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GABA Supplementation and Growth Hormone Response

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Abstract

The secretion of growth hormone (GH) is regulated through a complex neuroendocrine control system, especially by the functional interplay of two hypothalamic hormones, GH-releasing hormone and somatostatin. These hormones are subject to modulation by a host of neurotransmitters and are the final mediators of endocrine and neural influences for GH secretion. Interest in the possible role of γ-aminobutyric acid (GABA) in the control of GH secretion began decades ago. However, interest in its role as an ergogenic aid is only recent. It is well accepted that GABAergic neurons are found in the hypothalamus and recent evidence suggests its secretion within the pituitary itself. Inhibition of GABA degradation and blockade of GABA transmission as well as administration of GABA and GABA mimetic drugs have all been shown to affect GH secretion. However, there are many controversial findings. The effects may depend on the site of action within the hypothalamic-pituitary unit and the hormonal milieu. Experimental and clinical evidence support the presence of a dual action of GABA – one mediated centrally, the other exerted directly at the pituitary level. The two sites of action may be responsible for excitatory and inhibitory effects of GABA on GH secretion. This chapter will outline the anatomical basis for possible influences of GABA on GH secretion and present evidence for a role of GABA in the control of GH release by actions at either hypothalamic or pituitary sites. The potential ergogenic benefits of oral GABA supplementation will also be discussed.

Growth Hormone

Growth hormone (GH) is a peptide hormone that plays an important role in the growth and maintenance of skeletal muscle, stimulating increases in muscle and cartilage protein synthesis, fatty acid use, and cellular amino acid uptake [1]. Secreted by somatotropic cells of the anterior pituitary, it exhibits a great deal of molecular heterogeneity and circulates in multiple forms, only some of which are biologically active [2]. This has physiological significance, as the different forms have been shown to have different effects on lipid, carbohydrate and protein metabolism. In the adult human, approximately five pulses of GH are secreted during a 24-hour

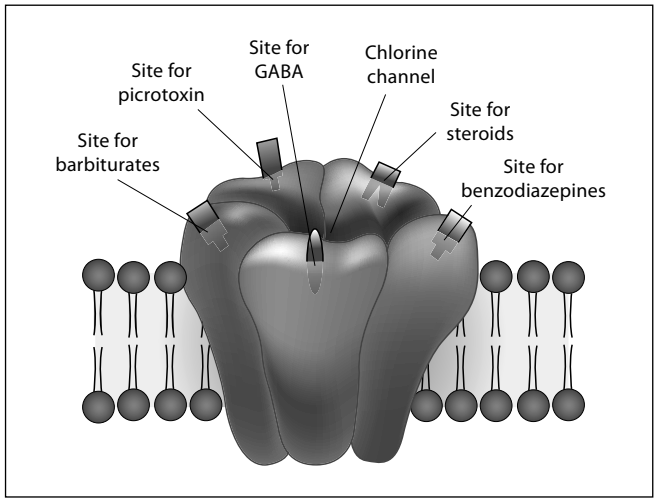

Fig. 1. The $GABA_A$ ligand-gated chloride ion channel receptor complex [from http://thebrain.mcgill.ca/flash/i/i_04/i_04_m/i_04_m_peu/i_04_m_peu.html].

period with a larger peak occurring at the onset of sleep at night [3]. However, several stimuli, including exercise [4] and amino acid administration [5] purportedly alter this pattern. GH secretion is regulated through a complex neuroendocrine control system that includes two main hypothalamic regulators, GH-releasing hormone (GHRH) and somatostatin (SS), exerting stimulatory and inhibitory influences, respectively, on somatotropic cells. Until recently, GH secretion was thought to be determined simply by the balance between these two hypothalamic peptides. It is now accepted that GH secretion is also influenced by other peptides produced in the periphery such as ghrelin [6]. Regardless of the stimulus, GHRH and SS are considered the final mediators of pituitary GH secretion and are subject to modulation by other hypothalamic peptides and by complex networks of neurons and neurotransmitters.

γ-Aminobutyric Acid

γ-Aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the central nervous system. Endogenously, it is synthesized from the decarboxylation of glutamate by the enzyme glutamic acid decarboxylase (GAD) and is metabolized to succinate by the sequential actions of GABA transaminase and succinic semialdehyde dehydrogenase. Neurons that secrete GABA are referred to as GABAergic neurons and have chiefly inhibitory actions, as receptor binding at pre- and postsynaptic membranes results in the opening or closing of ion channels. Two general classes of GABA receptors have been identified – $GABA_A$ (fig. 1) in which the receptor is part of a ligand-gated chloride ion channel complex [7], and $GABA_B$ metabotropic

receptors [8]. The $GABA_B$ receptors are guanine-nucleotide-binding proteins coupled to second messenger generating systems that open potassium channels. Thus, receptor binding generally results in the influx of negatively charged chloride ions or the efflux of positively charged potassium. $GABA_B$ receptor binding can also decrease the cell's conductance to calcium. More recently, a third GABA receptor has been suggested and labeled as $GABA_C$ [9]. Like $GABA_A$, it is part of a ligand-gated chloride channel complex. However, some simply consider it a subtype of the $GABA_A$ receptor complex, as a number of $GABA_A$ and $GABA_B$ subtypes have been identified [7, 8]. Once secreted, the synaptic actions of GABA are terminated by degrading enzymes and the high-affinity uptake systems (GABA transporters) of glial cells and neurons that can repackage it into vesicles [10].

Multiple feedback mechanisms control GABA concentration [11]. It is most highly concentrated in the substantia nigra and globus pallidus of the basal ganglia, followed by the hypothalamus, the periaqueductal grey matter and the hippocampus [12]. There are several ways of increasing GABAergic activity in the human brain and a number of GABA agonists have been identified, such as muscimol, benzodiazepines (e.g. diazepam), barbiturates (e.g. phenobarbital), propofol and progabid. These directly increase inhibitory chloride conductance or upregulate the effect of synaptic released GABA on the $GABA_A$ receptor. Muscimol binds to the same site on the $GABA_A$ receptor complex as GABA itself, while benzodiazepines and barbiturates bind to separate regulatory sites on the receptor complex. Thus, muscimol can enhance chloride conductance independent of GABA, while the other drugs only affect the efficacy and potency of GABA once it binds to the receptor. Progabid is also considered a $GABA_B$ agonist, while the drug baclofen is a selective $GABA_B$ agonist. Other drug types include GABA transporter blockers, which prolong the action of GABA in the synaptic cleft by inhibiting its uptake. Vigabatrin and sodium valproate are drugs that inhibit GABA transaminase and slow the degradation of GABA. Valproate is also thought to stimulate GABA synthesis. Both mechanisms, increasing synthesis or decreasing degradation, would increase intra- and extracellular GABA concentrations.

GABA and Pituitary Function

There is more than adequate anatomical evidence that GABA is involved in the regulation of many pituitary hormones both centrally and at the level of the gland itself. Inhibition of GABA degradation and blockade of GABA transmission as well as administration of GABA and GABA mimetic drugs have all been shown to affect pituitary hormone secretion [13–31]. While not completely understood, GABA may act at different sites within the hypothalamic-pituitary unit and these actions may also depend on the hormonal milieu. There is a remarkable density of GABAergic endings in the arcuate and periventricular nuclei and these endings are in synaptic contact

with other hypothalamic cells, including those that produce dopamine and releasing and inhibiting regulatory hormones [32, 33]. A vast majority of neurons from these nuclei terminate in the median eminence where they release regulatory hormones into the hypophyseal portal blood. They express multiple receptors for different neurotransmitters and their location in the median eminence brings them in contact with a host of other neurotransmitters and nerve endings [34–36]. Collectively they are referred to as the tuberoinfundibular system, which provides a major pathway for the release of GHRH, SS and other compounds and their influence on pituitary function. There are GABAergic fibers that also project from the arcuate and periventricular nuclei and terminate in the median eminence. Thus, the appropriate secretion of releasing and inhibitory compounds, such as GHRH and SS, can be regulated by different neurotransmitters within the nuclei and within the median eminence, including GABA [34–36]. This supports the central role of GABA and its influence on hypothalamic-pituitary function.

In addition to GABA's central effect, there is sufficient evidence for its direct influence on pituitary cells, as GABA receptors have been identified on gonadotropes, corticotropes and somatotropes and fairly high concentrations of GABA have been measured within the gland itself [16, 35, 37]. The physiological sources of pituitary GABA are not completely established, but it is generally accepted that it is synthesized by hypothalamic neurons and reaches the pituitary by two possible routes. The first involves secretion of GABA into the hypophyseal portal system and the second involves direct innervation of endocrine cells within the intermediate lobe. As mentioned above, the tuberoinfundibular pathway contains GABAergic fibers that terminate at the median eminence. Like dopamine, GHRH and SS, GABA secreted from these nerve endings can be released into the portal blood and transported to the anterior pituitary. This theory is supported by elevations in portal blood GABA observed following electrical stimulation of the median eminence [38] and inhibition of GAD [23]. These findings coupled with the presence of relatively high concentrations of GABA observed within the anterior pituitary in the absence of GAD [35], strongly suggest that GABA is indeed secreted into the hypophyseal portal vessels. Additionally, the number of GABA-binding sites within the anterior pituitary has been shown to increase following lesions of the median eminence [39]. This suggests an upregulation of the receptors following the elimination of the GABA which normally reached the receptors via the portal blood. Thus, it is likely that the hypophyseal portal vessels are the primary source of pituitary GABA. However, hypothalamic GABAergic axons can also directly reach and terminate on endocrine cells of the intermediate lobe [40] and, more recently, evidence suggests that GABA can actually be produced and stored within the pituitary gland itself [41]. The endocrine cells were also found to express $GABA_A$ and $GABA_B$ receptor subunits. Taken together, the data strongly imply the existence of novel autocrine and paracrine modes of regulation of pituitary function by GABA (fig. 2).

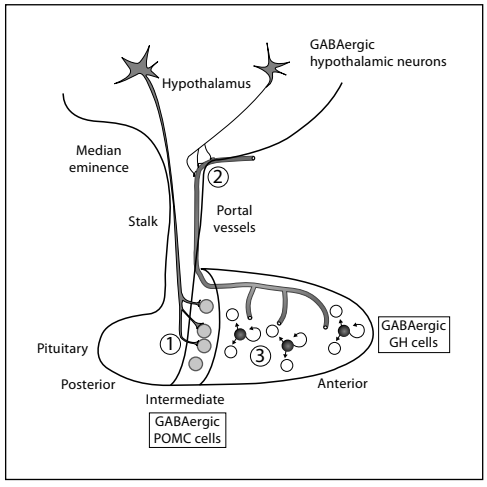

Fig. 2. Neuronal ((1)), neurohemal ((2)), and novel para/autocrine ((3)) control of pituitary function by GABA [from 41].

GABA and Growth Hormone Secretion

The actual role of GABA on GH secretion has been a source of considerable controversy, as numerous mechanisms of action have been proposed and a dual effect appears to exist. As mentioned above, GABA can act centrally by interfering with the activity of other neurotransmitters associated with GH secretion like dopamine [18, 24]. The centrally acting dopamine antagonist pimozide has been shown to blunt the GH response to GABA [18]. This was not observed when the peripheral dopamine antagonist domperidone was administered. However, the GH response to GABA was not completely eliminated by pimozide, suggesting that other mechanisms participate in the neuroendocrine effect of GABA. Early studies utilizing an intraventricular method of GABA administration indicate that it exerts a dose-related stimulatory effect on GH secretion [29, 30]. The effects were blocked by the $GABA_A$ antagonist bicuculline [30]. In a similar study, Willoughby et al. [31] observed an immediate increase in GH secretion when muscimol was injected directly into the periventricular area. Likewise, Spencer et al. [27] observed a rapid increase in plasma GH following intraventricular administration of GABA (10 mg). However, administration of 100 mg was inhibitory and decreased GH secretion. A plausible explanation for these observations would be the inhibition of SS release by GABA [31, 33, 42]. Not all studies are in agreement however [43].

In addition to central action, there is evidence that GABA can act directly on pituitary somatotropes [14, 16]. For example, stimulation of GH secretion has been observed in vitro following infusion of GABA directly into the pituitary [16]. The effect was purely stimulatory and transient, peaking at approximately 4 min and lasting approximately 20 min. Increases were also observed following muscimol administration. The response to muscimol was reduced when bicuculline

was administered, while baclofen had no effect on GH secretion. Additionally, the addition of benzodiazepine and secobarbital (barbiturate), which are known to potentiate the GABAergic response, enhanced the GH response to muscimol. Using a similar technique, Acs et al. [14] observed a dose-dependent increase in GH secretion following GABA infusion. Administration of a $GABA_A$ channel blocker diminished the GH response to GABA by 60%. A desensitization of the receptors was also suggested as a gradual decrease in GH secretion was observed following prolonged stimulation with GABA. Similar results have been reported elsewhere [15].

Inhibitory actions by GABA on GH have also been described and appear to occur centrally [20]. Diazepam has been shown to inhibit GH secretion by inhibition of dopaminergic transmission [24]. Likewise, intravenous administration of muscimol has been shown to inhibit secretory peaks of plasma GH [22]. In that study, GH inhibition was also observed when brain GABA levels were increased by injecting γ-acetylenic-GABA. Conversely, an intravenous injection of bicuculline triggered an early rise in plasma GH. It is plausible that GABA inhibits spontaneous GH release by inhibiting the secretion of GHRH [17]. It has been suggested that this dual effect by GABA on GH secretion might be explained by the location of action. Fiók et al. [22] reported poor penetration of GABA into the brain parenchyma following intraventricular injection. They suggested that GABA, when given intraventricularly, suppresses the activity of SSergic neurons in the periventricular region thereby leading to an elevation in GH secretion. On the other hand, it has been suggested that when GABA mimetic drugs are given peripherally, they reach the site of origin of GHRH neurons in the arcuate nuclear region and inhibit the release of GHRH, resulting in a fall in plasma GH.

GABA Supplementation

GABA is commercially available in its synthetic form as a nutritional supplement and is marketed as an anabolic agent via its ability to enhance endogenous GH production. There is evidence for this claim as both subcutaneous [13] and intravenous [27] administration of GABA has been shown to enhance GH secretion. The elevations following subcutaneous injection occurred in a dose-dependent fashion with the peak response occurring 20 min after injection. Administration of GHRH antibody did not interfere with the GH secretion, suggesting that GHRH has only a minor, if any role in GABA-induced GH secretion, at least when administered peripherally. It must be noted that both of these studies used an animal model and a parenteral route of administration. While studies investigating oral administration in humans are limited, the results favor GABA supplementation. Oral administration of sodium valproate [28] and baclofen [25] has been shown to stimulate GH secretion. Likewise, significant elevations of plasma GH have been observed following a single 5 g oral

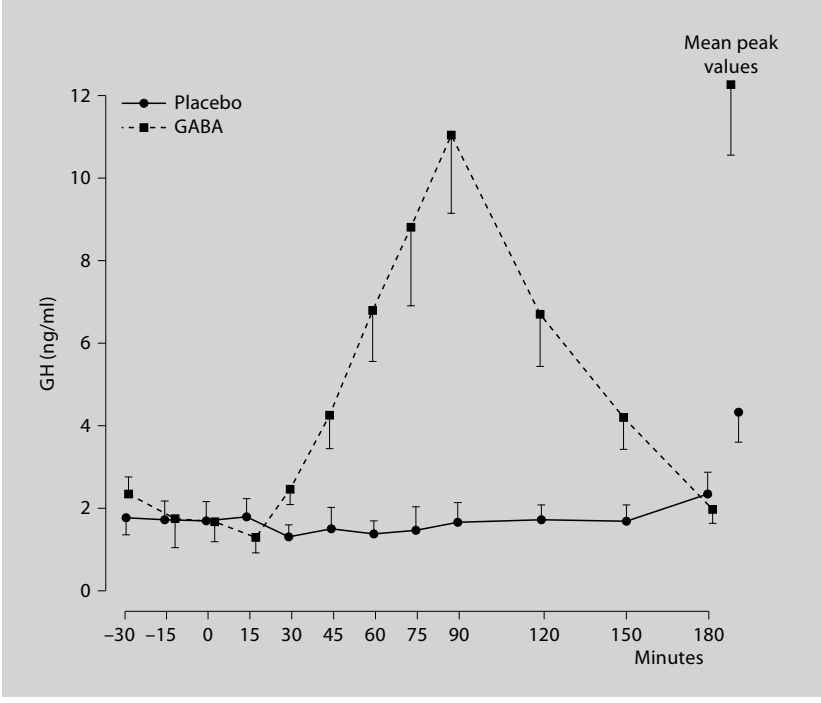

Fig. 3. Resting plasma GH pattern after oral administration of 5 g GABA or placebo [from 19].

dose of GABA [19]. The acute increase was observed in all 19 of the subjects studied (fig. 3). However, administration of 18 g GABA daily for 4 days by 8 additional subjects caused a significant blunting of the overall GH response to insulin hypoglycemia. In a similar study, Cavignini et al. [18] observed a significant elevation in GH following oral administration of 5 g GABA. More recently, 3 g of oral GABA has been shown to increase GH secretion [26]. In that study, an augmentation of the resistance exercise-induced GH response was also observed (fig. 4a, b). However, conflicting results regarding the response during cycling exercise have been reported when valproate is ingested [21, 28]. Steardo et al. [28] observed a significant increase in resting GH concentrations following valproate ingestion, while the GH response to a 20-min bout of cycling was markedly inhibited by it (fig. 5). To the author's knowledge, these are the only studies to investigate the effects of GABA during exercise, with only one investigating true GABA administration [26].

Peripherally administered GABA does not easily cross the blood-brain barrier and the perikarya of hypothalamic secretory neurons are localized in areas protected by this barrier. However, the axon terminals of these neurons are localized in the median eminence, which lacks the blood-brain barrier. It is known that intravenous radioactive GABA readily accumulates in the median eminence [44]. Thus, the action of GABA in this area might account for the central effect when administered

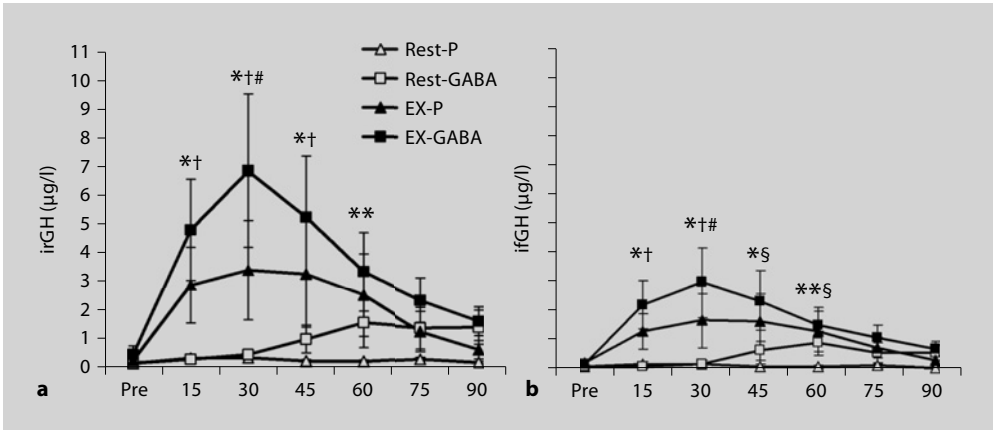

Fig. 4. Immunoreactive growth hormone (irGH) (**a**) and immunofunctional GH (ifGH) (**b**) time-point concentrations for the rest-placebo (P), rest-GABA, exercise (EX)-P, and EX-GABA conditions. * EX-GABA different from rest-P and rest-GABA ($p < 0.01$); † EX-P different from rest-P and rest-GABA ($p < 0.05$); # EX-GABA different from EX-P ($p < 0.05$); ** EX-GABA different from rest-P ($p < 0.01$); § EX-P different from rest-P ($p < 0.05$) [from 26].

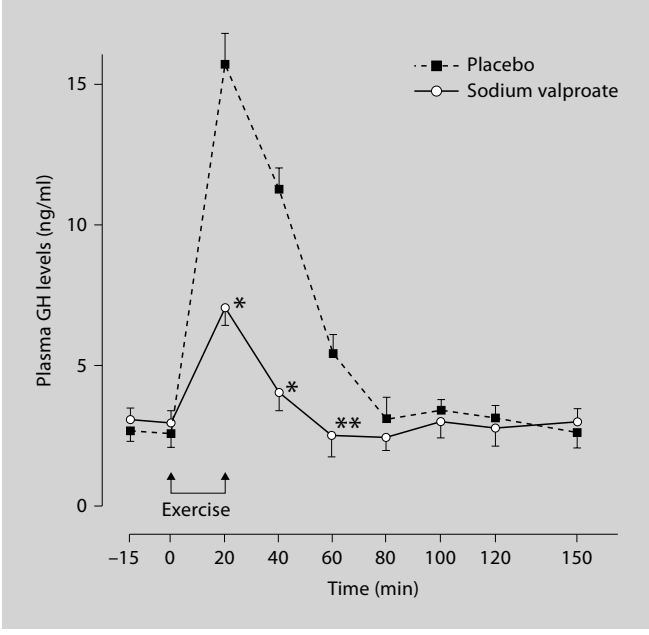

Fig. 5. GH response to cycling exercise following oral administration of sodium valproate or placebo [from 28].

peripherally. Likewise, the pituitary gland sits outside the blood-brain barrier, allowing for direct action by peripheral GABA. Researchers investigating the effects of oral GABA on GH have failed to assess the GABA concentration of the plasma. Thus, it is possible that oral GABA undergoes liver-induced biotransformation to other amino acids which may also stimulate GH secretion [5]. Regardless of the mechanisms

involved, it seems that GABA ingestion results in increased GH concentrations, both at rest and after resistance exercise.

Conclusion

The precise nature of GABA's effect on GH secretion as well as its mechanism of action remains to be clarified. As GABA ingestion apparently stimulates GH release, it is certainly possible that GABA induces lipolytic effects and skeletal muscle protein accretion, via mechanisms directly and/or indirectly related to GH release [1]. However, the anabolic and lipolytic values of the relatively small GABA-induced GH responses remains unclear. It is plausible that GABA supplementation stimulates GHRH or ghrelin secretion and/or suppresses SS release, as previously demonstrated in animal models. To date, no studies have investigated the ergogenic value of GABA ingestion. Given the acute GH responses to GABA ingestion, studies designed to determine the effects of longitudinal GABA supplementation on anthropometric and performance measures are warranted.

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