ECRONICON OPEN ACCESS

EC DIABETES AND METABOLIC RESEARCH
Guest Editorial

Association Between the Route of Hypoxia and the Development of Insulin Resistance

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Received: April 17, 2021; **Published:** April 19, 2021

The HIF pathway has recently been discovered to play an essential role in pancreatic beta cell function. Four independent studies have described the effect of HIF activation on beta cells in mice. In these studies, the Cre-loxP system was used to conditionally inactivate the VHL gene in beta cells, since VHL mutant mice are lethal in embryonic stages [1,2].

The Cre-loxP system is a genetic tool that allows the inactivation or activation of the gene of interest in a specific tissue or cell type without affecting its activity in the rest of the body. The elimination of VHL specifically in beta cells causes the activation of HIF1 and this causes the mice to develop glucose intolerance. Analysis of beta cell function in these mice revealed that, although basal insulin production and secretion were unaffected, beta cells did not secrete insulin in response to increased glucose concentration. This was due to defects in ATP production, membrane depolarization, and calcium mobilization in response to glucose [3].

These results are consistent with older studies conducted in *in vitro* cultures that showed that beta cells lost their ability to secrete insulin in response to glucose under hypoxic conditions. Endocrine beta cells detect glucose concentrations and respond by secreting the appropriate amount of insulin through a mechanism that requires glucose metabolism. Glucose is transported into the beta cell by the type 2 low-affinity glucose transporter (GLUT-2) and metabolized, causing an increase in the intracellular ATP/ADP ratio. This produces the closure of ATP-sensitive potassium channels causing a depolarization of the cell membrane and the opening of calcium channels. The increase in intracellular Ca^{++} levels is the direct stimulus of insulin secretion, an almost exclusive metabolic characteristic of beta cells is the low (practically null) activity of lactate dehydrogenase and monocarboxylate transporters, a mechanism that favors oxidative respiration. glucose and which appears to be critical for the precise functioning of insulin secretion in response to glucose [4].

In VHL-deficient mice, beta cells showed alterations in the expression of genes related to glucose transport, glycolysis, and pyruvate utilization. Activation of genes related to lactate production and secretion and an increase in lactate secretion were also observed. These results indicated that activation of the HIF pathway caused a change from aerobic to anaerobic metabolism despite the presence of normal oxygen levels, an effect similar to the Warburg effect observed in tumors [5].

This increased anaerobic metabolism blocks the insulin secretion capacity in response to glucose from beta cells, highlighting the close relationship between intracellular glucose metabolism and the regulation of insulin secretion. In addition to glucose metabolism, HIF activation appears to affect many other cellular functions in beta cells [6].

All these studies carried out in animal models show the importance of the HIF pathway in beta cell function and raise the possibility that changes in HIF levels may influence the deterioration of beta cell function (dysfunction) during the development of type 2 diabetes.

Beta cells are very sensitive to hypoxia and, in fact, the pancreatic islets are highly vascular. In some animal models of type 2 diabetes, such as Zucker rats and Goto-Kakizaki rats, there is increased expression of HIF target genes and glycolytic metabolism in pancreatic islets. It has been hypothesized that the increased islet size that occurs is a compensation for increased insulin resistance, which can lead to poor vascularization and consequent hypoxic stress [7].

On the other hand, it is well known that beta cells have a very high oxygen consumption at high glucose concentrations, which can potentially cause a transient decrease in intracellular oxygen levels. In fact, HIF accumulation and activation of a significant number of HIF target genes have been observed in beta cells (rat and human) in hyperglycemia. The HIF pathway can be activated by other stimuli in addition to hypoxia, some of these stimuli are pathophysiological conditions associated with type 2 diabetes and that could, therefore, cause the activation of HIF in beta cells. ROS (reactive oxygen species) levels seem to regulate HIF levels, probably by inhibiting the prolyl hydroxylases that act on HIF [8].

The chronic hyperglycemia observed in diabetic patients causes increased ROS production and it would be interesting to determine if HIF is activated in the beta cells of these patients. Nitric oxide is another factor described as an activator of HIF independent of the presence of oxygen, also acting on prolyl hydroxylases, and it has been described that in islets of type 2 diabetics there is an increase in nitric oxide production. In recent years there have been a large number of studies, both in cell lines and *in vivo*, that have shown that cytokines activate the HIF pathway. In fact, a very recent study suggests that HIF may mediate cytokine-induced beta cell dysfunction [9].

Together, all of these observations suggest that activation of the HIF pathway could contribute to the deterioration of beta cell function during the development of type 2 diabetes.

Conclusion

The activation and inactivation of the HIF pathway in different organs causes them to develop insulin resistance, which makes it possible to determine that this pathway may be the cause of the deterioration of beta cells, which, as is known, are responsible for the production of the insulin hormone, which metabolizes glucose in the blood and prevents hyperglycemia from occurring. This research generates the idea of how type 2 diabetes occurs, which is characterized by having a development since adolescence and being the most common.

The decrease in HIF levels in the liver of mice fed a high-fat diet improves insulin resistance, this being a possible therapeutic use.

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Volume 5 Issue 4 April 2021
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