Molecular Mechanism of Corticosteroid-Induced Hyperglycemia

Destika Ambar Sari[1], Galih Samodra[1], Ikhwan Yuda Kusuma[1]*

[1]Department of Pharmacy, Faculty of Health, Universitas Harapan Bangsa Purwokerto, Jl. Raden Patah No. 100, Kedunglongsir, Ledug, Banyumas Regency, Central Java 53182, Indonesia

*Corresponding Author. Email: ikhwanyudakusuma@gmail.com

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 examine 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. Corticosteroids 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, corticosteroids can cause hyperglycemia through mechanisms in the liver, skeletal muscle tissue, adipose tissue, and pancreatic beta cells.

Keywords: kortikosteroid, glucocorticoid, hiperglikemia, molekuler

Introduction

Corticosteroids are synthesized from cholesterol and produced by the cortex of the adrenal glands. The secretion of steroid hormone is influenced by adrenocorticohormone (ACTH) originated from the anterior pituitary [1]. Steroid hormones are divided into two major groups, glucocorticoids and mineralocorticoids. Glucocorticoids have important effects on carbohydrate metabolism and immune function, whereas mineralocorticoids have strong

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effects on fluid and electrolyte balance [2]. The use of glucocorticoids reached 0.9% displaying the highest use rate of 2.5% in individuals 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 onset of hyperglycemia [4].

A meta-analysis study reported that 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]. The administration of dexamethasone has proven to increase blood glucose levels by affecting insulin signal transduction through the insulin growth factor 1 (IGF-1) pathway and also induce P85α and phosphatidylinositol 3 kinase (PI3K) [7]. In addition, dexamethasone also increase the expression of MAP kinase phosphatase 3 (MKP-3) protein-mediated by forkhead box protein O1 (FOXO1). FOXO1 overexpression inhibited MKP-3, which causes fat accumulation and triggered insulin resistance [8].

Based on the description above, it can be seen that glucocorticoid corticosteroids have great potential to increase blood glucose levels, so this review aims to examine the effect of corticosteroids on increasing glucose levels through a molecular approach based on literature studies.

Methods

The initial search was done by searching for information sources through the PubMed, Science Direct, and Google Scholar databases. Keywords used were "Glucocorticoid-induced hyperglycemia", "Glucocorticoid effect on skeletal muscle", "Glucocorticoid effect on adipose tissue", and "Glucocorticoid effect on pancreatic beta-cell". The selected articles were articles published in 2010-2020.

The inclusion criteria applied were male gender human and test animals receiving corticosteroids. Whereas the exclusion criteria were male gender humans who had a family history of diabetes. Exclusion criteria were determined based on testing on humans or healthy test animals, which are expected to show a real hyperglycemic effect and show significance.

Articles obtained from various databases with details: PubMed (n=4543), Science Direct (n=1032), and Google Scholar (n=56). Further screening was done, 1256 articles showed duplication, and the remaining 4375. Next, title and abstract selection were applied based on inclusion and exclusion criteria, 4365 articles were eliminated, and 10 articles were obtained which were further analyzed.

Glucocorticoids effects on liver

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Glucocorticoids affect the liver by increasing endogenous plasma glucose (EGP) production. Insulin secreted in response to food or carbohydrates in suppressing EGP production, is disturbed by the presence of glucocorticoids which have opposite properties to insulin [9]. Although in low doses, the administration of prednisolone 7.5 mg was proven to interfere with insulin's ability in suppressing EGP production, resulting in an increase in blood glucose levels after receiving prednisolone for two weeks [10].

Glucocorticoids increase blood glucose production through upregulation of gluconeogenesis. Dexamethasone can increase blood glucose levels [11]. Glucocorticoids affect gluconeogenesis by activating phosphoenolpyruvate carboxylase (PCK) and glucose-6-phosphatase (G6PC). PCK plays an important role in increasing blood glucose levels because PCK is an enzyme needed to produce glucose-6-phosphate. Without PCK, glucose-6-phosphate will not be released and the glucose-6-phosphate enzyme will not be able to remove the phosphate, which allowing the release of glucose into the circulation [12]. Another study found the effect of dexamethasone administration in increasing blood glucose levels in the presence of glucose 6 phosphatase C2 (G6PC2) induction, which can reduce the sensitivity of glucose-stimulated insulin secretion (GSIS) to glucose [13] and increase the expression of Krüppel-like factor 9 (KLF9) [11].

Table 1. Mechanisme of action glucocorticoid-induced hyperglycemia

Drugs	Mechanism of action	Referensi
Dexamethasone	In the liver, glucocorticoids increase gluconeogenesis by increasing the expression and activity of phosphoenolpyruvate carboxylase and glucose-6-phosphatase and increasing 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 that inhibit certain proteins along insulin signal transduction pathways.	[14]
Dexamethasone	In visceral adipose tissue, glucocorticoids increase lipolysis in mature adipocytes through increased transcription and expression of adipose protein triglyceride lipase and hormone sensitive lipase.	[15,16]
Dexamethasone	The effect of using glucocorticoids on pancreatic beta cells is to directly inhibit the beta cell response to glucose through the role of protein kinase B (AKT) and protein kinase C (PKC).)	[17,18]

Glucocorticoids effects on skeletal muscle tissue

Glucocorticoids not only affect the liver but also on skeletal muscle tissue. Skeletal muscle tissue is the most important site for insulin-mediated glucose disposal. Skeletal muscle tissue can stimulate insulin for taking glucose, glucose oxidation, and glycogen synthesis through phosphorylation of several proteins [19]. Prednisolone 30 mg can cause impaired glucose disposal, increased basal glucose oxidation, and disturbed 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 certain proteins along insulin signal transduction pathways. This impact on suppressing glucose uptake mainly through 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 cause a decrease in 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 in adipose tissue proven to have a contradictory role in lipid metabolism by causing increased lipolysis and visceral adiposity. In vivo and in vitro studies showed that administration of glucocorticoids in rats for 10 days resulted in increased visceral adiposity, circulating free fatty acids, increased intracellular triglyceride deposition in liver and muscle. The increase in visceral adiposity that occurs together with the increase in circulating free fatty acids and ectopic lipid deposition showed that these mice developed insulin resistance and at risk for the development of type 2 diabetes [20].

In addition, glucocorticoids increase lipolysis in mature adipocytes tissue through increased transcription and expression of protein adipose triglyceride lipase and hormone sensitive lipase [21]. Adipose triglyceride lipase activities is regulated by interaction with the protein activator gene identification-58 (CGI-58) and the inhibitory protein G0/G1 switch 2 gene (G0S2) [15]. The 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

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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 stated that the administration of prednisolone in high doses of 37.5 mg per day for five days was proven to show a prolipolytic effect in adipose tissue through an increase in protein kinase A (PKA) signaling on perilipin-1 phosphorylation and hormone sensitive lipase along with changes in the CGI58 and G0S2 mRNA transcript. The suppression of PKA-mediated perilipin-1 phosphorylation showed glucocorticoid-induced insulin resistance. In addition, prednisolone 37.5 mg also increased cell-death including DNA fragmentation factor α–like effector (Cide) - CideA and CideC [22]. Cide protein plays an important role in the regulation of fat storage and lipolysis [23]. Cide protein is intended to protect lipids from lipase activity as well as interact with perilipin-1 to promote lipid formation [24]. Cide protein also promotes fat storage by the fat formation and lipolysis inhibition [25]. Moreover, Cide protein also damages adipose triglyceride lipase by its down-regulation [24].

Glucocorticoids effects on pancreatic beta cells

Another effect caused by glucocorticoids is reducing production and releasing insulin by pancreatic beta cells, resulting in reduced insulin sensitivity and triggering insulin resistance. The administration of prednisolone for two weeks can increase the glucose under curve area and decrease C-peptide levels [26]. Glucocorticoids increase blood glucose through increasing potassium outflow by reducing cell membrane depolarization and limiting calcium influx [27]. Another result obtained was that dexamethasone can compensate for peripheral insulin action. Dexamethasone-induced rats showed higher serum insulin levels. Emerging hyperinsulinemia is an adaptation that occurs in response to the emergence of insulin resistance [28].

In addition to triggering insulin resistance, glucocorticoids can also damaging beta cell function. The use of dexamethasone resulted in an increased of homeostasis model assessment of insulin resistance (HOMA-IR) by 2.2 times and an increased in the homeostasis model assessment of b cell (HOMA-B) value about 50% [29]. Another study stated that prednisolone 75 mg can reduce 25-50% beta cell function [26]. Moreover, prednisolone also reduced the potentiation factor ratio of pancreatic beta cells [30]. The glucocorticoids effects on beta cell function occurs by interfering with insulin signaling when acetylcholine is downregulated in insulin release as well as regulation of alpha 2 adrenergic receptors [31].

Another effect that appear from the use of glucocorticoids on pancreatic beta cells is directly inhibiting the beta cell response to glucose through the role of protein kinase B (AKT) and protein kinase C (PKC). Dexamethasone can cause an increase in blood glucose due to an

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increase in AKT [17]. AKT deactivates AS160, which causing an inhibitory effect on insulin secretion. AKT also activates mTOR, which supports beta cell growth. In beta cells, increased glucose in nicotinamide adenine dinucleotide phosphate NAD(P)H is mostly from mitochondrial. 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 protein kinase C (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].

From the above studies description, related to the effects of the glucocorticoids-induced hyperglycemia, it can appear in the liver, skeletal muscle, adipose tissue and pancreatic beta cells. The effects are a reduction in the effect of insulin on endogenous glucose plasma (EGP), stimulating gluconeogenesis, reducing insulin-stimulated glucose uptake in skeletal muscle and adipose tissue, and interfering with pancreatic beta cells' sensitivity and action.

Conclusion

Glucocorticoids induce hyperglycemia by several mechanisms: i) increasing endogenous plasma glucose and stimulating gluconeogenesis in the liver, ii) increasing the production of non-esterified fatty acids that affect insulin receptor substrate-1 signal transduction in skeletal muscle, iii) increasing lipolysis, iv) increasing visceral adiposity as well as the transcription and expression of adipose triglyceride lipase protein and hormone-sensitive lipase in adipose tissue, v) reducing insulin sensitivity thus triggering insulin resistance, vi) directly inhibits beta-cell response to glucose through the role of kinase C protein in pancreatic beta cells.

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Contributors

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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