CHAPTER – 2

GAMMA-AMINOBUTYRIC ACID (GABA) and its effects

2.1 Neurotransmitters

Neurotransmitters are the most common class of chemical messengers in the nervous system. Based on their chemical nature, neurotransmitters can be subdivided into two major groups (Fig: 2.1.1) - biogenic amines and small amino acids [20, 87].

![Image of neurotransmitters differentiation](image)

**Fig: 2.1.1. Differentiation of neurotransmitters based on their chemical structures.**
A neuroactive substance has to fulfill certain criteria before it can be classified as a neurotransmitter.

- It must be of neuronal origin and accumulate in presynaptic terminals, from where it is released upon depolarization.

- The released neurotransmitter must induce postsynaptic effects upon its target cell, which are mediated by neurotransmitter-specific receptors.

- The substance must be metabolically inactivated or cleared form the synaptic cleft by re-uptake mechanisms.

- Experimental application of the substance to nervous tissue must produce effects comparable to those induced by the naturally occurring neurotransmitter.

2.1.1 Gamma-Aminobutyric Acid (GABA)

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). It is found mainly in the brain and is an agonist at three receptor subtypes. Altered GABAergic function (GABA-activated neurotransmission) in the brain is believed to responsible for the development of some neurological and psychiatric disorders in humans in [21].
In addition to its positive effect on the nervous system, medical studies have also proven GABA to have many other important positive effects on the body following supplementation. First, GABA naturally stimulates the anterior pituitary gland to secrete higher levels of Human Growth Hormone (HGH). Second, studies have shown GABA to improve sleep cycles leading to more restful sleeping and more interesting, vivid dreaming. Third, GABA has shown powerful stabilizing effects on blood pressure. Finally, research has demonstrated GABA to be a very effective analgesic, eliminating pain from chronic conditions such as arthritis and lower back pain. GABA receptors have been detected in the endocrine glands, smooth muscles, and the female reproductive system [49].

GABA is the second most common neurotransmitter chemical in the human brain. GABA is an inhibitory neurotransmitter- it calms and reduces the activity of neurons. Some anti-anxiety medications work by promoting greater availability of GABA to brain cells.
While many of the basic functions of GABA have become better understood in the last decade, scientists continue to make new discoveries about GABA and the multiple types of GABA receptors, each of which can play a different role in neural cells.

**Fig: 2.1.1 Chemical structure of Gamma-aminobutyric acid**

IUPAC name - Gamma aminobutanoic acid

Molecular formula C$_4$H$_9$NO$_2$

Molar mass 103.12 g/mol

Melting point 203.7 °C, 477 K, 399 °F
2.2  GABA neurocircuits controlling the Hypothalamic-Pituitary-adrenal axis

![Diagram of brain regions including hypothalamus, pituitary, and other related structures.]

2.3 History of GABA

Gamma-aminobutyric acid (GABA) is an amino acid neurotransmitter synthesized by decarboxylation of glutamate by the enzyme glutamic acid decarboxylase (Figure 2.3.1). GABA had been long known to exist in plants and
bacteria, where it serves a metabolic role in [31]. However, GABA was not accepted as neurotransmitter until the 1960's after a great deal of physiological experimentation.

In [31] observed that an unknown compound from horse brain inhibited the crayfish stretch receptor when applied exogenously [80]. They further demonstrated that chemically synthesized GABA could inhibit the crayfish stretch receptor [35]. This observation prompted to propose that GABA was acting as an inhibitory neurotransmitter in the brain [49]. However, GABA's extraordinary qualities soon became a burden to its acceptance into the pantheon of neurotransmitters; its enormous abundance in the vertebrate brain-1000-fold higher than known monoamine neurotransmitters, its simple structure and and its role in the Krebs cycle (the "GABA shunt") suggested that it was likely to be involved in metabolism rather than signaling.

Finally, GABA was not found in significant concentrations in any invertebrates. Thus, GABA did not act as a neurotransmitter in organisms that made it; and it was not found in organisms in which it acted. GABA no longer fulfilled the qualifications of a neurotransmitter and by 1960 it had been demoted to a mere metabolite in [125].
2.4 Classification of three GABA Receptor Subtypes

GABA is important for the overall balance between neuronal inhibition and excitation, and is an agonist at three receptor subtypes: GABA$_A$, GABA$_B$, and GABA$_C$ receptors in [78]. The notion of GABA$_A$ and GABA$_B$ were introduced by [125], based on the discovery of difference between GABA-mediated activation of bicuculline-sensitive chloride channels and GABA-mediated activation of cation channels.

These two receptors are pharmacologically, electrophysiologically and biochemically different. The GABA$_A$ is a ligand-gated chloride ion channel, and has a number of binding sites for other ligands, including benzodiazepines,
barbiturates, convulsants such as picrotoxinin.

2.4.1 GABA_A receptors

Electrophysiological recordings from Ascaris by del Castillo demonstrated that GABA application inhibits body muscles by opening chloride channels in [78]. It is now known that these actions of GABA are mediated by the GABA_A receptor, a GABA-gated chloride channel in [88]. In vertebrate neurons, chloride ions are pumped out of the cell; thus, activation of GABA receptors will permit chloride to
diffuse into the cell, hyperpolarize the membrane and decrease the excitability of the cell.

This type of inhibition is called hyperpolarizing inhibition. In some cells, internal chloride is at concentrations higher than the equilibrium potential. In these cases, opening chloride channels caused an efflux of this anion, creating an inward current, and depolarizing the membrane. Nevertheless, this depolarization still inhibits muscle contraction because the increase in chloride conductance creates a 'current shunt' for excitatory currents. Specifically, the abundance of open chloride channels clamps the membrane voltage at the chloride equilibrium potential and 'shunts' further depolarization.

In addition, the weak depolarization caused by chloride conductance inactivates Na\(^+\) channels. This type of inhibition is called depolarizing inhibition. Thus, activation of GABA receptors will inhibit cell activity whether it hyperpolarizes or depolarizes the cell. GABA receptors are probably the most common kind in the mammalian nervous system. It is estimated that close to 40% of the synapses in the human brain work with GABA and therefore have GABA receptors.
Figure 2.4.1 GABA receptors are channel receptors

This means that when GABA binds to them, they change shape slightly to allow ions to pass through their central channel. This channel mainly allows negatively charged chloride neurons to enter the neuron, thus reducing its excitability.

Because of this property of the GABA channel receptor, GABA is classified as an inhibitory neurotransmitter, as opposed to excitatory neurotransmitters, such as glutamate, which augment the nerve impulses in the neuron.
2.5 GABA Metabolism

2.5.1 Figure GABA Metabolism

GABA, the major inhibitory neurotransmitter in brain, is synthesized primarily from glutamate, the major excitatory transmitter, through glutamic acid decarboxylase (GAD) which is a marker for GABAergic neurons. In the mammalian brain, GAD exists in two major isoforms, namely GAD65 and GAD67, which are products of two independently regulated genes, gad2 and gad1,
respectively in [111]. Invertebrates only have one isoform of GAD. GABA is transported in vesicular inhibitory amino acid transporters to the synaptic cleft, where it can interact with its receptor (GABA-R). GABA can activate ligand-gated ion channels (GABAAR and GABACR) and G-protein coupled receptors (GABABR). Alternatively, it can be transported by GABA transporters (gat) back to the presynaptic terminal (recycling) or to the glial cells for degradation.

The first enzymatic degradative step of GABA involves the enzyme GABA-transaminase (GABA-T), which utilizes a-ketoglutarate from the Krebs cycle to regenerate a molecule of glutamate for every molecule of GABA that is catabolised. Hence, the vital neurotransmitter pools of GABA and glutamate are constantly replenished and tightly regulated. The product of the GABA-T reaction is succinic semialdehyde (SSA), which is normally converted into succinate via the enzyme succinic semialdehyde dehydrogenase (SSADH). Succinate enters the Krebs cycle where a-ketoglutarate is formed.

The ongoing conversion of glutamate to GABA and back to glutamate is known as the GABA shunt. In addition, the major precursor of glutamate, glutamine, is synthesized in glial cells. This is transported to neurons, where glutamate and then GABA are metabolized. GABA undergoes reuptake in the glia and is converted to glutamine, which constitutes the GABA shuttle.
2.6 Gamma-aminobutyric acid receptor life cycle

2.6.1 Beyond the nervous system

GABAergic mechanisms have been demonstrated in various peripheral tissues and organs including, but not restricted to the intestine, stomach, pancreas, Fallopian tube, uterus, ovary, testis, kidney, urinary bladder, lung and liver.

In 2007, an excitatory GABAergic system was described in the airway epithelium. The system activates following exposure to allergens and may
participate in the mechanisms of asthma. GABAergic systems have also been found in the testis and in the eye lens.

2.6.2 Structure and conformation

GABA is found mostly as a zwitterion, that is, with the carboxyl group deprotonated and the amino group protonated. Its conformation depends on its environment. In the gas phase, a highly folded conformation is strongly favored because of the electrostatic attraction between the two functional groups. The stabilization is about 50 kcal/mol, according to quantum chemistry calculations. In the solid state, a more extended conformation is found, with a trans conformation at the amino end and a gauche conformation at the carboxyl end. This is due to the packing interactions with the neighboring molecules. In solution, five different conformations, some folded and some extended are found as a result of solvation effects.

The conformational flexibility of GABA is important for its biological function, as it has been found to bind to different receptors with different conformations. Many GABA analogues with pharmaceutical applications have more rigid structures in order to control the binding better.

2.6.3 GABA neurons in nematodes

To identify the GABA-containing cells in C. elegans, wild-type animals were stained with antibodies against the neurotransmitter. Antibody staining revealed that 26 of the 302 neurons present in C. elegans express the neurotransmitter GABA (Figure 2.6.1A). These 26 GABA neurons are comprised
of 6 DD, 13 VD, 4 RME, RIS, AVL and DVB (Figure 2.6.1 B). These neurons fall into different classes based on their synaptic outputs: the D-type neurons, that is, the 6 DD and 13 VD motor neurons, innervate the dorsal and ventral body muscles, respectively; the 4 RME motor neurons innervate the head muscles; the AVL and DVB motor neurons innervate the enteric muscles; and RIS is an interneuron.

Although Ascaris and C. elegans are diverged by 500 million years, their nervous systems are remarkably conserved. In Ascaris, a nearly equivalent set of 26 major GABA-synthesizing neurons were identified by immunostaining in [106]. In the ventral nerve cord 6 DD-like and 13 VD-like cells express GABA. In the head, there are 4 RME-like cells and in the tail a DVB-like cell. Variable staining was observed for additional cells in the head; although there are 6 bilaterally symmetric cells which stained in the cephalic ganglia, they do not appear to be homologs of AVL and RIS.

![Figure 2.6.1, A & B, The GABA nervous system](image)
2.7 Psychoneuroendocrinology

Psychoneuroendocrinology is the clinical study of hormone fluctuations and their relationship to human behavior. It may be viewed from the perspective of psychiatry, where in certain mood disorders, there are associated neuroendocrine or hormonal changes affecting the brain. It may also be viewed from the perspective of endocrinology, where certain endocrine disorders can be associated with psychiatric illness. Brain dysfunctions such as in the hypothalamus can affect the endocrine system, which in turn can result in psychiatric symptoms. This complex blend of psychiatry, neurology and endocrinology is needed to comprehensively understand and treat psychiatric illnesses of a non-psychological etiology.

2.7.1 Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder

Premenstrual dysphoric disorder (PMDD) is a more severe form of premenstrual syndrome affecting 3-8% of women in their reproductive years. PMDD mood disturbances are more severe than those of PMS. The most common symptom is irritability. Many women also report depressed mood, anxiety, or mood swings. These symptoms emerge one to two weeks preceding menses and resolve completely with the onset of menses.

By definition, this mood disturbance results in marked social or occupational impairment, with its most prominent effects in interpersonal functioning. PMDD is a psychiatric diagnosis and is considered to be one of the affective disorders, classified in the DSM-IV-TR as "depressive disorder not otherwise specified." PMDD can be distinguished from other affective disorders primarily by the cyclical
nature of the mood disturbance. Unlike other affective disorders, mood symptoms are only present for a specific period of time, during the luteal phase of the menstrual cycle. Additionally, these mood symptoms do not occur in the absence of a menstrual cycle, as during reproductive events such as pregnancy or menopause.

### 2.7.2 Postpartum Depression (PPD)

Postpartum psychiatric illness is typically divided into three categories:

1. postpartum blues
2. postpartum depression and
3. postpartum psychosis.

It may be useful to conceptualize these disorders as existing along a continuum, where postpartum blues is the mildest and postpartum psychosis the most severe form of postpartum psychiatric illness.

50 to 85% of women experience postpartum blues during the first few weeks after delivery. Given how common this type of mood disturbance is, it may be more accurate to consider the blues as a normal experience following childbirth rather than a psychiatric illness. Rather than feelings of sadness, women with the blues more commonly report mood lability, tearfulness, anxiety or irritability. These symptoms typically peak on the fourth or fifth day after delivery and may last for a few hours or a few days, remitting spontaneously within two weeks of delivery.

Postpartum depression is clinically indistinguishable from depression occurring at other times during a woman's life. Especially with milder cases, it may
be difficult to detect postpartum depression because many of the symptoms used to
diagnose depression (i.e., sleep and appetite disturbance, fatigue) also occur in
postpartum women in the absence of depression. The Edinburgh Postnatal
Depression Scale is a 10-item questionnaire that may be used to identify women
who have PPD. On this scale, a score of 12 or greater or an affirmative answer on
question 10 (presence of suicidal thoughts) raise concern and indicate a need for
more thorough evaluation.

Postpartum psychosis is the most severe form of postpartum psychiatric
illness. It is a rare event that occurs in approximately 1 to 2 per 1000 women after
childbirth. Its presentation is often dramatic, with onset of symptoms as early as the
first 48 to 72 hours after delivery. The majority of women with puerperal psychosis
develop symptoms within the first two postpartum weeks in [124].

2.8 GABA's role in the Brain

GABA is made in brain cells from glutamate, and functions as an inhibitory
neurotransmitter – meaning that it blocks nerve impulses. Glutamate acts as an
excitatory neurotransmitter and when bound to adjacent cells encourages them to
“fire” and send a nerve impulse. GABA does the opposite and tells the adjoining
cells not to “fire”, not to send an impulse.

Without GABA, nerve cells fire too often and too easily. Anxiety disorders
such as panic attacks, seizure disorders, and numerous other conditions including
addiction, headaches, Parkinson's syndrome, and cognitive impairment are all
related to low GABA activity. GABA hinders the transmission of nerve impulses from one neuron to another. It has a calming or quieting influence. A good example to help understand this effect is caffeine. Caffeine inhibits GABA release. The less GABA, the more nerve transmissions occur. Think what too much coffee feels like: that is the sensation of glutamate without enough GABA [88].

The functions that GABA has in the brain are;

- Decreases neuron activity
- Suppresses over firing of nerve cells
- Essential for brain metabolism
- Aids in proper brain functioning
- Is a neurotransmitter in the central nervous system

Stimulates the pituitary gland to secrete (release) more human growth hormone

2.8.1 Human Growth Hormone

There is evidence that getting extra GABA into the brain increases Human Growth Hormone. Injections of GABA directly into the brain increase Growth Hormone in rats. Baclofin, a drug analog of GABA that does reach the brain, increases HGH so it makes sense that GABA would do the same.
2.8.2 GABA effects on the Brain

GABA is the second most common neurotransmitter chemical in the human brain. GABA is an inhibitory neurotransmitter—it calms and reduces the activity of neurons. Some anti-anxiety medications work by promoting greater availability of GABA to brain cells. While many of the basic functions of GABA have become better understood in the last decade, scientists continue to make new discoveries about GABA and the multiple types of GABA receptors, each of which can play a different role in neural cells in [71].

2.8.3 Increase GABA levels in the Brain

GABA and is an amino acid found in the central nervous system. GABA works by lowering brain activity and helps you feel calm. People who lost their job can be a great factor to be stressed, or people who are overly anxious or easily overwhelmed may suffer from the reduced production of GABA in the brain. If the production of GABA is sufficient or healthy, this can aid you in sleep, blood pressure, and relieve pain. To test your GABA levels, a simple urine or saliva test
can determine the levels. This test will also determine whether an increased GABA production is needed.

2.8.4 GABA effects

May reduce symptoms of alcohol withdrawal.

May reduce symptoms of anxiety.

May help some schizophrenics.

May help to reduce high blood pressure.

May increase the effect of insulin so is useful for diabetics but not for hypoglycemia.

May suppress appetite.

May help with premenstrual symptoms.

Helpful for some cases of depression.
2.8.5 GABA side effects:

GABA has little to no side effects. Some sleepiness has been reported. A second approach to enhancing the GABA system includes supplementing with GABAs precursors and potentiators. These include the amino acids listed below. These amino acids freely cross the blood brain barrier and are a safe, effective option for patients using or considering prescription medications or large doses of GABA.

2.8.6 Increasing GABA Naturally

It's possible to increase the amounts of GABA in the body naturally by eating foods rich in glutamine. Foods rich in glutamine are oranges, brown rice, oats, citrus fruits, lentils, spinach, almonds and walnuts. A person with a GABA deficiency can take GABA supplements that come in tablet, capsules, powder or a tea form.
2.8.7 The Effects of GABA on children

For those children who suffer from hyperactivity disorder, taking a GABA supplement daily may help to alleviate the condition and provide a calming affect to the child. GABA supplements have also been known to promote clear thinking and alertness. Learning disabilities in children have been related to ADD and hyperactivity, making GABA supplements helpful. Hyperactivity and learning disabilities result from an imbalance in the brain from a deficiency of neurotransmitters.

2.8.8 The Effects of GABA on weight loss

GABA is the chemical in the body that helps to control stress and inhibit brain activity. Using this neurotransmitter helps to cut down on cravings while lifting our spirits. GABA works double time as an antidepressant and aid to weight loss. Research has shown that GABA is effective for weight loss because it helps our body burn fat.
2.8.9 **GABA most startling effect is in body fat loss**

Modern advances in medical research have uncovered a number of previously unknown facts concerning fat storage and energy utilization by the body. Recent studies have found that higher level of circulating Human Growth Hormone was associated with less body fat and a better lean tissue/stored fat ratio. Additionally, stimulating naturally the levels of Human Growth Hormone led to a marked decrease in fat storage and greater feelings of energy and vigor. HGH is a hormone that is widely known for its powerful anabolic (muscle building) effects as well as its lipotropic (breakdown and utilization of body fat) effects. The overall result of these effects is an increase in lean tissue mass and a decrease in body fat.

Human Growth Hormone (HGH) is produced, stored and secreted by the pituitary gland located at the base of the brain. As you advance in age, HGH is able to continue to be made and stored by the brain, however, it's level of secretion (release into the bloodstream) falls way off. This lack of circulating HGH is the factor that scientists now believe is responsible for the tendency of older individuals to have increased difficulty losing body fat. GABA signals the pituitary to naturally release HGH. Studies have shown that 90 minutes following GABA supplementation, HGH levels increase over five times the previous levels.

2.8.10 **GABA and Pregnancy**

GABA is a "natural" product, it should not be assumed that these supplements are safe to take during pregnancy. GABA supplements may affect
levels of various hormones in the body, many of which are important for a successful pregnancy. Therefore, if you are using GABA and pregnancy occurs, make sure to talk to your healthcare provider.

This is a mistake many pregnant women make. Pregnancy often limits the prescription and nonprescription drugs that a woman can take. As a result, pregnant women often seek safe alternatives, sometimes assuming that dietary supplements are always safe. This is simply not the case. Dietary supplements can be marketed in the United States without any evidence that they are safe, or even effective, for anyone, including pregnant women.

2.8.11 GABA and Breastfeeding

GABA is safe for use while breastfeeding. Because this supplement may affect the levels of various hormones, nursing women are typically advised to avoid GABA. Breastfeeding women should talk to a healthcare provider about the potential risks of GABA use in their particular situation.

2.8.12 GABA and Stress in Everyday Life

GABA plays an important part in helping the brain to regulate the body's internal rhythm and provides people with the ability to manage stress with a better mental focus. Stress is part of everyday life and at times can lead to anxiety and an overactive mind. When this happens, it's hard to stay focused and easy to become frazzled. Too much stress can even lower your immune system and increase your risk of getting sick.
GABA is a natural alternative to taking medications for anxiety and anti-depressants. If you suffer from any of these symptoms, talk to your doctor and ask to have your neurotransmitter levels and hormone levels checked to see if you have an imbalance. GABA has not been tested in pregnant or breast-feeding women, children, or people with liver or kidney disease.

2.8.13 Role of GABA receptors in disease and treatment

GABA plays an important role in many different behavioral and physiological mechanisms including locomotor activity, feeding behavior, aggression, sexual behavior, mood, regulation of pain sensitivity, cardiovascular regulation and thermoregulation. Abnormalities in GABAergic signaling play a role in several disorders including anxiety disorders [71], sleep disorders, epilepsy, tremor, alcoholism, and schizophrenia. For this reason, the GABA system has been targeted for development of drugs that treat these disorders. Most of the pharmacological manipulation of the GABA system has focused on agonizing the effects of GABA, in particular by enhancing the effects of GABA at GABA receptors. GABA receptor agonists have a wide range of clinical uses such as anticonvulsants, anesthetics, anxiolytics, muscle relaxants, sedative/hypnotics and depressants. However, many GABAergic drugs have untoward side effects or high abuse potential that results in psychological and physical dependence. Therefore, the development of more selective drugs that produce the desired effect without unwanted side effects is under pursuit.
2.8.14 GABA levels in Human Disease

Low levels or decreased GABA function in the brain is associated with several psychiatric and neurological disorders, but most primarily anxiety, depression, insomnia, and epilepsy.1-6 Currently, many popular anti-anxiety drugs – the sedative-hypnotics – interact primarily with GABA receptors. These drugs include the benzodiazepine drugs like alprazolam (Alprazolam, Xanax) and diazepam (Valium); as well as drugs like flurazepam (Dalmane); quazepam (Doral); temazepam (Restoril); triazolam (Halcion); zolpidem tartrate (Ambien); and baclofen (Kemstro, Lioresal).

All of these drugs mimic the effects of GABA in a much distorted manner and are associated with significant risks and side effects. Problems with these drugs include the fact that they are highly addictive and are very poor candidates for long term use. Common side effects include dizziness, drowsiness, and impaired coordination and it is important not to drive or engage in any potentially dangerous activities while on these drugs. Alcohol should never be consumed with these drugs as it could be fatal.

Recently, there has been renewed interest in studying the role of GABA in depression as preclinical studies have suggested that GABA levels are decreased in patients suffering from depression.3-5 The role of GABAergic dysfunction in mood disorders was first proposed 20 years ago. Now various antidepressant drugs have
been shown to be effective in unipolar and bipolar patients not only by affecting monoaminergic and serotonergic activity, but also by increasing brain GABAergic activity. GABA is also being investigated for its potential antihypertensive effects.

2.8.15 Pharmagaba: Effects on EEG

Electroencephalogram (EEG) is a well known measure of brain waves activity. The four major brain waves are classified according to their frequency: alpha (less than 8–13 Hz), beta (more than 13 Hz), theta (less than 4–8 Hz), and delta waves (less than 4 Hz). Each wave’s type is associated with a certain mental status. Delta and theta occur during deep sleep and early stages of sleep, respectively. Alpha is generated in relaxed and effortless alertness, while beta is seen in highly stressful situations and where there is difficulty in mental concentration. Therefore, the ratio of alpha to beta waves has been used as indices of relaxation, arousal, anti-stress, and better concentration.

Research has shown that PharmaGABA quickly (i.e. within 5 minutes) and efficiently increases the alpha to beta brain waves ratio – a state often achieved by meditation and characterized by being relaxed with greater mental focus and mental alertness. In one study conducted at the University of Shizuoka, 13 healthy Japanese volunteers, 7 males and 6 females, aged from 21 to 35 years, were enrolled. Two hours before the study they were forbidden to eat, drink or use any form of tobacco. EEG tracings were recorded before and after each of three administrations.
The order of testing for each volunteer administered 200 mL of distilled water was as follows:

(i) only distilled water;

(ii) containing 100 mg of PharmaGABA; and

(iii) containing 200 mg L-theanine (an amino acid from green tea known to increase alpha brain waves).

Tests of the 3 administrations were separated by 7-day intervals. EEG recordings were obtained with the subject resting quietly with closed eyes. EEG tracings were made before administration, then at 0, 30 and 60 minutes after each administration for 5 minute recording sessions. Alpha and beta waves were calculated as a percentage between pre- and post-administration values. Alpha/beta ratios have been calculated as a ratio between alpha and beta percentage values. As apparent in Figures 1 and 2, PharmaGABA produced significant effects on both increasing alpha waves and decreasing beta waves. As a result there was a highly significant increase in the alpha to beta wave ratio.

2.8.16 The use of GABA at novus

- Because of our unique DNA and the way that each of us metabolize drugs, each of us may have different amounts of GABA in the brain but we are still considered to be operating “normally.”
• Unfortunately, there are no accepted medical tests to determine if we have too much or too little GABA activity.

• In addition, it appears that people who are nutritionally deficit and dehydrated often have problems with the operation of GABA in their brains.

• Since almost all of our patients are nutritionally deficient and dehydrated when they arrive at Novus, our Medical Director has implemented the addition of GABA to the IV therapy given to our patients.

• The purpose is to provide a more natural boost to the GABA in the brain and to allow the calming effect of GABA to make the detoxification process more comfortable.

• In addition, the extra GABA will help reduce the anxious feelings experienced by many of our patients who are concerned about how they will feel without drugs.

**The first is neuron**

• A neuron is another name for a nerve cell.

• Nerve cells float in fluid.

• Each neuron has an axon-a thread-like part of the cell that sends signals from the cell body, and a dendrite-a part of the cell that receives signals from other neurons.

• The neurons are not touching and the space between the cells is called the synapse.
• Electrical signals are sent through the synapse to a receptor, a place on a cell that can produce a certain effect—like the production of adrenaline if someone is frightened.

The second term is central nervous system (“CNS”)

• The CNS is composed of the brain and the spinal cord.

• The CNS transmits signals to the rest of the body using chemical messengers called neurotransmitters.

• Neurotransmitters are stored in vesicles—hollow sac-like structures inside the cells.

• These neurotransmitters carry a message from a neuron to receptors on another neuron.

• The action of the neurotransmitters on the receptors has been likened to a key being inserted in a lock.

• When the key is turned the lock opens and the neurotransmitters activate the receptors, which in turn creates an effect in the body.

• Then many of the neurotransmitters return to the releasing vesicles to be used again.
2.9 GABA affect Psychology and Physiology

Because GABA is an inhibitory neurotransmitter, it is involved in processes in which neural activity is reduced, such as anxiety reduction, calming, and release of tension.

Some anti-anxiety medications like benzodiazepines and barbiturates primarily work by increasing the amount of GABA in the synapses that is available to bond to GABA receptor sites. Alcohol also promotes the influx of chloride ions into brain cells, and so amplifies the normal effects of GABA. Caffeine, on the
other hand, reduces the available GABA in the synapse, promoting effects like nervousness, anxiety, and difficulty sleeping.

The calming and inhibitory effects of GABA upon neuronal activity also has important physiological effects. For example, the cardiac vagal neurons (CVNs) are areas of the brain that moderate and slow heart rate, keeping it from becoming too rapid. GABA's inhibitory effect upon these neurons can cause heart rate to increase. Medications that act upon GABA receptors are known as "GABAergic" drugs.

2.9.1 Treatment for Anxiety

There are several treatments for relief from the disruptive symptoms of anxiety, including prescription drugs, hypnosis and breathing exercises. Prescription drugs such as Xanax can cause drowsiness and lethargy, making it difficult to function normally. Treating anxiety with GABA supplements is designed to increase GABA levels in the body. GABA has a soothing, calming and relaxing effect on the body, which efficiently reduces anxiety levels without any hangover symptoms.

2.9.2 Benefits of GABA

- Induces relaxation and sleep. Stops racing thoughts and calms the mind for relaxing, restful sleep.
• GABA is a safe, naturally occurring non-essential amino acid that is safe to use. Unlike Valium and other drugs, there are no side effects with normal dosages of 500-2000 mg.
• Promotes fast relief of tension and anxiety. If you have a highly stressful job or lifestyle, GABA is essential for maintaining a positive calm mood.
• Non-Addictive. Unlike Valium and other calming drugs, GABA produces calming effects naturally without with drawl symptoms.
• Substance abuse victims. Due to it's calming effects, this nutrient interrupts thought patterns and mood swings that send us into destructive behavior patterns.
• Treats many psycho disorders like, schizophrenia, depression, mania, anxiety and bi-polar disorders. Dosages are generally large for these victims since their levels for this nutrient are generally very low.
• Increases sense of well being.
• Reduces muscle tightness and tension.
• Increases HGH (human growth hormone) production.
• Helpful in the treatment of epileptic seizures.
• Aids in ADHD hyperactivity.
• Builds muscle.
• Helpful in mental blocks and thinking disorders. Because of its calming effects, the brain can effectively focus and work better.
• Reduces high blood pressure
• Helps reduce fat and promotes weight loss.
• Useful for enlarged prostates.
Low levels of this amino have been found in people with Multiple Sclerosis (MS), action tremors and other disorders of movement.

2.9.3 Negative Side effects to GABA

There are no negative side effects possible with the use of GABA, however, some beginning users report mild tingling about the face and neck as well as a brief but noticeable change in heart rates or breathing patterns.

2.9.4 Yoga and GABA

One of my standard recommendations for people who have anxiety or depression is to practice yoga. There are controlled clinical trials demonstrating its efficacy, and who hasn't felt that amazing sense of serenity and well-being after a particularly good yoga class? Part of treating anxiety is to bring people down from the state of constant alertness, to help someone be comfortable in his or her own skin for once. Yoga, through the process of holding (sometimes) uncomfortable positions and breathing through the stress, is a direct physical practice teaching you to get through a psychological stress. Eastern ways of viewing stress as a wave to allow to crash over you and pass by rather than as something you can fight off or entirely prevent can be helpful tools for learning to cope.
Yoga has been shown to increase the level of gamma-aminobutyric acid, a chemical in the brain that helps to regulate nerve activity. GABA activity is reduced in people with mood and anxiety disorders, and drugs that increase GABA activity are commonly prescribed to improve mood and decrease anxiety.