Intracellular events in diabetes mellitus – Behind the scenes

Diabetes mellitus had a global prevalence of 8.5% in 2014; in other words 422 million people were affected. This chronic metabolic disease is not only common in wealthy countries, but it is also rising in those of middle and low income. The World Health Organization (WHO) declared diabetes as one of the leading causes of death in the world.1

Although diabetes does not have a uniform clinical picture, in recent decades it has been divided into two main types. Type 1 diabetes represents 5-10% of all diabetes incidences. This immune-mediated form is caused by the disability of the patients’ pancreas to produce insulin. In contrast, type 2 diabetes, which is mainly acquired during adulthood affects 90-95% of diabetes mellitus patients, is characterized by insulin resistance.2 Today, there is no longer such a strict separation between these two types; more detailed classifications have been made. Such forms as pregnancy-induced diabetes (gestational diabetes mellitus) or types depending on genetic defects called maturity-onset diabetes of the young (MODY) are now included. Nevertheless, all patients more or less suffer from elevated blood glucose levels, leading to outcomes ranging from mild effects to organ damage and failure or even death if untreated.1,2 This review will give a short overview of the latest reports published in Acta Physiologica about the research on cellular mechanisms and potential interventions of diabetes.

Blood glucose level always needs to be strictly regulated. For this purpose glucose is transported into pancreatic β-cells.3 Membrane-bound glucose transporters (GLUT) ensure glucose uptake for a proper insulin secretion and glucose metabolism. Besides the classical signalling molecules like transporters, enzymes or transcription factors, other molecules are involved in this signalling pathway as well. Alam et al. studied the influence of keratin 8 (K8), a cytoskeletal filament on diabetes mice models. In their diabetes 1 model, a complete loss of K8 in knockout mice K8-/- was shown to result in GLUT2 mislocalization4, a heterozygous knockout (K8+/−) still maintained a normal glucose/insulin regulation. Furthermore, there was no effect on their type 2 diabetes mice model. Interestingly, decreased K8 led to a significantly higher type 1 diabetes susceptibility in mice.5

In addition, to regulate blood sugar level, other human cells—like muscle or fat cells express GLUT receptors in order to absorb and metabolize glucose. GLUT12 expression in mouse adipocytes was analysed by Gil-Itrube and colleagues.6 They found that GLUT12 and GLUT4 localize to the plasma membrane upon insulin stimuli.8 Since in a previous study GLUT4 was observed to be less expressed in obese insulin resistant patients,7 Gil-Itrube’s group screened for GLUT12 expression levels in obese mice. Strikingly, insulin sensitivity was reduced by decreased membrane-expressed GLUT12. The same was proven for human cells, making this receptor a promising target for treatment of type 2 diabetes.6,7

Located next to the above mentioned pancreatic insulin secreting β-cells are their opponents: pancreatic α-cells. Glucagon is released by α-cells and has effects that are mostly adversary to those of insulin. These include increasing blood sugar levels via secretion from the liver and glucose synthesis.8 Both cell types do not only manipulate blood sugar by their secreted molecules but also influence each other. A study measured glucagon receptor (Gcgr) expression via RT-qPCR analysis and found 25-fold increased Gcgr expression levels in β-cells compared to α-cells.9 With another interesting method—real-time bioluminescence recording—they checked for glucagon’s ability to synchronize β-cells. To measure bioluminescence signals in real-time, they used fusion proteins from cellular clock genes coupled to a luciferase reporter.9 Insulin release is not only highly regulated but also depends on a circadian rhythm.10 With their measurements Petrenko et al. proved that glucagon was able to synchronize and establish an oscillating circadian rhythm in β-cells.9

Furthermore, Green, who reviewed on “Cellular models for β-cell function and diabetes gene therapy”11, highlighted glucagon-like peptide 1 (GLP-1) as a potent β-cell regulating hormone. For instance, GLP-1 pushes insulin biosynthesis and regulates glucose-dependent insulin release. GLP-1 analogues are successfully used to treat type 2 diabetes.11 Interestingly, these molecules showed comparable effects on β-cell circadian rhythms as previously reported for glucagon.9

Naturally GLP-1 is secreted for example by L-cells, which belong to the diffuse endocrine system and are located in the intestine.12 In case such an important incretin hormone is shortened because of a specific behaviour, serious consequences to the host can occur. A classical Western diet comprises many saturated fatty acids (FA), like palmitate.
Martchenko et al. tested the influence of palmitate on GLP-1 expression in murine L-cells. Treatment with palmitate led to an impaired circadian secretion of this molecule. Further, mitochondrial respiratory function was likewise diminished by this saturated FA.12

Mitochondria are the most important cell organelles in terms of ATP production and energy supply. The increased coverage with FAs results in accumulation of metabolic intermediates leading to a state of lipotoxicity that further causes mitochondrial dysfunction,13 such as leak respiration. Uncoupling of respiration and dissipation of energy in form of heat is needed to create an optimal energy balance and body weight control. For this purpose uncoupling proteins (UCPs) play an essential role.14 On the other hand, increased leak respiration will lead to pathologic conditions. Friederich-Persson and co-workers studied UCP-2, which is the only isoform of UPCs expressed in the kidney. In a type 1 diabetes mouse model, they found that UPC-2 expressing mice indicated enhanced leak respiration. In contrast, UCP-2 -/- depleted mice did not show such an effect, assuming UPC-2 as a potential target to address diabetic nephropathy. Additionally, respiratory uncoupling in diabetic mice led to proteinuria, kidney hypertrophy and increased oxygen consumption, which results in kidney tissue hypoxia.15

Two recent animal studies focused on potential diabetes treatments to reduce kidney failure. Especially the renin-angiotensin-system (RAS) plays a major role in renal blood pressure and water homeostasis. Takenaka et al. detected elevated angiotensin II levels and angiotensinogen expression in diabetic mice affecting eg glomerular filtration rate (GFR) and albuminuria. These elevated values could be lowered with klotho protein supplementation,16 a protein whose expression is reduced in type 2 diabetic rats.17 Another approach is based on RAS-associated Angiotensin (1-7) peptide. By administering Angiotensin (1-7) via renal artery infusion in rats, GFRs decreased. Nevertheless, oxygen consumption further increased and tissue hypoxia was not prevented.18

Moreover, surgical interventions have been developed in order to treat diabetes and its causes. Gastric bypass surgery helps patients to lose weight. Obese patients with and without diabetes, who underwent gastric bypass surgery were tested for skeletal muscle insulin resistance. Interestingly, after surgery insulin sensitivity noticeable improved. But this was not related to skeletal muscle mitochondrial respiratory capacity.19 To achieve a more positive progress in this direction, additional physical training must be performed by the patient. The results of Axelrod and colleagues on initially sedentary adults revealed several beneficial physiological changes. Amongst other findings they detected enhanced oxidative capacity, glycolytic activity and overall increased whole-body insulin sensitivity.20 These effects were confirmed by a study investigating the outcome of high-intensity interval training (HIIT) in a cohort of type 2 diabetes patients.21

Even if people currently do not have diabetes, preventive measures should still be taken, especially concerning type 2 diabetes. Indeed, without suffering from obesity, external influences that we cannot control ourselves have an impact on our health, such as shift work.13 Bescos et al. investigated the influence of shift work on healthy adults. Alarming, only four days of simulated shift work already reduced insulin sensitivity by 25%, with the night shifts showing the greatest effects.22 For this purpose, again sport, particularly HIIT, was reported to have many favourable results on test persons. A lot of points already discussed in this review were shown to be improved like GLUT receptor expression, muscular oxygen uptake and whole-body insulin sensitivity.23

Taken together, these studies show that diabetes mellitus, a widespread disease, is a frequently and intensively studied topic. Analogues of GLP-1, here described as a β-cell synchronizer, are already used to treat diabetes patients. Future studies, including clinical trials, will show whether GLUT12 as a promising target or klotho protein for supplementation will also bring positive effect for humans. Furthermore, exercise improved overall health in general and reduced the risk to acquire type 2 diabetes shown in the publications reviewed, a tip that everyone should take to heart.

CONFLICTS OF INTEREST
The authors declare no conflict of interest.

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