Title: The role of pancreatic islet cell glutamate receptors in endocrine hormone secretion and in the development of diabetes.

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Abstract: After a meal our body turns food into sugar, celled glucose. Cells rely on a constant supply of glucose as a major source of energy. Therefore it is essential that the human body maintains blood glucose level in a very narrow range. Insulin and glucagon are the hormones that make this happen. Both hormones are secreted from small groups of cells (islet cells) present within the pancreas. Insulin and glucagon are both secreted in response to blood glucose levels, but in opposite fashion: high blood glucose (e.g. after a meal) stimulates insulin secretion from beta-cells (a type of islet cell) and inhibits glucagon release from alpha-cells. At low blood glucose (e.g. between meals and during exercise), more glucagon is secreted and the amount of insulin release goes down. Insulin is required for the uptake of glucose into cells, which lowers blood glucose. In contrast, glucagon stimulates glucose release from the liver into the bloodstream. It is the relative balance of insulin and glucagon secretion and interplay between islet cells that ultimately determines if a patient develops diabetes (persistently high blood glucose level due to insufficient production of insulin) or hypoglycaemia, both of which are potentially serious health problems. As a common chronic disease that affects several organs, diabetes has a profound impact on the population worldwide. Diabetes affects 6% of the adult UK population and therefore the associated healthcare cost is enormous. Improved treatment or the prevention of diabetes requires better understanding of the way insulin and glucagon secretion is regulated in pancreatic islets.

In the brain neurons communicate with others by releasing neurotransmitters and activating their receptors in neighbouring cells. The most important excitatory neurotransmitter is glutamate. Previous studies established that islet cells have much in common with neurons. For example, islet cells respond to glutamate through the activation of various glutamate receptors (GluRs) that appear to be involved in the regulation of hormone secretion. However, very little is known about the structure and functional properties of islet cell GluRs. This research project aims to define the physiological role of GluR subtypes (AMPA, kainate and NMDA receptors) in the regulation of insulin and glucagon secretion in pancreatic islet cells. Additional we aim to establish the role of GluRs in the autoimmune destruction of insulin secreting beta-cells in type 1 diabetes (T1D). The molecular organisation, distribution, pharmacological and functional properties and regulation of iGluR subtypes (AMPA, kainate and NMDA receptors) will be studied in human and rodent islets of Langerhans, glucagon secreting alpha-cells and insulin releasing beta-cells using a combination of molecular, pharmacological, biochemical and histological approaches. New pharmacological tools (e.g. biotin-tagged photoreactive affinity ligands and high affinity subunit specific antagonists), wide range of extensively characterised antibodies, transgenic mice and sensitive assays will enable the systematic characterisation of iGluRs in different cell types of the islets of Langerhans. GluR autoantibodies will be investigated in newly diagnosed T1D patients and the anti-GluR antibody binding sites determined by SPOT-peptide synthesis. The study will reveal key features of the expressed iGluRs and their involvement in endocrine regulation. It is likely that these receptors participate in the pathomechanism of diabetes mellitus and they should also be considered as potentially important pharmacological targets for future treatment strategies.