Single-Molecule Combinatorial Therapeutics for Treating Obesity and Diabetes

Matthias Tschöp[1] and Richard DiMarchi[2]

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It will soon be 100 years since Frederick G. Banting, Charles Best, James Collip, and John J.R. Macleod in 1921 demonstrated that extracts of the pancreas had breathtaking beneficial effects to restore the health of patients with diabetes (1,2). While their breakthrough revolutionized the medical management of diabetes, the disease continues today to spread worldwide (3) along with a global increase in obesity. Novel unimolecular gut hormone polyagonists have shown unique potential to reverse obesity and diabetes in animal models and are currently being assessed in multiple clinical trials for their efficacy and safety (4).

INSULIN IS NOT THE CURE

Insulin replacement therapy currently remains a central pillar of diabetes management while additional antidiabetes medicines enhance production, secretion, and action of insulin to improve disease management and enhance patient care. Enormous progress has been made in the precise and continuous quantification of blood glucose, which, together with next-generation insulin pumps, has enabled closed-loop delivery systems, a sizable step forward in the direction of automatized insulin therapy. The cure still remains elusive, and prevalence of the disease continues to rise across the globe, frighteningly so at an accelerated pace in some of the most populous countries. How can it be that a century after the discovery of insulin, the occurrence of disease is increasing with no cure to stem the epidemic in sight?

The vast majority of diabetes worldwide is constituted of what was traditionally characterized as adult-onset, type 2 diabetes (T2D). This form of diabetes is clearly driven by another pandemic—that of obesity—and to an increasing extent is no longer an adult-onset disease. While the specific molecular mechanisms by which obesity is promoting the diabetes epidemic remain unclear, there is no controversy that in the absence of obesity, the magnitude of the diabetes problem would be far less significant and more manageable. However, despite decades of intense, targeted research, we have failed to deliver safe and efficacious antiobesity therapeutics that reverse morbid obesity or even lesser forms of the disease to normal body weight. There is no advanced medicinal development candidate with curative potential, not even one with the promise to manage obesity in a comparable fashion to the treatment of diabetes with insulin.

A RAPIDLY CLOSING WINDOW?

Has the fight against obesity been lost and with it our chances to reverse the T2D pandemic? Considerable worldwide public health efforts promoting healthier lifestyles via education and public policies have not stemmed the increase in diabetes prevalence. While this certainly should not lessen our resolve to identify alternatives to pharmaceutical intervention, it does underscore the increased importance and urgency to identify therapeutics with curative potential. At this point it appears possible that such a discovery remains the only way to save coming generations from an unimaginable health crisis. The urgency of the situation is magnified by recent insights in epigenetics research. A growing body of data supports a model where daily environmental and behavioral factors can significantly alter stable heritable traits to change protein expression, which cannot be explained by changes in DNA sequence. Changes in histone code or DNA methylation patterns are frequently considered to be the basis of such epigenetic modifications (5). Such molecular alterations may promote diabetes susceptibility in subsequent generations, rendering them less likely to respond to novel prevention medicines with otherwise curative potential discovered using current models of the disease. Therefore, there is unprecedented urgency in the scientific community to sufficiently address the pandemic until more creative public policy and effective education might deliver a significant epidemiological impact.

[1]Institute for Diabetes and Obesity, Helmholtz Diabetes Center, and German Diabetes Center, Helmholtz Zentrum München, Neuherberg, Germany, and Division of Metabolic Diseases, Technische Universität München, Munich, Germany
[2]Department of Chemistry, Indiana University, Bloomington, IN, and Novo Nordisk Research Center Indianapolis, Indianapolis, IN

Corresponding author: Matthias Tschöp, tschoep@helmholtz-muenchen.de.

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INDIRECT BRAIN TARGETING WITH MULTIPLE SIGNALS

Almost a quarter of a century ago, significant hope and enthusiasm were triggered by Friedman's discovery of the adipocyte-derived hormone leptin (6). It suggested the existence of a hormone with sufficient pharmacological effect to manage severe body weight disorders in a fashion analogous to insulin treatment of severe diabetes. Unfortunately, only a very small number of obese patients directly benefit from leptin therapy; the majority of the obese population did not improve in response to treatment. Still, this unique hormone, which physiologically regulates appetite and energy metabolism, taught us several important points. Most importantly, the seminal role of the central nervous system as the key organ in the regulation of food intake, body weight, energy balance, and system-wide cellular metabolism was embellished. Similar insights were gained from identification of the gastric-derived peptide ghrelin as an endogenous hunger hormone, which along with leptin serves to control body weight. Today, when accounting for the entirety of data available through genome-wide association studies, it appears quite clear that obesity as the epidemiological driver of the T2D pandemic is predominantly a brain disease. Most of the single nucleotide polymorphisms identified through obesity genetics studies and confirmed in ever larger human populations pertain to proteins expressed or exerting their most important functions in the brain (7). Therefore, it seems inevitable that the discovery of obesity therapeutics would need to target brain pathways. Recent research advances provide reason for optimism. While currently approved medicines offer insufficient efficacy to reverse the global epidemic, surgical interventions such as Roux-en-Y gastric bypass or sleeve gastrectomy can successfully reverse most human forms of obesity and diabetes. Of particular interest to metabolism researchers is that improved glucose homeostasis occurs rapidly, even preceding significant weight loss. This observation suggests that molecular signals emanating from bariatric surgery may directly improve systemic glucose metabolism, independent from weight loss. The essential molecular mechanisms mediating appetite and metabolism improvements following such surgery remain largely unknown but continue to be intensely studied (8). The consensus opinion suggests that several pathways are involved and that central nervous system circuits governing appetite and systemic metabolism are indirectly modulated via gut-derived neuroendocrine signals. Although there are a growing number of proponents calling for broader use of bariatric surgeries to treat both morbid obesity and diabetes (9), these surgical interventions are highly invasive, irreversible, and not risk free. Possible long-term complications range from bowel obstruction and dumping syndrome to diarrhea, gallstones, and hypoglycemia. In addition, surgery is not appropriate for all patients with obesity or diabetes, and even if it were, there is insufficient infrastructure (surgeons, surgical space, and financial resources) to address an epidemic of global disease.

HARNESSING GUT–BRAIN COMMUNICATION WITH UNIMOLECULAR POLYAGONISTS

Beginning in 2003, with the goal of engineering novel agents with a superior potency and safety profile, we envisioned molecules modulating several gut-derived signals and thereby indirectly adjusting the control of appetite and metabolism in the brain and other metabolic control organs. Glucagon-like peptide 1 (GLP-1) receptor agonists target hypothalamic control circuits, offer proven metabolic benefits as well as pancreatic incretin action, and induce a small to modest loss of body fat in most patients. Our key approach was to significantly enhance the efficacy and action profile of incretin-like agents by engineering peptides to also include glucagon action. At the time, this strategy seemed counterintuitive to academic and pharmaceutical communities, as all glucagon-based research was focused on hyperglycemia, not obesity, and directed exclusively to antagonism at the glucagon receptor (10). How could it be a winning strategy for a new antiobesity drug to include actions of a hormone most widely known for its ability to increase hepatic glucose output? Intriguingly, the action profile of glucagon includes modulation of many metabolic processes beyond glycogenolysis and gluconeogenesis. Among those, lipolysis in adipose tissue, appetite suppression in the central nervous system, and promotion of energy expenditure recruited our interest to integrate glucagon action into unimolecular polyagonist peptides. We hoped that these desired metabolic actions would synergize with the classic benefits offered by incretin biology while simultaneously GLP-1 agonism would counterbalance the diabetogenic liability of glucagon to provide a therapeutic of superior efficacy in its metabolic profile. The first encouraging studies showed that comparably adding the nine–amino acid COOH-terminal tail that differentiates exendin from GLP-1 to glucagon provided a soluble, stable, and selective glucagon agonist that exemplified glucagon's weight loss–inducing efficacy (11). Subsequent discovery of several dual GLP-1/glucagon coagonists showed in preclinical models that a much larger loss of fat mass can be achieved than is otherwise possible with monoagonists (12). Interestingly, the superior weight loss of such glucagon-based dual agonists is fractionally dependent on the functional integrity in FGF21 signaling, suggesting a mutual mechanistic interaction between these two fasting hormones (13). The importance of glucagon action within a fully effective dual-agonist peptide is further exemplified by the gut peptide oxyntomodulin, which shows impotent in vivo metabolic effect that is GLP-1 receptor mediated (14). It fails to achieve metabolic benefits comparable to the best dual glucagon/GLP-1 agonists. Aiming to generate an expanded portfolio of drug candidates with tailored action profiles geared toward individual patient needs, we subsequently designed dual agonists combining the action

of the two most prominent physiological incretins (GLP-1 and glucose-dependent insulinotropic polypeptide [GIP]). Such dual incretins, or twincretins, also exhibited metabolic profiles superior to those of monoagonists but differed significantly from those of glucagon-based drug candidates (15). Importantly, numerous biological lessons were learned along the way in the study of these agents. Among those were paradigm shifts in viewing the pharmacological potential of glucagon action and, similarly, the superiority of GIP receptor agonism to previous attempts to antagonize GIP action. In each instance, predictions for pharmacology based on phenotypes in global mouse knockouts were misleading. Furthermore, preclinical observations revealed that simultaneous GLP-1 and GIP effects reveal metabolic and body weight effects that largely remain silent in the study of monoagonists. In order to achieve the optimal therapeutic benefits of glucagon action while maximizing incretin action and glycemic counterbalance, the search for balanced triple gut hormone agonists subsequently emerged about a decade ago. Balanced, fully potent triagonist peptides, when studied in animal models of obesity and diabetes, suggest that unifying the hormone actions of GLP-1, GIP, and glucagon achieves a body weight and metabolic impact reminiscent of the benefits in bariatric surgery (16). Importantly, such triagonist peptides are comparable in molecular size of endogenous glucagon and do not differ from endogenous gut hormones more than exendin-based drugs from human GLP-1.

TOWARD PERSONALIZED PRECISION MEDICINES FOR DIABETES AND OBESITY

Sufficiently powered clinical studies will demonstrate whether gut hormone polyagonists can reverse the obesity and diabetes pandemic. In parallel, more and more evidence suggests that obesity and diabetes are heterogeneous disease entities consisting of several populations of differing disease subtypes. While the conditions of some patients seem to be clearly driven by morbid obesity, others are affected by pancreatic failure, fatty liver disease, or less well-established pathophysiological conditions such as hypothalamic inflammation. A new generation of precision medicines may need to target each disease subtype in an appropriately personalized manner. With these needs in mind, we pioneered another series of novel metabolic disease drug candidates. Here we chemically fused steroid hormones such as estrogen or thyroid hormone onto gut hormone peptides. With this novel strategy, we pursued two goals. On one hand, this approach offered more possible hormonal combinations to be assessed for hidden synergistic profiles. On the other hand, the gut peptides would serve as "trojan horse" shuttles and deliver powerful nuclear hormones selectively to metabolically relevant cells while keeping them away from cells where they might have toxic effects. Several of these drug candidates have been discovered and show additional potential in the treatment of obesity and diabetes. Among them, GLP-1–based estrogen delivery improves hypothalamic neuropeptide balance and decreases body fat mass (17), and glucagon-based targeting of thyroid hormones improves liver lipid metabolism and atherosclerosis while minimizing adverse effects such as inappropriate increase in body temperature (18). Should clinical studies confirm the beneficial properties of such integrated peptide/small molecule conjugates, a plethora of additional combinations could be considered. However, what is missing are biomarkers offering refined diagnostics that would enable the most intelligent use of metabolic precision medicines. In this regard, cancer therapy is more advanced and illustrates what might be possible in a comparative sense. Oncology has access to data derived from sequencing of tumors, which can inform targeted precision therapy. Metabolic disease research is currently far more empirical, but a more descriptive collection of diagnostically relevant information such as organ imaging or basic blood chemistry coupled with precision medicines could constitute the future.

CONCLUSION

We find ourselves at a precarious point where our direction has been enlightened by the advances in modern-age biology but challenged by the global pandemic of disease and the uncertain consequence it represents for future generations. The importance of novel therapeutics with the potential to cure obesity and diabetes cannot be overstated, and the certainty of these being discovered removed from the urgency has never been greater. What we have witnessed is that through the coordinated action of multiple hormones, often in a targeted fashion, much enhanced efficacy can be achieved and is often devoid of classic toxicity. Within the complexity of polyagonism resides the performance that we most need to address the epidemic of disease. Whether polyagonist-based therapies provide clinical benefits approaching what has been observed in multiple preclinical species will be determined, and we remain optimistic.

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