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Received: 21 February, 2018

Accepted: 27 March, 2018

Published: 29 March, 2018

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Keywords: Stress; Glucose metabolism; Allostasis

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Mini Review

Stress and Glucose metabolism: A Review

Abstract

Stress is an inescapable fact of life. The perceived stress induces endocrine alterations characterized by the activation of hypothalamo-pituitary-adrenal axis and sympathetic adreno-medullary axis. The glucocorticoids and catecholamines which are secreted in response to stress induce variations in the physiology and behavior that help the individual to adapt to changing demands of the body. Glucocorticoids are known to play a central role in inducing the stress related pathophysiology. These hormones induce hypermetabolism in order to cope up with the increasing energy demands of the body. However when the stress is persistent the body adapts itself to continuous demands and starts regulating the metabolism at higher levels than the normal, termed as allostasis. This overwhelming load on the body will predispose the individual for the development of diseases. This mini-review focuses on long term chronic stress induced alterations in glucose metabolism and development of insulin resistance and glucose intolerance as a result of long term allostatic regulation.

Introduction

It is hard to dispute that most of us live at breakneck speed where numerous family, social and work obligations can easily overpower precious time and resources. This causes both physical and emotional stress that can take great toll on health [1]. Hence the field of biology of stress has been extensively studied by many researchers all over the world. However many of the aspects of stress remain obscure. Stress is a non-specific response of the body to any stimuli [2]. This review focuses on different pathways of glucose metabolism under long term chronic stress and its impact.

Stress is a state of threatened homeostasis which delineates the metabolic pathways in order to meet the increased demands of the host. The ability to cope with these changes is crucial for healthy life. The events that evoke stress response are called stressors which can be external or internal [3]. The external factors may be physical injury, extreme climatic conditions, etc. and the internal factors may be infections, hypoglycaemia, etc. or psychological factors (personal issues viz. job, health or finances, etc.) [4]. Stress may be acute i.e. exposure for a short duration or chronic i.e. long persistent stress. Acute stress is adaptive in nature and enables the organism face emergency situation precisely, flight or fight responses whereas the chronic stress is shown to have deteriorating effects on the health.

Stress, neuroendocrine axis and glucocorticoids

It is known that stress activates hypothalamo-pituitary-adrenal axis. The brain circuits that initiate and maintain

stress response are located in the hypothalamus, which include paraventricular nuclei, locus ceruleus and the central sympathetic nervous system [5,6]. Stress activates the paraventricular nucleus (hypothalamus) in the brain and stimulates endocrine and neural mechanisms leading to an increase in the concentrations of stress hormones viz. glucocorticoids and catecholamines. Precisely, the activated paraventricular nucleus neurons secrete corticotropin releasing hormone (CRH) which regulates the adreno-corticotrophic hormone (ACTH) release from the anterior pituitary. ACTH acts on the adrenal cortex to release glucocorticoids [7,8]. These neuroendocrine changes seem to lack habituation and possibly there was an abnormal hypothalamo-pituitary-adrenal axis (HPA axis) activation in response to repeated stress [9]. In addition, sympathetic nervous system is activated which releases norepinephrine direct to the circulation and epinephrine from the adrenal medulla. It is demonstrated that glucocorticoids and catecholamines act synergistically during stress [10] (Figure 1).

Catecholamines act transiently during the initial exposure to stress and at later stages would be accompanied by the secretion of glucocorticoids. Glucocorticoids are generally referred to as stress hormones [11] as their secretion will be high under stressful conditions. Glucocorticoids elicit their action by binding to glucocorticoid receptors (GRs) that regulate various physiological functions viz., inflammation, gluconeogenesis and adipocyte differentiation etc. [12]. Upon binding with ligand, it is dimerized and translocated into nucleus where it binds to glucocorticoids (GCs) response elements (GREs) and bring out the gene expression of the target genes.

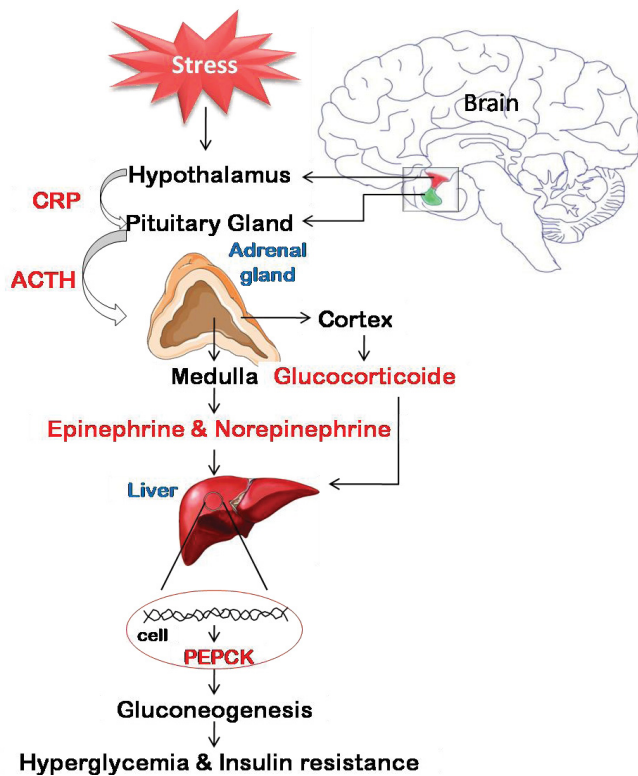


Figure 1: Hypothalamo-pituitary-adrenal axis under chronic

The mechanisms of stress induced alterations in glucose metabolism leading to hyperglycaemia are also elucidated which involve the changes in different pathways. The chronic stress is reported to cause hypermetabolism characterized by enhanced glycolysis, gluconeogenesis, altered glucose uptake and reduced glycogenesis. Persistent stress predispose to the development of chronic illness accompanied by the metabolic dysregulation.

Glucose uptake and aerobic oxidation of glucose under stress

An important outcome of chronic stress is hyperglycemia. This may be due to either reduced uptake of glucose by cells or increased synthesis of glucose. Hyperglycemia is the immediate effect of stress as it serves energy to meet the energy requirements of the body to chronic stress. In an attempt to maintain the glucose homeostasis in response to elevated adrenocortical activity during stress, all the glucose pathways would be affected. Glucose uptake in the body is facilitated in 2 ways viz., facilitated diffusion and secondary active transport. The facilitated diffusion is against concentration gradient which may be insulin mediated or non-insulin mediated glucose uptake. The secondary active transport is seen predominantly in kidney involves the use of ATP [13].

GLUT receptors play a vital role in the uptake of glucose from the blood stream. There are 14 different types of glucose transporters, however the GLUT 1 -4 are significantly studied [14]. GLUT-1 and GLUT-3 are shown to have high affinity for glucose and GLUT-1 is the major receptor that acts in brain and GLUT-2 is responsible for the uptake of glucose in pancreas.

The GLUT-4 is insulin sensitive and is predominantly involved in receptor mediated glucose uptake in muscle [15]. Counter regulatory hormones such as stress hormones (glucocorticoids and catecholamines) and glucagon are reported to inhibit insulin induced glucose uptake [16].

Glucose taken up by the cells enters glycolytic pathway. The end product of glycolytic pathway the pyruvate is metabolized either aerobically completely to carbon dioxide and water or anaerobically to lactate [13]. Under anaerobic conditions pyruvate is converted into lactate by the action of the enzyme lactate dehydrogenase. Under physiological conditions there will be equilibrium between the concentration of lactate and pyruvate. However under chronic stress conditions there will be increased concentrations of pyruvate and lactate [17-19] together with increased activity of lactate dehydrogenase (LDH) [20-22]. Under stressful conditions, the pyruvate produced by glycolysis may be channeled towards the production of glucose or it might end up in producing high lactate because of the reduced activity of pyruvate dehydrogenase (PDH). Reduced pyruvate dehydrogenase activity has been observed under chronic stress condition [23,24]. Stress is known to alter PDH activity [25] by increasing the concentration of pyruvate dehydrogenase kinase which inactivates PDH by phosphorylating it [26]. In spite of this, the activity of tricarboxylic acid (TCA) cycle will be high during stress because of the availability of substrates for TCA cycle by the oxidation of lipids (Nelson and Cox, 2004). Further the increased activity of TCA cycle provides substrates for gluconeogenesis. It is reported that stress induces lipolysis [27,28] and proteolysis which further elevate the concentration of the substrates for gluconeogenesis [29-31]. In addition, chronic stress caused hyperlactatemia an indication of hypermetabolism.

Glycogenesis and glycogenolysis during chronic stress

Chronic hyperglycemia during stress not only affects the glucose uptake and utilization but also enhances the synthesis of glucose endogenously. During normal conditions, the dietary glucose and endogenous glucose synthesized by the liver lead to the formation of glycogen in the liver. Stress is known to inhibit the glycogenesis in liver and skeletal muscles by inhibiting activity of glycogen synthase. The activity of glycogen synthase is inhibited by its phosphorylation by glycogen synthase kinase 3 (GSK-3) [32].

Glycogenolysis is the process of release of glucose from the glycogen. This usually occurs during starvation. Under stress, the glycogenolysis occurs to meet the increased energy demands by the body to withstand the perceived stress. A number of studies have shown the decreased liver glycogen content in response to chronic stress. For instance, our study [24] wherein rats were exposed for restraint and forced swimming every day for 2, 4 or 24 weeks, a reduction in hepatic glycogen content was observed. In addition, Kuznetsov and his coworkers [33] subjected rats to hypokinetic stress for 5, 15, 30, 45 and 60 days which resulted in decreased liver glycogen content.

Gluconeogenesis during chronic stress

Gluconeogenesis is synthesis of glucose from non-

carbohydrate precursors [13]. Under normal conditions the gluconeogenesis occurs during starvation to supply glucose to the cells, especially the brain which is dependent on the glucose. Stress increases the hepatic glucose production by increasing the activities of key gluconeogenic enzymes viz. phosphoenol pyruvate carboxy kinase (PEPCK), pyruvate carboxylase, fructose 1,6 bisphosphatase (FBPase) and glucose-6-phosphatase (G6Pase). All these key regulatory enzymes are transcriptionally regulated by glucocorticoids. Stress increases the transcription of PEPCK genes [12,34]. CREB, C/EBP and FOXO1 are the transcription factors which induce PEPCK genes under stress conditions [35]. It is reported that 7 fold over expression of PEPCK causes hyperglycaemia and 2 fold over expression causes insulin resistance [35]. Glucocorticoids also stimulate the expression of pyruvate carboxylase [29] and glucose-6-phosphatase [36]. In addition stress increases the activities of aminotransferases, glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT) [22,37] which further increase the concentration of substrates like pyruvate and oxaloacetate for gluconeogenesis. In addition to these, glucocorticoids are known to increase the blood glucose levels under stressful conditions by not only increasing gluconeogenesis but also by reducing insulin sensitivity. The glucocorticoids exert this action by antagonizing insulin stimulated translocation of glucose transporters from intracellular compartments to plasma membrane [12,38-40]. A similar mechanism is responsible for the glucocorticoid induced insulin resistance in the skeletal muscles [41].

Glucose metabolism, allostasis and allostatic load

The concept of allostasis was introduced by Sterling and Eyer in 1988 [42]. Allostasis is maintenance of physiological variables at altered level, different from the homeostatic set point in response to perceived or anticipated challenges or stressors. It regulates the metabolism by altering the biochemical pathways to achieve stability. Indeed the state of allostasis has been demonstrated by us in rats that were exposed to chronic stress [24]. In this study consistent hyperglycemia was observed in rats for 24 weeks, following exposure to restraint for 1 h followed by forced swimming for 15 minutes after a gap of 4 hours every day for 2, 4 or 24 weeks. The hyperglycemia was accompanied by altered pathways of glucose metabolism, predominantly increased activity of gluconeogenic enzymes. An exaggerated response of the body to persistent stress may lead to allostatic load i.e. altered physiological processes that may cause damage to the system [43]. For instance in our study [24] prolonged hyperglycemic condition due to stress was accompanied by insulin resistance and failure to tolerate glucose as shown by OGTT in rats. Thus when stress is persistent and it is prolonged for a long duration, the adaptive processes in the body become maladaptive resulting in pathophysiology. Brunner and coworkers has hypothesized [44] that neuroendocrine axis activated in response to stress stimuli plays a major role in the development of metabolic syndrome. In fact, many researchers have shown the development of insulin resistance and metabolic syndrome in response to chronic stress [12,45-49]. Therefore it is inferred that when the system is unable to cope

up with the continuous demands, allostatic load might become overwhelming that predisposes the body for the development of the diseases.

Conclusion

It is evident from the above discussion that chronic stress has adverse effects on the glucose metabolism. The alterations that are observed during chronic stress appear to be due to allostatic regulation in response to demand on the body. However, long term allostatic regulation leads to allostatic load resulting in pathophysiological conditions such as metabolic syndrome. Since stress is an inescapable fact of life, one should aim at managing the stress. Non-pharmacological intervention and stress management would prove beneficial in controlling the deleterious effects of stress. Future studies should be aimed at developing a novel strategy to suppress the activation of HPA axis and sympathetic nervous system due to stress, so as to prevent deleterious effects of glucocorticoids on carbohydrate metabolism.

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