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Insulin secretion and sensitivity
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Summary

In this thesis, the effect of potassium channel modulating agents on insulin secretion and insulin sensitivity has been investigated. Studies were performed in healthy volunteers, in patients with essential hypertension, which is associated with insulin resistance and hyperinsulinemia, in patients with non-insulin-dependent diabetes mellitus, a condition that combines resistance to insulin and a defect in insulin secretion by the pancreatic β cell, and in patients with hypokalemic periodic paralysis, a disease in which abnormalities in insulin release may be involved. This summary attempts to answer the questions, that are put forward in the introduction.

In chapter 1 the clinical role of the ATP-sensitive potassium channels is reviewed. Knowledge about the K⁺[ATP] channels has grown in the past decade, due to techniques for their assessment (isotope flux studies and the voltage-clamp technique), and the development of drugs that can either open or close these cell membrane structures. These K⁺[ATP] channel opening- and closing drugs and their (possible) effects on insulin release and insulin sensitivity are discussed. K⁺[ATP] channel opening drugs are effective in lowering blood pressure and in the management of ischemic heart disease. They are as effective in achieving adequate blood pressure control as calcium channel blockers. The possibility is discussed, that these agents could diminish insulin release in vivo by opening pancreatic β cell K⁺[ATP] channels, an effect formerly described in in vitro studies. K⁺[ATP] channel blocking drugs, better known as sulphonylurea derivatives (SU), are used for the management of NIDDM. They enhance insulin release in NIDDM patients, improving metabolic control. The hypothesis, that SU worsen cardiovascular mortality, is not supported by convincing data. The future place of SU in clinical practice will depend on the outcome of long-term studies like the UKPDS and on the development of other treatment strategies in NIDDM.

Chapter 2 describes, using intravenous glucose tolerance tests, that the acute administration of the potassium opener pinacidil, an antihypertensive drug, has no significant effect on insulin secretion, nor on glucose disappearance rate in hypertensive patients.
Previous data indicated that pinacidil deteriorates glucose tolerance by lowering plasma insulin levels, as measured by ivGTT’s in healthy subjects. To confirm this, insulin release and insulin sensitivity were studied in 10 hypertensive patients and in 10 matched control subjects using the hyperglycemic glucose clamp technique, as the ‘gold standard’ for the assessment of insulin secretion, yielding more precise results than the ivGTT (chapter 3). In the hypertensive subjects fasting insulin levels were significantly higher than in the control subjects, pointing to insulin resistance. The K⁺[ATP] channel opener pinacidil did not change insulin release, neither in the hypertensives, nor in the controls. However, pinacidil did enhance insulin sensitivity. This effect could be related to the vasodilative action of pinacidil, enhancing glucose uptake in muscle. So, based on the findings of our experiments, pinacidil has a profile, that makes it an eligible antihypertensive drug in patients with hypertension with or without NIDDM.

In chapter 4 four patients with hypokalemic periodic paralysis (HOPP), a rare inherited disease, characterized by transient attacks of muscle weakness, were studied with the hyperglycemic clamp technique. In HOPP, abnormalities in insulin release and in K⁺[ATP] channels could be involved. Insulin secretion and sensitivity appear to be normal in HOPP. Hyperglycemia did not provoke paralytic attacks and did not result in a decrease in muscle strength. Pinacidil may enhance muscle strength in those HOPP patients, who have partial paralytic attacks. This has to be confirmed in a larger group of HOPP patients in different stages of the disease, who take pinacidil for a longer period.

In NIDDM, first phase insulin secretion is diminished or absent, while second phase insulin release is markedly reduced. Sulphonylureas exert their effect by closure of the K⁺[ATP] channels of the pancreatic β cell, which results in insulin exocytosis. There may be differences in the various SU in stimulating first and/or second phase insulin release and with respect to stimulation of insulin release at high blood glucose levels. In chapter 5 the influence of oral administration of the SU glibenclamide on first and second phase insulin secretion was examined at submaximally (8 mmol/l) and maximally (>30 mmol/l) stimulating blood glucose levels in 12 healthy volunteers, using the primed hyperglycemic glucose clamp technique.
Summary

Glibenclamide increases second phase insulin secretion only at a submaximally stimulating blood glucose level without enhancement of first phase insulin release, and has no additive effect on insulin secretion at maximally stimulating blood glucose levels. These findings are in accordance with the theory glibenclamide acts via a mechanism similar to glucose, since a blood glucose level > 30 mmol/l represents the maximally stimulating glucose concentration. Furthermore, glibenclamide did not change insulin sensitivity in this acute experiment. Hyperglycemic clamp studies in patients with non-insulin-dependent diabetes mellitus could be performed to confirm these findings in NIDDM.

Chapter 6 describes studies with the SU gliclazide in 12 patients with long-lasting NIDDM. Gliclazide has previously been shown to enhance first phase insulin release in healthy subjects. After reaching stable euglycemia (blood glucose 4.6 mmol/l) with the hyperinsulinemic euglycemic clamp technique, the effect of 160 mg gliclazide on first and second phase insulin secretion during a 4 hr hyperglycemic clamp (blood glucose 8 mmol/l) was studied in a randomized, double blinded, cross-over study design. No evidence of an effect of gliclazide on first phase insulin secretion was found in these patients with long-standing NIDDM, who had an inconsiderable - 15% of normal - first phase. On the other hand, second phase insulin release showed a marked and sustained increase during the last 3 hours of the hyperglycemic clamp. So, after gliclazide has closed the ATP-sensitive potassium channel of the β cell, resulting in an influx of calcium ions, the cascade which results in first phase insulin release apparently is blocked, whereas stimulation of second phase insulin release is intact.

In chapter 7 the suppression of plasma free fatty acids (FFA) and triglycerides by acute hyperglycemia-induced hyperinsulinemia as well as baseline plasma lipids, plasma LCAT and CETP activity were studied in 8 patients with essential hypertension and in 8 matched control subjects. Essential hypertension is associated with abnormalities in FFA and triglyceride metabolism. During a 3 hr hyperglycemic clamp (blood glucose 10 mmol/l) plasma FFA and triglycerides decreased to a lesser extent and remained higher in the hypertensive patients, despite similar plasma insulin levels. Baseline plasma FFA, total cholesterol and HDL cholesterol were not different between the groups, but plasma triglycerides tended to be
higher in the hypertensive patients. The plasma LCAT/CETP ratio was higher in the hypertensive patients. So, in essential hypertension the action of insulin on FFA metabolism is impaired, which is likely to contribute to higher plasma triglycerides. In turn, higher triglycerides influence the HDL lipid composition, either directly or via an effect on the plasma LCAT/CETP ratio.

Final remarks

Potassium channel blocking agents (sulphonylureas) are widely used in the treatment of type 2 diabetes mellitus. Recently, interest has grown in the effects of SU on ATP-sensitive potassium channels of other organs, such as the myocardial cell and the vascular cell. In this aspect, differences have been found between the SU glibenclamide and glimepiride; glibenclamide blocks vascular ATP-sensitive potassium channels, whereas glimepiride does not have this property. Experiments with SU on myocardial cells indicate that they may increase cardiac ischemia and infarct size by inhibition of the reflectory vasodilation during cardiac oxygen depletion. Other studies suggest a cardioprotective effect of SU on rhythm disturbances of the heart, for example during myocardial infarction. Outcomes of prospective clinical studies are needed to define the clinical relevance of these in vitro findings. The recently cloned SU receptor (SUR) and its isoforms in various organ cells could also be of great importance in the understanding of the action of SU on different organs. Because the majority of NIDDM patients use SU to treat their disease, it is important that questions concerning possible cardiovascular effects of these drugs in man will be answered in the near future.