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Review

Strategy for limiting food intake using food components aimed at multiple targets in the gastrointestinal tract

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ABSTRACT

Background: Maintaining body weight homeostasis is a huge challenge for many people in developed as well as developing societies, where overweight and obesity are fast increasing. New strategies are needed to combat this trend.

Scope and approach: In this review we examine the effectiveness of the various approaches to modulating food intake. We analyze several pharmacological treatments that act on the brain and gut, focusing specifically on those that act on the gastrointestinal tract in order to change enteroendocrine hormones.

Key findings and conclusions: An initial review of the pharmacological approaches to limiting food intake in humans shows that acting on specific targets of the central nervous system (CNS) is not very effective. Instead, surgical approaches that limit the functionality of gastrointestinal fragments, which concomitantly changes the profile of secretion of several enterohormones, are the most effective. Since effectiveness seems to be mediated by multiple targeting, we review the bioactivity of various food-related compounds for different functions of the gastrointestinal tract. Treatments that limit ghrelin production within a threshold and activate anorexigenic enterohormones seem to be the most effective. We therefore suggest that an integrative approach based on the modulation of multiple targets with foods could help to limit food intake.

1. Introduction

The homeostatic regulation of body weight is a dynamic balance between energy income and outcome that works by controlling food intake and energy expenditure. Imbalances in this system result in a body weight that is above or below its optimum value, thus compromising physical wellbeing (Hill, Wyatt, & Peters, 2012). An optimum body weight has been defined as a Body Mass Index (BMI) ranging from 20 to 25 kg/m^2. Values above and below these boundaries are defined as overweight and underweight, respectively. Obesity is defined for BMI values above 30 kg/m^2 (World Health Organization, 2000).

Overweight and obesity are a major risk of health problems such as cardiovascular diseases, type-2 diabetes, osteoarthritis as well as cancers such those of the endometrium, breast and colon (World Health Organization, 2015). In the last few decades, the prevalence of overweight and obesity has increased dramatically in both developed and developing societies, rising from 25% of the world's population for overweight in 1980 to the current figure of 35% [5]. This increase coincides accurately with the prevalence estimations made in 2005, which predicted that by 2030 38% of the world's population will be overweight and 20% will be obese. Overweight is therefore currently the fifth leading risk of deaths worldwide and is directly related to other major risks such as high blood glucose and cholesterol levels and high blood pressure (G. Stevens, 2009).

To find an explanation of why body weight is not properly corrected by the body's homeostasis, we should bear in mind that obesity and overweight are complex multifactorial problems that include biological, socio-economic, cultural and psychological aspects (Marks, 2015; Smith & Cummins, 2009). Two main models attempt to explain it (reviewed in detail in (Speakman et al., 2011)). The set point model tries to solve biological aspects. It suggests that there is an active feedback mechanism linking adipose tissue (stored energy) to intake and expenditure via a set point, presumably encoded in the brain (Kennedy, 1953). An alternative

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model, to explain the socio-economic a psychological aspects, is "the settling point model". It is based on the idea that there is passive feedback between the size of the body stores and aspects of expenditure. Although both models have respective limitations to solve the problems. Another approach is to consider human evolution, which may help us to understand part of the inadequate adjustment in body weight homeostasis. Humans have suffered multiple ecological and feeding stresses, so the energy homeostatic system is biased toward weight gain in order to enable the body to store energy and ensure survival (Hill et al., 2012; Mangine et al., 2012). It is generally currently accepted that the main causes of the large increase in the incidence of obesity in industrialized countries are related to high calorie consumption and low physical activity (Prentice & Jebb, 2004, pp. 98–104).

Despite the complexity of this issue, the main advice given to individuals on how to manage their body weight is to engage in regular physical activity and to limit the consumption of energy-dense food (World Health Organization, 2015). Although the first-line treatment for combating obesity consists of promoting lifestyle changes, dietary lifestyle interventions may be poorly effective in reducing body weight in the long term (Curioni & Lourenc, 2005). Alternative, e.g. pharmacological, treatments could complement lifestyle interventions aimed at reducing and sustaining body weight. The 2015 Endocrine Society Clinical Practice Guideline recommended pharmacotherapy as an adjunct to lifestyle modification for promoting weight loss in obese people (Apovian et al., 2015). In this context, existing strategies for avoiding overconsumption include blocking intestinal lipid absorption (Sjöström et al., 1998), increasing the oxidation of lipid body composition (Hursel & Westerterp-Plantenga, 2010), and suppressing appetite (Fidler et al., 2011). Maintaining their optimum body weight is an even greater challenge for individuals who achieve weight loss (Elfhag & Rössner, 2005).

Though great advances have been made in our understanding of food intake processes, their complexity makes it difficult to solve the problem. Analysis of existing treatments suggests that an approach aimed at acting on several targets could produce a net effective change in food intake that would prevent excessive body weight accumulation and avoid related pathologies. This multiple targeting could be achieved through the administration of food components.

2. Complexity of appetite-regulation processes

The cyclic food intake patterns of humans are regulated by a wide range of factors that involve physiological, psychological and behavioral processes (Halford, Boyland, Blundell, Kirkham, & Harrold, 2010). The sum of these processes, named appetite, reflects our resulting desire to eat food. One of the main factors that influences appetite is hunger, the conscious sensation that reflects a mental urge to eat, which directly determines when and how much we consume. Another factor is the satiating power of food, which is the capacity of food to suppress hunger by means of several processes that are roughly classified as cephalic, sensorial, cognitive, post-ingestive and post-absorptive. The operation of these processes has been collectively referred to by Blundell (Blundell, Green, & Burley, 1994) as the satiety cascade. Technically, the conscious sensation opposite to hunger is called satiation during the course of the meal and satiety during the inter-meal periods. Satiation, therefore, brings an eating period to its termination while satiety determines how long the inter-meal period will last.

When searching for agents to act on food intake processes, there are two main target organs: the brain and the gastrointestinal tract. It is beyond the scope of this manuscript to review the central mechanisms by which these organs participate in controlling food intake (both are reviewed in numerous published papers (Chambers, Sandoval, & Seeley, 2013; Horvath, Diano, & Tschöp, 2004; Williams, 2012)). However, for clarification: Fig. 1 shows the main hormonal circuits initiated at the stomach, the small intestine, the pancreas and the adipose tissue that impact on the sensations of hunger and satiety exerted via hypothalamic neuroendocrine pathways (adapted from (Chambers et al., 2013)); and Figs. 2 and 3 shows the main molecular mechanism that senses food components at the gastrointestinal wall and initiates several chemical signals that reach the centers of the brain via the blood or the nerves (adapted from (Engelstoft et al., 2013; Farré & Tack, 2013)).

3. Pharmacological management of body weight via mechanisms for controlling food intake

Two main strategies have been designed from the known physiological mechanisms that regulate food intake: the first is to directly influence the central mechanisms that control food intake and the second is to indirectly influence them via gastrointestinal signals.

3.1. Drugs acting on the central nervous system (CNS)

Several areas of the brain participate in controlling food intake, the most clearly defined of which are hypothalamic centers (Chambers et al., 2013; Morton & Schwartz, 2006). These centers receive input signals from several peripheral areas and produce output orders to regulate food intake (Fig. 1).

Several studies are currently based on MC4R or Y5 signaling. In studies of rodents, several MC4R agonists led to an effective reduction in food intake when administered centrally (Kumar et al., 2009) or peripherally (Skowronski et al., 2014). However, whether MC4R agonists can be applied to humans is less clear because of the difficulty in avoiding undesirable side effects. LY2112688 is a highly selective MC4R agonist that produces a limited reduction in food intake in obese subjects, but it also causes headache, asthenia, nausea and diarrhea (Kievit et al., 2013). RM-493, also called MK-0493 or BIM-22493, is another MC4R agonist that in preclinical tests in macaques moderately reduced food intake but also produced nausea and vomiting over a certain dose (Kievit et al., 2013). These negative effects led to the rejection of RM-493 as an effective weight-reducing agent in healthy obese humans (Krishna et al., 2009). However, it is currently involved in phase-II trials in MC4R haploinsufficient (Prader-Willy syndrome) and POMC-null obese subjects (NCT02311673 and NCT02507492, respectively), where it is expected to reduce food intake and become an effective treatment in these special cases of obesity.

Like MC4R agonists, several Y5 antagonists reduce food intake and body weight in murine models (Ishihara et al., 2006) but their applicability in humans is unclear. MK-0557 is an orally-delivered, highly-selective Y5 antagonist. However, after three intervention studies it was concluded that the effects of MK-0557 were not clinically significant and research was discontinued (Erondu et al., 2007). The Y5 antagonist S-2367 has been tested in obese humans in phase-II trials over 60 weeks. The patients benefited from this treatment, which significantly lowered body weight compared to a placebo (George, Rajaram, & Shanmugam, 2014). Immediately after these trials, the effects of S-2367 were tested alone or in combination with the lipid absorption blocker Orlistat in 486 subjects under a reduced-calorie diet (NCT01126970). However, no results have yet been reported for this study and research on S-2367 seems to have been discontinued.

Specifically targeting the CNS to prevent side effects is a huge challenge, as has been proven by studies of Sibutramine (James