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REVIEW

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Molecular mechanism of corticosteroid-induced hyperglycemia

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Abstract: Corticosteroids are widely used as strong anti-inflammatory and immunosuppressive drugs to treat various diseases. However, the use of corticosteroids can cause several side effects, such as hyperglycemia. This review aims to discuss the effect of corticosteroids on increasing glucose in molecular levels based on literature studies. A literature searching was carried out on the PubMed, Science Direct, and Google Scholar databases published in 2010-2020. Glucocorticoids can cause an increase in blood glucose levels by several mechanisms. In the liver, glucocorticoids increase endogenous plasma glucose and stimulate gluconeogenesis. Glucocorticoids increase the production of non-esterified fatty acids which affect the signal transduction of insulin receptor substrate-1 in skeletal muscle. In adipose, glucocorticoids increase lipolysis and visceral adiposity through increased transcription and expression of protein adipose triglyceride lipase and hormone-sensitive lipase. In pancreatic beta cells, glucocorticoids directly inhibit the beta cell response to glucose through the role of protein kinase B and protein kinase C. At the molecular level, glucocorticoids can cause hyperglycemia through mechanisms in the liver, skeletal muscle tissue, adipose tissue, and pancreatic beta cells.

Keywords: glucocorticoid, hyperglycemia, insulin resistance, insulin signalling pathway

Introduction

Glucocorticoids are synthesized from cholesterol and produced by the cortex of the adrenal glands. The secretion of these hormones is regulated by adrenocorticotropic hormone (ACTH) secreted by the anterior pituitary gland [1]. Steroid hormones are categorized into two primary groups: glucocorticoids and mineralocorticoids. Glucocorticoids have important roles in carbohydrate metabolism and immune function, whereas mineralocorticoids have strong effects on fluid and electrolyte balance [2]. Glucocorticoids are used by up to 0.9 percent of the population, with the highest usage of 2.5% among aged 70 to 79 years [3]. Although glucocorticoids are used widely as an anti-inflammatory and immunosuppressive, glucocorticoids have a strong impact on glucose metabolism that contributes to the new-onset hyperglycemia [4].

A meta-analysis study reported that prevalence of glucocorticoid-induced hyperglycemia level was 32.3% [5]. Glucocorticoids can increase blood glucose levels by up to 68%, with an average increase of 140 mg/dL [6]. Dexamethasone administration has been shown to increase blood glucose levels by affecting insulin signaling pathway and inducing P85α, a regulatory subunit of phosphatidylinositol 3-kinase (PI3K) [7]. In addition, dexamethasone also increases the expression of MAP kinase phosphatase 3 (MKP-3), mediated by forkhead box protein O1 (FOXO1). FOXO1 overexpression induces MKP-3 expression, resulting in fat accumulation and insulin resistance [8]. Given the great potential of corticosteroids to increase blood glucose levels, this review aims to dexamine the effect of corticosteroids on glucose levels at a molecular level.

Methods

An initial search was conducted through the PubMed, Science Direct, and Google Scholar databases. The keywords used included "glucocorticoid-induced hyperglycemia", "glucocorticoid effect on skeletal muscle", "glucocorticoid effect on adipose tissue", and "glucocorticoid effect on pancreatic beta-cell". The selected articles were those published between 2010 and 2020.

Table 1. Mechanism action of glucocorticoid-induced hyperglycemia

Drugs	Mechanism of action	References
Dexamethasone	In the liver, glucocorticoids increase gluconeogenesis by increasing the expression and activity of PCK and G6PC, leading to an increase hepatic glucose output.	[12]
Prednisolone	Elevated levels of non-esterified fatty acids increase the risk of accumulation from intramuscular lipids, fatty acyl-CoA, diacylglycerol, and ceramides, which inhibit specific proteins involved in insulin signal transduction pathways.	[14]
Dexamethasone	In visceral adipose tissue, glucocorticoids promote lipolysis in mature adipocytes by augmenting the transcription and expression of adipose protein triglyceride lipase and hormone-sensitive lipase.	[15,16]
Dexamethasone	The effect of using glucocorticoids on pancreatic beta cells directly inhibits the beta cell response to glucose through the role of PKB (AKT) and PKC.	[17,18]

Glucocorticoid effects on liver

Glucocorticoids affect the liver by increasing endogenous glucose plasma (EGP) production. Insulin, which is secreted in response to food or carbohydrates to suppress EGP production, is disrupted by the presence of glucocorticoids due to their opposing properties [9]. A two-week administration of a low dose prednisolone (7.5 mg) has been shown to interfere insulin's ability to suppress EGP production, resulting in an increased blood glucose levels [10].

Glucocorticoids increase blood glucose production through upregulation of gluconeogenesis [11] (Table 1). Mechanistically, glucocorticoids activate phosphoenolpyruvate carboxylase (PCK) and glucose-6-phosphatase (G6PC). PCK plays an important role in increasing blood glucose levels because it is the enzyme needed to produce glucose-6-phosphate. Without PCK, glucose-6-phosphate is not formed, and the phosphate cannot be removed, preventing glucose release into circulation [12]. Another study reported that dexamethasone administration can elevate blood glucose levels by inducing glucose-6-phosphatase C2 (G6PC2), reducing the sensitivity of glucose-stimulated insulin secretion (GSIS) to glucose [13], and increase the expression of Krüppel-like factor 9 (KLF9) [11].

Glucocorticoids effects on skeletal muscle tissue

Glucocorticoids also impact skeletal muscle tissue, the primary site for insulin-mediated glucose disposal. Skeletal muscle tissue can stimulate insulin for glucose uptake, glucose oxidation, and glycogen synthesis through phosphorylation of various proteins [19]. A dose of 30 mg prednisolone can cause impair glucose disposal, increase basal glucose oxidation, and altere insulin's ability to suppress whole-body lipolysis and plasma levels of non-esterified fatty acids [10].

Increased levels of non-esterified fatty acids can increase the accumulation risk of intramuscular lipids, fatty acyl-CoA, diacylglycerol, and ceramides that inhibit specific proteins in insulin signal transduction pathways. The effect on suppressing glucose uptake mainly through the inhibition of glucose transporter-4 (GLUT4) translocation to muscle cells. Intramuscular lipids can activate various serine kinases, such as c-Jun amino-terminal kinase (JNK) and IκB kinase (IKK), which phosphorylate serine residues on insulin receptor substrate-1 (IRS-1) and decrease insulin signal. IRS-1 is responsible for transmitting signals from insulin, such as insulin growth factor-1 (IGF-1), through activation of the phosphatidylinositol-3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways [14].

Glucocorticoids effects on adipose tissue

Glucocorticoids play a contradictory role in lipid metabolism within adipose tissue, causing increased lipolysis and visceral adiposity. *In vivo* and *in vitro* studies have demonstrated that a 10-day administration of glucocorticoids in rats resulted in increased visceral adiposity, circulating free fatty acids, increased intracellular triglyceride deposition in liver and muscle. The simultaneous increase in visceral adiposity, circulating free fatty acids, and ectopic lipid deposition indicates that these mice developed insulin resistance and at risk for the development of type 2 diabetes mellitus [20].

Additionally, glucocorticoids increase lipolysis in mature adipocytes tissue through increased transcription and expression of adipose triglyceride lipase and hormone sensitive lipase [21]. Adipose triglyceride lipase activity is regulated by the interaction between

protein activator gene identification-58 (CGI-58) and the inhibitory protein G0/G1 switch 2 gene (G0S2) [15]. This interaction result is the inability of CGI-58 to activate the hydrolysis triacyl glyceride mediation. Whereas in adipose triglyceride lipase and G0S2 cause interactions that can inhibit G0S2 in its lipolysis activity. This means that an increase in adipose triglyceride lipase level in adipose tissue occurs simultaneously with an increase in CGI-58 and a decrease in G0S2, thereby triggering an increase in the non-esterified fatty acids level [16].

Another study found that the administering prednisolone at high doses of 37.5 mg per day for five days exhibited a prolipolytic effect in adipose tissue through an increase in protein kinase A (PKA) signaling on perilipin-1 phosphorylation and hormone sensitive lipase, alongside changes in the CGI58 and G0S2 mRNA transcript. The suppression of PKA-mediated perilipin-1 phosphorylation demonstrated glucocorticoid-induced insulin resistance. Additionally, prednisolone 37.5 mg increased cell-death including DNA fragmentation factor α–like effector (Cide) – CideA and CideC [22]. Cide proteins play an important role in regulating fat storage and lipolysis [23]. Cide proteins protect lipids from lipase activity as well as interact with perilipin-1 to promote lipid formation [24]. Cide proteins also promote fat storage by inhibitinf lipolysis [25]. Moreover, Cide proteins can downregulate adipose triglyceride lipase [24].

Glucocorticoids effects on pancreatic beta cells

Glucocorticoids also reduce the production and release of insulin by pancreatic beta cells, resulting in reduced insulin sensitivity and triggering insulin resistance. A two-week administration of prednisolone can increase the glucose under curve area and decrease C-peptide levels [26]. Glucocorticoids increase blood glucose levels by increasing potassium efflux, reducing cell membrane depolarization, and limiting calcium influx [27]. Another finding showed that dexamethasone can compensate for peripheral insulin action. Dexamethasone-induced rats exhibited higher serum insulin levels. The resulting hyperinsulinemia is an adaptive response to insulin resistance [28].

In addition to causing insulin resistance, glucocorticoids can also damage beta cell function. Dexamethasone use led to a 2.2-fold increase in the homeostasis model assessment of insulin resistance (HOMA-IR) and a 50% increase in the homeostasis model assessment of b cell (HOMA-B) value [29]. Another study reported that 75 mg of prednisolone can reduce beta cell function by 25-50% [26]. Moreover, prednisolone also diminisehd the potentiation factor ratio of pancreatic beta cells [30]. Glucocorticoids effect beta cell function by interfering with insulin signaling when acetylcholine is downregulated in insulin release, as well as regulating of alpha 2 adrenergic receptors [31].

Another effect of glucocorticoids on pancreatic beta cells is the direct inhibition the beta cell response to glucose through the roles of protein kinase B (AKT) and protein kinase C (PKC). Dexamethasone can cause increased blood glucose levels due to elevated AKT [17]. AKT deactivates AS160, inhibiting insulin secretion. AKT also activates mTOR, which supports beta cell growth. In beta cells, the increase in nicotinamide adenine dinucleotide phosphate NAD(P)H from mitochondrial source is primarily due to glucose. NAD(P)H is one of the mitochondrial signaling factors used for insulin release during glucose stimulation. Increased production of NAD(P)H will affect mitochondrial function in the phosphorylation of PKC, which is significantly increased. PKC can be activated by the phospholipase C pathway, which produces diacylglycerol and inositol 1,2,5-triphosphate. In addition, PKC also induces the release of intracellular Ca2+ [18].

Conclusion

In summary, the effects of the glucocorticoids-induced hyperglycemia can be observed in the liver, skeletal muscle, adipose tissue, and pancreatic beta cells. These effects include a reduction in insulin's effect on endogenous glucose plasma (EGP), stimulation gluconeogenesis, a decrease in insulin-stimulated glucose uptake in skeletal muscle and adipose tissue, and interference with pancreatic beta cells' sensitivity and action. By understanding the the mechanisms behind glucocorticoid-induced hyperglycemia, researcher can manipulate towards more effective treatment strategies for those condition's affected.

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Declaration of conflict interest

None.

Author contributons

DAS: conceptualization, investigation, resources, data curation, visualization. GS: formal analysis, writing-reviewing editing, supervision. IYS: methodology, investigation, resources, writing – original draft, writing - review and editing, supervision.

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