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REVIEW ARTICLE

"The Human Pancreatic Alpha Cell in Health and Disease": A Clinician's Perspective

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Historical Background

When Banting and Best injected extracts from pancreatic tissue intravenously or subcutaneously into diabetic dogs and humans, a marked reduction in blood sugar was noticed (reflecting the hypoglycaemic action of insulin). However, this was often preceded by a small transient elevation of blood sugar, which was initially thought to be caused by epinephrine. A few years later, this phenomenon was ascribed to a glucose-mobilizing substance, later named 'glucagon'.[1,2] It took almost three further decades before the pancreatic α-cells were identified as being the source of glucagon, and hypoglycaemia documented as a trigger for the release of this hormone.[3,4]

Physiology

Pancreatic islets are tiny islands of endocrine cells in the pancreas. The islets contain four major types of cells. They are as follows:

1. **Alpha cells (α-cells):** 25% of the total, secrete glucagon.
2. **Beta cells (β-cells):** 60% of all the cells of the islets, lie mainly in the middle of each islet and secrete insulin and amylin.
3. **Delta cells (δ-cells):** about 10%, secrete somatostatin.
4. **Gamma cells (γ-cells)**: 05%, secrete pancreatic polypeptide.

Glucose homeostasis requires a carefully orchestrated balance between the release of insulin and glucagon by β- and α-cells, respectively, in pancreatic islets. After a carbohydrate enriched meal(Figure 1), glucose stimulates insulin secretion while inhibiting glucagon secretion. During fasting (Figure 2), the rate of insulin secretion drops ensuring slow glucose utilization, whereas that of glucagon secretion rises to promote gluconeogenesis, thereby preventing hypoglycaemia.

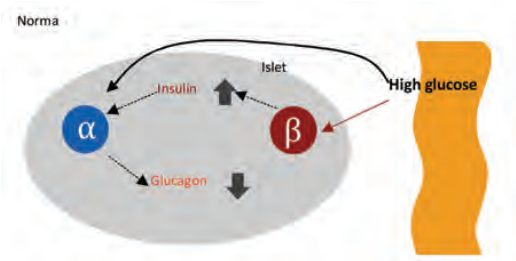

Figure 1. Glucose Homeostasis Following a Carbohydrate Rich Meal

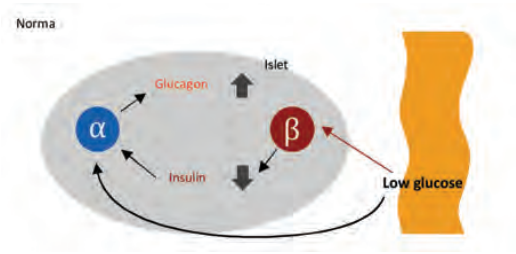

Figure 2. Glucose Homeostasis During Fasting

Glucagon plays a key role in glucoregulation[5,6] (Figure 3) by ensuring hepatic glucose production adequate to maintain glucose concentrations within the normal range between meals.

- In the resting state and between meals, glucose used by the body is replaced by the liver, either via glycogen lysis (use of stored glycogen reserves) or gluconeogenesis (new glucose synthesis).
- Glucagon activates enzymes that convert amino acids from the blood into glucose. The glucose is then released into the circulation for use by body cells,which reduces blood amino acid concentrations and increases blood glucose concentrations.
- Glucagon activates enzymes that convert stored triglycerides into free fatty acids and glycerol. Free fatty acids can be used directly by muscles and most other cells to generate ATP. Additionally, some of the free glycerol released into the bloodstream travels to the liver, which converts it into glucose.
- Glucose enters the extracellular glucose space from the liver and is removed by the brain and extra neural tissues under the influence of insulin.

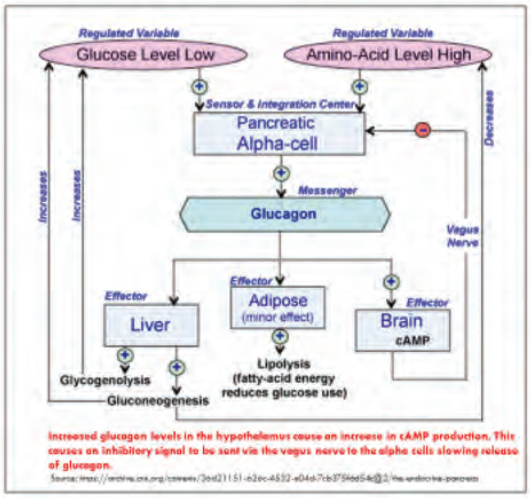

Figure 3.Glucoregulatory Role Of Glucagon

- Glucagon mediates about two-thirds of resting glucose production.[7]
- Hyper- and hypoglycaemia are prevented by this balance between hepatic glucose production and total glucose utilization. The islets sense even small changes in circulating plasma glucose levels and in response precisely alter the glucagon to insulin ratio to maintain a hepatic glucose production rate equal to total glucose utilization, which is about 10 g/h in the resting state (Figure 4).

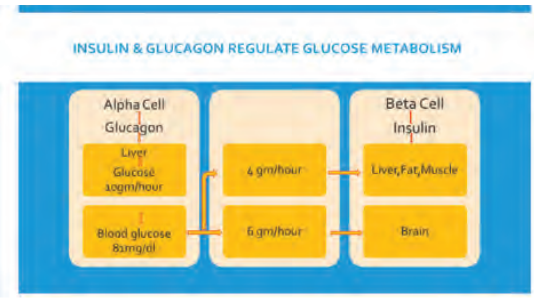

Figure 4. How insulin and glucagon work together

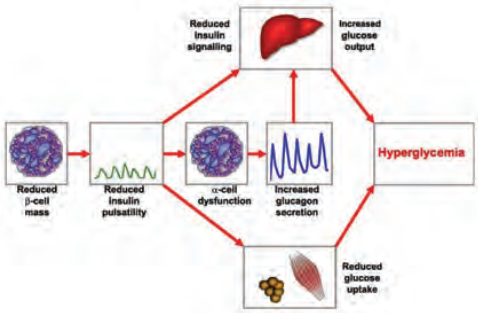

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Figure 5.Reduced pulsatile insulin and exaggerated glucagon concentrations in T2 DM

Pancreatic islet dysfunction leads to insufficient insulin, elevated glucagon and hyperglycemia in T2DM. (Figure 5). In normal physiological conditions alpha cells produce glucagon but in conditions of beta cell injury they also produce glucagon-like peptide-1 (GLP-1), a growth and survival factor for beta cells. Under conditions of beta cell stresses such as glucotoxicity, pregnancy, or streptozotocin, alpha cells respond by proliferating and produce GLP-1, a growth and survival hormone for beta cells, suggesting the existence of an islet-intrinsic adaptive response of alpha cells to beta cell stress and injury.

A hallmark of both type 1 (T1D) and type 2 diabetes (T2D) is a variable but definite increase in alpha cell mass in the islets that equals or exceeds

the loss of beta cell mass. These new findings suggest a major role for alpha cells in the islets, hitherto unappreciated, which is to serve as guardians or protectors of beta cells to preserve the capacity for the islets to produce insulin hormone.[8]

Marroqui et al[9] have been able to decipher how alpha cells survive metabolic stress better by expressing higher amounts of survival factors than beta cells. The researchers observed higher amounts of Bcl-xL (Bcl2l1) in alpha cells than in beta cells. Alpha cells are also preserved in T1D. This may be due to the specificity of the immune response to beta cell antigens such as proinsulin. The islets are infiltrated by immune cells that secrete a range of cytotoxic proteins however these perhaps act as onlookers and do not damage the alpha cells. These findings explain a possibility that alpha cells may also survive better in an inflammatory environment such as in T1D. In a recent proteomic study of alpha and beta cell lines, a major difference was recorded in the defense of alpha cells and beta cells against reactive oxygen species due to variation in expression of superoxide dismutase 2, a major scavenging enzyme.[10]

The role of hormone glucagon has long been undermined and under recognized while being dubbed as a minor contributor to metabolic derangements seen in diabetes. A major, yet poorly understood, feature of T2D is the excessive hepatic glucose production and the corresponding insulin resistance leading to fasting hyperglycaemia. A host of research carried out to identify the physiological and molecular mechanisms responsible for this impairment has led to the emergence of several consenting hypotheses.

Most widely accepted among these is the increased daily and unregulated plasma glucagon concentration in T2D patients.

In fact, glucagon excess, rather than insulin deficiency, is absolutely indispensable for occurrence and worsening of diabetes. Hypotheses and evidences supporting this concept include the following:

(a) Glucagon increases hepatic glucose and ketone production, catabolic features present in insulin deficiency.
(b) Hyper-glucagonaemia plagues every form of poorly controlled diabetes.
(c) The glucagon suppressors, leptin and somatostatin, suppress all catabolic manifestations of diabetes.

REGULATION OF GLUCAGON SECRETION

Whereas the mechanisms by which glucose regulates insulin secretion from the β-cells have been well established,[11,12] factors regulating glucagon secretion from α-cells in response to glucose belong to the most debated aspects of islet cell biology.[13,14] The tricky question is whether the secretion of glucagon by α-cells is auto-regulated by an intrinsic mechanism or by factors released from other cells within the islets (paracrine mechanisms).

Paracrine Regulation of Glucagon secretion

The suggestion that paracrine factors influence glucagon secretion is supported by reports that isolated α-cells (that no longer have paracrine input) are unable to respond appropriately (i.e. decreasing their activity and glucagon secretion) to increased glucose concentrations.[15]Somatostatin (SST) has been proposed to be a paracrine regulator of glucagon secretion with an important role for inhibiting glucagon secretion during hyperglycaemia.[16]

Intrinsic Regulation of Glucagon Secretion

Pancreatic α-cells, like β-cells, are electrically excitable. At low concentrations of glucose, when the secretion of glucagon is stimulated, α-cells fire continuous overshooting action potentials (APs).

The discharge of high-voltage APs opens voltage-gated Ca^{2+} channels (VGCCs) to allow influx of extracellular Ca^{2+} into the cytosol. This results in an elevation of the intracellular Ca^{2+} concentration and provides Ca^{2+} signals that trigger glucagon granule exocytosis. Pharmacological studies have confirmed that there are at least four different VGCCs (T, L, N, and P/Q-type Ca^{2+} channels) expressed in the α-cells.

When the circulating glucose level rises, glucagon secretion is suppressed. This is likely to be via the reduction of P/Q-type Ca^{2+} channel activity in α-cells. The change of membrane potential is a result of glucose metabolism or transport (via electro genic

sodium-glucose co-transporter 2 transporters).[17,18]

Both intrinsic and paracrine mechanisms seem to be simultaneously functional within certain ranges of glucose concentrations while regulating glucagon secretion from the pancreatic islet α-cells. Of particular note is the physiological role played by intra-islet somatostatin signalling. In addition to its ability to inhibit action potential firing (which is only transient), intra-islet somatostatin also exerts a more sustained inhibitory effect on the exocytosis of glucagon.[19]

Alpha Cells in Type 1 Diabetes

Type 1 diabetes mellitus (T1DM) patients experience rampant glycemic variability requiring them to constantly monitor glucose level in order to respond to and correct major glycemic fluctuations with supplemental insulin or glucose, severely compromising their quality of life. An overwhelming possibility of a causal relationship between the volatility and the loss of paracrine control of glucagon secretion by insulin exists as T1 DM patient's islets are devoid of beta cells.

It needs to be appreciated that, when hyperglycaemia is unaccompanied by an increase in insulin, it paradoxically stimulates rather than suppresses glucagon secretion, accounting for the exaggerated post- prandial hyperglycaemia of T1DM.

High incidence of hypoglycaemia in Type 1 diabetics which usually is precipitated by physical exertion or delayed meal intake is explained by the subnormal counter regulatory glucagon secretion and by high injected insulin levels in the brain suppressing glucagon secretion by a central neural mechanism.[20,21]

Glucagon Suppression as a Therapeutic Strategy

In T1D, an ideal strategy would be to use insulin in doses that meet the requirements of peripheral tissues but are not high enough to suppress excess glucagon release from the alpha cells and to reassign the duty of alpha cell suppression to a noninsulin agent, such as leptin. Somatostatin has been explored in the past, but side effects have limited its use. Amylin is another glucoregulatory beta cell hormone that is normally co-secreted with insulin in response to meals and is deficient in patients with T1D. It has been co administered with prandial insulins to address hyperglucagonaemia of T1D.

Equally relevant to the treatment of T2D, are studies aiming to understand the physiological regulation of glucagon secretion and the corresponding impairment during diabetes. Glucagon secretion by α-cells is an immediate response to low blood glucose levels. Abnormal secretion of glucagon and other counter-regulatory hormones is a hallmark of T1D and T2D and a major limitation to the use of strong hypoglycemia agents. Insufficient insulin secretion and insulin resistance are exacerbated in T2D by too much glucagon secretion during hyperglycaemia and too little during hypoglycemia. In diabetes there is an increase in the number of δ-cells.[22-25]The resultant hypersecretion of SST may, via binding to SSTR2 and activation of GIRK (G-protein coupled inwardly rectifying K^+ channel) channels, suppress glucagon secretion.

Current Therapeutic Options to Suppress α-Cell Hyperactivity in T2D

Over the past decade, in cretin based therapies have succeeded in normalizing plasma glucagon concentrations of type 2 diabetic patients, mostly through the activation of portal and brain glucose sensors by the hormone GLP1, thus also proving to be a rewarding strategy to combat iatrogenic hypoglycaemia. The quest for an ideal combination of glucose-lowering agents (which should have complementary mechanisms of action that address multiple pathophysiologic pathways, can be used at all stages of the disease, and be generally well tolerated with lowered risk of hypoglycaemia, cardiovascular events, or weight gain, the combination should also provide conveniences for patients, such as oral dosing, single-pill formulations, and once-daily administration, potentially translating to improved adherence) ends with two classes of glucose-lowering agents that meet these criteria: the sodium glucose

cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Bottom Line

The persistent euphoria since the discovery of insulin in 1922 has eclipsed the vital role of glucagon secreted by the alpha cells in glucose homeostasis. Even though we are approaching a century of insulin monotherapy use, we have failed to accept that insulin replacement alone cannot normalize glucose levels in T1DM and no intensive efforts to reduce or block glucagon actions in diabetes have yet been undertaken. Such insulin centric reluctance to accept the pathophysiologic importance of diabetic hyperglucagonaemia has deprived millions of diabetes patients of optimum therapeutic management. Hence, strategies aiming to normalize glucose-regulated glucagon secretion remain important milestones for the treatment of diabetic patients and in the prevention of iatrogenic hypoglycaemia.

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