A Biochemist's Experience with GABA

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Abstract *This paper examines the clinical applications of gamma-aminobutyric acid (GABA) for the treatment of anxiety, as well as the relationship between GABA and allopregnanolone, a primary metabolite of progesterone. For many years I have been involved in biochemical research of GABA, looking at its elemental structure as well as its permeability across the blood/brain barrier. While it is clear that GABA is helpful for the treatment of anxiety, the current laboratory evidence is insufficient to confirm the uptake and absorption of GABA into the brain, as it appears to act on the central nervous system directly without crossing the blood/brain barrier. A "new" form of GABA, produced from* Lactobacillus hilgardii, *is being marketed as the only form of GABA that crosses the blood/brain barrier. Having studied the molecule for years, I submit that GABA is not a typical left-right rotatory molecule, but rather is part of a macromolecular complex whose biochemical functions are independent of rotation. Because this new form of GABA is no different from pharmaceutical grade GABA in its molecular structure and mechanism of action, it is illogical to contend that it crosses the blood/brain barrier. Additionally, growing GABA from a culture is dangerous because of the potential for bacterial contamination.*

Introduction

Gamma-aminobutyric acid (GABA) is a biochemical molecule that has a profound effect on the central nervous system (CNS). While other amino acids act on the CNS (e.g., L-taurine has a calming effect on the amygdala), GABA is unique, in that it is both an amino acid and neurotransmitter. Biochemically, the root of anxiety is an overfiring of nerves, leading to a feeling of being overwhelmed. Often, when the receptors for the CNS are filled with GABA, this overfiring stops and anxiety can be assuaged.

GABA's Mechanism of Action

While the mechanism of action of GABA is not completely understood, it appears to act on the CNS directly without crossing the blood/brain barrier. In the CNS, the $GABA_A$ receptor (often referred to as $GABA_AR$) is inhibitory, meaning that when GABA binds to it, the result is a calming effect on the body. The $GABA_AR$ is a pentameric (i.e., five-sided) structure comprised of combinations of alpha and beta subunits. Each subunit in turn is comprised of four trans-membrane spanning alpha-helices, which pass through and form a central chloride ion channel. The active site (binding site for GABA) is the alpha-4 subunit which is located between the alpha and beta subunits. When two GABA molecules bind together in this site, the molecule opens the channel and allows chloride ions to flow. This hyperpolarization results in neuroinhibition, or a sensation of calm. All of this is done without the GABA molecule actually crossing the blood/brain barrier.

The $GABA_AR$ also contains several allosteric binding sites which are the target of many current anti-anxiety medications, such as benzodiazepines, barbiturates, ethanol and some neuroactive steroids. When these molecules

bind to the allosteric sites of the $GABA_AR$, the receptor again changes shape and opens the chloride channels.[1] These drugs work by further enhancing chloride influx.[2] By changing the shape of the $GABA_AR$, these drugs might also inhibit the ability of endogenous GABA in the body to bind to the active site of the molecule, thus interfering with the body's natural ability to balance neurotransmitters. This may be the basis for some of the addictive properties of these drugs.

GABA Modulation

While GABA affects both men and women, the hormones progesterone and estradiol are both major modulators of this process, leading to the hypothesis that GABA may function somewhat differently in women than in men. Progesterone produces a breakdown product, allopregnanolone, which enhances the calming effect of GABA. Current research suggests that in the presence of allopregnanolone, GABA binds more easily to the alpha-4 subunit of the $GABA_AR$. Without enough allopregnanolone, GABA does not bind as easily, and this leads to many of the symptoms of progesterone deficiency including severe anxiety, premenstrual syndrome, and post-partum depression.[3]

It is also postulated that hypothalamic cells treated with estradiol will respond to GABA as excitatory rather than inhibitory.[4,5] In my work, I believe that the balance between estrogen and progesterone is critical, and this is one example where upsetting that balance can lead to many problems for women. I have worked with a number of women who are dealing with anxiety and other issues of perimenopause, and have found GABA to be of key importance. Here, I present two patient cases that depict how GABA was used clinically to reduce their anxiety.

Case #1

Elaine was an architecture professor at a prestigious design school. For years she had assumed she was simply a "type-A personality." Then in her early forties, she started experiencing panic attacks, periods when she felt that she could not get enough air. Her long-time internist prescribed venlafaxine and alprazolam, which helped with the depression, but she felt like she was on a roller coaster of anxiety masked by an almost catatonic state as she steadily became dependent on these drugs. As she was in her forties, the time of drug dependency correlated with stage two of perimenopause, which is marked by declining progesterone. She tried to reduce her alprazolam dependency but could not. She had repeated visits to the local emergency room, claiming to her family that she was having severe menstrual cramps, when in fact she was having acute anxiety.

She came to me on the recommendation of one of her emergency room doctors. I started her on a withdrawal protocol from the alprazolam, which had to be done slowly and carefully, and at the same time I gave her a powder-filled capsule (750 mg) of pharmaceutical grade GABA. She was instructed to mix the GABA in water and sip it over 10-20 minutes, which reduces possible side effects of cutaneous flushing and neurologic tingling. Within half an hour, her level of calmness noticeably increased and she was astounded that she could feel that level of calmness without the feeling of being drugged. She was maintained on the 750 mg/day of GABA mixed in water. She was also prescribed bio-identical progesterone (not synthetic progestins found in birth control pills) to potentiate the therapeutic effects of GABA and reduce her perimenopausal symptoms. Doses of 750-1000 mg of GABA, up to three times daily, are ideal for stopping panic attacks. Some clinicians use more but I have found higher doses to be unnecessary for most women, especially if progesterone is used. (Men may need more than 750 mg/day, though not often). Higher daily doses of GABA appear to affect hyperpolarization more significantly.

I followed Elaine for over five years. She improved using a combination of hormones, GABA, and therapy. As Elaine got her anxiety under control, she was able for the first time, to get in touch with the much deeper depression and feelings of alienation that had been haunting her since early adolescence.

Case #2

In high school, Lilly struggled with extreme premenstrual syndrome, which caused severe, painful cramps, combined with powerful feelings of anxiety, and obsessive/compulsive thinking. This left her feeling as if her head were disconnected from her body. At times, she felt as if she was drowning in her emotional world. During her twenties, therapy helped but it was the later combination of biochemical support and talking about her feelings that allowed her to see life more clearly.

Lilly also had a curvy body, typical of women who tend toward estrogen dominance in their younger years (i.e., she had far more estrogen relative to progesterone). Many women at mid-life and younger have serious deficits of progesterone that impact everything from irregular cycles to mood issues, leading to symptoms like irritability, anxiety and an overt sharpness of the tongue.

Initially, Lilly responded well to bio-identical progesterone and 400 mg/day of GABA in a blend with other nutrients and herbs to potentiate its therapeutic effects (i.e., 100 mg of magnesium, 100 mg of glycine, 10 mg of vitamin B_6, 140 mg of glutamine, 150 mg of passion flower herb powder, and 150 mg of primula veris officinalis herb powder). The combination of GABA and bio-identical progesterone helped Lilly immensely.

I have been following Lilly for many years now. I have observed similar curvy, big- breasted women as they move into perimenopause and menopause. While these women tend toward estrogen dominance and respond beautifully to progesterone when they are younger, as they age and get closer to late perimenopause, their cells demand more estrogen because that is what they were used to. As primary estradiol plummets, they experience a shift from anxiety to more of a flat affect. The estrone goes up, the estradiol goes down, and brain fog and depression set in. This is why there is such a crucial need to manage anxiety in its early stage since later the chemical changes precipitate a need for more estrogen. In Lilly's case, she responded well to progesterone when she was younger, and then needed increased estrogen as she moved through menopause. GABA was an integral part of managing these physiologic transitions.

A New GABA?

There is a "new" natural form of GABA, manufactured from *Lactobacillus hilgardii* (the bacteria used to ferment vegetables in the preparation of the traditional Korean dish, kimchi). This form of GABA is marketed as being unique because it is harvested in a culturing process, similar to the way Kimchi is grown. There are also numerous ads stating that it is proven to cross the blood/brain barrier and that it increases brain alpha-waves and lowers beta-waves, creating significant physical relaxation while maintaining mental focus.

While it is true that GABA is an amino acid, it is not an alpha amino acid and not a protein amino acid. The molecule is not chiral, so there are no L- and D- forms, and no left-right rotation. There is no possibility of non-superimposable mirror images to exist. To observe asymmetry, there has to be at least one asymmetric center–GABA has none. This new form of GABA is therefore no different from pharmaceutical grade GABA in its molecular structure and mechanism of action, and therefore it is illogical to contend that it crosses the blood/brain barrier.

Pharmaceutical grade GABA is synthesized, and not made by fermentation, as most of the alpha amino acids are. Based on historical problems with producing amino acids from culture, I believe this process is potentially a dangerous medium for GABA synthesis because of the possibility for bacterial contamination, as happened some years ago in Japan when tryptophan was manufactured this way.

Conclusion

GABA is nature's way of calming the nervous system. I have found GABA to be extremely useful in the treatment of anxiety. It is a safe and non-addictive treatment with far fewer side effects commonly seen

with traditional pharmacological agents. For women in perimenopause, its effectiveness is enhanced by the addition of bio-identical progesterone.

Statement of Informed Consent

Written consent was obtained from these patients for publication of this report.

Competing Interests

The author declares that she has no competing interests.

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