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Metabolic Function of Glucocorticoid and Significant Relation between Glucocorticoids and Weight Loss

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Introduction

The adrenal cortex produces glucocorticoids under the control of the hypothalamic-pituitary-adrenal (HPA) axis, which is predominantly controlled by the hypothalamic-pituitary-adrenal (HPA) axis. In brief, the hypothalamus releases corticotropin-releasing hormone (CRH) and vasopressin, which work together to trigger the secretion of stored adrenocorticotropic hormone (ACTH) from corticotrope cells in the anterior pituitary gland. The blood then transports ACTH to the adrenal cortex, where it drives the production of corticosteroids like cortisol from cholesterol.

However, it was only recently discovered that ACTH-independent mechanisms are also involved in the fine-tuning and regulation of the adrenal system. A temporal lag between stimulus-induced changes in circulating ACTH and corticosteroid levels, adrenal corticosteroid metabolism and kinetics, and plasma protein binding are all examples of this. Furthermore, under pathological situations, dysregulation of glucocorticoid secretion is found. In obesity, for example, some human investigations show an increase in cortisol release directly from the adrenal gland, while circulating plasma levels remain normal, possibly due to a faster metabolic clearance rate. Adrenal secretions have been shown to be influenced by a number of growth factors, neuropeptides, cytokines, and adipokines. Adrenocortical cells, in turn, express receptors for each of these substances.

Glucocorticoids' metabolic function

Glucocorticoids play a role in metabolism, inflammation, cardiovascular health, and behaviour. As a result, they affect the transcription of a wide range of genes, including cytokines and chemokines, receptors, enzymes, adhesion molecules, and inhibitory proteins, as discussed previously. High glucocorticoid levels were linked to the metabolic syndrome in clinical studies, proving their function in diabetes and obesity. Glucocorticoids' metabolic effects are linked to physiological pathways linked to hepatic and peripheral insulin resistance, hyperglycemia, and dyslipidaemia. Glucocorticoids activate PEPCK and glucose-6-phosphatase in the liver, which stimulates gluconeogenesis (G6Pase).

Furthermore, glucocorticoids increase lipolysis in adipocytes during fasting, resulting in the production of glycerol for gluconeogenesis and free fatty acids for oxidation and utilisation as energy. Although glucocorticoids are necessary for maintaining lipid homeostasis, too much of them can cause an increase in circulating free fatty acids and lipid build-up in the skeletal muscle and liver, both of which are linked to insulin resistance. Excess glucocorticoids can block the translocation of GLUT4 glucose transporters to the plasma membrane in response to insulin in rat skeletal muscle, resulting in insulin resistance. Glucocorticoids cause adipocyte differentiation in human adipose tissue, resulting in increased adiposity and insulin resistance [1].

Glucocorticoids have also been linked to the development of the pancreas. Dexamethasone treatment decreased B-cell insulin content, and examination of embryonic pancreata from glucocorticoid-treated animals revealed a decrease in insulin-producing cells and an increase in exocrine cells, possibly due to down-regulation of pancreas maturation transcription factors like Pdx1, Pax6, and Nkx6.1. However, islets from Wistar rats given dexamethasone for 5 days revealed increased insulin release in response to glucose, as well as an increase in the number of insulin granules docked at the plasma membrane in -cells. High fat-induced -cell failure was reversed in transgenic mice overexpressing 11B-HSD1 specifically to the -cell. The growth of the -cell population and the function of tiny islets, both of which are linked to the protein kinase A and p21 signalling pathways, contributed to this.

Weight Loss and Glucocorticoids

Diet and Exercise: Cortisol production rate, free cortisol levels, and metabolic clearance rate did not change in males who lost weight after 6 months of dieting as compared to baseline. However, when weight loss and body fat reduced, cortisol production and free cortisol levels increased, but adipose 11B-HSD-1 levels declined, relative to baseline. Men did not show any difference in cortisol levels after a week of calorie restriction. These findings were also explored in overweight/obese post-menopausal women who had lost weight through diet, with mixed results. In one study, 11B-HSD1 expression in adipose tissue reduced after weight loss, and this decrease was linked to a decrease in BMI between baseline and six months after starting the diet [2].

Cortisol levels rise within minutes after a meal, indicating that glucocorticoids respond quickly to changes in nutritional status. Given the disparities across studies and the variations in human and rodent data, it became evident that the type of meal in each diet needed to be described, and specific dietary macronutrients' effects on metabolism needed to be explored.

Exercise, in addition to diet, is a popular weight-loss treatment. Exercise, on the other hand, is a type of metabolic stress that can activate the HPA axis and raise glucocorticoid levels in the bloodstream. The significance of this has been investigated by separating acute intense and chronic voluntary exercises in rats on the treadmill, where intense exercise studies have shown higher corticosterone levels in urine, enlargement of the adrenal glands, and reduced adrenal sensitivity to ACTH, as indicated by a low ACTH-to-glucocorticoid ratio, whether regular and voluntary exercise increased adrenal sensitivity, demonstrating that long-term training balances glucocorticoid fluctuations. Although increasing glucocorticoid concentration can be harmful to pancreatic -cells alone, frequent exercise can improve insulin sensitivity and glucose tolerance, which may be due to tissular, rather than systemic, glucocorticoid metabolism [3].

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Gender and adiposity location appear to have an impact on the results as well. It's vital to realise that not all people with obesity have the same cortisol secretion and metabolism, especially at the beginning. Chronic cortisol measurement, maybe employing hair cortisol measures, which have been proved to be an unique and accurate approach to detect average systemic cortisol levels, may give a more appropriate and ubiquitous means to report changes in glucocorticoid metabolism.

Bariatric Surgery: In people with morbid obesity, bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB), results in long-term weight loss, as well as dramatic and rapid improvements in T2DM, dyslipidemia, hypertension, and a considerable reduction in cardiovascular disease and death. Although the effects of RYGB on diabetes were initially attributed to significant weight reduction following post-operative dietary restriction and/or absorption, the same effect was observed in rodents that did not lose weight, suggesting a weight-independent mode of action. Furthermore, the advantages might be seen within hours or days, long before significant weight loss has happened [4].

This observation has now led to various investigations into the glucoregulatory role of the gastrointestinal tract, including the involvement of a rise in observed post-operative GLP-1 concentration, in an effort to better understand the underlying processes of diabetes remission. This includes the "hindgut hypothesis," which claims that euglycaemic effects result from the faster delivery of nutrients to the distal intestine, where GLP-1 is largely released, which improves glucose metabolism by enhancing the insulin signal. Glucocorticoid metabolism has been connected to bariatric surgery in several studies, most notably in the context of post-operative adipose tissue reduction.

The activity of 11B-HSD1 in subcutaneous adipose tissue was reduced, as seen by the tissue's F/E. In addition, total urine cortisol metabolites were lower, implying a decrease in HPA axis activation. Both mRNA expression and urine and adipose tissue F/E, as well as positive changes in insulin sensitivity, circulating leptin and adiponectin, and peripheral glucocorticoid metabolism, have been reported to show a decrease in subcutaneous adipose tissue 11B-HSD1 activity at 1 and 2 years after gastric bypass surgery in humans. Furthermore, rather than cortisol, intra-adipose cortisone levels showed the most evident changes, suggesting that the altered glucocorticoid metabolism after weight loss could represent an adaptive response to insufficient adipose cortisol levels [5].

Glucocorticoids are steroid hormones that play an important role in maintaining homeostasis. Their physiological and therapeutic activities have made them important pharmacological targets, especially as anti-inflammatory drugs. Nonetheless, their negative effects, particularly in terms of metabolism, might be severe.

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