NUTRACEUTICAL RESEARCH

Review Article

# Tryptophan in the Serotonergic Control of Pancreatic Functions in Stress: Implications for type 2 Diabetes

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**ABSTRACT**

Type 2 diabetes (T2D), a metabolic disorder, is highly prevalent in every society and people of every economic status are affected. Stress related epigenetic factors are known to increase risk for diabetes. Treatment response of this lifelong metabolic disorder highly depends on comorbid conditions, which worsens the treatment outcome and increases mortality. Novel, comorbidity related, drug targets for treating diabetes are therefore highly needed. In this context, a role of serotonin (5-hydroxytryptamine; 5-HT), a biogenic amine seems important. Acting centrally, serotonin is implicated in a number of stress related mental illnesses. The synthesis of serotonin also occurs intracellularly in the pancreatic beta cells, where it is co-localized with insulin and regulates serotonylation-dependent insulin secretion. In addition, serotonin present in the blood circulation can also modulate insulin release from beta cells through autocrine and paracrine signals. The synthesis of serotonin depends upon the availability of its precursor tryptophan, which is an essential amino acid. Tryptophan obtained from dietary proteins is largely utilized via hepatic kynurenine pathway. Evidence suggests that stress-induced sustained increases of circulating glucocorticoid (GCs) can further enhance utilization of tryptophan via kynurenine pathway; the availability of tryptophan for serotonin synthesis is therefore decreased. This article targets effects of stress-induced sustained increases of GCs on circulating tryptophan and intracellular serotonin in the pancreatic beta cells and suggests that together with blood glucose levels, circulating levels of serotonin, tryptophan and kynurenine should be considered as biochemical markers for therapeutic intervention in diabetes.

**Keywords:** Pancreas, Stress, Serotonin, Diabetes, Glucocorticoids, Tryptophan, Kynurenine



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## INTRODUCTION

Type 2 diabetes (T2D) is a metabolic disease which is highly prevalent in every society and people of every economic status are affected [1]. It is a life time disease which arises because of deficits in the secretion of insulin or its action. Together with exercise, weight and dietary control, insulin injections and oral glucose lowering compounds are prescribed for diabetes patients. Most of these oral treatments are associated with adverse effects such as weight gain, hyperinsulinemia, muscle weakness and increase in LDL cholesterol [2]. Insulin is usually added to an orally prescribed drug if glycemic control is not adequate [3]. Insulin therapy is also associated with hypoglycemia and weight gain [3]. In addition, treatment response of this lifelong disease highly depends on comorbid conditions such as obesity and depression [4-5]. The co-morbidity of diabetes with depression or obesity or both [4] worsens the treatment outcome and increases mortality. Novel drug targets for treating this metabolic disease are therefore highly needed.

Serotonin (5-hydroxytryptamine; 5-HT), a biogenic amine, is synthesized in the brain as well as in the peripheral tissues. It acts as a neurotransmitter in the brain and is highly involved in responses to stress, depression, obesity and therapeutic effects of antidepressant as well as antiobesity drugs [6-7]. In addition, an association of stress with type-2 diabetes is also becoming increasingly recognized. Evidence suggests that epigenetic /environmental factors which produce stress enhance risk not only for mental illnesses but a risk of type-2 diabetes is also increased [8].

Preclinical investigations are also indicative of a link between diabetes and stress. Thus, experimental diabetes produced by the administration of streptozotocin was also associated with the expression of depression like behavior, and it was reversed by insulin [9]. Exposure to chronic mild stress produced depression like behavior of higher intensity in diabetic than non-diabetic rats [10]. Moreover, rats exposed to repeated immobilization stress and chronic unpredictable mild stress exhibited progressively disturbed glucose metabolism [11]. Treatment with some oral hypoglycemic agents decreased incidents of depression in diabetic patients [12], and modulated anxiety/depression like behavior in experimental animals [13-14]. In addition, serotonin has been also shown to have a role in the amelioration of glycemic and renal profiles, and in the modulation of sympathetic tone in type 1 diabetes in rats [15].

It is now well established that exposure to an acute stress episode triggers activity of hypothalamic-pituitary-adrenal (HPA) axis. This results in an increase in the release of glucocorticoid (GC) hormones from the adrenal cortex, which helps in enhancing energy production to meet the stress demand. On the other hand, chronic stress-induced long-term increases of GCs produce deficits in serotonin neurotransmission to play an important role in the precipitation of mental illnesses [16].

Evidence supports an association of T2D not only with stress but also with circulating GCs [16]. These steroid hormones regulate multiple aspects of glucose homeostasis such as gluconeogenesis, glycogenolysis, and glucose uptake by tissues and release of insulin and glucagon from the pancreas. The increases of circulating GCs following exposure to an acute stress episode and their effects on glucose homeostasis are considered adaptive as these effects help preserve circulating glucose for brain during stress. On the other hand, persistent increases of GCs, which occur during chronic stress, produce physiological and transcriptional dysregulation [16] of enzymes involved in glucose metabolism to lead to type-2 diabetes.

In addition, there is evidence that plasma tryptophan concentration is also reduced when circulating GCs are higher [17]. This occurs because hepatic utilization of tryptophan is highly enhanced in presence of GCs. A large part of circulating tryptophan is normally utilized via kynurenine pathway located in the liver. GCs are known to produce an increase in the activity of enzymes which metabolize tryptophan via kynurenine pathway [18] to potentially reduce available tryptophan for the synthesis of serotonin and release of insulin from pancreatic beta cells. Co-localized with insulin in the pancreatic beta cells; serotonin is known to regulate insulin secretion through serotonylation [19].

In view of improving therapy in diabetes, the present article addresses potential mechanism involved in the effects of stress or of circulating GCs on the availability of tryptophan for serotonin synthesis and on serotonergic control of pancreatic functions, which have been given little attention. Hopefully, the understanding of this mechanism will help to develop better treatment strategies and novel pharmacological agents for treating T2D and diminishing escalating rise of this life-long disease.

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## SEROTONIN SYNTHESIS AND FUNCTIONS

Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from the essential amino acid l-tryptophan (Figure 1). The synthesis takes place in two steps in the presence of a hydroxylase (tryptophan hydroxylase; TPH) and a decarboxylase (L-aromatic amino acid decarboxylase; AADC) [20]. It is synthesized in the brain as well as in the peripheral tissues but central and peripheral pools of serotonin is separated from each other by blood brain barriers (BBBs). TPH, the rate limiting enzyme of serotonin synthesis is present only in cells that synthesize serotonin. Peripheral TPH (TPH1) and central TPH (TPH2) encoded by different genes, synthesize 5-HT from peripheral and centrally available tryptophan. Central 5-HT is synthesized largely in the midbrain and hindbrain raphe neuronal cells and functions as a neurotransmitter to play an important role in emotional control [21]. Serotonergic system is therefore targeted for treating depression, anxiety and psychosis. In addition, it is also highly involved in the elicitation of satiety signal and onset of sleep. Serotonin is also synthesized in the enteric nervous system, where it acts to largely affect neural modulation of gut smooth muscles and bowl function.

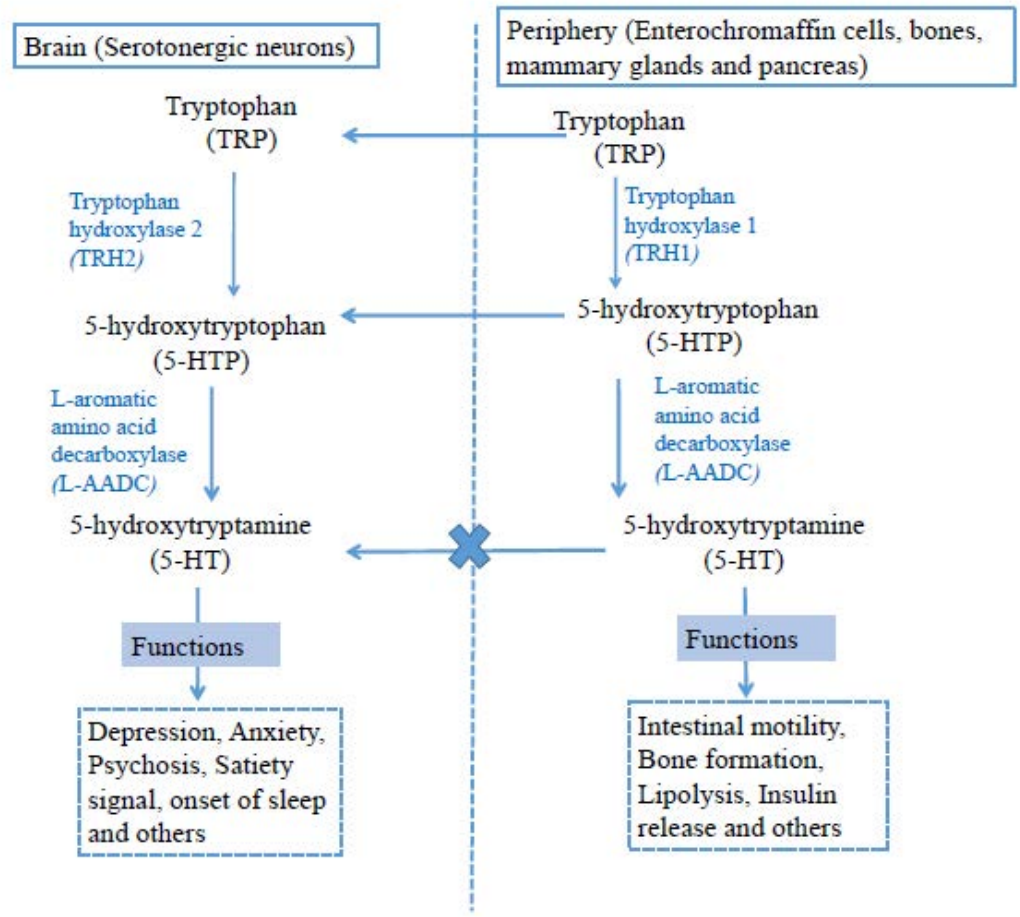


**Figure 1.** Synthesis of serotonin from tryptophan in the brain and in the peripheral tissues and their important functions: The enzyme TRH1 and TRH2 are highly localized in the serotonin producing cells and this is the slowest (rate limiting) step of biosynthesis. Therefore 5-HTP is produced only in serotonin producing cells but L-AADC is present in nearly all tissues and can convert 5-HTP to 5-HT almost immediately. Tryptophan and 5-HTP can cross blood brain barriers but 5-HT cannot, therefore central and peripheral pools of 5-HT are separate. Some important functions of central and peripheral 5-HT are also shown.

Peripherally serotonin is synthesized in many tissues such as bone, mammary glands, the pancreas, but the enterochromaffin cells (ECs) of gastrointestinal (GI) epithelium is the major site where about 90% of serotonin synthesis occurs [22]. Stored in the blood platelets it is released at different tissue sites including the pancreas to control many serotonin- mediated



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functions. Peripheral functions of serotonin include intestinal motility, bone formation, lipolysis and others including insulin release from the pancreatic beta cells [23]. The synthesis of 5-HT also occurs in the pancreatic beta cells, where it is stored and released with insulin. Intracellular 5-HT, stored with insulin, regulates insulin exocytosis while extracellular 5-HT acts via 5-HT receptors to modulate insulin secretion [24]. Degradation of central as well peripheral serotonin occurs by monoamine oxidase (MAO) and aldehyde dehydrogenase (ADH) to 5-hydroxyindole acetic acid (5-HIAA), but in the periphery serotonin is also metabolized by glucuronidation.

Centrally produced serotonin represents only 5% of its total synthesis, while most of the serotonin is produced in the peripheral tissues. About 98% of entire serotonin is present in the peripheral tissues, but it cannot pass through the blood-brain barrier making the two systems functionally independent [22]. Tryptophan, the sole precursor of peripherally and centrally produced serotonin [25], is obtained (Figure 2) from dietary proteins [26]. Plasma levels of tryptophan play an important role in the regulation of 5-HT biosynthesis [25].

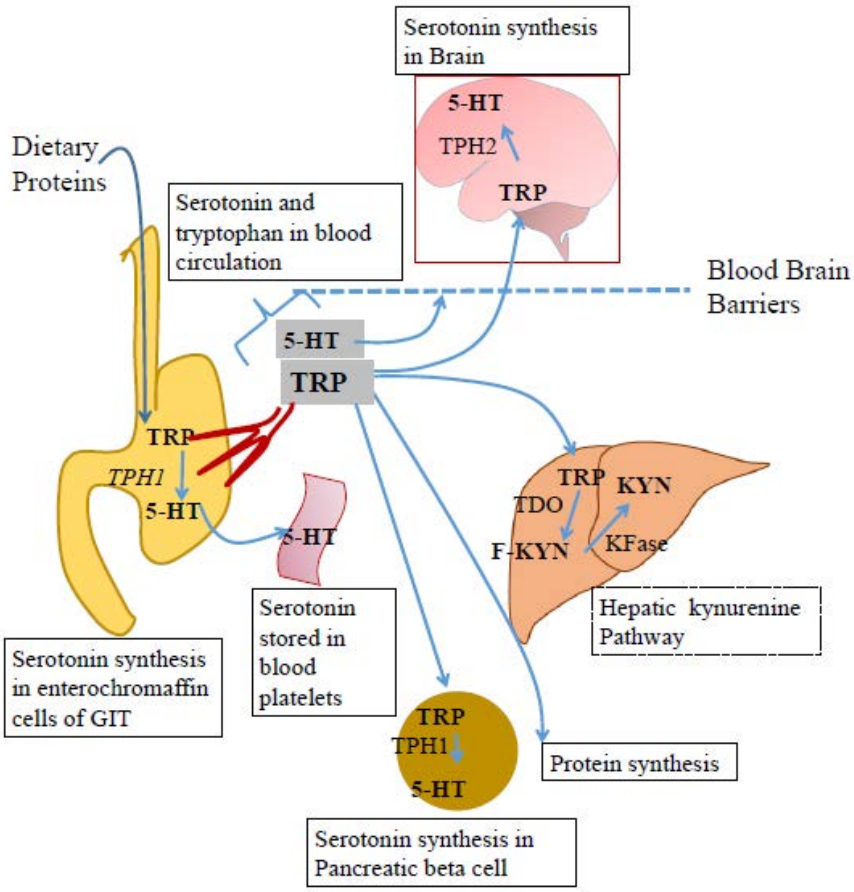


**Figure 2.** Schematic diagram showing the utilization of dietary tryptophan for serotonin synthesis in the periphery and in the brain. The source of tryptophan is dietary. Synthesis of serotonin from tryptophan in the enterochromaffin cells of the GIT, pancreatic beta cell and serotonergic neuron is also shown. It is not synthesized in the blood platelets but taken up by platelets it is transported to various tissue sites. Tryptophan is also essential for protein synthesis but quantitatively its utilization via kynurenine pathway is most important. Tryptophan (TRP); 5-Hydroxytryptamine (5-HT; serotonin); Tryptophan hydroxylase (TPH), tryptophan 2,3-dioxygenase (TDO); Kynurenine (KYN), formyl-kynurenine (F-KYN); Kynurenine formamidase (Kfase).

An essential role of circulating tryptophan is to provide a pool for the synthesis of proteins (Figure 2). But quantitatively, most prevalent metabolic pathway of tryptophan is the synthesis of kynurenine, which accounts for approximately 90% of tryptophan degradation in the liver [18,27]. In the first step of this pathway tryptophan is oxidized to N-formylkynurenine in presence of enzymes tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO) which is then

hydrolyzed to stable compound, kynurenine in presence of enzyme kynurenine formamidase [27]. TDO, the first enzyme of tryptophan catabolism, is present primarily in the liver, and is highly activated by circulating GCs. Physiological or pharmacological activation of kynurenine pathway decreases circulating tryptophan because a large part of tryptophan is metabolized via kynurenine pathway; serum serotonin levels are also reduced [28,29].

## SEROTONIN IN PANCREATIC ISLETS

The co-localization of serotonin with insulin in pancreatic islets was reported in 1968's [30]. Later studies showed that serotonin was released together with insulin from pancreatic beta cells during glucose stimulated insulin secretion (GSIS) and that synthesis of serotonin from tryptophan also occurred locally in these cells [24,31-32]. Studies reporting presence of enzymes for 5-HT synthesis and break down in the pancreatic beta cells [33-36] also supported the idea that 5-HT was synthesized locally in these cells.

Both TPH1 and TPH2 are present in pancreatic beta cells [32,36-37]; but there is evidence that TPH1 selectively catalyzes the first step of 5-HT biosynthesis in these cells. Thus, an inhibition of TPH1 activity resulted in inhibition of 5-HT secretion from beta cells [33]. 5-HT synthesized locally in pancreatic beta cells is stored in secretary granules and released with insulin [36]. Released serotonin can be efficiently taken up by an efficient reuptake mechanism [33], while enzymes which can convert 5-HT to 5-HIAA, MAO-A and MAO-B are also present in pancreatic beta cells [36]. In addition, known types and subtypes of 5-HT receptors are expressed in pancreatic islets [33,38-40] suggesting that the release of serotonin and insulin from pancreatic beta cells is dependent on 5-HT receptor dependent signals. Substantial evidence supports the notion that serotonin synthesized intracellularly in the beta cells as well as that present extracellularly can control insulin secretion [40,41].

## MECHANISM OF GLUCOSE STIMULATED INSULIN SECRETION (GSIS)

Pancreatic islets are parts of the pancreas having groups of spherical endocrine cells clusters surrounded by supporting mass of exocrine cells [42]. Hormones produced in pancreatic islets are secreted directly into the blood stream. Pancreatic beta cells which make up 65-80 percent of total islets produce insulin, an anabolic hormone, which controls storage of carbohydrates and lipids. The stimulus for insulin release is an increase in the concentration of glucose in circulating blood. The released hormone facilitates glucose uptake and utilization by peripheral tissues and circulating glucose concentration is maintained within normal range. Glucagon, a hormone produced by the alpha-cells of pancreatic islets, is released in response to low levels of glucose in circulation. It acts to facilitate glycogen lysis; glucose stored in the liver as glycogen is therefore released to prevent blood glucose levels dropping too low. About 15-20 percent of total pancreatic islets are comprised of alpha cells. Other cell types namely delta cells, gamma cells and epsilon cells are also present which produce somatostatin, pancreatic polypeptide, and ghrelin [43].

Insulin release is tightly regulated by mechanisms sensing blood glucose which enters in the beta-cell through a glucose transporter [44]. Intracellular metabolism of glucose generates ATP; this results in the shutdown of ATP-sensitive potassium channels (KATP-channels) and subsequent depolarization of plasma membrane of the beta-cell. Consequently, voltage-dependent calcium channels (VDCC) open, allowing influx of calcium ions in the beta cell. This is followed by an enhanced release of calcium ions from the endoplasmic reticulum. Higher intracellular calcium triggers exocytosis accompanied by insulin release [45]. Thus, postprandial increases of plasma glucose enhance insulin secretion, which acts to reduce hepatic glucose production and facilitate glucose uptake by skeletal muscles and adipose tissues [46].

## INTRACELLULAR SEROTONIN AND THE CONTROL OF INSULIN SECRETION

In vitro studies conducted during 1970s and 1980s suggested a role of serotonin in the control of insulin secretion from beta cells. Later studies reported that in conditions which impose greater metabolic need, more 5-HT is synthesized in the islet to enhance insulin secretion for maintaining glucose homeostasis. Thus more 5-HT is synthesized in beta cells during pregnancy and following intake of high fat food [33,47]. Enhanced 5-HT synthesis in these conditions has been shown to depend on 5-HT2B receptor signals. These studies show greater expression of 5-HT2B receptor mRNA and enhanced beta cell growth in pregnant rodents [39], while SB204741, a specific 5-HT2B receptor antagonist has been shown to block these effects during pregnancy. Factors which decrease 5-HT synthesis, such as restricting dietary intake of tryptophan or

inhibiting TPH activity has been also shown to block beta cell growth and impair glucose homeostasis in pregnancy [48].

Another supporting evidence is expression of diabetes like symptoms in mice deficient in TPH1 (Tph1−/−) [24, 49]. Moreover, factors which increase 5-HT synthesis, such as systemic administration of 5-hydroxytryptophan (5-HTP) and pargyline, which respectively are serotonin precursor and MAO inhibitor and increase intracellular 5-HT, produce a speedy hypoglycemic effect and rapid rise in plasma insulin in mice [24].

The enzyme TPH1 is also rate limiting enzyme of serotonin biosynthesis in the enterochromaffin cells of the GIT. Selective deletion of TPH1 in the enterochromaffin cells produces no effect on insulin levels. Conversely, selective deletion of TPH1 in the pancreatic beta cells is reported to decrease circulating insulin and impair glucose tolerance in mice [48]. Moreover, intracellular serotonin concentration in these animals has been found to correlate positively with insulin secretion, thereby strengthening the view that intracellularly synthesized serotonin enhances insulin secretion. The mechanism of intracellular 5-HT dependent insulin secretion is shown to be a receptor-independent covalent coupling of 5-HT with the small GTPases Rab3a and Rab27a [24]. The coupling called serotonylation promotes insulin granule exocytosis (Figure 3).

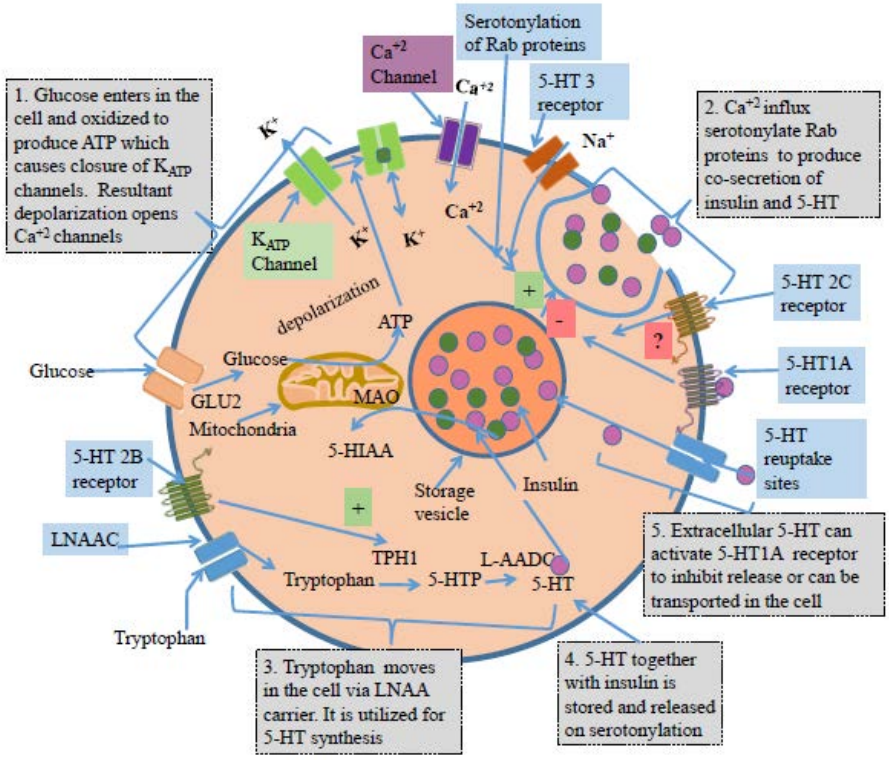


**Figure 3.** Schematic diagram of a beta pancreatic cell showing intracellular 5-HT synthesis, storage and release with insulin. Tryptophan taken up by beta cells is utilized for 5-HT synthesis which is stored in vesicles with insulin. Glucose transported via GLU2 produces ATP, which causes closure of KATP channel to generate depolarization potential. This opens voltage dependent Ca+2 channel and influx of Ca+2 produces serotonylation of proteins essential for insulin release by exocytosis. 5-HT co-released with insulin is either transported back via high affinity transporters or remains extracellularly to activate receptors on the beta cells. Activation of 5-HT2B receptors enhances beta cell proliferation and 5-HT synthesis. 5-HT3 receptor activation enhances serotonylation and co-release of insulin and 5-HT. Activation of 5-HT1A receptors (negatively coupled with adenylate cyclase) decreases co-release of insulin and 5-HT.

An increase in pancreatic beta cell production and enhanced insulin release during pregnancy is also associated with greater expression of TPH and enhanced serotonin concentration in these cells [48]. High-fat diet–fed mice with selective deletion of beta cell TPH1 exhibit a progressively impaired glucose tolerance and deficits of in insulin secretion, suggesting that 5-HT produced in beta-cells plays an essential role in insulin release.

## EXTRACELLULAR SEROTONIN IN THE MODULATION OF PANCREATIC FUNCTION

Not only intracellular but extracellular serotonin has been also shown to modulate insulin. These studies are relevant that serotonin can produce a stimulatory or an inhibitory effect on insulin release. The finding that a decrease in insulin secretion from rat insulinoma cell line (INS1) occurs following application of serotonin directly on these cell lines [24] suggests that 5-HT present extracellularly in circulation can reduce insulin secretion. When serotonin is applied directly to non-diabetic human islets, it results in an inhibition of insulin as well as glucagon secretion. This effect of serotonin is highly reduced in islets from T2D individuals [33,40], suggesting impaired 5-HT dependent signaling in T2D.

Serotonin is known to act through at least seven types and fifteen subtypes of receptors. These 5-HT receptors except 5-HT3 are G protein coupled receptors. The 5-HT3 receptor is a ligand gated ion channel (Table 1 and Figure 3). Gene and protein expression studies show presence of 5-HT1A, 5-HT1D, 5-HT1F, 5-HT2B and 5-HT3 receptors on pancreatic islets. These studies show that 5-HT1A, 5-HT1D, 5-HT2B and 5-HT3 receptors are primarily expressed on beta cells, [34-37] while 5-HT1F receptors are expressed on alpha cells [33].

**Table 1.** 5-HT receptor mediated influences on the secretion of insulin or glucagon

| Receptor Type | G protein or ion channel | Localization on pancreatic islets | Effect on insulin or Glucagon release | Reference |
|---|---|---|---|---|
| 5-HT1A | Gi | Primarily on beta cells but also on alpha cells | Inhibit insulin secretion | [24,40] |
| 5-HT1D | Gi | Primarily on beta cells but also on alpha cells | Inhibit insulin secretion | [40,51] |
| 5-HT1F | Gi | Primarily on alpha cells | Inhibit glucagon secretion | [33] |
| 5-HT2A | Gq | Primarily on beta cells but also on alpha cell | Enhance insulin secretion | [40,51] |
| 5-HT2B | Gq | Beta cells | Enhance insulin secretion and beta cell expansion | [33,39,47] |
| 5-HT2C | Gq | Beta cells | Inhibit insulin secretion | [40,41] |
| 5-HT3 | Ca | Beta cells | Enhance insulin secretion | [34,48,50] |

The inhibitory effects of extracellular 5-HT on insulin release are produced by the stimulation of 5-HT1A receptors located on pancreatic beta cells [24,40] which subsequently decreases membrane depolarization (Figure 3). The other type of receptor present on pancreatic beta cells is 5-HT3 receptor. Activation of this receptor type depolarizes plasma membrane of pancreatic beta cells, resulting in the facilitation of voltage-dependent calcium entry for promoting insulin exocytosis (Figure 3). The finding that mice deficient in 5-HT3 receptor become glucose intolerant during pregnancy [50] also supports a role of 5-HT3 receptor in GSIS. Other investigations on the role of 5-HT3 receptor in GSIS report that 5-HT3 receptor knockout mice if challenged with a high-fat diet display impaired first phase insulin secretion in vitro [34,48].

Activation of 5-HT2C receptors on beta cells is also linked with a decrease in insulin release. These investigations show that the expression of 5-HT2C receptor is higher in pancreatic islets of diabetic mice, while administration of a 5-HT2C antagonist produces a dose-dependent increase in insulin secretion from these cells [40,41]. These studies therefore tend to suggest that an upregulation of 5-HT2C receptor in pancreatic beta cells can reduce insulin secretion in diabetes. Greater expression of 5-HT1D and 5-HT2A receptor in beta as well as alpha pancreatic islets is reported to occur in type 2 diabetes [51].

Altogether, unlike intracellular serotonin which produces an increase in insulin release by serotonylation or due to an increase in beta cell mass, extracellular serotonin can enhance or inhibit insulin release. Activation of 5-HT1A and 5-HT2C receptors is linked with a decrease in insulin release, while 5-HT3 receptor activation produces tonic influence on membrane depolarization and consequently on insulin release. Pancreas also receives serotonergic input from vagus and enteric nervous system. Serotonin released from these intra-pancreatic nerves can enhance or attenuate insulin release depending on the expression 5-HT receptors on beta-cells.

There is evidence that serotonin can also change glucagon secretion from pancreatic alpha cells. Serotonin released with insulin from beta cells can act on neighboring alpha cells to inhibit glucagon release. This effect of serotonin is produced by the activation of 5-HT1F receptor and subsequent decrease in intracellular cAMP resulting in an inhibition of glucagon secretion. A diminished serotonergic control of alpha cells enhances glucagon secretion to produce glucose blindness and diabetes [33].

## ACTIVATION OF HPA AXIS: A PHYSIOLOGICAL RESPONSE TO STRESS

Roles of HPA axis and of sympathetic nervous system in responses to stress are well established [16]. Stress activates HPA axis (Figure 4) resulting firstly in an enhanced formation and release of corticotrophin releasing factor (CRF) from the hypothalamus. CRF acts on the pituitary to increase adrenocorticotrophin (ACTH) production and release, which subsequently acts on the adrenal glands to increase production of GCs and mineralocorticoids (MCs) hormones from its cortical region [52]. Long term increases of circulating GCs can produce insulin resistance to lead to diabetes [16].

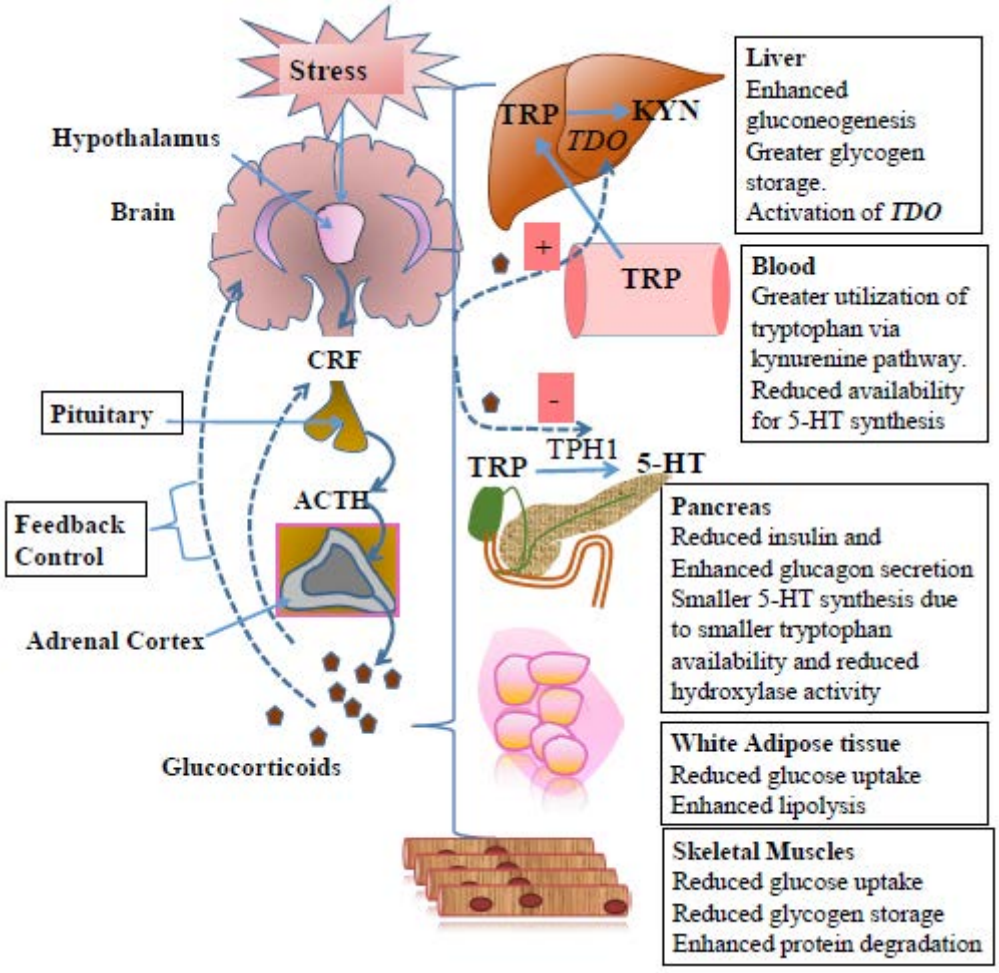


**Figure 4.** Stress-induced increases in circulating glucocorticoids and their subsequent effect on glucose homeostasis and 5-HT synthesis in the pancreatic beta cells. Stress activates hypothalamic-pituitary-adrenocortical (HPA) axis, resulting in an increase in levels of circulating glucocorticoids (GCs). Repeated stress decreases the efficacy of GC-mediated feedback control over the HPA axis to produce a sustained increase in circulating GCs and sustained hyperglycemia. Tryptophan levels in the circulation are reduced because of its greater utilization via hepatic kynurenine pathway. Synthesis of serotonin in beta cells is reduced because of a decrease in the activity of tryptophan hydroxylase and smaller tryptophan availability. Abbreviations: ACTH, adrenocorticotrophin; CRF, corticotropin-releasing factor; TRP, tryptophan; TPH1, tryptophan hydroxylase 1; TDO, tryptophan 2, 3-dioxygenase; 5-HT, 5-hydroxytryptamine.

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Cortisol is the main GC in humans while corticosterone is the GC of rodents and the synthesis of these steroid hormones take place from cholesterol [53]. Their synthesis and release in to the blood circulation follows a characteristic circadian pattern; according to which it is higher in the morning and smaller in the evening. These hormones play a highly significant role in maintaining energy balance and metabolic demand in response to stress stimuli as well as in normal conditions [54]. A stress episode increases circulating GCs, which mobilize glucose and fatty acids to provide more energy to meet the stress requirement. Shortly thereafter, a fast feedback regulatory mechanism at the level of hypothalamus and pituitary is activated to restore energy balance and terminate GC response to stress [55]. Thus, in animals exposed to a 2nd stressor, a little later after the first episode of stress, increases of CRF as well as GCs are not very high suggesting that this fast feedback effect is mediated via receptors in the hypothalamus. Exogenous GCs if administered immediately before exposing to stress also produce similar reduction in stress-induced increases of GCs. It has been also shown that these short-term effects of GCs are not produced by the changes at the level of transcriptional factors; and that transcriptional modulation takes place after long-term exposure to GCs.

## GLUCOSE HOMEOSTASIS IN STRESS

An important role of GCs in stressful condition and also in starvation is to facilitate sustained supply of glucose for the brain. This goal is achieved (Figure 4) by decreasing glucose uptake, primarily by the skeletal muscles and adipose tissue, and promoting gluconeogenesis in the liver. That GC receptor signaling is essential for glucose homeostasis has been also shown suggesting an essential role of GCs in glucose homeostasis. Following termination of GC-response to an acute stress via fast feedback control [56], effects of stress on glucose homeostasis are also terminated. On the other hand, chronic stress downregulates fast feedback regulatory control on the activity of HPA axis, and stress effects on circulating GCs become long lasting [56]. These sustained higher circulating GCs producing sustained hyperglycemia leads to diabetes.

The metabolic effects of GCs on glucose homeostasis are opposite to that produced by insulin. Insulin facilitates glucose utilization by changing the activities of metabolic pathways at the level of transcription, translation or at post-translational stage [57]. GCs interfere with these signaling cascades to reduce insulin-mediated cellular uptake of glucose and its utilization by skeletal muscles. Excessive increases of GCs therefore counteract the effects of insulin on glucose disposal to lead to hyperglycemia. For example, insulin increases utilization of glucose by skeletal muscles and adipose tissue, while GCs reduce it. A number of studies show that GCs enhance hepatic glucose production while insulin is known to inhibit it [58]. In addition, evidence suggests that GCs impair serotonin mediated pancreatic functions to predispose to diabetes in chronic stress (Figure 4).

## STRESS AND GLUCOCORTICOIDS IN THE SEROTONERGIC CONTROL OF BETA CELL FUNCTION

Considering that intracellular as well as extracellular serotonin can modulate insulin secretion from the beta cells as well changes in beta cell are also produce [24], it becomes objectively important to understand the effect of GCs on serotonin level. There are reports that the expression and activity of enzymes TPH1 and TPH2, as well as serotonin synthesis in pancreatic islets are highly reduced in mice treated with GCs [58]. Conversely, an increase in the expression of both of these 5-HT synthesizing enzymes in mice deleted for GR in the pancreas has been also shown. These studies suggest that chronic stress and associated long-term enhancements in circulating GCs can decrease intracellular 5-HT stores in beta cells. A subsequent decrease in insulin secretion can therefore produce hyperglycemia and diabetes.

Apart from a decrease in the activity of TPH (Figure 4), another factor which plays a pivotal role in decreasing intracellular serotonin in pancreatic islets in stress is the availability of tryptophan. Major portion of tryptophan which is present in blood circulation is metabolized to kynurenine in the liver. Chronic stress-induced sustained increases of GCs causing sustained activation of kynurenine pathway [59,60] can potentially reduce availability of tryptophan for 5-HT synthesis. A decrease in serotonin synthesis therefore occurs not only in the brain [25] but is also expected to occur in the pancreas (Figure 4).

A single exposure to acute stressor such as immobilization stress, cold stress and forced running, increases TDO activity in the liver. The effect is produced by the GCs released from HPA axis in response to stress [62]. Thus, administration of a high-dose GC hormone, such as hydrocortisone or dexamethasone, produces an increase in TDO via transcription of the gene coding for TDO in the liver [18]. Moreover, exposure to 2h/day restraint stress for 10 days resulted in an enhancement

in the circulating corticosterone and decrease in tryptophan concentration in rats, while the expression of TDO in the liver and cerebral cortex also increased [62]. In addition, co-treatment with allopurinol, a TDO inhibitor, resulted in a reduction in chronic stress-related increase in circulating kynurenine concentrations. These studies are relevant that chronic stress-induced depletion of circulating tryptophan can decrease intracellular serotonin in pancreatic beta cells to impair insulin secretion (Figure 4). Associated decrease in extracellular 5-HT can also modulate serotonin receptor mediated signals on pancreatic beta or alpha cells to modulate glucose homeostasis.

## CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion a large body of evidence supports the notion that extracellular as well as intracellular serotonin is involved in the control of pituitary function. Intracellular serotonin seems to enhance insulin release but extracellular serotonin can enhance or impair insulin release, which depends upon the type of 5-HT receptor activation. The activation of 5-HT3 receptor on pancreatic beta cells enhances depolarization dependent insulin release but activation of 5-HT1A as well as 5-HT2C receptor reduces insulin secretion. In addition, extracellular serotonin can also increase release of glucagon from pancreatic alpha cells.

Stress-induced increases of GCs can produce a direct effect on pancreatic function by impairing depolarization-induced serotonin release from the beta cells. In addition, GCs can reduce serotonergic tone by reducing the availability of tryptophan for serotonin synthesis and decreasing the activity of rate limiting enzyme of serotonin synthesis. It suggests that together with blood glucose levels, circulating levels of serotonin, tryptophan and kynurenine should be considered as biochemical markers for therapeutic intervention in diabetes. The knowledge contained here-in can help develop better treatment strategies and novel pharmacological agents for improving treatment of this life-long disease. Further, it is essential to note that the mechanism by which 5-HT can modulate insulin release and its effect on glucose homeostasis are not yet fully explored and exciting results from related future studies are highly needed. For example, GPR119, a cannabinoid receptor-like class A G protein coupled receptor is also highly expressed in pancreatic beta cells. GPR119 is activated with lipid metabolites and its activation has been shown to promote GSIS from beta cells [63]. Future studies on any potential relationship of GPR119 receptor activation and serotonin mediated signaling can further help identifying mechanism involved in GSIS from pancreatic islets.

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## DECLARATION OF INTEREST

The author reports that there is no conflict of interest

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