

Relation between vitamins of the b complex, GABA and glutamate, and their role in neurocognitive disorders -Brief review

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Abstract

Vitamins, especially the water-soluble complex of vitamins B, are highlighted in the daily clinical practice. Numerous studies emphasize the need for supplementation, mainly in groups with deficiency of these vitamins, such as the elderly, pregnant women, children and patients with diseases associates with cognitive disorder. Thiamine (B1), a vitamin of the diet, is an important cofactor for the three key enzymes involved in the citric acid cycle and the pentose phosphate cycle. Pyridoxine (B6) and cobalamin (B12) act in the CNS as a cofactor in the metabolism reactions of homocysteine. Deficiency of some neurotransmitter precursors can also cause symptoms of attention deficit hyperactivity disorder in children, especially amino acid and vitamin B deficiency. Inhibitory and excitatory neurotransmitters regulate diverse behavioral processes, including sleep, learning, memory and sensation of pain. They are also implicated in many pathological processes, such as epilepsy and neurotoxicity. Studies suggest that the excitatory amino acids may play a role in learning and memory. The binding of glutamate to its receptor triggers molecular and cellular events associated with numerous physiological and pathophysiological pathways, including the development of an increased sensation of pain (hyperalgesia), brain neurotoxicity or synaptic alterations involved in certain types of memory formation. Between the two major classes of neuroactive amino acids, γ -aminobutyric acid (GABA) is the major inhibitory amino acid. It is known that GABA plays a fundamental role in encoding information and behavioral control, in the regulation of motor function and in motor learning. The inter-relationships between diet, the brain and behavior are complex. However, micronutrients are known to have a direct influence on cognitive function through their involvement in the energy metabolism of neurons and glia cells, the synthesis of neurotransmitters, receptor binding and the maintenance of membrane ion pumps.

Keywords: GABA; Glutamate; Vitamins B; Neuroplasticity; Neurotransmission.

1. Introduction

The inter-relationships between diet, the brain and behavior are complex. However, micronutrients are known to have a direct influence on cognitive function through their involvement in the energy metabolism of neurons and glia cells, the synthesis of neurotransmitters, receptor binding and the maintenance of membrane ion pumps. Vitamins have potential benefits for cerebral function, since their deficiencies are characterized by dramatic neurological manifestations. In the first part of this article, the current knowledge of the physiological roles of some vitamins of the B complex most closely associated with cognitive performance will be reviewed, with particular reference to the central nervous system (CNS). In the second part of this article, the physiological roles of two main neurotransmitters of the CNS are discussed as well.

2. Vitamins B

Vitamins, especially the water-soluble complex of vitamins B, are highlighted in the daily clinical practice. Numerous studies emphasize the need for supplementation, mainly in groups with deficiency of these vitamins, such as the elderly, pregnant women,

children and patients with diseases associates with cognitive disorder [1], [2].

Clinical evidence shows that all B vitamins have a fundamental role in neurotransmitters, lipids and proteins metabolism, and act differently in various enzyme systems, participating as co-enzymes in the activation of numerous metabolic processes [3], [4]. Demonstrations found in scientific papers related to B vitamins deficiencies are, mostly, neurological and cardiovascular [5]. Being water soluble, these vitamins are not considerably stored in the body, so that a daily supply through diet is critical to prevent deficiencies. The main sources of these vitamins are red meat [6].

2.1. Thiamine

Thiamine (B1), a vitamin of the diet, is an important cofactor for the three key enzymes involved in the citric acid cycle and the pentose phosphate cycle. Thiamine is vital to the maintenance of cellular oxidative metabolism and synthesis of nucleotides in the developing brain [7], [8] as well as in adults [9], [10].

The deficiency in cellular metabolism and oxidative stress in Alzheimer's disease is very similar to that induced by thiamine deficiency. Clinical and experimental evidences have demonstrated that patients with Alzheimer's disease also show a downregulation (low hippocampal neurogenesis) [11], besides dependent oxidative metabolism and reduced thiamine [12], [13]. Other experiments show that mice with deficiency of thiamine produce a pathological

change Alzheimer's-like, with a selective neuronal loss [14]. Therefore, hippocampal neurogenesis is vulnerable to thiamine deficiency.

The hippocampus has been recognized as the structure related to learning and memory; it plays a key role in neural plasticity induced in physiological conditions as well as pathological conditions. The correlation between hippocampal neurogenesis and cognitive function naturally awakened enormous research interest [15], [16], [17]. Experimental evidence has shown that the newborn neurons in the hippocampal dentate gyrus have the potential to become synaptically integrated [18], [19], [20], [21] and achieving neuronal characteristics morphological, biochemical and electrophysiological normal [22], [23], [24].

Furthermore, thiamine plays an important role in the synthesis and decomposition of acetylcholine (ACh). ACh is synthesized in neurons from choline and acetyl coenzyme A (CoA) by the enzyme choline acetyltransferase. Acetyl-CoA is derived primarily from oxidative decarboxylation reaction of pyruvic acid. Thiamine pyrophosphate (TPP), an active type of thiamine, is a coenzyme key to this reaction of oxidative decarboxylation. The thiamine deficiency leads to inhibition of ACh synthesis due to the reduction of acetyl-CoA. Moreover, such a deficiency weakens the inhibitory effect of thiamine on the activity of acetylcholinesterase and accelerates the inactivation of ACh. Therefore, inhibition of ACh synthesis may contribute to cognitive dysfunction induced by

thiamine deficiency [25]. All this functional mechanism is summarized in Figure 1.

Zhao et al. (2008) [25] explored the influence of thiamine deficiency (DT) in the pathological pre-injury stage in the early neurogenesis and the correlation between affected neurogenesis and cognitive dysfunction. The mouse experimental model DT was fed a diet with thiamine depletion. The functions of learning and memory of mice with DT were tested with the Y-maze scale. Neurogenesis was studied with the immunohistochemical markers BrdU, PCNA, Dcx and NeuN. The results showed a significant decrease in learning ability and neurogenesis in the hippocampus simultaneously from the ninth day of treatment (D9) when the models showed loss of cholinergic neurons and reduction of hippocampal cells. Administration of thiamine in the diet reversed learning ability, as well as the decrease in hippocampal neurogenesis induced by DT in the early pathological pre-injury phase [25]. In a clinical study by Benton et al., (1995), involving one hundred and twenty young adult women with ingestion of 50 mg thiamine, the treated group had a significant improvement in mood (after 2 months use) and in time reaction compared to the control group (placebo) [26]. Several authors have demonstrated effects and various concentrations of thiamine use, as shown in Table 1.

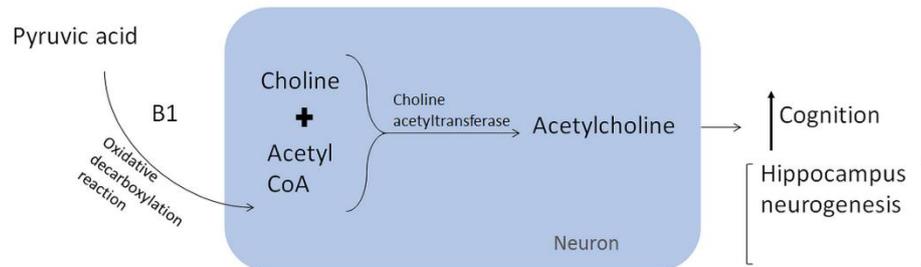


Fig. 1: Mechanism of Action of Thiamine.

Table 1: Clinical Studies of Thiamine Deficiency and Supplementation.

Author	n	Dose (mg)	Time	Effect
Brožek et al. (1957) [27]	10	Privation	15-27 days	Anorexia, muscle weakness, irritability, depression.
		5	9-21 days	Improvement of symptoms observed in the deprivation of this vitamin.
Benton et al., (1995) [26]	129	14	4 months	Improved mood in women.
Smidt et al., (1991) [28]	80	10	6 weeks	Increased sense of well-being and decrease fatigue.
Heseker et al., (1990) [29]	1081	Privation	2 months	Introversion, inactivity, fatigue, decreased confidence and mood.
		3		Increased sociability, sensitivity and mood.
		120		Adequate amount of thiamine = normal children.
Harrell (1946) [30]		0,9 (girls)	1 year	Taller children, with better vision, faster reaction times and better results on memory and intelligence tests.
		2 both sexes		

2.2. Pyridoxine and cobalamin

Pyridoxine (B6) and cobalamin (B12) act in the CNS as a cofactor in the metabolism reactions of homocysteine [31]. Homocysteine (HCl) is a sulfhydryl amino acid formed from the demethylation of methionine and is metabolized by two pathways: the remethylation (dependent on vitamin B12 and folic acid) and the transsulfuration (dependent on vitamin B6) [32]. The mechanisms of action cited below are summarized schematically in Figure 2.

Cobalamin (B12) passes through the blood-brain barrier bound to transcobalamin II protein (TC2) forming the cobalamin-TC2 complex, which crosses the barrier by endocytosis, using the high affinity cell surface receptor [33]. Pyridoxine (B6) is absorbed from the gastrointestinal tract and converted in the liver into pyridoxal 5'phosphate, the enzyme non-specific alkaline phosphatase.

In blood, the same enzyme removes phosphate, producing pyridoxal, which is then transported by the blood-brain barrier [34].

B6 is a cofactor in the synthesis of cysteine from Hci. Cysteine is a glutathione precursor, which is an antioxidant substance, and acts by inhibiting Hci oxidant action [2]. B6 and B12 also act as cofactors in the S-adenosyl-methionine synthesis (SAM), which is an enzymatic cofactor of glutathione production [35]. SAM is also a precursor in the synthesis of melatonin, produced in the pineal gland. Melatonin has an antioxidant role, as glutathione [36]. In fact, studies show that SAM synthesis can enhance cognitive performance [37]. It also adds the fact that B6 and SAM are essential cofactors in the pathway of synthesis of epinephrine, which is involved in learning processes and memory consolidation [38], [39].

Diets deficient in B6 and B12 induce in mice high levels of HCY in plasma and high levels of amyloid-beta, neurotoxicity indicative for leading to neuronal apoptosis caused by oxidative stress [40]. Added to this, in vitro experiments show that supplementa-

tion with B6 and B12 can treat diseases related with dementia by reducing the amyloid-beta accumulation in the cortex and hippocampus [41]. It was concluded that high levels of homocysteine (HCY) in plasma are directly related to deficiency of vitamins B6 and B12 [2].

Other clinical studies evaluated the rate of brain atrophy in Alzheimer's patients who have low levels of HCl, after treated with B6 (pyridoxine) and B12 (cobalamin). The results showed that the rate of atrophy and cognitive impairment declined in 85 patients treated, after 2 years [42]. In another study of these same authors carried out in 2012 included 133 patients with Alzheimer's disease who were treated with B6 and B12. In this evaluation, cognitive decline caused by the disease was retarded in the end of 2 years of treatment [43]. In another study, 211 young, adult and old women were tested with B6 and B12 supplementation to assess the association between cognition and vitamins B. The processing speed

and working memory were used as parameter. The result was positive, there was improvement in memory and learning of young women, after 35 days of treatment [44]. Furthermore, a clinical study of association between the high concentration of Hci in plasma and cognitive performance evaluated 87498 individuals presenting a associatin of 7-8% of Hci levels with cognition [45]. Deficiency of some neurotransmitter precursors can also cause symptoms of attention deficit hyperactivity disorder in children, especially amino acid and vitamin B deficiency [46]. Therefore, supplementation with vitamins B6 and B12 provide improvement in cognition and learning, as they assist in the processes of synthesis of those neurotransmitters that are directly involved in cognitive processes of brain [47]. Table 2 outlines some clinical studies with different doses of supplementation of vitamins B6 and B12.

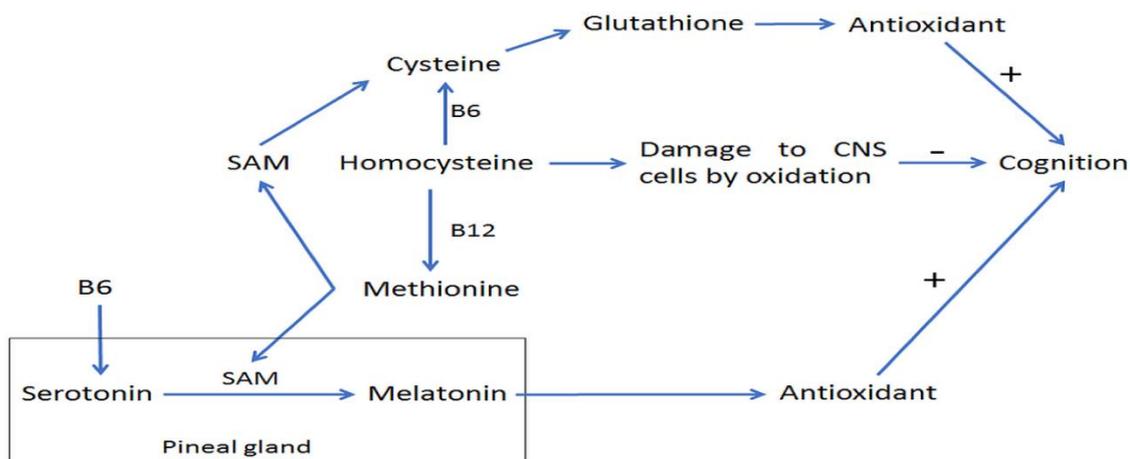


Fig. 2: Mechanism of Action of B6 and B12.

Table 2: Clinical Studies of B6 and B12 Vitamins.

Author	B6 Vitamin	B12 Vitamin	Time	Patients	Results
Smith et al., 2010 [42]	20mg	0,5mg	24 months	85	Brain atrophy rate and cognitive impairment decreased
Jager et al., 2012 [43]	20mg	0,5mg	24 months	133	It was slowed cognitive decline caused by the disease
Bryan et al., 2002 [44]	75mg	15µg	35 days	211	Supplementation with B vitamins shows positive results on memory and learning

3. Neurotransmitters aminoacids

The central nervous system (CNS) shows high concentrations of certain aminoacids which bind to postsynaptic receptors, acting thus as inhibitory or excitatory neurotransmitters.

Inhibitory and excitatory neurotransmitters regulate diverse behavioral processes, including sleep, learning, memory and sensation of pain. They are also implicated in many pathological processes, such as epilepsy and neurotoxicity. The interactions between ion channels, receptors that regulate these channels and aminoacid neurotransmitters in the CNS are the molecular basis of these processes. This section will discuss the operation of the two major systems of aminoacid neurotransmission in the CNS, which involve the gamma-aminobutyric acid (GABA) and glutamate.

3.1. Glutamate

Excitatory aminoacids have been proposed as the main neurotransmitter of the central nervous system. Studies suggest that the excitatory aminoacids may play a role in learning and memory [48]. The binding of glutamate to its receptor triggers molecular and cellular events associated with numerous physiological and pathophysiological pathways, including the development of an increased sensation of pain (hyperalgesia), brain neurotoxicity or synaptic alterations involved in certain types of memory formation [49].

The glutamate synthesis proceeds via two distinct pathways. In one of these pathways, alpha-ketoglutarate formed in the citric acid cycle is transaminated to glutamate in the nerve endings in the CNS. Alternatively, the glutamine produced and secreted by the glial cells is transported in the nerve endings and converted into glutamate by glutaminase [49]. There are two isoforms, D-glutamate and L-glutamate.

L-Glutamate is the most abundant free amino acid in the brain and the predominant excitatory neurotransmitter in the CNS of vertebrates. Among its many functions, the L-glutamate plays a critical role in the synaptic plasticity and its maintenance [50]; also contributes to learning and memory through changes in the use of synaptic efficacy, such as maintenance of long-term potential [51]. In nerve terminals, L-glutamate is stored in vesicles and released by a mechanism dependent on calcium. Once in the synaptic cleft, L-glutamate binds to and activates postsynaptic glutamate receptors. Although many different subtypes of glutamate receptors have been identified [52] ionotropic receptors have been the most extensively studied. They are subdivided into three classes: the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), kainate and NMDA (N-methyl D-aspartate) receptors, the NMDA being the most important. The functions of the NMDA receptors are as sodium and calcium transporter, having five separate binding sites, each of which is affected by different substrates susceptible to alter the receptor affinity. L-glutamate action is ended by removal of this substance from the synaptic cleft by

neuronal and glial presynaptic uptake systems of high affinity, several of which have previously been cloned [53], [54], and [55]. The voltage dependent blockade of the NMDA receptor by Mg^{2+} and its high permeability to Ca^{2+} make inherently appropriate the indications for a role in mediating synaptic plasticity. The flow of ions through the channel operated by the NMDA receptor is normally only achieved in the presence of a strong local depolarization induced, e.g., by Na^{2+} influx due to activation of glutamate receptor AMPA type [56]. Thus, two simultaneous processes are required for physiological activation of NMDA receptor learning channel, allowing the translation of quantitative information [57]. The regulatory mechanisms of neuronal genes triggered by binding to the NMDA receptor become important to understand the mechanisms of learning, memory and other long-term adaptive changes in neurons. The neurotransmitter glutamate stimulates rapid and transient induction of several genes including the proto-oncogene *c-fos* [51] and the promoter *Zif-268* [58]. The *c-fos* is the most commonly used markers for neuronal plasticity. While a study on the *c-fos* gene provides information about the neural

plasticity, *Zif-268* has been implicated in long-term memory consolidation process [58], [59]. The *c-fos* promoter contains several critical regulatory elements, including the serum response element (SRE) that mediate transcription induced by glutamate in neurons. Transcription factors of serum response factor (SRF) and Elk-1 can mediate transcription of SRE in cortical neurons by glutamate induction. There are at least two distinct pathways, through which glutamate signals act through the SRE: a path SRF-dependent, which can operate in the absence of elk; and an Elk-dependent pathway. The activation of the Elk transcription dependent pathway seems to require phosphorylation of Elk-1 by extracellular signal regulated kinases (ERKs), providing evidence for a physiological role of ERK in glutamate signaling in neurons. Taken together, these findings suggest that the SRF, Elk and ERK pathways may play an important role in neuroplasticity [51]. Figure 3 shows the summarized Mechanism of Action of L-glutamate at NMDA receptors.

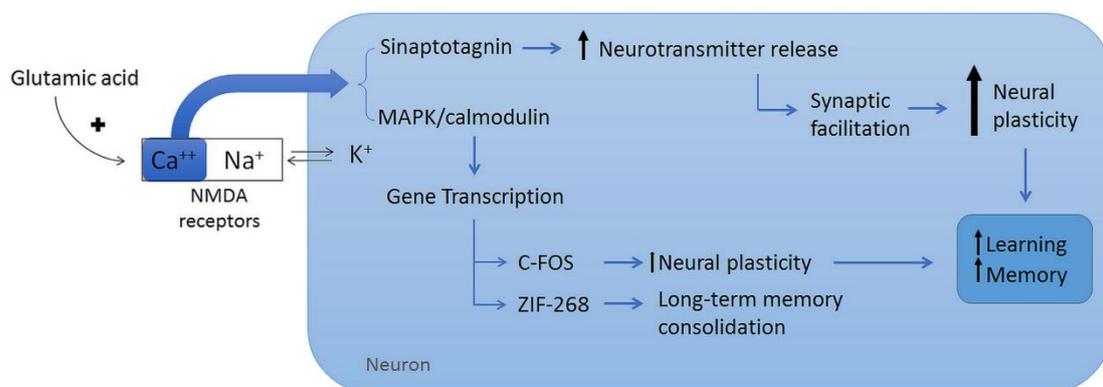


Fig. 3: Mechanism of Action of L-Glutamate.

The plasma concentrations of L-glutamate can fluctuate during the day as a result of changes in the diet, metabolism and protein turnover. If these changes were directly transferred to the interstitial space of the brain, they would have effects on neuronal synaptic communication [60].

Consequently, the passive flux of many polar solutes such as L-glutamate, is very limited. To compensate the limited passive exchange, the cells that make up the external layer of the blood-brain barrier (BBB) contain different levels (20 or more) of specific transport systems, which regulate the solute flux from blood to the cerebrospinal fluid and brain interstitial fluid and again out [60].

The first transport systems to be proposed were identified based on the results of uptake studies in vivo [61], [62], [63]. Such carriers include X2 system, that acts independently of sodium, promoting absorption with high affinity to amino acid with anionic side chains, including L-glutamate and L-aspartate [60].

Although such an arrangement helps to protect the greater part of the brain from the plasma changes of circulating L-glutamate, there are some brain areas that contain no BBB, allowing rapid uptake of L-glutamate from the circulation [64]. These are collectively known as circumventricular organs and include the median eminence, area postrema, subfornical organ, organ subcommissural, pineal gland, pituitary and organum vasculosum of the terminal blade [65]. Uptake rates in the brain to small solutes in these areas are greater than the BBB by 10 to 1000 times [64], [65], [66], [67]. Once inside the brain extracellular fluid, solutes can move into adjacent brain areas via intercellular diffusion or by flow along the Virchow-Robin spaces. Such movement has been documented for glutamate and aspartate in animals after high-dose administration amino acids [68], [69]. The result is that certain areas of the brain are vulnerable to fluctuations in the acute glutamate concentration in plasma of great magnitude as a result of "flooding" from the circumventricular organs [60].

There are recent hypotheses that suggest a critical role of glutamate receptors in memory potentiation and retention in the hippocampus, in long term. Flood et al (1990) trained rats to avoid shock [48]. After the formation of learning they injected intracerebroventricularly agonists and antagonists of various classes of glutamate receptors. The retention test (specific memory acquisition) was assessed one week after training. NMDA receptor agonists have been able to improve memory retention in a dose-dependent manner. L-glutamate, but not D-glutamate, increased memory retention. Administration of antagonists 24h after training did not impair memory retention [48]. Vogel et al. (1966) reviewed a large number of clinical studies in which glutamic acid was administered in healthy subjects and individuals with mental retardation, who underwent tests [70]. The authors concluded that glutamic acid reduces the severity of mental retardation, resulting in better performance in intelligence tests in both subject populations.

3.2. GABA

From the two major classes of neuroactive aminoacids, γ -aminobutyric acid (GABA) is the major inhibitory [49], [71]. It is known that GABA plays a fundamental role in encoding information and behavioral control [72], in the regulation of motor function [73], [74], [75] and in motor learning [76], [77]. Further important, GABA appears to be also involved in action selection processes [78] and inhibition of responses that occur in fronto striatal circuits [79] and are likely to play key role in neuromodulation of action control processes [78], [80], [81].

GABAergic neurons play an important role in the control mechanisms in various centers of the stem and hypothalamus. If its activity within these structures is compromised, abnormally increased responses can be observed, for example: emotional reactivity, cardiac and respiratory functions, food and water intake functions,

sweating, insulin secretion, gastric acid release and colonic motility [82].

GABA synthesis is mediated by glutamic acid decarboxylase (GAD), which catalyzes the decarboxylation of glutamate to GABA, in the GABAergic nerve endings [83] (Fig. 4). Therefore, the amount of GABA in the brain tissue correlates with the amount of functional GAD, which requires pyridoxal phosphate (Vitamin B6) as a cofactor. In response to an action potential GABA release occurs into the synaptic cleft by fusion of vesicles containing GABA in the presynaptic membrane [49], [84], [85], [86].

The end of the GABA action in the synapse depends on removal of the extracellular space. Neurons and glial cells take GABA by specific GABA transporters (GAT). Inside the cells, the widely distributed mitochondrial enzyme GABA-transaminase (GABA-T), catalyzes the conversion of GABA to succinic semialdehyde (SSA), which is subsequently oxidized to succinic acid by the SSA dehydrogenase (SSADH), entering hereafter in the Krebs cycle, which is transformed into α -ketoglutarate. Thereupon, GABA-T regenerates glutamate from α -ketoglutarate [49], [84], [85], [86] (Fig. 4).

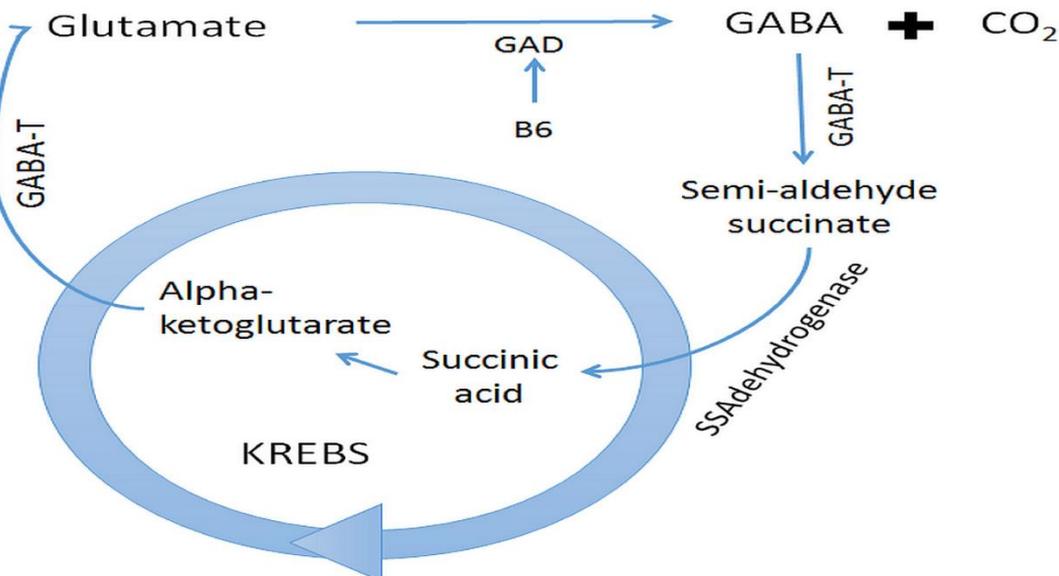


Fig. 4: Mechanism of Action of GABA.

The CNS cell membranes of most neurons and astrocytes of vertebrates express GABA receptors and, because of this, these receptors influence in several functions and neural circuits [87, 88]. There are two types of GABA receptors. The ionotropic GABA receptors (GABA_A and GABA_C) consist of membrane proteins of multiple subunits, which bind to GABA, opening an intrinsic chloride ion channel [89]. The metabotropic GABA receptors (GABA_B) are heterodimeric receptors coupled to G-protein that affect neuronal ionic currents via second messengers [49], [90], [91]. The most abundant GABA receptors in the CNS consist of the ionotropic GABA_A [90].

The inhibitory postsynaptic current (IPSC) consists of quick responses triggered by very short bursts (high frequency) of GABA release in the synapse. The prolonged occupation of the agonist's sites by GABA also leads to a desensitization of the GABA_A receptor, a transition to an inactive state on the agonist [91]. The selective activation of chloride channels (crescent conductance) deviates neuronal transmembrane voltage to the equilibrium potential of the Cl⁻ (-70 mV) [92]. This flow hyperpolarizes Cl⁻ or stabilizes the postsynaptic cell close to its membrane potential in normal resting (V_m ~ 65 mV), thereby reducing the likelihood that excitatory stimuli can initiate action potentials. The open Cl⁻ channels attenuate the change in membrane potential produced by excitatory synaptic currents, a so-called shunting effect. This process provides a molecular explanation for the inhibitory effects of GABA signaling through GABA_A receptors. [49], [93].

In the literature there are conflicting results about the GABA entry into the brain across the blood brain barrier (BBB). The BBB is a tightly sealed layer of brain endothelial cells that form solid joints and prevent the majority of solutes between the brain based on the size, charge and lipid solubility. However, as pointed out by Shyamaladevi and colleagues (2002), recent studies have shown that BBB is much more dynamic than was predicted in the past, and some solutes passages may occur by transcytosis, transport mediated by carrier, or simple diffusion of hydrophobic substanc-

es [94]. Although there is some evidence for only a limited GABA brain penetration [95], [96], a more recent study using rats has shown that GABA administration alone increased GABA concentration in brain, when compared with untreated mice [97].

Still on its effects, GABA has also been linked to the effectiveness of cascade action processes. Consistent with this hypothesis, Yildiz et al (2014) have shown by magnetic resonance spectroscopy (MRS) that superior performance of cascade action was associated with increased striatal GABA concentrations [98]. Another point, the active transcutaneous stimulation of the vagus nerve (tVNS) which increases the concentration of GABA and norepinephrine (NE), improved functions of response selection during the cascade action, compared with the stimulus simulation [99]. These results suggest a critical role of GABA in the neuromodulation of cascade action processes. They also suggest that the increase [98, 99] not too high [100] of GABA levels are associated with better performance of these cascade actions.

In another study, Steenbergen et al (2015b) aimed to provide converged and direct evidence about the possible key role of the GABAergic system in modulating the efficacy of cascade action [101]. To this end, the subject received a dose of 800mg of synthetic GABA [97], [102] or 800mg of microcrystalline cellulose (placebo). The results suggest that systemic administration of synthetic GABA directly influences the effectiveness of the cascade action as measured by a change stop test - a well established diagnostic index (Verbruggen et al, 2008). GABA appears to modulate the performance as much as a more parallel strategy of overlap (i.e., when the interruption of a current task and a change of alternative response were required simultaneously) and as a strategy more in series step-by-step is requested (ie when switching to the alternative response was required after the process stop now was over) [103].

Other studies have shown that psychological stress affect the secretion of salivary cortisol in response to the anticipation of negative events, such as academic tests [104, 105, 106, 107]. The

chromogranin A (CgA) and salivary cortisol are known stress markers in humans [108], CgA being ubiquitously secreted in several tissue types, including, as recently discovered, in the sub-mandibular glands [109], [110]. Kanehira et al (2011) observed that salivary secretion levels of chromogranin A were significantly lower in subjects who did intake 25 and / or 50 mg of GABA in comparison with the control group [111].

Other studies also report the GABA effect on relaxation and stress reduction. Abdou et al (2006) found that oral administration of GABA increased significantly alpha waves and decreased beta waves in the brain, and has maintained the levels of immunoglobulin A in saliva, when the subjects were subjected to stress conditions, such as crossing a suspension bridge [112]. This study showed that GABA could induce relaxation by decreasing anxiety while increasing immunity under stress conditions.

Kanehira et al (2011) determined in a study the effects of a drink containing GABA (control group = 0mg, group 1 = 25 mg, group 2 = 50mg of GABA) in feelings of individuals with chronic fatigue after the performance of a task [111]. Changes in mood measured by the Visual Analogue Scale and the Mood Profile (VAS and POMS) were significantly different in GABA 50mg group and the other two groups. Regarding the cortisol levels and CgA in saliva, an arithmetic task was made to induce mental stress. Samples of saliva control group showed a significant increase in CgA levels, while the group of 25mg GABA showed a significantly lower level of CgA. This trend was more pronounced in the 50mg GABA group. The results of cortisol were similar. In addition, the number of correct responses on tasks was significantly higher in the 50mg GABA group, whereas there was no marked difference in the comparison between the control group and the group 25mg GABA [111].

Recent evidence also suggests that a deficit in behavioral inhibition, common in patients with ADHD may be linked to a deficit in cortical inhibition of the GABAergic pathway. Experimental studies have shown that knockout mice for subtype 1 of GABA transporter (GAT1) gain hyperactive profiles and display an impaired memory, as well as low levels of concentration and attention with increased impulsivity [113].

Edden and coworkers (2012) compared two groups of children, one of healthy individuals and one of individuals with ADHD, using magnetic resonance spectroscopy (MRS) for measuring the volume of GABA concentration in the primary somatosensory and motor cortex. MRS showed that concentration of GABA in children with ADHD is reduced when compared with children with normal development, suggesting that there is a deficiency in GABA pathway [114]. These studies are summarized in Table 3.

Table 3: Clinical Studies of GABA

Autor	Patients	Dose (mg)	Effects
Steenbergen et al., 2015 [101]	30	800mg	Modulation of the efficacy of the cascade action.
Abdou et al., 2006 [112]	13	100mg	Increased alpha waves and decreased beta waves. Decreased anxiety, induction of relaxation.
	8		Increased immunity in stress situations.
Kanehira et al., 2011 [111]	30	25mg	Good performance in stress induction tests, decrease of physical fatigue.
		50mg	More precise performance in stress induction tests, as well as reduction of physical and psychological fatigue.

4. Conclusion

Because of their metabolic interdependence, the B complex vitamins have to be regarded as a functional unit whose individual members act like links in a chain of biochemical reactions. Four major mechanisms can be identified by which micronutrients in-

fluence cognitive function: through their role in neurotransmitter synthesis; by neuronal membrane and receptor modification; by influencing brain energy requirements; and via their role in Hcy metabolism.

Inhibitory and excitatory neurotransmitters regulate diverse behavioral processes, including sleep, learning, memory and sensation of pain. They are also implicated in many pathological processes, such as epilepsy and neurotoxicity. Clinical evidence shows that all B vitamins have a fundamental role in neurotransmitters, lipids and proteins metabolism, and act differently in various enzyme systems, participating as co-enzymes in the activation of numerous metabolic processes

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