AUCTORES
Globalize your Research

Journal of Neuroscience and Neurological Surgery
Elizaveta I Bon *

Open Access

Review Article

The Place of Mood Stabilizers in The Treatment of Anxiety Disorders

Bon E.I., Rai K.O

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus

***Corresponding Author:** Elizaveta I Bon, Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

Received date: March 22, 2024; Accepted date: April 10, 2024; Published date: April 29, 2024

Citation: Bon E.I., Rai K.O, (2024), The Place of Mood Stabilizers in The Treatment of Anxiety Disorders, *J. Neuroscience and Neurological Surgery*, 15(3); DOI:**10.31579/2578-8868/312**

Abstract

Mood stabilizers are used to treat bipolar disorder, but some drugs, in particular valproate, have anti-anxiety activity. This property is determined by the effect of valproate on the GABAergic system. Gamma-aminobutyric acid is involved in neurotransmission through interneuronal synapses in areas of the brain that control mood, such as the striatum, globus pallidus, and cerebral cortex. One of the most widespread mediators that plays a central role in the pathophysiology of anxiety disorders is the gamma-aminobutyric acid (GABA) system. This fact allows us to consider valproic acid as the drug of choice in the treatment of anxiety disorders.

Key Words: normotimics, mood stabilizers, valproic acid, VPA, gamma-aminobutyric acid, GABA, GABA receptors, anxiety disorder.

Introduction

Normotimics, mood stabilizers, are psychotropic drugs primarily used for treating bipolar disorder in acute phases or for maintenance therapy to prevent relapse. [1]

Some normotimic drugs have additional valuable psychotropic properties. For example, valproates exhibit not only normotimic but also pronounced anxiolytic and antipanic activity, allowing their use in panic disorder, anxiety disorders, and when anxiety is present in the structure of another mental illness.

Valproic acid (VPA), a short-chain branched fatty acid, is the drug of choice for the treatment of epilepsy and may act as a mood stabilizer. There are three pathways for the metabolism of valproic acid: glucuronidation, mitochondrial oxidation, and cytochrome P450-mediated oxidation. In this case, glucuronidation is 50%, mitochondrial oxidation is 40%, and oxidation by cytochrome P450 is 10%, respectively. Serum contains 70–94% VPA bound to albumin. The half-life of VPA is 13-18 hours.[2]

The mechanism of action of VPA includes:

Inhibition of gamma-aminobutyric acid (GABA) transaminase:

VPA inhibits the function of the GABA transaminase enzyme, which is responsible for the degradation of GABA, the predominant inhibitory neurotransmitter in the brain. As a result, the level and activity of GABA increases, which leads to increased inhibition of neuronal functions. In neuropathic pain, VPA causes neurogenic inflammation through GABA-A receptor-mediated inhibition.

Enhances GABA synthesis by increasing the expression and activity of glutamic acid decarboxylase (GAD). This enzyme is responsible for converting glutamate, which in turn is one of the main excitatory neurotransmitters in the brain, into GABA. This leads to increased levels and activity of GABA.

VPA inhibits GABA succinate semialdehyde dehydrogenase (SSA-DH). This enzyme is responsible for the accumulation of gamma-aminobutyric acid through its maintenance.

Valproic acid inhibits the action of histone deacetylases enzymes (HDAC). Acts mostly on HDAC1. Histone diacelase 1 is the main enzyme regulating gene expression. Recently, inhibition of this enzyme occurs as a result of recent changes in chromium, which affect the transcription of many genes. This may explain VPA's effects on mood.

Inhibition of sodium channels that are potential dependent: the main effect of valproic acid is the effect of the penetration of sodium ions into neurons, ultimately reducing neuronal excitability and firing rate.

VPA affects the function of calcium sources, such as T-type, L-type and N-type calcium compounds. These functions include a range of functions: neuronal signaling and neurotransmitter release, gene expression and cell survival.[4]

VPA can also inhibit the TCA (tricarboxylic acid cycle) at the alpha-ketoglutarate dehydrogenase stage.

Due to the action of valproate on the GABAergic system, it can act as an anxiolytic in anxiety disorders. A special place is occupied by inhibition of gamma-aminobutyric acid transaminase, a derivative of GABA synthesis, and inhibition of succinate semialdehyde dehydrogenase.

The GABAergic system is responsible for the synthesis and degradation of gamma-aminobutyric acid, as well as its release and interaction with receptors.[5]

The GABAergic system consists of the following components:

1. GABA

2. glutamate decarboxylase

3. GABA-A receptors,

4. GABA-B receptors

5. GABA transporters (GAT). [5]

Gamma-aminobutyric acid (GABA) or 4-aminobutyric acid is part of the group of non-protein amino acids and contains four carbons. GABA is the main inhibitory neurotransmitter in the central nervous system.[6]

Gamma-aminobutyric acid is involved in neurotransmission through interneuronal synapses in the brain and also coordinates brain activity. Some of which control mood, such as the striatum, globus pallidus and cerebral cortex. [7][8]

The biosynthesis of gamma-aminobutyric acid begins with glutamate under the action of the enzyme glutamate decarboxylase. Glutamate decarboxylase (GAD English glutamate decarboxylase) consists of two isoforms: GAD65 and GAD67. GABA can be synthesized in two ways. Direct synthesis from glutamic acid is catalyzed by GAD65 or GAD67, and synthesis from glutamic acid produced by trichloroacetic acid is catalyzed by the GAD67 isoform. [9]

GABA is then converted into succinate semialdehyde due to metabolic processes. Under the action of GABA transaminase and succinate semialdehyde dehydrogenase, succinate semialdehyde is converted to succinate. Therefore, by acting on these enzymes, valproic acid promotes the accumulation of GABA in the central nervous system. [3]

GABA receptors are inhibitory pentameric ligand-dependent receptors that influence the resting potential through the influx of chloride ions. However, if chloride accumulates intracellularly, it can depolarize the membrane, changing the intracellular concentration and making the Nernst potential less negative. When the Nernst chloride potential becomes less negative than the resting membrane potential, the opening of GABA receptors causes chloride efflux instead of influx, resulting in membrane depolarization instead of hyperpolarization.[10]

Cells that have GABA receptors on them can transmit the GABA-mediated signal in different ways, either using metabotropic or ionotropic receptors. There are two types of GABA receptors, GABA A and GABA B, which differ in their structure. Previously, there was another type of ionotropic GABA C receptor, but at this point in time it is classified as a subtype of GABA A receptor. [11] [8]

γ-aminobutyric acid subtype A receptors are well-known inhibitory neurotransmitter receptors in the central nervous system. They belong to the family of ligand-gated ion channels. GABA A are heteropentamers, which are formed from 19 subunits: six α (alpha1-6), three β (beta1-3), three γ (gamma1-3), three ρ (rho1-3) one δ (delta), ε (epsilon), π (pi) and θ (theta). Due to this, there are many isoforms of the receptor. The genes responsible for the synthesis of subunits are located on chromosomes 4, 5, 15 and X of the human genome. Each of these isoforms may exhibit different pharmacological and physiological properties. In humans, most GABA A receptors consist of two α subunits, two β subunits, and one γ subunit. [8]

GABA B receptors belong to the group of metabotropic receptors and are heterodimeric, coupled through G proteins with potassium and calcium channels. GABA B receptors are located not only in the central nervous system, but also outside it, unlike GABA A receptors. [11] [12]

GABA B receptors exert their inhibitory effect through activation of K + channels, inactivation of Ca 2+ channels and inhibition of adenylate cyclase. GABA B receptors are strict heterodimers that are formed by the assembly of subunits R1 and R2, each of which consists of three domains: a long extracellular N-terminal domain or otherwise the Venus flytrap domain, which contains a binding site, a heptahelical transmembrane domain and a C- terminal intracellular tail. The Venus flytrap domain of the R1 subunits binds to ligands but not to the R2 subunits, although they have similarities. R2 subunits couple to G protein, providing slow and long-lasting G protein-mediated inhibitory signals.[13]

GABA transporters play a huge role in GABA homeostasis.

There are four GABA transporters GAT1, GAT2, GAT3 and BGT-1. GATs are expressed in presynaptic neurons as well as surrounding astrocytes. GAT1 is a GABA transporter that is highly expressed, in contrast to GAT2, which has the lowest expression. Inhibition of GABAergic signaling by GABA occurs in two ways. One of them involves either transport back to the releasing neuron, which takes up 80%, the second involves transport into the surrounding glial cells, which takes up 20%, where it is further metabolized into glutamine. [14]

One of the most common biomarkers of anxiety disorders is the gamma-aminobutyric acid (GABA) system. An imbalance between excitatory and inhibitory CNS neurotransmitters has been found in patients with anxiety disorders, especially panic disorder. [15]

Also, a connection between anxiety disorders and GABA is indicated by the response to treatment with anxiolytics, as well as studies of the mechanism of action, genetic engineering and neuroimaging studies of the GABA receptor. The overall results indicate a relative deficit in GABA neurotransmission, which may be enhanced by the use of a drug such as valproate, which increases brain GABA levels or neurotransmission by influencing GABA metabolic pathways. [16] Oral GABA supplementation has also been shown in studies to reduce anxiety in people under stress.[19]

Based on the data, animal studies were conducted

The effect of valproic acid on the activity of enzymes responsible for further metabolism of GABA was studied using mouse brain homogenates [17]

Numerous studies have documented an increase in GABA concentrations in the brain of rodents following VPA administration. [18]

In mice, valproate showed an anxiolytic effect in a mirror chamber test. VPA produced behavioral changes very similar to those caused by lorazepam, supporting the use of valproate in anxiety disorders. [20]

Human studies have shown

Use of valproate in a translational human model of anxious behavior. Valproate had an anxiolytic effect.[21]

The effectiveness of valproic acid in participants with social anxiety disorder showed that there were changes in the primary outcome measures from baseline in the Liebowitz Social Anxiety Scale total score. The results of this open-label study indicate the effectiveness of valproic acid for the treatment of social anxiety disorder.[22][23]

Thus, mood stabilizers, in particular valproic acid, have an anxiolytic effect due to their effect on the GABA-erinic system. Therefore, valproic acid can be considered as a drug of choice in the treatment of anxiety disorders.

References

1. Chen CK, Yang SY, Park SC, Jang OJ, Zhu X, Xiang YT, Ouyang WC, Javed A, Sayeed Khan MN, Grover S, Avasthi A, Kallivayalil RA, Chee KY, Chemi N, Kato TA, Hayakawa K, Pariwatcharakul P, Maramis M, Seneviratne L, Sim K, Lin SK. (2023). Clinical use of mood stabilizers beyond treatment for bipolar disorder: The REAP-MS study Asian J Psychiatr Jul:85:103613.
2. Ayesha Safdar and Fatima Ismail. (2023). A comprehensive review on pharmacological applications and drug-induced toxicity of valproic acid. Saudi Pharm J. Feb; 31(2): 265–278.
3. Masum Rahman; Ayoola O. Awosika; Hoang Nguyen. Valproic Acid.Last Update: August 17, 2023.
4. Demetra J. Mills. (2021). The Aging GABAergic System and Its Nutritional Support. J Nutr Metab. 2021: 6655064. Published online 2021 Apr 25.
5. Yu Shan, Jianan Zhao, Yixin Zheng, Shicheng Guo, Steven J. Schrodi and Dongyi He. (2023). Understanding the function of the GABAergic system and its potential role in rheumatoid arthritis. Front Immunol. 14: 1114350. Published online 2023 Feb 7.
6. Hellen A. Oketch-Rabah, Emily F. Madden, Amy L. Roe, and Joseph M. Betz Evasio Pasini, Academic Editor, Francesco S. Dioguardi, Academic Editor, and Giovanni Corsetti, Academic Editor. (2021). United States Pharmacopeia (USP) Safety Review of Gamma-Aminobutyric Acid (GABA). Nutrients. Aug; 13(8): 2742. Published online 2021 Aug 10.
7. Jung Goo Lee, Young Sup Woo, Sung Woo Park, Dae-Hyun Seog, Mi Kyoung Seo, and Won-Myong Bahk. (2022). Neuromolecular Etiology of Bipolar Disorder: Possible Therapeutic Targets of Mood Stabilizers. Clin Psychopharmacol Neurosci. May 31; 20(2): 228–239. Published online 2022 May 31.
8. Amr Ghit, Dina Assal, Ahmed S. Al-Shami, and Diaa Eldin E. Hussein. (2021). GABAA receptors: structure, function, pharmacology, and related disorders. J Genet Eng Biotechnol. Dec; 19: 123. Published online 2021 Aug 21.
9. Yu Shan, Jianan Zhao, Yixin Zheng, Shicheng Guo, Steven J. Schrodi, and Dongyi He. (2023). Understanding the function of the GABAergic system and its potential role in rheumatoid arthritis. Front Immunol. 14: 1114350. Published online 2023 Feb 7.
10. Sager Nawafleh, Abdallah Barjas Qaswal, Aiman Suleiman, Obada Alali, Fuad Mohammed Zayed, Mohammad Abu Orabi Al-Adwan, and Mo'ath Bani Ali, Anna Pannaccione, Academic Editor. (2022). GABA Receptors Can Depolarize the Neuronal Membrane Potential via Quantum Tunneling of Chloride Ions: A Quantum Mathematical Study. Cells. Apr; 11(7): 1145. Published online 2022 Mar 28.
11. Erwan Sallard, Diane Letourneur, and Pascal Legendre. (2021). Electrophysiology of ionotropic GABA receptors. Cell Mol Life Sci. 78(13): 5341–5370. Published online 2021 Jun 1.
12. Styliani Vlachou. A Brief History and the Significance of the GABAB Receptor. (2022). Curr Top Behav Neurosci 52:1-17.
13. Miho Terunuma. (2018). Diversity of structure and function of GABAB receptors: a complexity of GABAB-mediated signaling. Proc Jpn Acad Ser B Phys Biol Sci. Dec 11; 94(10): 390–411.
14. Manan Bhatt, Laure Gauthier-Manuel, Erika Lazzarin, Rocco Zerlotti, Christine Ziegler, Andre Bazzone, Thomas Stockner, and Elena Bossi. (2023). A comparative review on the well-studied GAT1 and the understudied BGT-1 in the brain. Front Physiol. 14: 1145973. Published online 2023 Apr 13.
15. Jeffrey R. Strawn, MD and Amir Levine, MD. (2020). Treatment Response Biomarkers in Anxiety Disorders: From Neuroimaging to Neuronally-Derived Extracellular Vesicles and Beyond. Biomark Neuropsychiatry. Author manuscript; available in PMC 2020 Dec 1. Published in final edited form as: Biomark Neuropsychiatry. Dec; 3: 100024. Published online 2020 Jul 17.
16. Charles B Nemeroff. (2003). The role of GABA in the pathophysiology and treatment of anxiety disorders. Psychopharmacol Bull 37(4):133-46.
17. M C Sawaya, R W Horton, B S Meldrum. (1975). Effects of anticonvulsant drugs on the cerebral enzymes metabolizing GABA. Epilepsia Nov;16(4):649-55.
18. Todd D. Gould, Guang Chen, and Husseini K. Manji. (2012). Mood stabilizer psychopharmacology. Clin Neurosci Res. Author manuscript; available in PMC Jun 14.
19. Zhou Heli, Chen Hongyu, Bao Dapeng, Tan Yee Shin, Zhong Yejun, Zhang Xi, and Wu Yingying. (2022). Recent advances of γ-aminobutyric acid: Physiological and immunity function, enrichment, and metabolic pathway. Front Nutr. 9: 1076223. Published online Dec 22.
20. A Padovan Lang , L de Angelis. (2003). Experimental anxiety and antiepileptics: the effects of valproate and vigabatrin in the mirrored chamber test. Methods Find Exp Clin Pharmacol May ;25(4):265-71.
21. Dominik R Bach, Christoph W Korn , Johanna Vunder , Antonia Bantel. (2018). Effect of valproate and pregabalin on human anxiety-like behaviour in a randomised controlled trial. Transl Psychiatry Aug 16;8(1):157.
22. Gustavo Kinrys , Mark H Pollack, Naomi M Simon, John J Worthington, Antonio E Nardi, Marcio Versiani. (2003). Valproic acid for the treatment of social anxiety disorder. Int Clin Psychopharmacol May ;18(3):169-72.
23. Chih-Ken Chen , Shu-Yu Yang , Seon-Cheol Park , Ok-Jin Jang , Xiaomin Zhu , Yu-Tao Xiang , et al,(2023). Clinical use of mood stabilizers beyond treatment for bipolar disorder: The REAP-MS study. Asian J Psychiatr Jul:85:103613.

DOI: 10.31579/2578-8868/312