SHORT COMMENT FOR NATURE REVIEWS ENDOCRINOLOGY

Targeting simultaneously GLP-1, GIP and glucagon receptors : a new paradigm for treating obesity and diabetes

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Standfirst :

An innovative unimolecular, polypharmaceutical strategy using a well-balanced monomeric peptide triagonist targeting three metabolically-related hormone receptors (glucagon-like peptide-1, glucose-dependent insulinotropic poplypeptide and glucagon) appears the most effective pharmacological approach to reversing obesity and metabolic comorbidities in rodents and could open new perspective to tackle the dual obesity-diabetes burden in humans.

Bulleted point : Whereas inhibition of glucagon is classically considered as a potential target for treating diabetes mellitus, activating glucagon receptors simultaneously with GLP-1 and GIP receptors has the potential of treating both hyperglycaemia and weight excess, a strategy that opens a new paradigm in the management of obesity and type 2 diabetes.
50 words

Finan and colleagues reported the discovery of a new agonist acting simultaneously at three key metabolically-related peptide hormone receptors : glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors[1]. This rationally designed monomeric peptide that exerts a balanced agonism proved remarkable activity to reduce body weight, improve glucose control and reverse hepatic steatosis in various relevant models (either diet-induced or genetically determined) of obesity and diabetes in rodents. Through elegant studies using individual receptor-knockout mice, Finan and colleagues were able to demonstrate the presence of each constituent activity within the unimolecular triagonist and could ascertain some of the contribution of each constituent to the overall metabolic benefits induced by the monomeric peptide. The overall metabolic efficacy predominantly results from synergistic glucagon action to increase energy expenditure, GLP-1 action to reduce caloric intake and improve glucose control, and GIP action to potentiate the so-called incretin effect. Interestingly enough, the last two actions buffer against the diabetogenic effect of inherent glucagon activity of the peptide. Thus these preclinical studies in rodents suggest that this unimolecular, polypharmaceutical strategy has the potential to reversing obesity and related metabolic disorders[1]. Further studies should confirm whether this innovative pharmacological approach, which proved superior to any existing dual coagonists and best-in-class monoagonists in rodents, might be effective and safe to treat obesity and type 2 diabetes (T2DM) in humans and thus ultimately offer a valuable pharmacological alternative to bariatic surgery[2,3].

The dramatic rise of the twin epidemics, T2DM and obesity, is associated with increased mortality and morbidity and represents one of the most important public health challenges worldwide[4]. Striking parallel increases in the prevalence of the two entities reflect the importance of body fatness as a contributing factor to diabetes incidence and complications. Despite the importance of weight control strategies in the prevention and management of T2DM, long-term results are generally disappointing with lifestyle or available drug interventions[4]. Notably, therapeutic attempts to normalize body weight and glycaemia with single agents alone have generally been disappointing. Furthermore, most of

the classical glucose-lowering agents are accompanied by weight gain rendering even more challenging the management of most overweight/obese individuals with T2DM[4].

Incretin-based therapies are increasingly used in clinical practice for the management of T2DM[5]. Dipeptidyl peptidase-4 (DPP-4) enzyme rapidly degrades GLP-1 and GIP, two gastrointestinal hormones that potentiate insulin secretion in response to a meal. Therapeutic approaches for enhancing incretin action include degradation-resistant GLP-1 receptor agonists (incretin mimetics) and inhibitors of DPP-4 activity (incretin enhancers)[6]. Besides its incretin effect, GLP-1 suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. Both oral DPP-4 inhibitors (known as gliptins) and injectable GLP-1 receptor agonists exert a glucose-lowering effect with no or only a minimal risk of hypoglycaemia, the injectable agents being more potent than the oral compounds. Furthermore, while DPP-4 inhibitors are weight-neutral[7], GLP-1 receptor agonists significantly reduce body weight [8]. However, the amount of weight loss is generally moderate and could not compete with the drastic weight reduction induced by bariatric surgery. Benefits of bariatric surgery, however, extend well beyond weight loss and include dramatic improvement of T2DM. By recapitulation of the profound changes in the enteroendocrine responses secondary to changes in gastrointestinal anatomy, drugs based on gut hormones represent an exciting possibility for the treatment of T2DM and obesity[3,4]. Emerging data from preclinical studies supports the feasibility of using two or more agonists, or single co-agonists, for the treatment of obesity and T2DM[2].

. The therapeutic index of the triagonist developed by Finan and colleagues cannot be accurately determined from these preclinical studies. One crucial feature before using such a triagonist in humans would be to have a well-balanced glucagon activity. Indeed, glucagon is known as a counterregulatory hormone that exerts a potent hyperglycaemic effect by increasing hepatic glucose output through the stimulation of both glycogenolysis and gluconeogenesis[9]. Some experimental data suggested that glucagon suppression or inactivation may provide therapeutic advantages over insulin monotherapy[10]. Many attempts have been developed to inhibit glucagon secretion and/or action, with the aim of improving glucose control in T2DM, however without obvious success so far except the success story of incretin-based therapies[11]. The activation of glucagon receptor proposed by Finan and colleagues drastically contrasts with previous attempts to inhibit glucagon. The aim is that glucagon could exert some beneficial activities whereas its diabetogenic effects may be counteracted by the co-activation of GLP-1 and GIP receptors. Glucagon, at least partly by inhibiting orexin A secretion, may be interesting to increase energy expenditure and thus

promote weight loss, as recently shown in animals and humans, irrespective of changes in glucose or insulin levels[12]. Furthermore, recent data showed that coadministration of GLP-1 during glucagon infusion in humans results in increased energy expenditure, reduction in food intake and amelioration of hyperglycaemia[13,14]. Thus, GLP-1 protects against glucagon-induced hyperglycaemia whereas the glucagon-induced increase in energy expenditure is maintained. These observations support the concept of GLP-1 and glucagon dual agonism as a possible treatment for obesity and diabetes. Of note, GIP action to potentiate the incretin effect, as present in the new triagonist, could also contribute buffer against the diabetogenic effect of inherent glucagon activity[5]. Finan and colleagues are confident that the glucagon activity can be selectively fine-tuned with minimal structural or chemical change[1]. If it is the case, the ability to choose among several options that differ in their inherent molecular pharmacology would certainly increase the likelihood of ultimate success in humans.

Pharmacological outcomes of a particular target are often difficult to predict from targeted mutation animal models and safety issues are always critical in humans. Cardiovascular safety is becoming a major concern for the development of any new antidiabetic agent and glucagon is known to exert some cardiovascular effects whose action in humans remains to be better investigated. Furthermore, humans are not rodents from a metabolic point of view and many promising strategies to treat obesity and/or diabetes in rodents were not successful in human beings. Whether novel mechanisms identified in preclinical studies, such as that by Finan and colleagues[1], have potential translational relevance for the treatment of human disease would require extensive future studies[5]. Nevertheless, such studies targeting glucagon simultaneously with GLP-1 and GIP receptors open a new paradigm for the management of T2DM, especially when associated to obesity.

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Figure 1 : Complementary (but also opposing) effects of the individual components of a peptide triagonist targeting glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors with the potential of treating obesity and type 2 diabetes.

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