New therapeutic efforts and upcoming developments in the field of diabetes medicine and endocrinology

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I welcome the readers to the newest issue of Therapeutic Advances in Endocrinology and Metabolism. In this issue, two important therapeutic fields are addressed: In the diabetes area the pharmacologic improvement of insulin therapy and a specific cellular therapy for treating severe foot ulcers as a treatment option in complicated and therapy-resistant cases; in the field of specific endocrine and metabolic disorders, the pharmacologic treatment of the syndrome of inappropriate antidiuretic hormone (SIADH) which is also called the Schwartz-Bartter-Syndrome is extensively reviewed.

It is a sobering statistic: in an online survey of 500 patients with types 1 and 2 diabetes mellitus, 57% reported intentionally omitting their insulin injections. From a patient's perspective, avoiding hypoglycemia is a major concern and this is probably one of the main causes of non-adherence to this medication, resulting in poor glycemic control. A longer-acting basal insulin should, therefore, address this problem. The review by Ammar Wakil and Stephen Atkin in this issue looks at Degludec, a new long acting insulin with a longer half-life than others, a flat time-action profile (less likely to cause hypoglycemia) and less day-to-day variability, improving glycaemic control. Degludec is made by deleting a threonine residue from human insulin and adding an acyl side chain to a lysine residue, so that injection results in self-association and the formation of large soluble multi-hexamers – a subcutaneous depot. This promises better glycemic control compared with insulin glargine and patients have more choice as to the timing of their basal insulin dose.

Lower limb amputations as a result of non-healing foot ulcers in diabetic patients are regrettable, especially because they might have been avoided with more consequent and earlier treatment of the disease. In a letter to the Editor from the group of Matthias Weck, an emerging cellular therapy using platelet-rich plasma gel is described, and seems to provide previously unavailable ulcer management options to avoid limb loss.

Physicians haven't had a specific therapy for hyponatremia until the recent arrival of vasopressin receptor antagonists, the vaptans. Peter Gross contributes to the issue with a comprehensive review focusing on SIADH, accounting for one third of hyponatremia and serving as a general model for the disease. Misdiagnosis is common, and the author discusses the importance of demonstrating reduced effective serum osmolality in a given hyponatremia to exclude the possibility of a normoosmolar or hyperosmolar hyponatremia. It must be considered that a common circumstance of hyperosmolar hyponatremia is hyperglycemia. The introduction of parenteral (conivaptan) and orally available (tolvaptan) renal V-2 vasopressin receptor antagonists – collectively called vaptans - for the specific, easily titratable treatment of SIADH has been considered a breakthrough. The author gives detailed practical expert advice on their therapeutic use.

Further new upcoming developments in the field of diabetes medicine

Four very recent developments impressed me and will be topics in detail in future issues of Therapeutic Advances in Endocrinology and Metabolism:

First, Burant and colleagues published results of a phase 2 – trial investigating the first oral, highly potent, and selective free fatty acid receptor 1 (FFAR1)-agonist called TAK-875 which was the first of its class tested for glucose-lowering ability in patients with type 2 diabetes. In humans, FFAR1 expression is highest in β-cells of the pancreatic islets. Activation of this

GLP-1-agonists	DPP-4-inhibitors	glitazones	glitazars	$SGLT_2$-inhibitors	$FFAR_1$-agonists	$IL_{1\beta}$-mABs
PROs: - Glucose-dependent inhibition of glucagon-secretion - Emptying of stomach reduced - Appetite reduction (direct CNS-effect) - Weight reduction (- 2-3 kg) - Slow release formulation available	**PROs**: - Oral formulation available - Glucose-dependent improvement of insulin secretion and inhibition of glucagon-secretion - Approved for severe renal failure - Approved for monotherapy - No risk for hypoglycemia	**PROs**: - No increased CV-risk with pioglitazone - Improve insulin resistance - Valid secondary line treatment option if other drugs fail	**PROs**: - Combined $PPAR_\alpha$ and $_\gamma$-stimulation - Combine benefits of glitazones (glucose reduction) and fibrates (lipid profile improvement)	**PROs**: - Calory dumping - Weight reduction - Insulin-independent reduction of blood sugar - Combination therapy with other oral antidiabetics promising	**PROs:** - Dose-dependent improvement in glycemic control - Significant change in HbA_{1c} apparent in week 4→rapid onset of action - Low risk of hypoglycemia - So far excellent AE-profile on placebo level.	**PROs:** - Focusing the potentially central role of inflammation in pathophysiology of T2DM - Reduces CRP and IL-6 - Metabolically neutral - CANTOS-trial evaluates as secondary EP new onset of diabetes.
CONs: - Not approved for monotherapy. - Only injectable formulation available - Rare cases of pancreatitis and anaphylaxis reported - Nausea frequently reported	**CONs**: - No weight reduction. - No effect on stomach emptying and appetite - Rare cases of pancreatitis and anaphylaxis reported	**CONs**: - Only pioglitazone still available - Potentially increased risk for bladder cancer - Contraindicated in heart failure NYHA I-IV - Increased risk for bone fractures	**CONs**: - Only aleglitazar still in clinical development - Mura- and Tesaglitazar were stopped due to unfavourable AE*-profiles	**CONs**: - Increased rate of urinary tract and genital infections reported - Rare cases of bladder and breast cancer reported - FDA approval denied, new studies requested	**CONs**: - Variable weight gain points towards variability in response - Insulin resistance apparently unaffected	**CONs**: - Experimental therapy today under investigation. - Only moderate HbA1c-reduction

*Adverse event.

cell-surface receptor by fatty acids or synthetic ligands such as TAK-875 results in increased insulin secretion, but only in the presence of rising glucose concentrations. Although the exact mechanisms for augmentation of glucose-mediated insulin secretion by FFAR1 signalling remain unclear, the pathways appear distinct from other glucose-dependent insulin secretagogues, such as glucagon-like peptide-1 (GLP-1). In this trial, TAK-875 significantly improved glycaemic control in patients with T2DM with only minimum risk of hypoglycemia [Burant *et al*. 2012]. The authors consider the activation of FFAR1 a viable therapeutic target for the treatment of T2DM. Unquestionably unpleasant is the fact that TAK-875 increased bodyweight relative to placebo (>0.6 kg), an effect not dissimilar to that of the sulfonylurea glimepiride. A further potential limitation is that insulin resistance was apparently unaffected by TAK-875. This finding revisits the therapeutic conundrum in type 2 diabetes that chronically increased insulin concentrations can aggravate insulin resistance, which might offset early benefits of enhanced insulin secretion [Bailey 2012]. Further and larger phase III trials will teach us if FFAR1-agonists may have a role in the treatment of T2DM in the future.

Second, Ridker and colleagues recently introduced the CANTOS-trial, which investigates the inflammatory hypothesis of atherothrombosis and the role of hsCRP in clinical practice [Ridker *et al*. 2011]. Experimental evidence accumulating over the past quarter century has implicated IL-1 in atherothrombosis. Given the role of IL1-β in atherothrombosis, the use of IL-1β inhibition as a possible method to reduce vascular risk has generated considerable interest. Canakinumab is a human monoclonal antihuman IL-1β antibody of the immunoglobin G1/k isotype that is currently indicated for the treatment of IL-1β-driven inflammatory disorders. The primary objective of the CANTOS-trial is to determine whether long-term-treatment with canakinumab (50, 150, or 300 mg SC every 3 months) as compared with placebo will reduce rates of recurrent cardiovascular events among stable patients with postmyocardial infarction who remain at elevated vascular risk as gauged by increased levels of hsCRP (> 2 mg/L) despite usual care, including statin therapy. CANTOS will also address whether canakinumab will reduce the incidence of new onset diabetes. This latter secondary hypothesis reflects IL-1β's implication in autoinflammatory processes related to pancreatic dysfunction, insulin resistance, and diabetogenesis. If successful, CANTOS could not only affirm the inflammatory hypothesis of atherothrombosis but also provide an entirely novel cytokine-based therapy for the secondary prevention of cardiovascular disease and new-onset diabetes.

Third, a potential new drug target for the treatment of diabetes which is currently intensively investigated is osteocalcin. It is a noncollagenous protein found in bone and dentin. Undercarboxylated osteocalcin (uncOCN) has positive effects on the metabolic syndrome including improvement of insulin resistance, β-cell function and dyslipidemia. Osteocalcin acts as a hormone in the body, causing beta cells in the pancreas to release more insulin, and at the same time directing fat cells to release the hormone adiponectin, which increases the sensitivity to insulin [Lee 2007]. Undercarboxylated osteocalcin or analogs as injectable or small molecule agonists of the putative osteocalcin receptors might be potential approaches in the near future.

Fourth, it has been recently shown experimentally that reduced expression of the *Indy (= **I** am **N**ot **D**ead, **Y**et)* gene in *D. melanogaster* and *C. elegans* prolongs life span, and in *D. melanogaster* augments mitochondrial biogenesis in a manner akin to caloric restriction. However, the cellular mechanism by which *Indy* does this is still unknown. Experiments in a knockout-mouse model of the mammalian *Indy* (*mIndy*) homologue, *SLC13A5* demonstrated a profound effect of *mIndy* on mammalian energy metabolism and suggest that mINDY might be a therapeutic target for the treatment of obesity and type 2 diabetes in the later future.

The pros and cons of currently available treatment options have recently been discussed in detail [Schindler 2012]. Table 1 provides an overview of currently available therapies compared with future new therapies. The results of ongoing clinical trials will teach us how to treat diabetes mellitus in the future.

References

Bailey, C. (2012) Could FFAR1 assist insulin secretion in type 2 diabetes? *Lancet* Feb 27 EPub ahead of print

Birkenfeld, A.L., Lee, H.Y., Guebre-Egziabher, F., Alves, T.C., Jurczak, M.J., Jornayvaz, F.R. *et al.* (2011). Deletion of the mammalian *INDY* homologue mimics aspects of dietary restriction and protects against adiposity and insulin resistance in mice. *Cell Metab* 14: 184–195

Burant, C.,Viswanathan, P., Marcinak, J., Cao, C., Vakilynejad, M., Xie, B. *et al.* (2012) TAK-875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* Feb 27 EPub ahead of print

Lee, N.K., Sowa, H., Hinoi, E., Ferron, M., Ahn, J.D., Confavreux, C. *et al.* (2007). Endocrine regulation of energy metabolism by the skeleton. *Cell* 130: 456–469

Ridker, P., Thuren, T., Zalewski, A. and Libby, P. (2011) Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: Rationale and Design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J* 162: 597–605

Schindler, C., Barthel, A., Fischer, S., Bornstein, S. and Kirch, W. (2012) Benefits and risks of current pharmacotherapy in the treatment of type 2 diabetes. *Internist (Berl.)* Mar 4 EPub ahead of print