Obesity

Emerging Poly-Agonists for Obesity and Type 2 Diabetes

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Possibly as many as 2 billion adults currently have overweight or obesity, according to the World Health Organization, and obesity constitutes the most severe global health threat of our time. Dietary modifications and physical activity can promote weight loss, but adherence to these lifestyle modifications has so far proven impossible. Decades of research indicate that humans are evolutionarily wired to favor a positive energy balance and to stubbornly defend body weight gains (1).

Potent and safe pharmacological options that promote weight loss and improve metabolic health are urgently needed. Drugs currently available to treat obesity have limited efficacy and/or adverse side effects. Gastric bypass surgeries are by far the most effective obesity intervention, and they can produce sustained weight loss of up to 40% for most patients. However, financial cost and medical risk render these irreversible surgeries an unsuitable approach for large-scale intervention. Nonetheless, their robust efficacy demonstrates what is theoretically possible in terms of weight loss. Importantly, the metabolic benefits of gastric bypass surgery are not solely a result of changes in mechanical function of the gut but are likely due to alterations in complex neuroendocrine signaling patterns that alter appetite and energy expenditure (1). It is the concept of an adjusted hormonal profile following bariatric surgery that has led to the hypothesis that pronounced and sustained weight loss may be pharmacologically possible by mimicking several of these hormonal changes. To achieve clinically meaningful outcomes and to minimize regulatory complexities inherent to physical mixtures, we therefore designed multiple hormonal actions within single peptides. Identifying relevant combinations and balancing their activity to safely maximize body weight loss has been a near-Sisyphean journey. After more than a decade of painstaking efforts, several novel poly-agonists that have produced hitherto unparalleled preclinical results have progressed to clinical evaluation.

The starting point in our approach was provided by perhaps the most significant hormonal alteration following bariatric surgery, the marked increase in postprandial glucagon-like peptide 1 (GLP-1) secretion. Targeting both the central nervous system and pancreas, GLP-1 promotes satiety and insulin secretion. Currently available GLP-1 mono-agonist therapy provides a relevant but modest body weight loss of up to 10% in most patients with obesity (2). Determined to potentiate the metabolic benefits of GLP-1 receptor (GLP-1R) agonism with a nonredundant hormonal partner that promotes energy expenditure (3), we integrated a complementary and balanced glucagon receptor (GcGR) activity to a single molecule. We postulated that the glycemic benefits of GLP-1 could buffer the diabetogenic liability of unbuffered glucagon pharmacology and safely unleash its catabolic properties. This approach is diametrically opposed to the historical attempts to antagonize glucagon action. The first generation of balanced GLP-1/glucagon co-agonists was discovered early in the past decade, and they provided superior, synergistic, and safe body weight reduction of ~30% (Figure 1) following 1-month treatment in preclinical animal models of obesity (4).

Encouraged by this achievement, we sought to create a diverse portfolio of precision medicines capable of providing a more customized metabolic therapy. The generation of several innovative poly-agonists ensued, challenging certain dogma regarding the hormones that individually failed to produce meaningful results in treatment of metabolic diseases. A natural progression was the generation of "twincretin" molecules with balanced dual agonism at both major incretin receptor targets, GLP-1R and gastric inhibitory polypeptide receptor (GIPR). By utilizing insulintropic gastric inhibitory polypeptide (GIP) action (5), we aimed to amplify GLP-1 through the physiological benefits resident in the two natural incretins. The resulting series of GIP/GLP-1 co-agonist peptides markedly improved insulin secretion and glucose tolerance, without any appearance of hyperinsulinemia or hypoglycemia (6). Surprisingly, the GIP/GLP-1 co-agonists also produced synergistic and meaningful weight loss of 20% after 2 weeks of co-agonist administration in animals with obesity, partially through enhanced anorectic effects (Figure 1). The mechanisms behind this unexpected weight loss are subject to ongoing research, as this may reveal new avenues to modulate body weight in humans. Dual agonist peptides that possess balanced GIP or glucagon with GLP-1 for the treatment of obesity and diabetes currently constitute an area of sizable importance to pharmaceutical development, with numerous competing programs advancing to clinical study (7).

Building upon the independent success with dual agonists, we pursued single-molecule tri-agonists to simultaneously target

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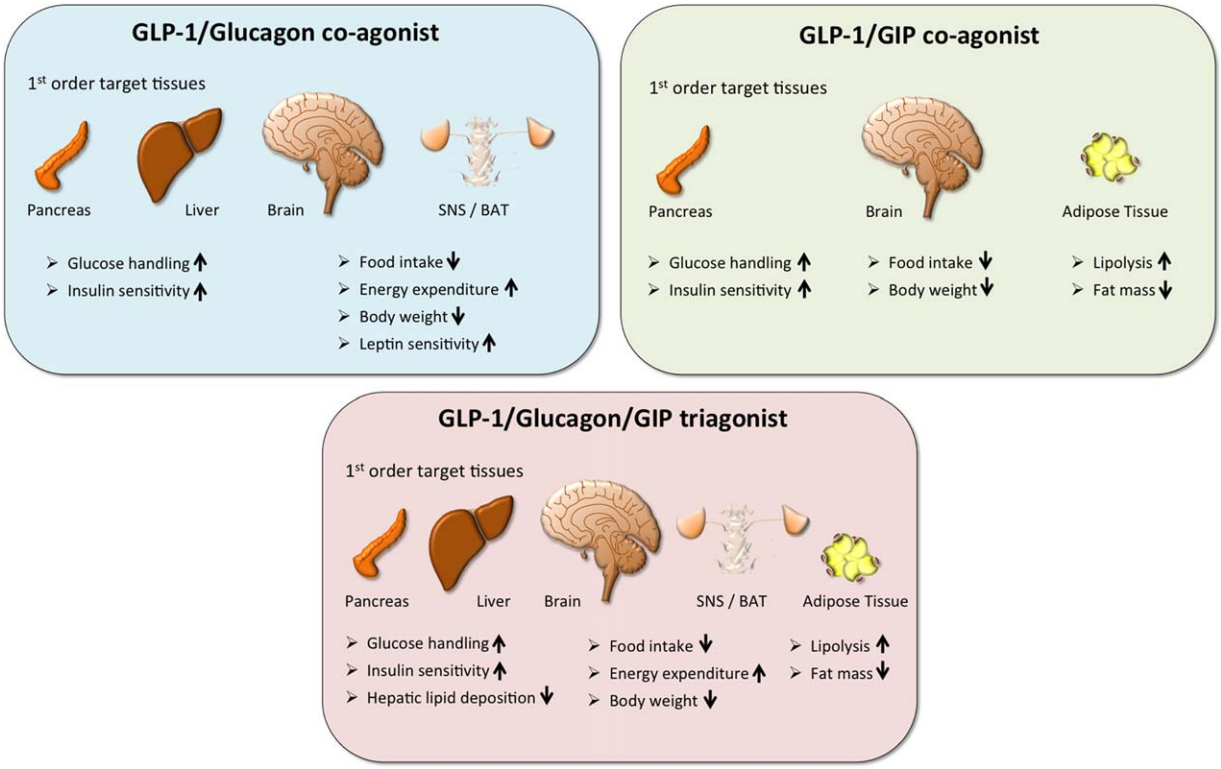

Figure 1 Poly-agonists for obesity and type 2 diabetes. SNS, sympathetic nervous system; BAT, brown adipose tissue.

GLP-1R, GIPR, and GcGR. MHT has been a member of the Novo Nordisk A/S advisory board and an SAB member of ERX Pharmaceuticals. The Institute for Diabetes and Obesity cooperates with Novo Nordisk and Sanofi-Aventis. Rationalizing that the dual incretin action could augment glycemia buffering, we were able to increase the relative glucagon activity and achieve further weight loss. This strategy holds unique promise, as these triagonists reverse the key aspects of the metabolic syndrome in rodent and nonhuman primate models of obesity and diabetes more effectively than any other previously reported agent (7,8). When compared to dual incretin co-agonists, these novel triple-acting peptides appear superior in correcting adiposity, hepatic steatosis, hyperphagia, and dyslipidemia associated with excessive body weight (Figure 1).

Realizing that hormonal poly-agonism is not restricted to peptide hormones and believing that we could safely integrate other molecular forms of hormone therapy, we directed our attention and expertise to specifically target discrete extracellular G-protein coupled receptors with specific nuclear hormones. Nuclear hormones,

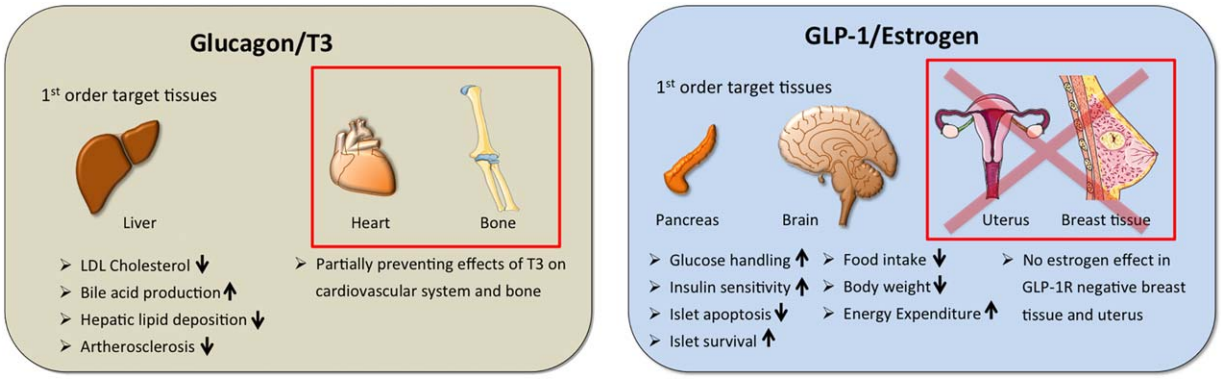

Figure 2 Conjugates for targeted delivery of nuclear hormones. LDL, low-density cholesterol; T3, triiodothyronine.

including estrogen, testosterone, and thyroid hormones, are potent modulators of energy metabolism but are well recognized to impact many other aspects of human biology (e.g., reproduction, immune function, growth). Their pleiotropic nature currently restricts their medical utility for the treatment of metabolic conditions. By chemically conjugating nuclear hormones to peptide hormones via stable peptide bonds, we envisioned that we could achieve an unparalleled selectivity through targeting of G-protein coupled receptors and thus enhance efficacy and safety. In a proof-of-concept study, we first utilized GLP-1 to deliver the steroid hormone estrogen selectively to GLP-1R–expressing tissues. Treatment of male and female mice with diet-induced obesity with the GLP-1/estrogen conjugate produced synergistic metabolic benefits relative to GLP-1 alone (Figure 2). Importantly, because estrogen activity was limited to GLP-1R–expressing tissues, none of the adverse gynecological or tumorigenic effects that are evident following unopposed estrogen monotherapy was detected in GLP-1/estrogen treated animals (9).

The prospect of using thyroid hormones in treatment of obesity has fascinated the clinical community for more than a century. The ability of the thyroid hormone triiodothyronine (T3) to robustly lower cholesterol is widely appreciated, but its deleterious chronic effects on the heart, muscles, and bones have curtailed such use in humans. Embellishing classical T3 therapy, we covalently linked T3 to glucagon to selectively deliver T3 action to specific glucagon-responsive tissues (10). This approach mainly circumvented the undesirable T3 action in tissues such as muscle and bone, while predominately focusing T3 pharmacology at the liver. The potential clinical benefit of such a glucagon/T3 conjugate was demonstrated in a mouse model of heart disease, in which coordinated pharmacology reversed arterial plaque formation, consistent with its beneficial levels on the plasma lipid profile. Glucagon/T3 also reversed hepatic steatosis in mouse models of fatty liver disease (Figure 2).

Over 25 years, the research community has collectively witnessed significant progress in defining the molecular pathways governing human energy metabolism, but we have struggled with first attempts to transform these insights to efficacious and safe medicines. The efficacy of bariatric surgery provides the standard to which medicinal intervention strives to achieve. It remains our belief that such performance requires poly-agonism and that our work of the past decade, largely preclinical in multiple species, provides possible direction and encouragement for the further integration of new mechanisms of action. As this approach progresses in clinical trials, there are several limitations that could thwart the successful translation from relatively short-term preclinical animal studies to chronic use in humans. The delivery route of subcutaneous injections, for example, could cause allergic reactions or even lead to the development of antibodies that neutralize endogenous hormones. Also, while conjoining multiple hormonal actions into a single drug has distinct regulatory advantages over classic combination treatment, the potency and intrinsic activity of each hormonal component is fixed and cannot be adjusted independently. For a comprehensive discussion of potential pitfalls, please refer to Tschoep et al. (7).

A central element to the success we have experienced has been the recruitment of substances and mechanisms previously thought to be ineffective, counterproductive, or unsafe. We have found that, through the coordinated action of multiple hormones, often in a targeted fashion, enhanced efficacy can often be achieved that is devoid of classical toxicity. Within the complexity of poly-agonism resides the performance that we most need to address the epidemic of obesity. The degree to which the therapy must be customized remains unknown, but this is not to be avoided, as the refinement to simpler approaches will inevitably derive from human experience. Once safety and primary efficacy have been firmly established, the customization of specific poly-agonism to suit the needs of individual patients will inevitably be pursued. O

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