METABOLISM CLINICAL AND EXPERIMENTAL XX (2015) XXX–XXX

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Incretin-based therapies for obesity treatment

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ARTICLE INFO

Article history:
Received 26 June 2014
Accepted 21 May 2015

Keywords:
Obesity
Treatment
Incretin
DPP-4
GLP-1

ABSTRACT

Currently, obesity and its associated complications are considered major public health problems worldwide. Because the causes are multifactorial and complex, different treatment methods are used, which include diet and exercise, as well as the use of drugs, although they can have adverse side effects. A new target for the treatment of obesity may be the incretin system, which consists of hormones that seem to contribute to weight loss. In this sense, some studies have shown a relationship between weight loss and drugs related to incretin system, including glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. The objective of this review is to summarize the association between the incretin system and obesity treatment.

1. Introduction

Obesity is a chronic disease characterized by abnormal or excessive fat accumulation, which is currently one of the most serious public health problems worldwide [1]. According to the World Obesity Federation, in 2012, 1.0 billion adults were overweight and more than 475 million were obese worldwide [2].

Obesity can be diagnosed by using body mass index (BMI), a formula based on weight in relation to height. Overweight is defined as a BMI between 25 and 29.9 kg/m^2; and a BMI of 30 kg/m^2 or higher is considered obese [1,2]. Obesity can lead to other illnesses, given that excess weight is a risk factor for developing coronary heart disease, diabetes, and hypertension [1].

The cause of obesity is multifactorial, and involves several factors in its development [2]. However, dietary patterns, which are generally characterized by high intake of energy-dense foods, and physical inactivity are still the main factors that contribute to excessive body weight or obesity [1,2]. Based on this knowledge, generally a combination of diet and physical activity is the cornerstone in the management of obesity [3]. According to a qualitative study on obese individuals, long-term orientation is required, linking diet to physical activity, to maintain a balanced body weight [4].

However, many patients do not achieve satisfactory results with diet and exercise. Thus, the use of drugs should be considered when other non-pharmacological measures fail [5]. Today, drug treatment for obesity is very common [6].

Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; BMI, body mass index; CNS, central nervous system; EMA, European Medicines Agency; FDA, US Food and Drug Administration; (Pro3)GIP, proline-3 gastric inhibitory polypeptide.

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http://dx.doi.org/10.1016/j.metabol.2015.05.012
0026-0495/

Studies have shown efficacy in weight loss, but their effect is diminishing with continuing treatment. In addition, drugs have adverse effects, which limits their clinical use [6,7]. Orlistat has been approved in Europe and the United States to treat obesity, but many patients cannot tolerate its gastrointestinal side effects [8]. Sibutramine was associated with adverse cardiovascular events [8]. Since the adverse effects of many drugs were so powerful that they affected tolerability and safety, many of them were withdrawn from the market, such as amphetamine [8].

Therefore, there is a lack of effective pharmaceutical strategies for the treatment of obesity, as well as various constraints related to existing drugs on the market. New therapeutic targets are being sought to treat this disease. In this context, drugs available for other purposes, with mechanisms known to affect glycemic control, have been identified and investigated as medications for weight loss [9,10], including medications that affect the incretin system [11–15].

Incretin-based medications mimic or act on glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and dipeptidyl peptidase-4 (DPP-4) (Fig. 1), and were primary developed for treatment of type 2 diabetes mellitus [16,17]. However, some extra-glycemic effects were observed, including the reduction in body weight [13,18,19]. Many studies have been conducted in this direction [18,19], and most recently, liraglutide, an incretin-based medication, was approved by the FDA, in December 2014, for treatment of obesity in the United States [20].

Among the effects of hormones that may be related to weight loss are slowing gastric emptying, increased satiety and food intake reduction [19,21,22]. Therefore, considering that obesity is a public health problem worldwide, with different causes and shortage of drugs for its treatment, and that the use of the incretin system may be an option, the objective of this review paper was to summarize the relevant literature on the incretin system and its potential use for obesity treatment. The review was conducted by searching PubMed and SciELO, collecting articles related to the topic published between the years 2002 to 2014. Original and review articles that addressed incretin-based therapies showing beneficial effects on reduction in body weight and potential cardioprotective effects were included. Clinical trials that evaluated only the effects of incretin-based therapies on blood glucose were excluded.

2. Incretin System

A complex set of physiological responses is activated after food ingestion, which provide neural and endocrine signals that regulate digestion, and absorption and assimilation of ingested nutrients [23]. Studies on glucose tolerance have demonstrated that plasma insulin levels were significantly higher after oral glucose administration compared with intravenous glucose administration. This increase in intestinal insulin secretion was attributed to incretins [23], which are hormones that are released by endocrine cells in the intestinal mucosa in response to food intake [16].

There are two main incretins secreted from the gastrointestinal tract, GLP-1 and GIP [24]. GIP is synthesized and secreted by K cells, whereas GLP-1 is produced and secreted by L cells [17]. Incretins stimulate glucose-dependent insulin secretion after food intake [17], and therefore, play an important role in the regulation of glucose homeostasis [16]. The increase in plasma concentrations of these hormones after food intake involves a combination of neural and endocrinal signals [25]. Incretins also affect glucagon secretion, with GIP stimulating, but GLP-1 inhibiting glucagon secretion [21]. Obese people, especially those with concomitant type 2 diabetes mellitus, have reduced levels of incretins [23,26], which may cause deterioration of glucose homeostasis [22].

Both GIP and GLP-1 receptors exert their functions by coupling to G-proteins [17]. GIP receptors are mostly expressed in pancreatic β-cells, and to a lesser extent, in the adipose tissue

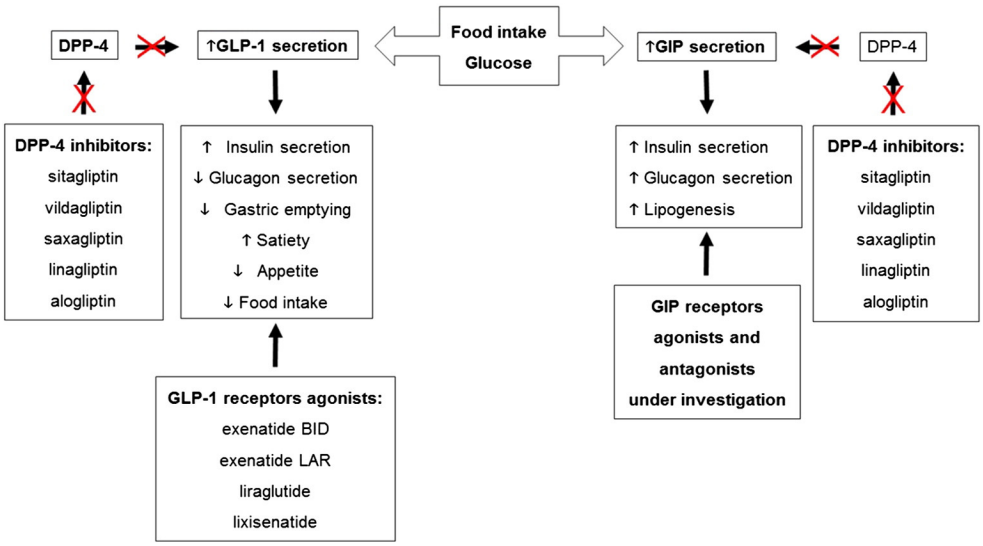

Fig. 1 – Incretin system and incretin-based therapies. GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulinotropic polypeptide; DPP-4: dipeptidyl peptidase-4.

Please cite this article as: de Mello AH, et al, Incretin-based therapies for obesity treatment, Metabolism (2015), http://dx.doi.org/10.1016/j.metabol.2015.05.012