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Novel pharmacotherapies for the treatment of Obesity and Diabetes

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Abstract

Since almost a decade our group has now, together with lead international scientists, revolutionized the concept of polypharmacology by generating peptides which combine, through intermixed sequence hybridization, the beneficial effects of several key metabolic hormones into a single hormone entity. In line with this notion, we have shown that a molecule with balanced dual--agonism at the receptors for GLP--1 and glucagon synergistically corrects diet-induced obesity and glucose intolerance in a variety of rodent models (Day et al., Nat Chem Biol. 2009). A molecule with balanced dual--agonism at the receptors for GLP--1 and GIP was further developed and demonstrated to substantially correct glucose metabolism in a variety of species, including obese and diabetic rodents, non--human primates and humans (Finan et al., Sci Transl Med 2013). Notably, the GLP--1/GIP dual-- agonist improved glucose handling with greater metabolic efficacy and with an unmet level of safety relative to best-- in-- class available FDA/EMA approved drugs for T2D (Finan et al., Sci Transl Med 2013). A single highly potent PK--optimized molecule with balanced triple agonism at the receptors for GLP--1, GIP and glucagon were further shown to correct obesity and glucose intolerance, to reverse insulin resistance and to improve lipid and cholesterol metabolism. The beneficial metabolic effects of this triple agonist were demonstrated in various mouse models of diet and genetically induced obesity (Finan et al., Nat Med 2015) and was shown to translate from obese rodents to non--human primates (Tschöp et al., Cell Metab 2016). Expanding the concept of polypharmacology, we recently reported GLP--1 mediated delivery of the nuclear hormone estrogen to selected tissues relevant in systemic energy metabolism control (Finan et al., Nat Med 2012). The tissue--specific delivery of estrogen thereby maximized its beneficial effects on metabolism and minimized its oncogenic potential in GLP--1R negative tissues, such as the uterus and the breast tissue. Building up on these findings, we recently report targeted delivery of dexamethasone via GLP 1 as the peptide carrier to improve hypothalamic inflammation (Quarta et al., Cell Metab 2017). In summary, our data emphasize the therapeutic utility of several novel unimolecular polypharmacotherapies for the treatment of obesity, type 2 diabetes and cardiovascular diseas.

Biography

Timo Müller has completed her Nutrition and Dietetics degrees (Post-Master's studies in International Nutrition). He is the Professor and Chairperson of Nutrition and Dietetics Department at Institute for Diabetes and Obesity (IDO), Germany. He has recently published her dissertation in the Type 2 diabetes risk gene Dusp8 regulates hypothalamic Jnk signaling and insulin sensitivity, and is a contributing Writer for newspapers and health magazines and has also published two vegetarian cookbooks. His professional experience includes Vegetarian Nutrition Consultant, Public Health Speaker and Program Planner for international and state-wide public health nutrition initiatives.

Publications

Type 2 diabetes risk gene Dusp8 regulates hypothalamic Jnk signaling and insulin sensitivity.
The extracellular N-terminal domain of G-protein coupled receptor 83 regulates signaling properties and is an intramolecular inverse agonist.
The extracellular N-terminal domain of G-protein coupled receptor 83 regulates signaling properties and is an intramolecular inverse agonist.
Age-dependent membrane release and degradation of full-length glycosylphosphatidylinositol-anchored proteins in rats.
Active integrins regulate white adipose tissue insulin sensitivity and brown fat thermogenesis

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