Alpha Cells, Glucagon and Type 2 Diabetes

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HISTORY AND INTRODUCTION

Type 2 diabetes is one of the most prevalent disease in the world, about 44 crore people living with it in 2014, with a prevalence rate of 8.5% among the adults over 18 years of age. It is projected to grow in future and become the 7th leading cause of death in the year 2030. Last few decades have improved our understanding of diabetes, though we are far from the knowing it fully. It was in the year 1869 that a young 22 year old German pathologist Paul Langerhans noted islands of different looking cells in pancreas which were later called islet of Langerhans. It took another 20 years to link these cells to diabetes. These weigh only about 2 mg but majorly control the glucose metabolism in our body. An out of the job orthopaedic Dr Banting, while preparing for a lecture in physiology had the bright idea of isolating the chemical out of pancreas (later called insulin) by tying the exocrine duct in the dog pancreas. He was assisted by Best an intern chosen by the toss of a coin. This was a landmark discovery and after some purifications done by Collip, insulin was tried in type 1 diabetic boy Leonard Thompsons in 1921 with miraculous results. Medical world almost believed that it had discovered the cause and treatment of diabetes. In 1923 just two years later Murlin et al suggested the existence of glucagon and in 1948 Sutherland et al talked about the alha cells and its association with glucose metabolism. In 1950 its amino acid sequence was deciphered, but it was forgotten for the next 50 years because of a large shadow of B cells and insulin. There is renewed interest in alpha cell in causation of diabetes and its treatment for the last 2 decades.

ROLE OF ALPHA CELLS IN HEALTH (TABLE 1)

The alpha cells are as much involved in glucose metabolism as B cells. In a fasting state when there is

Table 1: α-Cell Function regulation	
Stimulatory Factors (↑ Glucagon)	**Inhibitory Factors (↓ Glucagon)**
Hypoglycaemia	Glucose
Protein meal	Carbohydrate meal
Amino acids	Ketones
Stress; adrenaline (epinephrine)	Insulin
Sympathetic/ parasympathetic nerves	Somatostatin
GIP	GLP-1

deficiency of glucose in the blood, the alpha cells produce more glucagon. Glucagon is produced from proglucagon in the alpha cells. It is carried in the portal blood to liver where it affects hepatocytes through glucagon receptors. It orders liver to produce glucose by glycogenolysis and neoglucogenesis, thus bringing up the blood glucose levels. In experiments done to stop glucagon secretion by giving somatostatin and maintaining constant insulin levels it was proven that glucagon is responsible for 75% of hepatic glucose output. It also causes ketogenesis and has a very short half-life (like insulin) of 5 minutes. Alpha cells have insulin receptors and glucagon secretion is controlled by insulin level. Insulin inhibits proglucagon gene transcription and thus decrease glucagon secretion. The flow of blood in pancreas is from b cells to alpha cells thus promoting this paracrine relationship. There are other stimulants to glucagon secretions than low insulin levels eg. hypoglycaemia, stress through hypothalamus, protein meal and catecholamines.

In the post prandial state, exactly the opposite happens. Availability of carbohydrates in food stimulates insulin secretion from beta cells, which in turn brings down the glucagon secretion from alpha cells. Glucagon levels must come down in post prandial state otherwise hepatic glucose output won't come down and blood glucose levels will remain unduly high. In a post prandial state hepatic glucose output is suppressed 50% by increasing insulin secretion and 50% by lowering of glucagon levels. Other factors which inhibit glucagon secretion are carbohydrate meal directly, somatostatin and GLP.

GLUCAGON IN TYPE 2 DIABETES

Lets' review what happens in type 2 diabetes. There is a marked reduction in beta cells with amyloid deposition in pancreas. Unfortunately alpha cells population is not reduced as much. With the result that not only there is deficiency of insulin but also excess of glucagon. In fasting state glucagon levels are inappropriately high (50% more than in normal) which results in fasting hyperglycaemia. Similarly alpha cells are non-responsive to higher blood glucose in a post prandial state and continue to secrete high levels of glucagon. Does this happen only because of a paracrine effect of low insulin availability? This was thought true for a long time but some recent discoveries have questioned this hypothesis that inappropriate high levels of glucagon found in type 2 diabetes are secondary to low insulin levels only. The glucagon receptor null mice are those mice who have no receptors through which glucagon can work on their hepatocytes to increase blood

glucose. These mice do not develop diabetes even when all the beta cells are destroyed in them. GLP1 analogues decrease blood glucose through decreasing glucagon levels even in c peptide deficient type 1 diabetes. The interpretation of these two facts is that alpha cells dysregulation and its treatment may be independent of beta cell function.

IMPILCATIONS IN THE TREATMENT OF TYPE 2 DIABETES

There is a clear role of alpha cells and glucagon in causation of type 2 diabetes.

This was being neglected for three reasons in the past

A.   There was undue focus on insulin resistance and insulin deficiency.

B.   The methods to assess glucagon were not easy and reliable.

C.   The techniques to isolate the role of glucagon through the use of somatostatin were not refined

This defect needs to be addressed in management of type 2 diabetes. We have finally got some drugs which can correct this defect. These are 1. Drugs working through GLP axis eg. GLP1 analogues and DPP4 Inhibitors. 2. Amylin agonist eg. Pramilintide.

Another thing to keep in mind is its role in hypoglycaemia. The first response to hypoglycaemia in an individual is to stop the production of insulin which in turn stimulates glucagon. Glucagon is the main hormone to correct the blood glucose through increased hepatic glucose output. In those individual who are severely insulinopenic (long duration type 2 diabetics) there is no insulin to be decreased in event of hypoglycaemia due to which there is no robust secretion of glucagon and they suffer prolonged hypo.

FUTURE

Considering the role of glucagon in type 2 diabetes, there is a scope for glucagon receptor blockers in treatment. Many pharmaceutical companies are doing trials in these experimental drugs. We are likely to hear more about these drugs in near future. These drugs result in alpha cells hypertrophy, hyperglucagonimia and in experimental animals this has resulted in increased evidence of pancreatic tumours. The alpha cells and glucagon are finally being acknowledged as one of the pathophysiological defects in type 2 diabetes. Increased glucagon levels and non-responsiveness of alpha cells to blood glucose levels are as much responsible for hyperglycaemia as insulin defects. There are some evidences that this is independent of paracrine effects of low insulin levels. The drugs likely to counter this defect are in different phase of development and may hit the market in near future.

REFERENCES

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