Project 7: Investigation of alternative mechanisms involved in the anti-diabetic effects of dextromethorphan.

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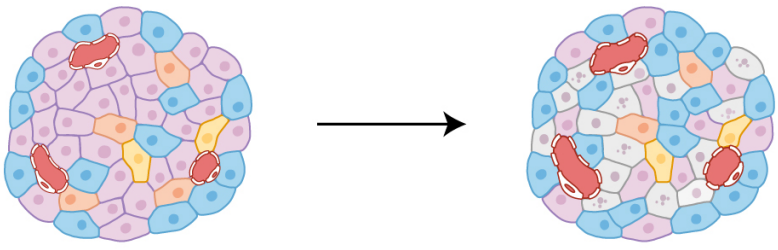
Background: T2DM develops when insulin resistance in organs, such as liver or skeletal muscle, is accompanied with a failure of the insulin-secreting pancreatic beta cells. The latter cells decline in their function, meaning they do not secrete sufficient insulin to sufficiently control blood glucose levels, and they decline in their survival, meaning that the beta cells start to die. In addition, the pancreatic beta cells dedifferentiate and become non-functional. This decline in beta cell function, survival and differentiation is progressive upon onset of T2DM and is believed to contribute to diabetes progression in humans with T2DM, often leading to insulin dependence. Notably, most oral anti-diabetic medication cannot stop this disease progression. Therefore, after some years of medical treatment, blood glucose concentrations return to those before anti-diabetic treatment. Thus, it is essential to identify and explore pathways in the beta cells that protect them from dysfunction, death and dedifferentiation, so that current oral anti-diabetic medication is successful for a longer duration, thereby avoiding the need for insulin injections.

Own previous work: We have previously found that NMDA receptors are expressed on pancreatic beta cells[1,2]. The most conserved subunits in pancreatic islets are the essential subunit GluN1 and two of its co-subunits, i.e. GluN2C and GluN2D[1,2]. Blocking NMDA receptors both genetically and pharmacologically increases glucose-stimulated insulin secretion and beta cell survival *in vitro* and *in vivo*[1-3]. In addition, the NMDA receptor antagonist dextromethorphan increases glucose-stimulated insulin secretion from pancreatic islets and enhances their viability. Dextromethorphan is the prodrug of dextrorphan, which inhibits NMDA receptor currents, but also acts on certain transporters (such as the sodium-dependent serotonin transporter) and other receptors (such as the σ1-receptor and μ-opioid receptor).

Aim of the project: Here we aim to dissect the molecular mechanisms underlying the anti-diabetic effects of dextrorphan in pancreatic beta cells. More specifically, we focus on how dextrorphan at low and high concentrations affects glucose-stimulated insulin secretion and pancreatic beta cell survival. The long-term goal of this project is to identify possible ways to generate anti-diabetic drugs that no longer exhaust pancreatic beta cells, but instead preserve their function as to prevent diabetes progression and insulin dependence in human individuals with type 2 diabetes mellitus.

Work program: The effects of dextrorphan on pancreatic islets and their targets will be studied *in vitro*, *in vivo* and *ex vivo*. A specific focus will be on insulin secretion from pancreatic islets, the role of alternative targets of dextrorphan as well as its effects on the electrophysiologic and metabolic properties of pancreatic beta cells. Genetic, pharmacologic, cell biological, and electrophysiologic methods will be applied. Both PhD and MD students are integrated in this project.



Development of diabetes mellitus due to pancreatic beta cell demise
(Illustration by Y. Koh)

References: [1]Marquard, Otter, Welters et al., Nat Med 2015. [2]Otter & Lammert, Trends Endocrinol Metab 2016. [3]Scholz et al., The NMDA Receptors (ed. Hashimoto) 2017.