Brief Communication

Sodium-glucose cotransporter-2 inhibition and the insulin: Glucagon ratio: Unexplored dimensions

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ABSTRACT

The sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a novel class of glucose-lowering drugs which act by inhibiting the reabsorption of filtered glucose from the kidneys. Their effect on insulin and glucagon levels has recently been studied but is not fully explained. This communication proposes various hypotheses: A direct effect of SGLT-2 inhibition on the alpha cell receptors, a paracrine or intra-islet mediated effect on alpha cell sensitivity to glucose, and a calorie restriction mimetic action, to explain the impact of these drugs on the insulin glucagon ratio.

Key words: Beta cell, canagliflozin, dapagliflozin, diabetes, empagliflozin, glucagon, insulin

Introduction

The sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a novel class of glucose-lowering drugs which act by inhibiting the reabsorption of filtered glucose from the kidneys. This effect is mediated by inhibition of SGLT-2 co-transporters, which are expressed in the proximal renal tubule. While their predominant mode of action is renal, SGLT-2 inhibitors appear to have effects on other parts of the glucose homeostatic system as well. Clinical data suggest an improvement in beta-cell function, perhaps mediated by reversal of glucotoxicity, and a reduction of insulin resistance, with SGLT-2 inhibition.[1]

Recent data, from studies performed with SGLT-2 inhibitors, have demonstrated a fall in insulin to glucagon ratio upon acute exposure to these drugs; the change is the ratio is contributed to increase in the glucagon and fall in the insulin level concentration. This change persists, though to an attenuated degree, even after 28 days of SGLT-2 inhibitor administration.[2,3]

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In 1966, the bihormonal hypothesis, proposed by Unger, clearly highlighted the important role of glucagon in the pathophysiology of diabetes.[4] Developments in this field, however, were overshadowed by insulin-centric research, though a few experts did highlight its significance. The inclusion of the alpha cell in de Fronzo's infamous ominous octet,[5] coupled with advancement in therapeutics such as glucagon receptor antagonists, and bihormonal bionic (two hormone) artificial pancreas devices,[6] has brought glucagon back to the center stage of diabetes research.

Alpha cell dysfunction develops in different ways in type 1 and type 2 diabetes. While type 1 diabetes subjects manifest an exaggerated glucagon response to arginine,[7] mediated by severe intra-islet deficiency of insulin, persons with type 2 diabetes may have alpha-cell resistance to insulin, which prevents insulin (whether endogenous or exogenous) from suppressing glucagon release in response to arginine.[7] The exact mechanism of alpha cell insensitivity is still not certain.

The insulin glucagon ratio (IGR) was a relatively frequently cited index in the literature from the 1970s

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and 1980s. IGR was assessed in various conditions, including nonglycemic states like burns and starvation, and dysglycemic syndromes including type 2 diabetes and gestational diabetes mellitus.[8-11]

Insulin glucagon ratio can be used as an index of anabolism, insulin is the most potent anabolic hormone in the body, and a high IGR reflects its action, as opposed to that of glucagon, which has glycogenolytic or catabolic activity in the liver.[11] Little attention has been paid to this index in recent years. However, this may be because of the development of more accurate indices and parameters which measure insulin sensitivity/resistance.

The challenges posed by recent understanding of SGLT-2 inhibition, however, have created interest in this index. SGLT-2 inhibitors have been reported to improve beta cell function and insulin sensitivity. There is, however, an associated rise in endogenous glucose production, noted both after acute and chronic administration of SGLT-2 inhibitor, which attenuates the glucose-lowering efficacy of the drug.[2] This supposedly paradoxical or "ambivalent" response is not explained easily. The Ferrannini *et al*. group suggest that this paradoxical response is a manifestation of an adaptive physiological response to loss of calories in the urine.[2]

We discuss the utility of the IGR in current diabetes management, and suggest three hypotheses in addition to those put forward by Bonner *et al*. and Ferrannini *et al*., to explain the effect of SGLT-2 inhibition on the index. Though no firm conclusions can be drawn from current data, available knowledge opens up exciting vistas for further research.

Hypotheses for Increase in Insulin Glucagon Ratio

Inhibition of sodium-glucose cotransporter 2 in alpha cell

Recently, the presence of SGLT-2 receptors in the alpha cell has been reported by Bonner *et al*.[12] The authors suggest that SGLT-2 expression in alpha cells, when down-regulated, is associated with an increase in the expression of SGLT 1 and glucagon genes, as well as genes related to hepatic gluconeogenesis.[12] The same research team reports that SGLT 1 and 2 gene expression is lower in islets of type 2 diabetes as compared to normal subjects. Lower gene expression is associated with increased glucagon gene expression. Similar results are obtained when SLCSA-2 gene is knocked out, or when it is inhibited with dapagliflozin.[13] This may explain the paradoxical increase in plasma glucagon and hepatic glucose production noted with SGLT-2 inhibition. The workers who have reported a fall in IGR upon exposure to SGLT-2 inhibitor, propose correction of hyperglycemia, and alleviation of "glucotoxicity" upon the alpha cell (mediated perhaps by paracrine effects), as a mechanism for the relative hyper-glucagonemia.[2]

Increase in alpha cell glucose sensitivity

Sodium-glucose cotransporter 2 inhibition leads to lowering of plasma glucose, which in turn brings counter-regulatory processes into motion. The first line of defense against hypoglycemia is a reduction in insulin levels, while the second line is an increase in glucagon, mediated by intra-islet sensing of glucose. The third line of defense, an increase in epinephrine release, is mediated by peripheral and central nervous system sensing. Though plasma glucose concentrations with SGLT-2 inhibition do not fall to hypoglycemic levels, or to levels which are thought to stimulate glucagon secretion (70 mg/dl), it is possible that relatively low intra-islet glucose concentrations or low intra-islet insulin release, have a paracrine effect upon the alpha cells. SGLT-2 inhibitors may increase the alpha cell's glucose sensitivity through receptor-dependent, or through receptor-independent modes of action. The latter may be a mechanism of action distinct from the alpha cell SGLT-2 receptor-based pathway suggested by Bonner *et al*.,[12] and may support the nonhypoglycemic pharmacodynamics of SGLT-2 inhibitors.

Calorie restriction mimetic action

The lowered IGR suggests a catabolic state, or more accurately, mimicry of calorie restriction. This may be construed as a beneficial action, designed to correct the "maladaptive anabolism" noted in obese type 2 diabetes. The lowering of IGR with SGLT-2 inhibitors may explain or may be a corollary of, weight loss noted with these drugs.

After 4 weeks, chronic treatment with SGLT-2 inhibitors total glucose disposal was reduced due to prolonged reductions in insulin and glucose with maintained energy expenditure.[2] The enzyme carnitine palmitoyl transferase 1 (CPT 1) acts as a gateway to the mitochondria to help allocate free fatty acids (FFAs) to either of two pathways: β-oxidation, or conversion to triacylglycerol.[14,15] It is possible that SGLT-2 inhibition may stimulate CPT 1, perhaps by suppressing malonyl coenzyme A (CoA) (a potent inhibitor of CPT 1), and diverts FFAs to β-oxidation, instead of fat deposition. This enzyme has been identified at the site of action of other classes of oral anti-diabetic drugs and will be discussed further. In preclinical animal models, FFA nutrient stimulate glucagon released from alpha cells at low or normal glucose level.[16] As SGLT-2 inhibitor treatment is known to increase plasma FFA levels,[2,3] further research is warranted on effect of FFA on alpha cell with the use of SGLT-2 Inhibitors.

Recent data which describe a reduction in IGR after SGLT-2 inhibitor empagliflozin treatment administration uses "estimated prehepatic IGR" calculated from plasma concentrations of insulin and glucagon.[2] It is possible that concentrations of the hormones and their gradient may differ if estimated through portal vein sampling. Accurate analysis, therefore, can be made only through portal vein sampling.

Comparison with Other Drugs

Sodium-glucose cotransporter-2 inhibitors can be compared and contrasted with existing classes of glucose-lowering drug. Glibenclamide has been shown to inhibit the CPT 1 gateway, thus diverting substrate toward the triacylglycerol production. This molecular mechanism of action may explain the weight gain associated with sulfonylurea use.[17]

Metformin, on the other hand, activates the CPT 1 gateway. By inactivating acetyl CoA carboxylase, which catalyzes the biosynthesis of malonyl CoA, it reduces malonyl CoA formation. This molecule acts as a substrate for *de novo* fatty acid biosynthesis and inhibits CPT 1. Lower malonyl CoA production allows the CPT 1 pathway to divert FFA to the β-oxidative pathway.[18] This explains the weight-reducing property of metformin. It is possible that SGLT-2 inhibitors act in a manner similar to that of metformin in addition to weight loss due to calories lost in the urine.

It must be mentioned here that metformin is a calorie restriction mimetic, with geroprotective effects.[19] Whether, currently available SGLT-2 inhibitors share similar properties remains the focus of future research. At the same time, it is prudent to clarify that the CPT 1 enzyme is not a homogenous entity. It has multiple isoforms, expressed in different organs, and much needs to be learnt about its biology.[20]

Another similarity of SGLT-2 inhibitors with metformin is that they are able to achieve incretin enhancement without causing hyperinsulinemia. This property contrasts with that of incretin-based therapies such as dipeptidyl peptidase 4 inhibitors and glucagon-like peptide-1 analogs.

Conclusion

Impact of SGLT-2 inhibition on the IGR throws up exciting possibilities for research. It supports a multifaceted effect of SGLT-2 inhibitors, beyond inhibition of co-transporter in proximal renal tubule and proposes that these drugs will be able to shift the body milieu from maladaptive anabolism in type 2 diabetes to adaptive metabolism.

The IGR should also be studied as a tool for research and clinical decision-making. Inclusion of plasma glucagon values or portal glucagon concentrations, in formulae or models created to measure insulin sensitivity, may improve their utility.

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