that finally destroys the islet of Langerhans, thus abolishing the secretion of insulin and glucagon. The aetiology of T1D is poorly understood; both genetic and environmental factors are causal agents. By contrast, type-2 diabetes (T2D) deals with an increasing need for circulating insulin (due to a loss of insulin sensitivity) that finally depletes beta cells, causing their 'blindness' to glucose level and their subsequent death. T2D aetiology is also quite undetermined, but it has an important genetic association, especially in certain ethnic groups. Obesity (in particular), aging and poor fetal development are associated factors implicated in T2D pathogenesis.

In spite of this simple and classical aetiological classification, there is an important body of evidence to support the existence of a wider range of pathological entities causing hyperglycaemia, and hence diabetes, which are not based on either autoimmunity or peripheral insulin-resistance; these therefore demand more specific therapeutic approaches. Examples are hyperglycaemia due to genetic disorders, such as maturity-onset diabetes of youth (MODY), genetic defects in insulin action, diseases of the exocrine pancreas, excessive secretion of hyperglycaemic hormones (e.g. cortisol, catecholamines, somatotropins) or gestational diabetes mellitus.

Although diabetic patients can perform normal daily tasks, there are several complications that greatly diminish life expectancy and cause an increased cost to national medical institutions.

As stated above, obesity is the main factor implicated in T2D pathogenesis; its increase has reached epidemic proportions worldwide, and it seem to be the driving force that lies behind an alarming explosion of T2D and cardiovascular diseases. Even more worrying is the increasing incidence of obesity in adolescents; this has increased by a factor of more than 10 in the past two decades, suggesting that the obesity epidemic has just only begun. According to the International Obesity Task Force, about 155 million school-age children worldwide are currently overweight, with 30–45 million classified as obese. In the European Union countries, the number of children affected by overweight and obesity is rising by nearly 400,000 a year, and already one child in four is overweight. Furthermore, recent studies have raised alerts about the dramatic increase in obesity-associated pathologies such as T2D, coronary heart disease, and fatty liver in the future adult population.[1–3] Unfortunately, there is increasing evidence to suggest that lifestyle adjustment is not sufficient to treat obesity, and hence a pharmacological approach is necessary. The pharmaceutical industry, convinced of this need, has long been exploring the possibility of a 'magic bullet' against obesity and, nowadays, the endocannabinoid system constitutes an interesting target, perhaps the most promising proposed so far for such an objective.[4–6] The cannabinoid CB1 receptor antagonist rimonabant has shown promising results in clinical trials tackling obesity. A worldwide phase-III trial named RIO (Rimonabant in Obesity) was developed to test the loss of body weight, the prevention of weight regain, as well as the changes in baseline of metabolically relevant biochemical and hormonal parameters.[7–10] This promising profile has allowed the approval of Acomplia (the commercial name of rimonabant) for medical use, and it is now licensed in many countries; however, some low-prevalence side-effects have been reported, mainly anxiety and depression, preventing final FDA approval and hence commercialization in the USA. Rimonabant is used as an adjunct to diet and exercise for the treatment of overweight or obese patients with associated conditions such as T2D and dyslipidaemia. In addition, other new CB1 antagonists have been developed in order to compete in this interesting business: e.g. taranabant is a new CB1 inverse agonist developed by Merck with a good profile similar to that of rimonabant.[11]