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Research Article

Role of Glucocorticoids and Stress in Pathogeny of Diabetes Mellitus and Related Disorders

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Abstract

Presented work aimed at preparing literature review that could describe the contribution of Glucocorticoids (GC) and stress to pathogeny of diabetes mellitus and related disorders: Metabolic syndrome and obesity. This review includes the following topics: Effects of GC and stress on glucose metabolism, the role of GC and stress in pathogenetic mechanisms of clinical and experimental diabetes, the importance of catecholamines and other stress hormones in mechanisms of hypo and hyperglycemia, interactions of GC with high-fat diet, contribution of GC to comorbidity of metabolic and neuropsychiatric disorders, metabolic consequences of prolonged GC treatment, the role of GC in programming/imprinting phenomena, the importance of stress proteins in pathogeny of metabolic disorders and modes of counteracting stress and GC in diabetes and related diseases. The conclusion is made about the necessity of more detailed evaluation of the effects of hormones having antistress properties, as applied to metabolic disorders.

Keywords: Diabetes mellitus; Glucocorticoids; Metabolic syndrome; Obesity; Stress

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Abbreviations

BDNF: Brain Derived Neurotrophic Factor

DHEA: Dehydroepiandrosterone

DOHaD: Developmental Origins of Health and Disease

DST: Dexamethasone Suppression Test

GC: Glucocorticoids

HPA: Hypothalamo Pituitary Adrenal (axis)

HSP: Heat Shock Proteins

iHSP70: Intracellular Hsp70

eHSP70: Extracellular HSP70

eHSP72: Extracellular HSP72

PEPCK: Phosphoenolpyruvate Carboxykinase

PPAR-alpha: Peroxysome Proliferator-Activated Receptor, Type Alpha

PPAR-gamma: Peroxysome Proliferator-Activated Receptor, Type Gamma

SAMS: Sympatho Adrenomedullary System

11beta-HSD1: 11beta-Hydroxysteroid Dehydrogenase Type 1

Introduction

Earlier we have briefly discussed the role of Glucocorticoids (GC) in mechanisms of aging and age-related diseases [1,2]. During such discussion it became clear that it is necessary to describe in more details the role of GC and stress in pathogeny of various diseases. Therefore, the presented work aimed at preparing literature review about the contribution of GC and stress to pathogeny of diabetes mellitus and related disorders, especially metabolic syndrome and obesity. Our choice of GC from the whole spectrum of stress hormones was justified, on one hand, by central positions occupied by GC in metabolic bioregulation and on the other hand, by the broad use of GC in various subfields of medicine as pharmacotherapeutic preparations, mainly with anti-inflammatory and immunosuppressive action. Therefore, it is necessary to consider possible diabetogenic GC action on patients with non-endocrine disorders.

Materials and Methods

For preparing bibliographic review we localized in various commercial databases and public domain of internet the evidence on the role of stress and GC in pathogenetic mechanisms of diabetes mellitus, metabolic syndrome and obesity during the last decades and predominantly in English language, using the key words indicated. Thereafter all the data obtained were sorted according to their degree of importance and reasoning, separating the discussion on clinical and experimental diabetes, metabolic syndrome and obesity, influence of high-fat diet, hypo- and hyperglycemia, finalizing with more complex topics on comorbidity with some neuropsychiatric disorders, the role of heat shock proteins and programming/imprinting phenomena and possible modes of counteracting stress and excessive GC action in diabetic patients.

Two types of stress as related to stress hormones and proteins

At present two main types of stress are considered: The physiologic and cell stress. The physiologic stress is systemic one and realized by means of hormones belonging to Hypothalamic Pituitary Adrenal (HPA) axis and Sympatho Adrenomedullary System (SAMS), first of all GC and catecholamines. On the other hand, cell stress is more localized one and effectuated by means of stress proteins, first of all Heat Shock Proteins (HSP) and metallothioneins. In this article we shall focus mainly on GC and HSP, although other stress hormones and proteins may be also important.

Effects of glucocorticoids and stress on parameters of glucose metabolism

At present GC are considered as functional insulin antagonists [3]. In fact, on systemic level these hormones cause insulin resistance and impaired glucose tolerance, increased gluconeogenesis and decreased glucose transport in targets organs for insulin [4,5]. Correspondingly, GC enhance glucose production in the liver and diminish its consumption in peripheral tissues [6]. These GC properties were confirmed in studies on healthy human volunteers and in experimental models of laboratory animals.

On the other hand, various stress types can increase the risk of diabetes in humans and animals. Really, chronic psychosocial stress in job place doubled the risk of type 2 diabetes in middle-aged women [7]. In experiments on laboratory animals restraint stress caused diabetes after partial resection of the pancreas [6].

The following section will discuss how stress or GC are associated with clinical diabetes and related disorders.

Role of glucocorticoids and stress in pathogenetic mechanisms of clinical diabetes, metabolic syndrome and obesity

First of all, subclinical hypercortisolism is more frequent in patients with type 2 diabetes, especially in the presence of diabetic complications [8]. Besides, stressor events of everyday life are able to increase the risk of diabetes, whereas surgical stress impairs glycemic control [6,9].

The increase in cortisol levels in blood may be responsible for the decrease in wound healing rate in diabetic patients [10]. In such patients the subjective perceptions of stress are enhanced, and coping processes are decreased [11].

In patients with metabolic syndrome urinary excretion of metabolites of cortisol and catecholamines is increased [12]. Besides, in such patients cortisol concentration in blood correlated to the degree of insulin resistance [13]. In obesity urinary excretion of cortisol metabolites is also increased [14]. Moreover, in obesity the relation between adrenal size and the risk of type 2 diabetes was revealed [15].

Special position is occupied by polycystic ovary syndrome that shares many features with metabolic disorders. In patients with such syndrome the enhanced reaction of hyperglycemia to dexamethasone administration was observed [16].

The role of catecholamines and other stress hormones in mechanisms of hypo and hyperglycemia, as well as other metabolic disorders

It is well known that hypoglycemia represents one of the most powerful stressors, being able to stimulate the secretion of GC, catecholamines, glucagon, vasopressin and other stress hormones. It was established also that repeated iatrogenic hypoglycemia provokes the disturbances of SAMS that result consequently in impaired capacity to recognize the foregoing hypoglycemia by patients [17].

On the other hand, acute stress-induced hyperglycemia may indicate enhanced risk of mortality and impaired functional recovery in non-diabetic patients [18]. Besides, prolonged hyperglycemia caused by chronic stress in rats can be considered as manifestation of allostatic load [19].

It is suggested that nearly all the components of metabolic syndrome are related to disturbances in SAMS [20], whereas diabetes of type 1 represents a state of excessive activity of this system [21].

Role of glucocorticoids and stress in pathogeny of experimental diabetes and metabolic disturbances related to high-fat diet

In rats and mice with experimental diabetes the levels of GC and adrenaline in blood are increased, and the reaction to restraint stress is enhanced [6,11]. Experimental diabetes potentiated adverse influence of chronic stress on hippocampus [22,23]. Hippocampal disturbances in animals with experimental diabetes were prevented by GC antagonist RU-486 [24].

Chronic moderate stress in mice with experimental diabetes leads to higher degree of hyperglycemia and to decrease in survival [25]. Probably, in diabetes GC have lost their homeostatic function and become the brain-damaging agents [26].

The most significant results were observed in the cases of combined influence of GC and high-fat diet. In fact, such combination provoked really dramatic enhancement of glucose and lipid levels in blood, as well as of insulin resistance [27]. Combined action of exogenous corticosterone and high-fat diet resulted in unusually rapid development of phenotype of metabolic syndrome or type 2 diabetes [28].

The question therefore emerges: How these data are applied to real clinical situations? As a matter of fact, GC possess orexigenic action enhancing appetite, especially as referred to highly caloric food stuffs, rich in carbohydrates and lipids [29]. In relation to this, it is very interesting that high cortisol level in blood of type 2 diabetic patients correlates to predominant choice of such products [30]. On the other hand, it was shown that high-fat diet consumption activates HPA axis [27] that results in creation of vicious cycle of positive feed forward influences. However, it is important to note here that the effects of GC on metabolism in peripheral organs should be considered also, besides their central influence on appetite.

In addition to important role of the diet, aging process in itself may be responsible for interactions between GC, stress and metabolic disturbances. Really, aging is accompanied by decreased efficacy of GC negative feedback mechanism and HPA axis hyperactivity. As a

result, in elderly patients with chronic diseases the progressive increase of cortisol levels in blood is observed, especially in the evening [1]. The important role in such disturbances is played by atrophic hippocampal changes that can favor the comorbidities with neuropsychiatric disorders.

Role of glucocorticoids in comorbidities of metabolic and neuropsychiatric disorders

Stress hormones appear to occupy central positions in the pathogeny of both metabolic syndrome or obesity and depression [31,32]. In diabetic patients the psychic depression is observed more frequently, with common pathogenic factors of such comorbidity being enhanced secretion of GC, catecholamines, glucagon and other stress hormones, as well as decreases in neurogenesis and in the level of Brain Derived Neurotrophic Factor BDNF [33]. The consequence of chronic hyperglycemia is accelerated brain aging. The risk of comorbid depression is enhanced by diabetes as chronic metabolic stressor; in both cases elevated cortisol level in blood and disturbances of its circadian rhythm and in the results of the test of suppressing cortisol secretion by Dexamethasone (DST) give the evidence of impaired negative feedback associated with hippocampal atrophy and worsened cognitive processes and memory. Moreover, patients with diabetes demonstrate more severe progressing of comorbid depression and 10 fold higher risk of suicide [34].

Approximately 25-60% of patients with bipolar disorder show the symptoms of metabolic syndrome. The enhanced blood levels of catecholamines and GC in such patients already in early stages of disease are considered to be the manifestation of allostatic load [35]. In schizophrenia it should be considered also that elevated activity of SAMS and HPA axis can provoke diabetogenic influence [36].

The following section will discuss the actions of exogenous GC used as pharmacotherapeutic agents.

Metabolic consequences of pharmacotherapy with exogenous glucocorticoids

The diabetes is considered as quite common complication of chronic influence of excessive GC and can be the risk factor of enhanced mortality. More than a half of patients with kidney disease demonstrate impaired tolerance to glucose and diabetes already after 10 weeks of treatment with prednisone, and higher GC dose results in more probable necessity to prescribe hypoglycemic peroral drugs [37]. Prolonged pharmacotherapy with GC is responsible for 2% of diabetes cases in ambulatory patients [38].

About 35% of patients with rheumatoid arthritis that use GC during prolonged period of time, demonstrate disturbances of glucose metabolism [39]. As some authors note, it can happen that using GC, the patients may “exchange” one disease (for example, bronchial asthma) to another (metabolic syndrome or diabetes) [40].

Therefore, it is critically important for physicians prescribing GC even in small doses to consider the risk of iatrogenic metabolic disorders [39]. However, only in transplantology there exist recommendations for regular checking blood glucose levels in the cases of prolonged GC treatment, but unfortunately, these recommendations do not consider that frequently GC do not alter basal glucose levels in blood [37].

Special position is occupied by pharmacotherapy with exogenous GC in perinatal period of development. In this sense, it was shown that administration of synthetic GC to premature infants leads to their decreased sensitivity to insulin [41]. These data are related to the evidence of important role of GC in phenomena of programming/imprinting.

Role of glucocorticoids in phenomena of programming/imprinting of metabolic disorders

In the frame of concept of Developmental Origins of Health and Disease (DOHaD) it was shown that dexamethasone administration to pregnant rats resulted in impaired glucose tolerance and insulin resistance in the offspring already in adult state, as well as in elevated expression of GC receptors and key enzyme of gluconeogenesis PEPCK in the liver [42]. The stress of pregnant rats also caused impaired glucose tolerance in the offspring already in aging period [43].

In general, the data obtained in different animal species show that the action of excessive GC in perinatal period of development provokes the progressing of metabolic disorders in later life. In this sense, it is interesting that in the individuals with low birth weight, higher activity of HPA axis is observed already in adult state, what can be responsible for the development of visceral obesity and metabolic syndrome [44,45].

Just recently we tried to attract the attention to insufficient description of cell stress mechanisms in the endocrinological literature [46]. In fact, contrary to hormonal mechanisms of so called physiologic stress, the role of cell stress in pathogeny of diabetes and related disorders is poorly studied yet.

The importance of stress proteins in pathogeny of metabolic disorders

It was shown that intracellular levels of HSP are low in clinical and experimental diabetes and in the cases of insulin resistance. This situation can enhance the vulnerability of diabetic patients to lesions of cells and tissues [47].

Relatively recently it was discovered that there exists non-classic, exosomal mechanism of release for one of principal components of the family of stress proteins-HSP70 from the cells to extracellular fluid. Besides, if intracellular HSP70 (iHSP70), for example, in leukocytes of peripheral blood, has anti-inflammatory action by means of inactivation of transcription factor NF-kappaB, in contrast, extracellular HSP70 (eHSP70) characterizes enhanced activity of immune system and inflammatory processes, therefore the relation eHSP70/iHSP70 can be used as indicator showing the tendency to generalized inflammation [48].

It seems that in diabetes the elevated relation eHSP70/iHSP70 occurs, what explains the vulnerability of diabetic patients to inflammatory complications. Moreover, it was shown that hypoglycemia, i.e., well-known stressor, leads to enhanced level of eHSP72 that appears to serve as danger signal to switching-on the mechanisms of defense against immune and metabolic disorders [49].

Undoubtedly, these interesting data can lead to the necessity of re-evaluating many established concepts on the role of GC and stress in mechanisms of metabolic disorders. However, as already it was

noted in our previous work [46], the obstacle on the way of such re-evaluation may be insufficiently studied interactions between the proteins and hormones of stress.

Finally, based on above mentioned facts, let's discuss how counteracting stress and excessive GC can help in the treatment of patients with diabetes and related disorders.

Modes of counteracting stress and glucocorticoids as possible means of treatment of metabolic disorders

One of such means may be the diet with low contents of carbohydrates and fat, that can prevent activation of HPA axis in patients with diabetes, as can be deduced from evidence mentioned above. However, in order to not provoke the undesirable disbalance of macronutrients (with excessive protein content in the diet), perhaps, the total caloric restriction is preferable in these cases. Another non-drug mode may be moderate but regular physical activity that in contrast to acute physical exercise is able to paradoxically decrease the secretion of stress hormones, as well as to diminish the relation eHSP70/iHSP70 [47,50]. Warm bath appears to do partially the same [47]. Behavioral training of relaxation may improve glucose tolerance and decrease the secretion of cortisol and catecholamines in hospitalized patients [6].

What for drugs, insulin appears to be the drug of choice for treating GC-induced hyperglycemia [51]. In addition, antidiabetic preparations, agonists of PPAR-gamma and clofibrate-agonist of PPAR-alpha are able to inhibit the enzyme 11beta-HSD1 that reactivates cortisol from inactive cortisone, what can promote the decrease in local cortisol production in adipose tissue [44]. In this sense, it was shown that inhibition of 11beta-HSD1 activity by carbenoxolone improves cognitive functions and memory both in patients with type 2 diabetes and in healthy elderly persons [52], whereas neuro active steroid DHEA decreases the activity of this enzyme in adipocytes [53]. It should be underlined that in general, novel inhibitors of 11beta-HSD1 represent promising tools of treating diabetes, obesity and other metabolic disorders [54,55].

On the other hand, antidiabetic preparation glyburide can enhance insulin secretion by means of antagonism on the level of alpha2-adrenergic receptors [6]. In this sense, it was noted long time ago that the importance of stress-limiting systems consists of the blockade of adrenergic effects of stress [56]. The modes of enhancement of such stress-limiting systems are the use of benzodiazepine preparations, e.g., Alprazolam [6], and the employment of antioxidants [57], considering also the capacity of excessive GC to provoke oxidative stress [58]. Nevertheless, it should be noted here that the use of various drugs like adrenergic blockers, benzodiazepines or antioxidants for counteracting stress or GC effects is only beginning to be considered, and a lot of investigative efforts are needed yet for clarifying this emergent topic.

Conclusion

Recently we discussed the modes of counteracting stress and GC in early ontogeny [59] and in aging [60,61]. Such modes include melatonin and neuroactive steroids, such as DHEA, as well as oxytocin, insulin-like growth factors and somatolactogens. However, growth hormone is considered to be the stress hormone and can induce insulin resistance [62]. It means that in future studies it will be important to discuss in more detail the action of such hormones, as referred to metabolic disorders.

On the other hand, hormetic phenomena should be taken into account, considering that mild stress may be beneficial, especially in aging [63]. However, future studies should establish more clearly the thresholds separating acute and chronic, as well as mild, moderate and intense stress types.

And finally, the role of epigenetic mechanisms in the effects of GC and stress during experimental and clinical diabetes should be investigated more thoroughly. At present there exist only scarce data, e.g., on methylation of promoters in the gene of 11beta-HSD1 [64], although, as related to DOHaD concept and aging, the promising epigenetic perspectives involving GC and stress are already emerging [65,66].

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Conflict of Interest

The author affirms that conflict of interests related to this work does not exist.

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