

A Negative Feedback Mechanism Between Brain Catecholamines and Gamma Amino Butyric Acid, Could Be a Central Defense Mechanism in Stress. A Review Article

Ali Esmail Al-Snafi

Department of Pharmacology, College of Medicine, Thi qar university, Nasiriyah, Iraq

Abstract: The most important hormones involved in stress are catecholamines (CA), adrenocorticotropin (ACTH) and glucocorticoids. These hormones guided many biochemical events resulted in hyperglycemia with a decrease in insulin dependent peripheral glucose utilization. Under these conditions, glucose utilization by non-insulin dependent tissues is increased. One of these tissues is central nervous system, since all nervous tissues except ventral hypothalamus do not require the presence of insulin for glucose utilization and metabolism. Increase of brain glucose level subsequently increase synthesis of gamma amino butyric acid (GABA). Elevation of GABA as a result of hyperglycemia, has inhibitory effect on the secretion of brain catecholamines. Therefore, it was expected that the negative feedback mechanism between central GABA and catecholamine represent a resistant mechanism against stress.

Key words: Adrenocorticotropin • ACTH • Glucocorticoids • GABA • Norepinephrine • NE • Insulin • hormones • Hypothalamus • Pituitary

INTRODUCTION

Gamma-amino butyric acid (GABA) is the main inhibitory neurotransmitter of the CNS. It plays a major role in the modulation of cognitive and behavioral processes. GABA receptor antagonists exert anxiogenic effects, while GABA receptor agonists reduce anxiety and stress responses. The hormones involved in stress include catecholamines (CA), adrenocorticotropin (ACTH) and glucocorticoids. These hormones associated with a complex biochemical events including participation of hypothalamus anterior pituitary, adrenal and pancreas. This paper postulated that this brain-endocrine integration which result in catecholamines-GABA negative feedback is a defence mechanism in stress.

Stress mediators and their effect on insulin release, activity and on plasma glucose level.

The three most important hormones involved in stress are catecholamines (CA), adrenocorticotropin (ACTH) and glucocorticoids. The release of ACTH from the pituitary is controlled by a peptide hormone, corticotropin releasing factor (CRF), arising from the

hypothalamus which reaches the pituitary by a portal circulation [1]. Releasing of CRF is stimulated by norepinephrine (NE) [2, 3]. On the other hand intracerebroventricular administration of nanomole amount of CRF into rat induces a long-lasting rise in plasma epinephrine (E), NE and glucose [4]. Both CA and CRF have additives stimulatory effect on corticotroph cell and might provide for a sustained release of ACTH that is resistant to feed back inhibition by glucocorticoids [3]. The stimulatory effect of CA on ACTH releasing is mediated by β_2 -adrenergic receptors and these receptors coupled to an Adenylate cyclase mechanism [1, 5]. CA also has indirect stimulatory effect on the excretion of ACTH mediated by α_2 -adrenergic receptors, since clonidin (α_2 agonist) has been shown to be capable of increasing β -endorphin from anterior pituitary of rats [6]. The substance which when injected intra-cisternally increased ACTH secretion in rats [2]. The previous immunohistochemical studies using antisera raised against ACTH and β -endorphin have revealed that such peptides are contained in the same granules in pituitary corticotrophs [8]. Brain serotonin also elevated in stress

Corresponding Author: Ali Esmail Al-Snafi, Department of pharmacology, College of Medicine, Thi qar University Chancellor of Thi qar UniversityUniversity of Thi qar, Near Thi qar Stadium, Iraq. Cell: +9647801397994.

[9] and it also has stimulatory effect on the excretion of ACTH, therefore antiserotonergic drugs, such as cyproheptadine and metergoline, are used in the treatment of Cushing's disease effectively [10, 11]. Glucocorticoids elevation in stress by the above mechanisms exerts many biological effects, among them is the decreasing of basal and insulin stimulated glucose uptake in peripheral tissues. Part of this effect is associated with a decrease in the number of insulin receptors (down regulation), while glucocorticoids also decrease glucose utilization indirectly by increasing free fatty acids which in turn decrease the sensitivity of insulin receptors (Randle effect) [12]. However the major basis of hyperglycemic effect of glucocorticoids is enhancement of gluconeogenesis by increasing the flow of amino acid substrate from muscle protein degradation and by inducing hepatic synthesis of gluconeogenic enzymes such as transaminases, pyruvate carboxylase and glucose-6-phosphates [12, 13].

Hyperglycemic effect of glucocorticoids may induce corticosteroid diabetes which is one of the manifestations of Cushing's disease. Furthermore, excessive administration of glucocorticoids can induce hyperglycemic coma [13].

The enhanced activation of sympathetic-adrenomedullary system in various stress conditions has been known for over half a century [1]. Peripheral catecholamines increase glycogenolysis mediated by α -adrenoceptor via calcium and β -adrenoceptor via cAMP, while catecholamines have a dual effect on insulin secretion, they inhibit insulin secretion via α_2 -adrenoceptors and stimulates it via β -adrenoceptor. However the net effect is usually inhibition [12]. The hypothalamic-growth hormone axis is particularly sensitive to the effect of stress. Human stress has a stimulatory effect on growth hormone [14, 15]. Growth hormone decreases glucose uptake by peripheral tissues and induces a form of secondary diabetes mellitus. Decreasing of glucose uptake occurs as a result of desensitization of insulin receptors by growth hormone. Growth hormone decreases glucose uptake by peripheral tissues and induces a form of secondary diabetes mellitus. Decreasing of glucose uptake occurs as a result of desensitization of insulin receptors by growth hormone. An additional inhibition of glucose uptake is refers to increased level of free fatty acids secondary to more rapid lipolysis in adipose tissue [12, 13]. A number of factors that increase in stress and inhibit the release of insulin and /or antagonize it's biological activities, like catecholamines, growth hormone and glucocorticoids,

stimulate glucagon, which is the most important physiological stimulus for glycogen degradation and release of glucose from the liver. its acts through its specific membrane receptors to increase adenylate cyclase activity and through cAMP to increase protein kinase activity, therefore systemic administration of glucagon induces a sharp increase in plasma glucose level [12, 16].

Elevation of brain CA during stress also stimulates thyroid stimulating hormone (TSH) secretion via interaction with α -adrenoceptors [17-19]. Krulich and colleagues [19] suggested that the effect of α -adrenergic tone on TSH secretion may be mediated via stimulation of thyroid releasing hormone (TRH) from hypothalamus, since both basal serum TSH level and the TSH response to TRH are declined by α -adrenoceptor bloker, phentolamine, and not affected by β -adrenoceptor blockers [17].

On the other hand prolonged administration of thyroid extract produced metathyroid diabetes, in addition human diabetes state is aggravated by hyperthyroidism and ameliorated by thyroidectomy [20], so that thyroid hormones are insulin antagonists [12]. Therefore hyperglycemia is one of the common manifestations of thyrotoxicosis [21].

Many data show that prolactin, both in animals and humans, is a true stress hormone as it is sensitive to various stressors [22]. Acute stress such as that occurring during obstetric and gynecologic intervention increases prolactin release [23, 24]. Prolactin has been shown to have diabetogenic effect in human [12, 25, 20]. It antagonizes insulin effect [12].

Elevation of peripheral CA during stress exerts inhibitory effect on secretion of somatostatin via α -adrenoceptor mechanism, by this mechanism CA abolishes the inhibitory effect of somatostatin on plasma ACTH, growth hormone and plasma glucose level [12].

As a result, all the above biochemical events associated with stress, induce a high degree of hyperglycemia with a decrease in insulin dependent peripheral glucose utilization. As a result, elevation of plasma glucose level can't exert stimulatory effect on insulin release (which has been under many inhibitory effects).

Hyperglycemia and Brain Gamma Aminobutyric Acid:

Under these conditions we postulate that glucose utilization by non-insulin dependent tissues is increased. One of these tissues is central nervous system, since all nervous tissues except ventral hypothalamus do not require the presence of insulin for glucose utilization and

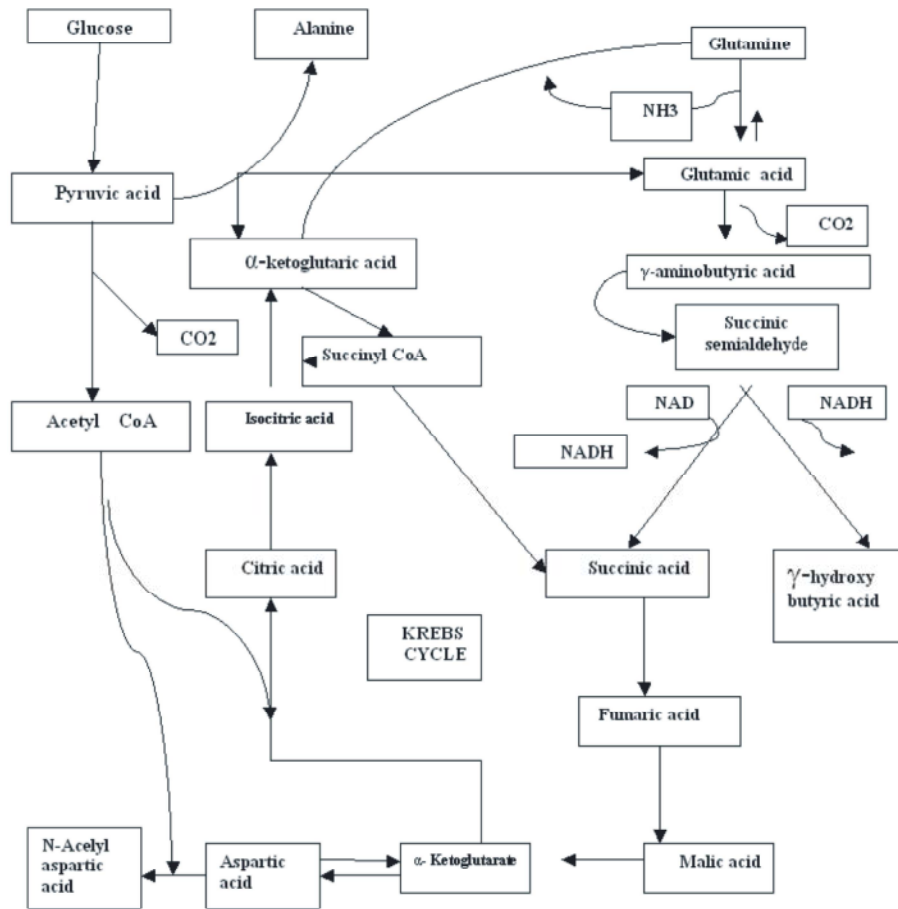


Fig. 1: The precursor of GABA, L-glutamic acid can be formed from glutamate by transamination from α -ketoglutarate

metabolism [27]. Increase of brain glucose level subsequently increase synthesis of gamma amino butyric acid (GABA) the evidences of this postulate were obtained from many previous studies.

Studies with (C14)-labeled glucose both *in vitro* and *in vivo* have indicated that carbon chain of GABA can be derived from glucose. Since GABA is intimately related to oxidative metabolism of carbohydrates in central nervous system by means of a (shunt) involving its production from glutamate. Its transamination with GABA- α -Ketoglutarate transaminase yielding succinate semialdehyde and regeneration glutamate [28]. The metabolism of GABA and its relationship to Krebs cycle and carbohydrate metabolism is mentioned in Figure 1.

Severe hyperglycemia seen at 5-minute following intravenous glucose injection produced a significant elevation of brain GABA, which is reflected in elevation of the minimum seizure threshold [29]. A previous study postulated that the lowering of seizure threshold occurs as a result of elevation of brain glycogen and ATP as an

energy source [30]. These results give strong evidence that the lowering of minimum seizure threshold related to increase synthesis of GABA and not to utilization of glucose as a source of energy for neurons. So the elevation of brain GABA is the same cause which reduces susceptibility and severity of seizures in the patient with diabetes mellitus [29, 31].

During hypoglycemia there is a marked reduction in the brain GABA level and this reduction is associated with increased brain excitability and level-dependent decreased seizure threshold [32, 23].

Effect of Brain GABA Elevation on Stress Mediators:

Elevation of GABA as a result of hyperglycemia, has inhibitory effect on the secretion of brain catecholamines, therefore GABA-agonist, such as benzodiazepines and barbiturates used effectively as antianxiety drugs in medical practice nowadays [34].

The inhibitory effect GABA on ACTH-cortisol secretion is obtained by acute and chronic administration of GABA degradation inhibitors such as sodium valproate

(GABA-transaminase inhibitor) and GABA-agonist such as diazepam [35]. Elevation of ACTH and increment of plasma cortisol following injection of CRH were depressed during antiepileptic treatment [36-39]. Furthermore, administration of GABA-agonists, baclofen or γ -vinyl-GABA in healthy subject decreases baseline plasma cortisol values and the response to insulin hypoglycemia [40]. GABA also induced reduction in the central serotonin activity [41]. Which increases during stress and exerts stimulatory effect on excretion of ACTH. previous study showed that GABA-agonist compounds inhibit secretion of growth hormone when given for prolonged time [42]. However, an opposite result was obtained by acute injection [36, 37]. GABA also inhibits prolactin secretion [43]. The rise in serum prolactin concentration induced by administration of haloperidol or morphine (to male rats) and during estrogen treatment (in ovariectomized female rats) as reduced by systemic injection of GABA-agonists, muscimol [44].

On the other hand injection of GABA or its agonists blunt the release of TSH in response to TRH [45, 46]. Diazepam has a pronounced inhibitory effect on triiodothyronine and thyroxine [47], while administration of GABA-agonists such as bicucullin and picrotoxin completely abolish the inhibitory effect of GABA administration on TSH response to TRH [48].

Therefore, we postulate that GABA is elevated as a result of hyperglycemia inhibits all stress mediators and subsequently decreases plasma glucose level, which in turn decreases GABA synthesis and abolishes its inhibitory effect on stress.

Therefore, the negative feedback mechanism between central GABA and catecholamine represent a resistant mechanism against stress and the pathological state may occurs as a result of desensitization of the receptors of mediators [1, 22].

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