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REVIEW ARTICLE

WHAT IS THE UNDERLYING CAUSE OF TYPE II DIABETES? – ARE CELLS PROTECTING THEMSELVES AGAINST THE REACTIVITY OFGLUCOSE?

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ABSTRACT

Through the last couple of thousand years, human food sources and availability have changed tremendously. Moving from a diet of hunter gathers, consisting of nuts, fruits, tubers and meat, to the farmers' diet of grains, milk, meat to this and last century, where among other processed foods there is the unlimited availability of refined sugar. This change in diet has been proposed as being the underlying reason for the dramatic increase in the prevalence of type II diabetes that we are observing world-wide in our time world health organization 2016. The question is what is the underlying molecular causeof this decease? One possibility proposed here is that type II diabetes might be a consequence of our cells trying to protect themselves from too high intra-cellular concentration of this reactive compound.

INTRODUCTION

Glucose is the preferred energy source of our cells; evident from the fact that we even have a taste receptor dedicated for detection of glucose (and closely related compounds) in our food (vigues *et al.,* 2009). The reason that glucose is our preferred energy source is that it is a reactive molecule that is readily oxidized under the release of energy. This reactivity of glucose can among other chemical reactions be observed from the damage that it does to the micro-cardiovascular system, nerves and kidneys of diabetes patients that have too high levels glucose circulating in their blood stream (American Diabetes Association, 2017; Patschan, Muller, 2016; Nukada, 2014). Indeed, the long-term exposure (3 months) of glucose in diabetes patients is measured by determination of the amount of non-enzymatic glucation of hemoglobin (HbA_{1c}) in the red blood-cells (Andel*, et al.,* 1981).The average life-span of red blood cells are about four months, thus, the usefulness of this marker for the determination of long-term (3 months) average exposure. When trying to understand the underlying molecular mechanism of type II diabetes it is important to keep this reactivity of glucose in mind (see below). When we eat food that contain glucose, the glucose is detected by taste receptors in the gut, as well as, when the compound is take up and transported into our blood stream, directly by the Islets of Langerhans cells also in our gut (Renwick, Molinary, 2010). This detection is leading the secretion of the hormone Insulin.

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Some of our tissues, including the liver, fat-cells (adipose tissue) and muscle cells, possess receptors on their surface that can bind insulin (Li, C., Zhang, 2000). Binding of insulin and subsequent receptor signalling leads to expression of proteins, enzymes that import the glucose into the cells for subsequent conversion into energy. The question is, if glucose is the preferred energy source, why are cells not expressing the genes required for import and utilization constitutively; here the reactivity of glucose might be the explanation. By regulating the expression of the genes required, the cells not only have the ability to turn the import on, but also to turn it off. Thus, if there is high concentration of glucose in the blood, and thus the intra-cellular concentration of glucose reaches a level that damages (through auto-catalytic glycation) cellular components then the cells might shut off uptake to protect themself. It is this possible shut off that might be the underlying cause type II diabetes. Cells regulate their genes in many different ways; for example involving activators and repressors, however, in the last couple of decades the importance of epigenetic marks has been revealed (Paluch*, et al.,* 2016). Genes can be silenced or activated by different enzymatic modifications to the DNA itself as well as the histones that are associated with the specific genetic locus to be controlled. Such modification are intricate parts of the mechanism that control gene expression; some can easily be reversed other are more difficult to reverse. Moreover, these DNA and histone modifications can be inherited though cell divisions (Lange; Schneider., 2010). And in some cases even through meiosis when gametes are formed (Campos, *et al.,* 2014). The latter is important as it means that this epigenetic

information can be transferred to the next generation. Several recent studies have established that there are epigenetic differences between patients with diabetes and the general population, suggesting that such modifications are somehow related to type II diabetes (Desiderio, *et al*., 2016; van Dijk, *et al.,* 2015). One possible explanation is that some the epigenetic marks required to shut off the genes required for import of glucose are difficult to reverse or are un-reversible, leading to a lack of or decrease ability of the cells to take-up glucose from the blood-stream in response to insulin or, in other words, to type II diabetes. Is there any evidence for this? As mentioned above, epigenetic modifications can be inherited from one generation to next, and with regard to type II diabetes there are several studies that show that the diet of the mother during pregnancy, both in humans and animal models, can affect the risk of the offspring developing diabetes type II later in life (Zheng, *et al*., 2014; Carolan-Olah, *et al*., 2015). If this explanation, that type II diabetes is due to silencing of genes involved in uptake of glucose, is correct, then it suggest that in some cases if not all the silencing might be reversible, and thus, that type II diabetes can be cured through changes in diet. Indeed, there are currently several studies looking specific diets to achieve this (Gow, *et al*., 2016; Lim, *et al*., 2011). Most likely, a diet that would force the cells to repeatedly attempt to activate the genes required for uptake of glucose, without the presence of too much glucose leading to the potential induction of gene shutoff, could be beneficial.

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