

Killing ourselves by Forgetting the Brakes

A deep dive into GABA,
Positive Allosteric Modulators,
and Natural Equivalents

Scott Sherr MD

Disclosures

- COO, Health Optimization Medicine and Practice
- COO, Troscriptions
- Founder, Integrative HBOT
- Cofounder, OneBase Health
- Dr. Alan Sherr

Top Symptoms of GABA deficiency

- Mental Health:
 - Anxiety, Fear, Depression, short temper, Phobias, impulsiveness / disorganization, addictions, migrains
 - Schizophrenia
 - OCD
- Systemic Symptoms:
 - IBS, Diarrhea, HTN, tinnitus, chronic pain, allergies, frequent urination, flushing/blushing, sweating, salt cravings, muscle tension, muscle wasting (or difficulty gaining muscle)

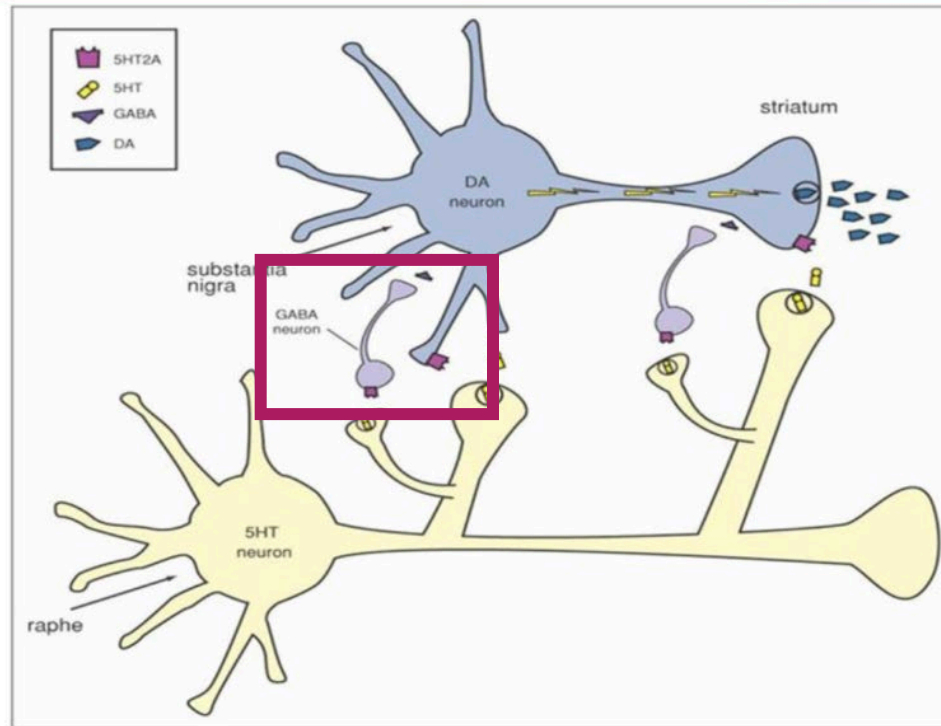
Anxiety

- In 2021, a sample of 1978 American men and women was prevalent in 42% of the population, with women more likely than men to have anxiety symptoms.
- The pandemic increased rates by 25%.
- People are self-medicating with food (→ Obesity), alcohol (→ Liver failure), and illegal drugs (→ Overdoses).
- Prescribed medications for anxiety (Xanax, Valium, Ativan, etc) and sleep (Ambien, Lunesta) are highly addictive, very difficult to stop, and are associated with increases in all-cause mortality.

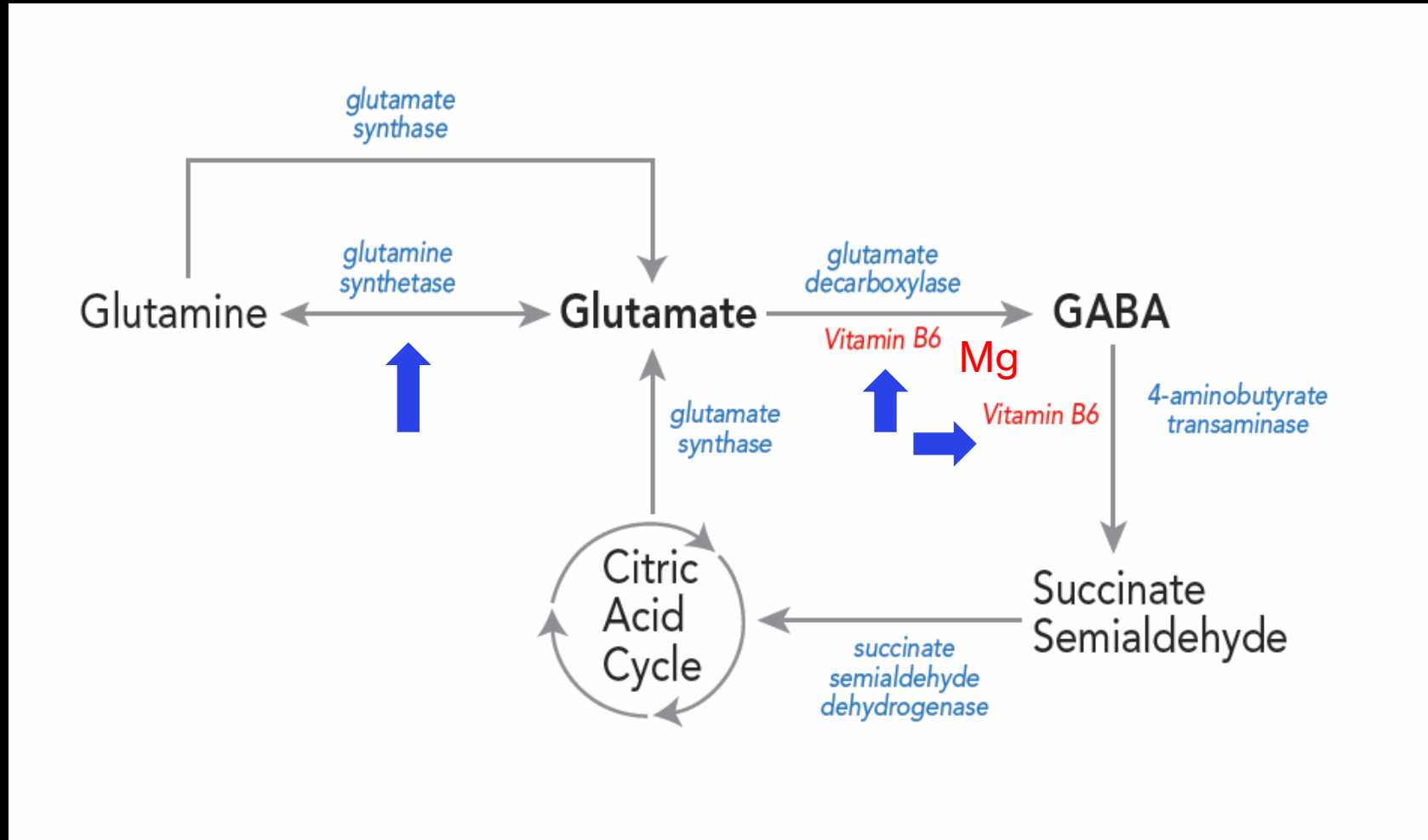
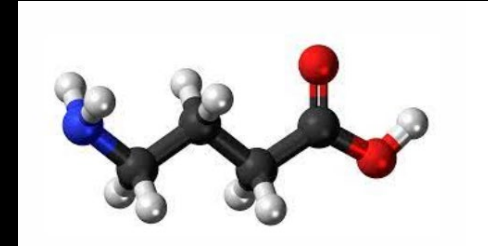
Depression

- Pre-pandemic, between 2015 and 2020, the incidence of depression rose to nearly 10% in American adults and almost 20% in teens and young adults (17%)
- Pandemic increased rates by 25%
- Depression is a primary driver of suicide and suicide attempts
- Often these patients turn to drugs, alcohol, and risky behaviors
- The drugs we use come with black box warnings of suicidality, especially in young people.

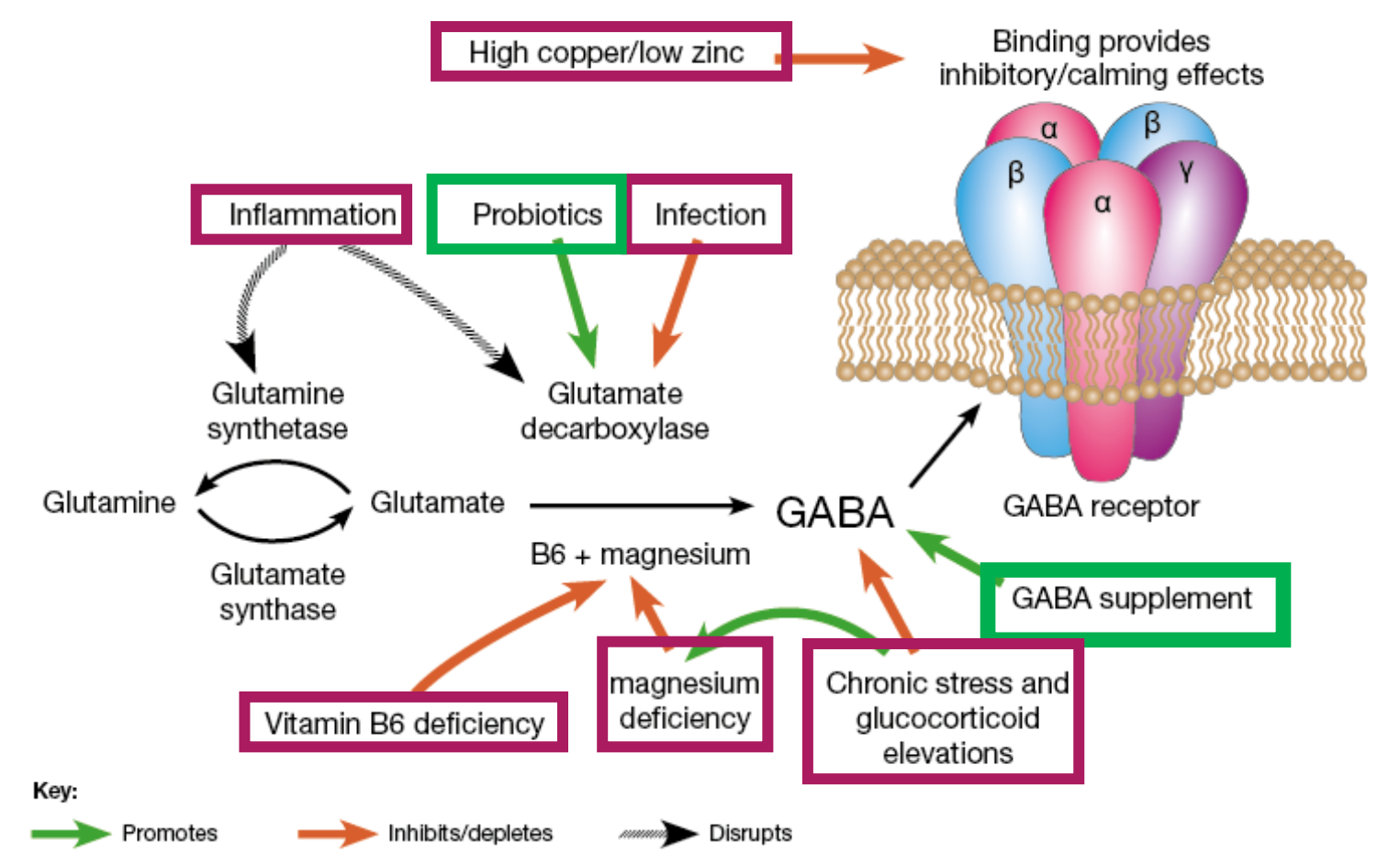
GABA Cells are Inter-neurons



GABA Synthesis



Factors Affecting GABA Synthesis

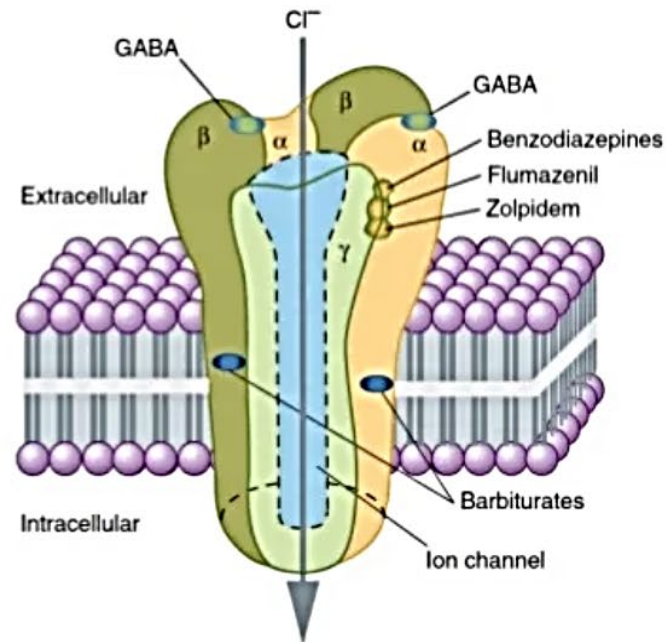


GABA Receptors

Gamma aminobutyric acid (GABA) is the major inhibitory neurotransmitter

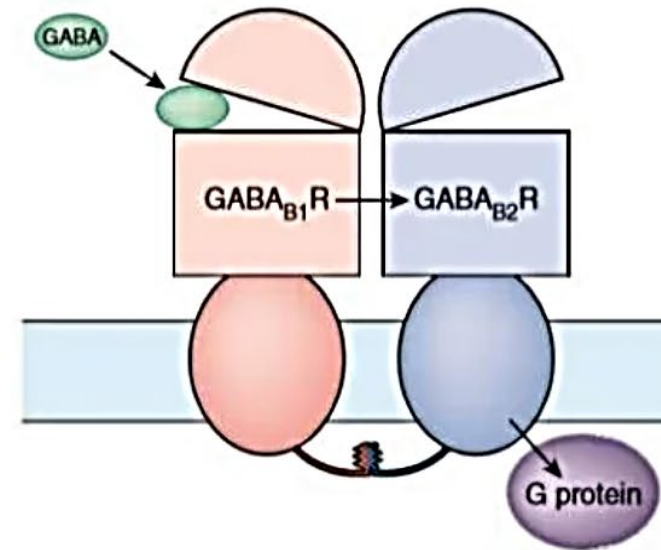
20% of CNS transmission

GABA A Receptors



Ionotropic (Cl^- channel)
Pentamer

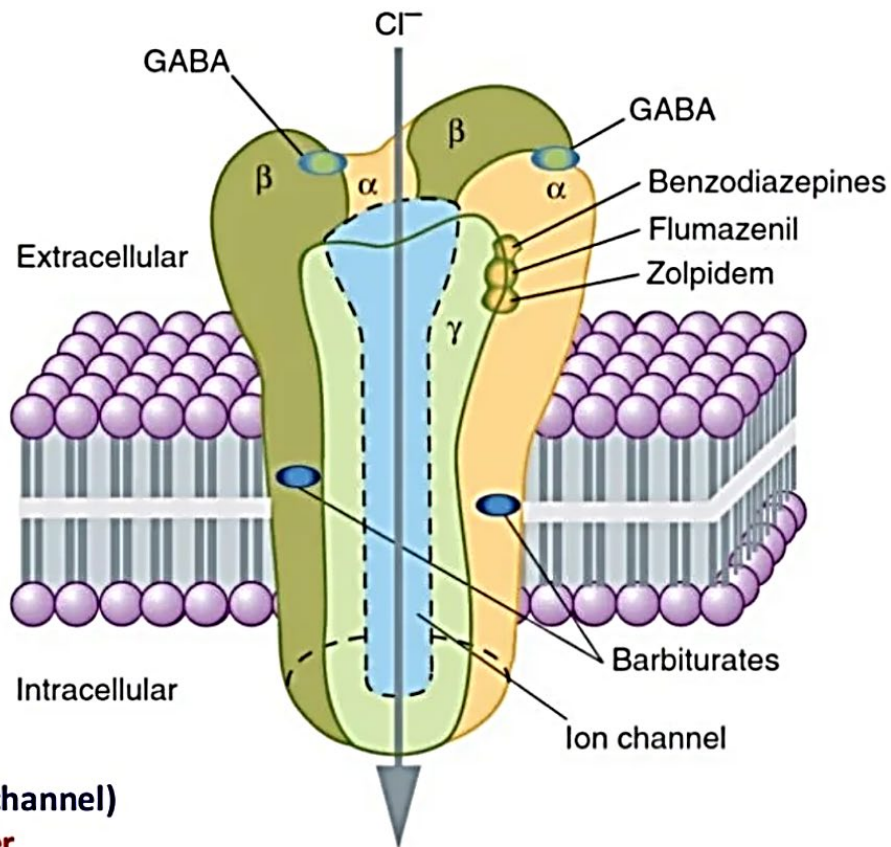
GABA B Receptors



Metabotropic (Gi-prot.)
Dimer

GABA A Receptors

GABAA receptor



Ionotropic (Cl^- channel)
Pentamer

The GABA_A receptors are made up of subunits which form a receptor complex. Humans have **19 receptor subunits** and are classified into α (1–6), β (1–3), γ (1–3), δ , ϵ , π , θ , and ρ (1–3). The function of the receptor is different according to how the pentameric complex is put together. The most common complex that includes around 40% of the GABA_A receptors is the **$\alpha 1\beta 2\gamma 2$** combination.

Mechanism of action

→ Activation of **GABA_A receptor**
(Endogenous – GABA, Inositol; Exogenous - Drugs)



→ Opening of central pore



→ **↑ influx of Cl⁻ ions** through the pore



→ Hyperpolarization of the neuronal membrane



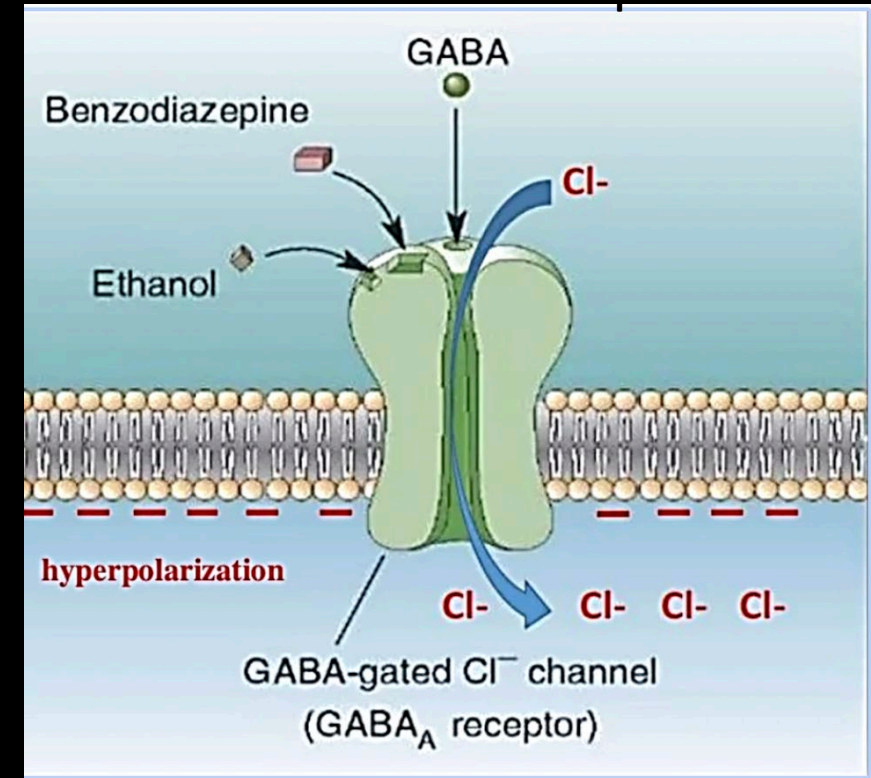
→ ↓ occurrence of action potential



→ **Inhibition of neurotransmission**
(early part of IPSP)

15

Mechanism of action: GABA A receptor

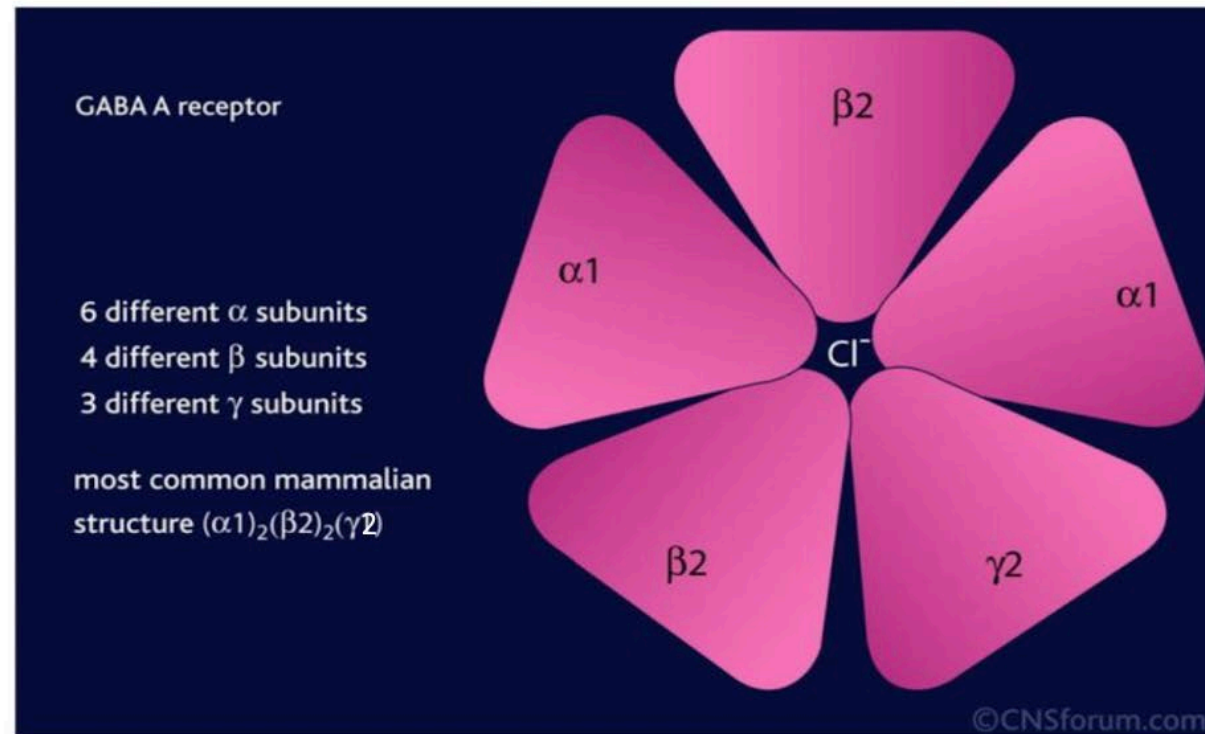


Receptor Selectivity

Selectivity for GABA-A Receptor Subunits

GABA A Receptors containing **Alpha 1** subunits are involved in SLEEP MODULATION

GABA A Receptors containing **alpha 2 or alpha 3** subunits are involved in EXPERIENCES of ANXIETY

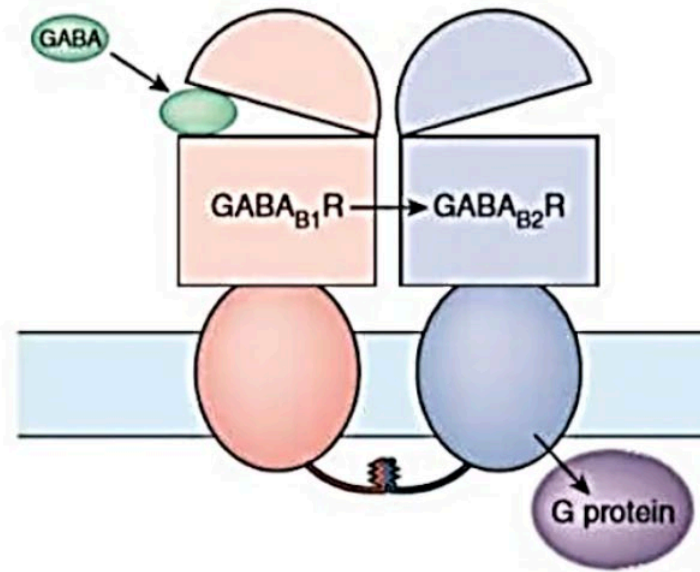


Composition, Distribution, and Major Functions of GABA_A Receptors

SUBUNIT COMPOSITION	LOCATION	FUNCTION
$\alpha 1\beta 2\gamma 2$	Widespread GABA Neurons	Sedation, anticonvulsant activity
$\alpha 2\beta 3\gamma 2$	Forebrain, spinal cord	Anxiety, muscle relaxant
$\alpha 2\beta 1\gamma 1$	Glia	
$\alpha 3\beta 3\gamma 2$	Cortex	Anticonvulsant activity
$\alpha 4\beta 2\gamma 2$	Thalamus	
$\alpha 4\beta 2/3\gamma 2$	Dentate gyrus	
$\alpha 4\beta 2\delta$	Thalamus	Tonic inhibition
$\alpha 4\beta 2/3\delta$	Dentate gyrus	
$\alpha 5\beta 3\gamma 2$	Hippocampus CA1 Sensory Ganglia	Tonic inhibition
$\alpha 6\beta 2/3\gamma 2$	Cerebellar granule cells	
$\alpha 6\beta 2/3\delta$	Cerebellar granule cells	Tonic inhibition
$\gamma 3, \theta, \epsilon$	Little information	

GABA B receptor

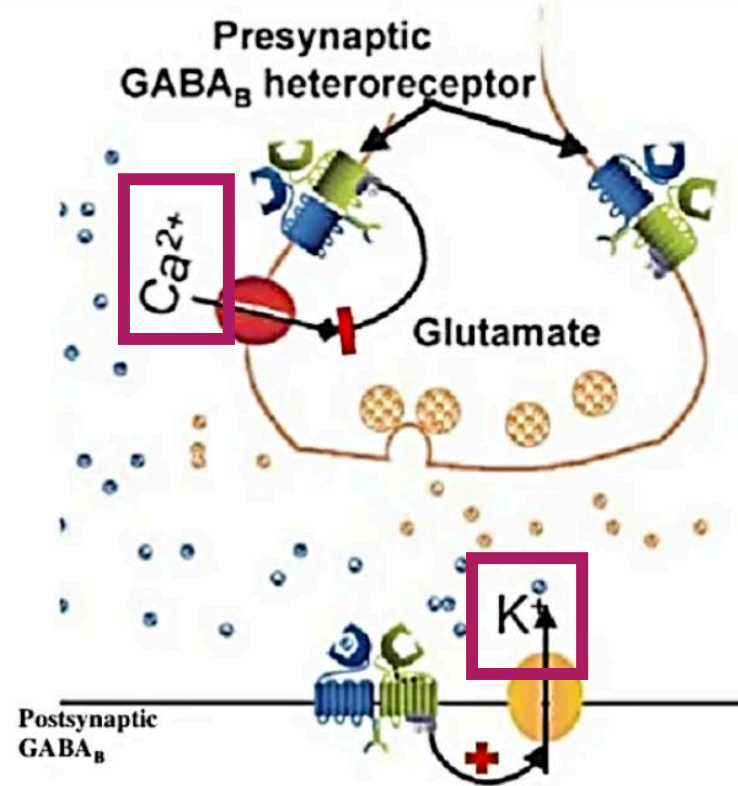
Dimer : 2 transmembrane domains: GABA_{B1} & GABA_{B2}



Metabotropic (Gi-prot.)

Coupled to Gi proteins → ↓CAMP →
inhibit Ca²⁺ channels (Presynaptic)
activate K⁺ channels (Postsynaptic)

GABA B Receptor Mechanism



Neuronal Inhibition

GABA_B receptors: Metabotropic (G-prot.) > in Spinal cord

Presynaptic ↓ Ca²⁺ influx → ↓ release of the excitatory transmitter glutamate.

Postsynaptic ↑ K⁺ outflux → hyperpolarization

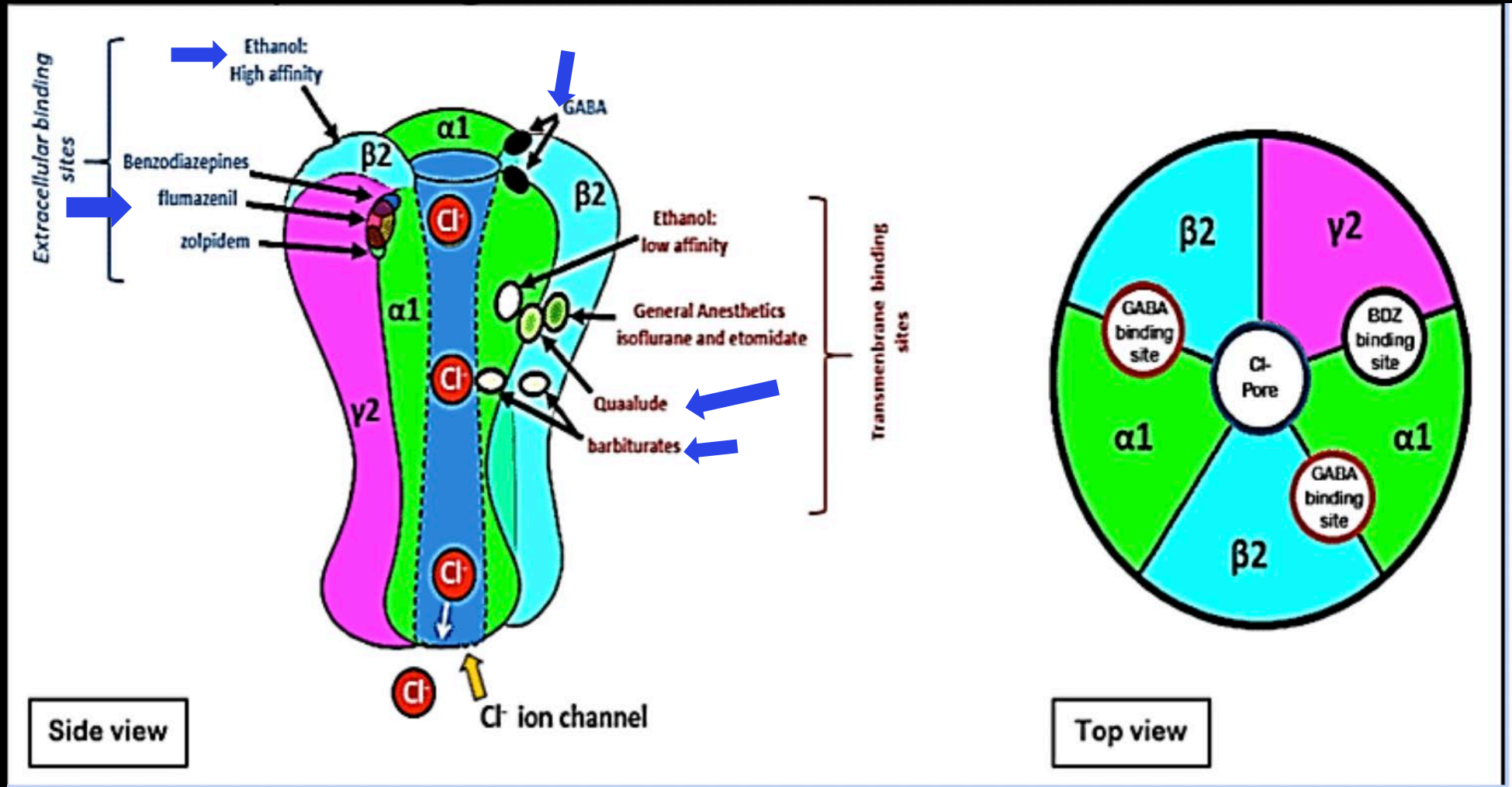
	GABA A	GABA B
Type	Ionotropic	Metabotropic
Location	Widespread; Post-synaptic	Widespread; Pre- & Post-synaptic
Structure	Pentamer	Dimer
MOA	Post-synaptic inhibition by - ↑ Cl⁻ influx	Pre-synaptic inhibition by – ↓ Ca²⁺ entry Post-synaptic inhibition by – ↑ K⁺ permeability
Endogenous agonist	GABA	GABA

	GABA A	GABA B
Pharmacological effects	<ul style="list-style-type: none"> ✓ Sedation ✓ Hypnosis ✓ Anxiolysis ✓ Anticonvulsant ✓ Amnesia ✓ Muscle relaxation ✓ Euphoria 	<ul style="list-style-type: none"> ✓ Central muscle relaxation ✓ Epileptogenesis ✓ Suppression of drug craving ✓ Antinociception ✓ Cognitive impairment ✓ Inhibition of hormone release

Receptor Ligands and Modulators

- Orthosteric Ligands: A chemical that interacts with the same binding sites as the natural endogenous chemicals found in our body. In this case, the natural chemical would be GABA
- Allosteric Ligand (or allosteric modulator): This is a chemical that works by modifying how the receptor behaves when it has been bound to an orthosteric ligand. The allosteric binding sites are distinctly separate from the site of the main neurotransmitter (GABA).
- Positive Allosteric Modulator (PAM): a modulating chemical that binds to an allosteric site and increases the affinity or the efficacy of an agonist for that receptor.

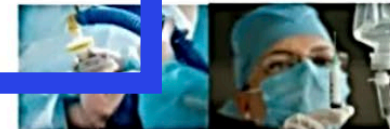
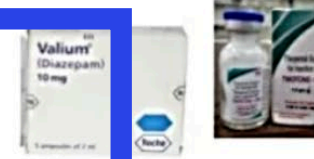
GABA A Receptor Ligands and Modulators



Drugs Acting on the GABA A receptor

A. Facilitating GABA A Action (Agonist) (+ve Allosteric Modulators)

1. Barbiturates (GABA mimetic)
2. Benzodiazepines (BZDs)
3. Z- Hypnotics (Zolpidem – Eszopiclone).
4. Alcohols, Acamprosate (Partial agonist)
5. IV Anaesthetics: etomidate, propofol & neuroactive steroids
6. Volatile Anaesthetics: isoflurane and enflurane



B. Antagonist at BZD site : Flumazenil (Antidote)

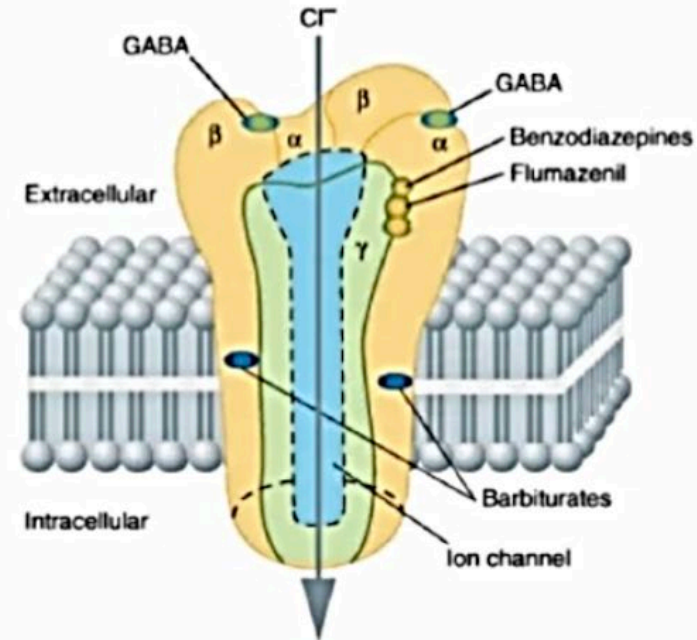
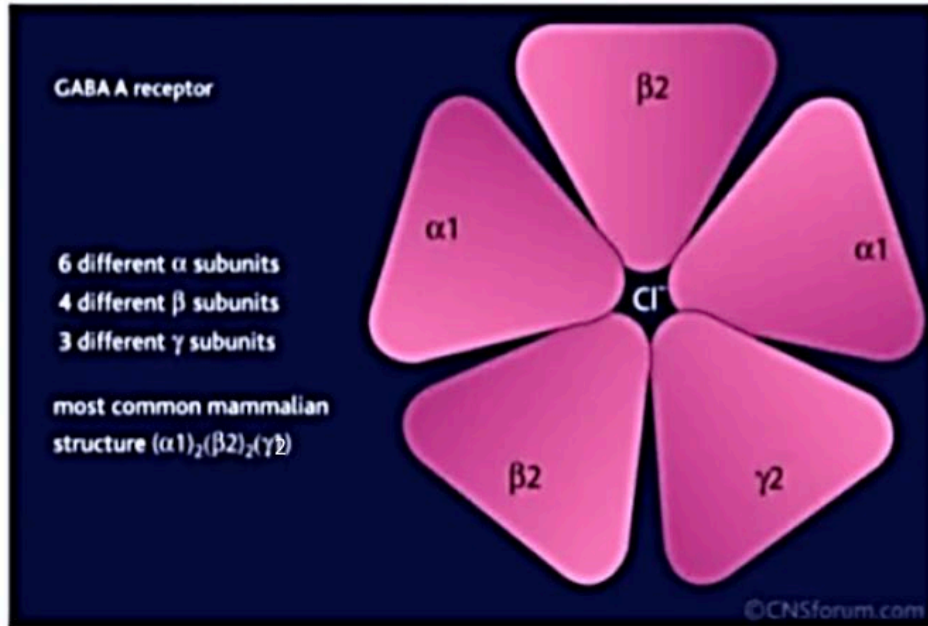
C. Inverse agonists at BZD site : β carbolines

D. GABA A receptor Blocker Bicuculline & Cl⁻ Channel Blocker Picrotoxin, PTZ Pentylenetetrazole

Benzodiazepines enhance GABA by increasing the frequency of Cl channel-opening.

GABA A receptors containing alpha 1 subunits are involved in sleep.

GABA A receptors containing alpha 2 or alpha 3 subunits are involved in anxiety.



Common BZ receptor subtypes in the CNS are designated as **BZ₁** or **BZ₂** depending on whether the binding site includes an α_1 or α_2 subunit, respectively.

- α_1 subunit is associated with sedation/hypnosis. (Z-Hypnotics)
- α_2 subunit has greater anxiolytic and muscle relaxation actions

Drugs acting on the GABA B Receptor

Drugs acting on GABA B receptor		
Agonists	Positive modulators	Antagonists
Baclofen GHB (γ -hydroxybutyrate)	BHFF, Fasoracetam, BSPP	Saclofen, Phaclofen, 2-OH saclofen, Homotaurine, CGP-35348
Others: Lesogaberan, Phenibut, Isovaline, SKF-97541		

Drugs acting on the GABA B Receptor: Baclofen

Baclofen

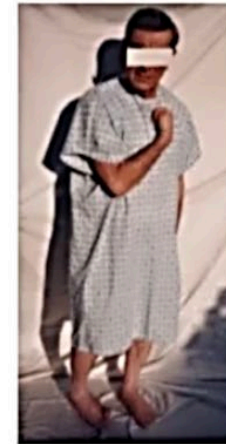
- Selective GABA_B agonist, muscle relaxant

Uses: Treatment of

- Spasticity (e.g. UMNL, CP)
- Skeletal muscle rigidity (e.g. PD, EPS)

Side effect:

- Sedation, weakness, ataxia,
- Can aggravate absence seizures (not used in epilepsy) “Epileptogenesis”



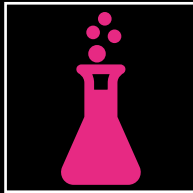
	GABA A	GABA B
Type	Ionotropic (Cl- Channel)	Metabotropic (Gi-prot.)
Structure	Pentamer (2 α , 2 β , 1 γ)	Dimer (B1&B2)
Location	Widespread; (mainly) Post-synaptic in CNS	Widespread; Pre- & Post-synaptic In CNS (>spinal cord)
MOA	Post-synaptic inhibition by - \uparrow Cl- influx	<u>Pre-synaptic</u> inhibition by - \downarrow Ca ²⁺ entry <u>Post-synaptic</u> inhibition by - \uparrow K ⁺ permeability
-Endogenous agonist - Drugs acting e.g.	GABA Barbiturates, BZD, Z-Hypnotics Anesthetics (IV, Volatile...)	GABA - Baclofen
Pharmacological Actions	<ul style="list-style-type: none"> ▪ Sedation, Hypnosis, Anxiolysis ▪ Anticonvulsant ▪ Amnesia ▪ Muscle relaxation ▪ Euphoria 	<ul style="list-style-type: none"> ▪ Central muscle relaxation ▪ Epileptogenesis ▪ \downarrow drug craving ▪ Antinociception ▪ Cognitive impairment ▪ \downarrow hormone release

Natural GABA Correction



Lifestyle modification

Diet
Exercise
Meditation



Metabolite Repletion

B6, Magnesium, Minerals, AA
levels
Fix a leaky gut

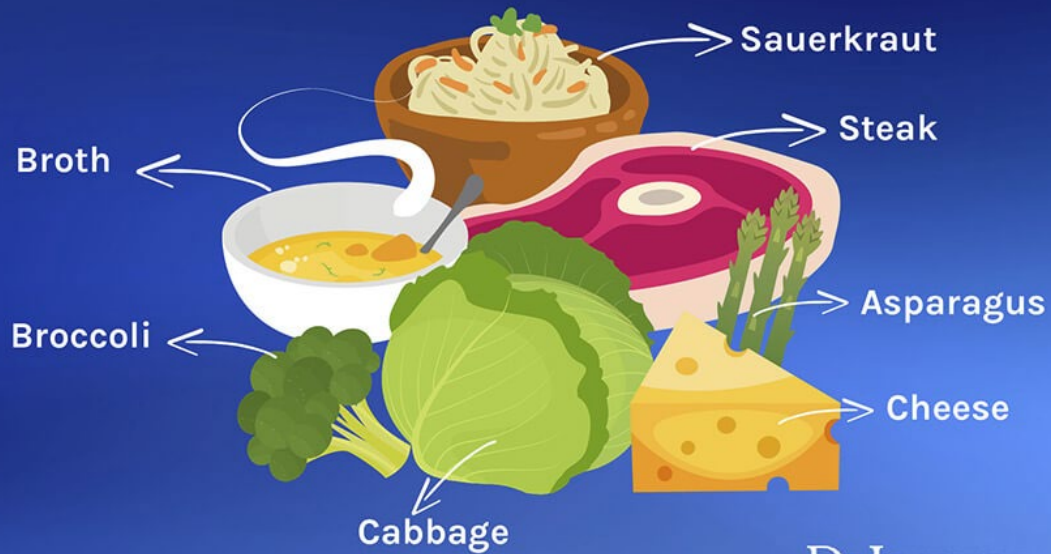


Supplementation

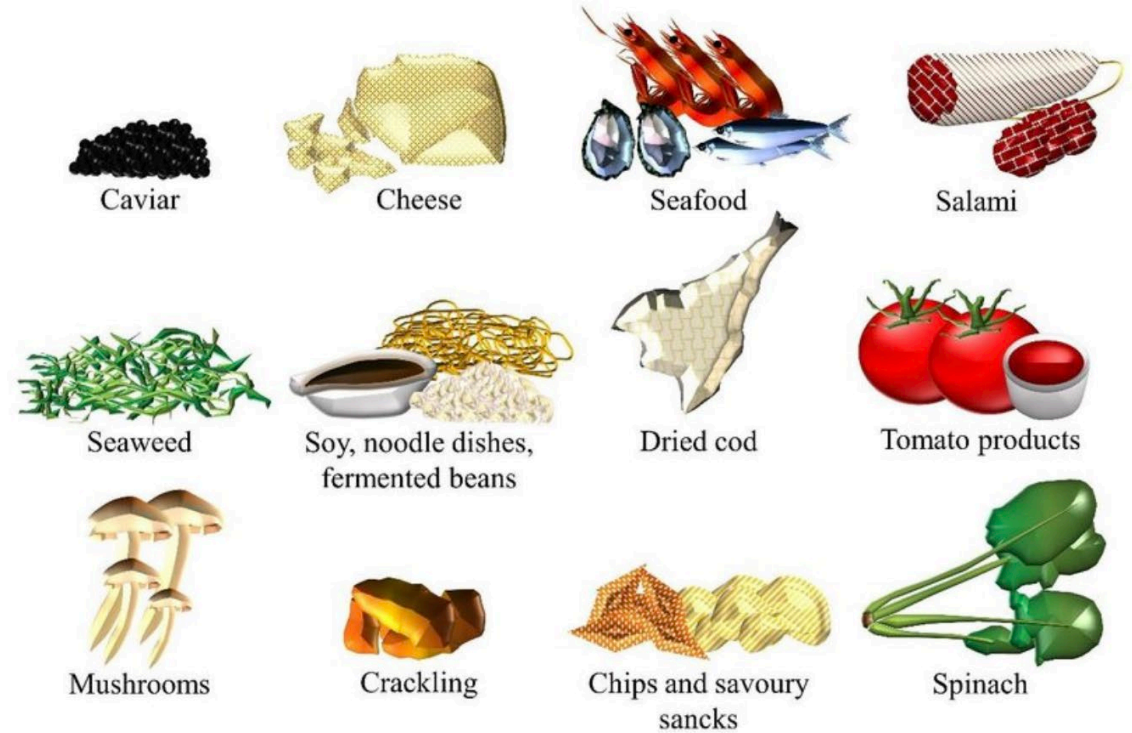
Does GABA itself get across
the BBB?

GABA Correction: Lifestyle Modification

10 Best Food Sources of Glutamine



DRJOCKERS.COM
SUPERCHARGE YOUR HEALTH



GABA Correction: Lifestyle Modification

The Journal of Neuroscience, February 24, 2016 • 36(8):2449–2457 • 2449

Cellular/Molecular

Acute Modulation of Cortical Glutamate and GABA Content by Physical Activity

 **Richard J. Maddock**,^{1,2} **Gretchen A. Casazza**,³ **Dione H. Fernandez**,^{2,3} and **Michael I. Maddock**²

¹Department of Psychiatry and Behavioral Sciences, ²Imaging Research Center, and ³Sports Medicine Program, University of California Davis Medical Center, Sacramento, California 95817

GABA Correction: Lifestyle Modification



🏠 [The Journal of Alternative and Complementary Medicine](#) > [Vol. 13, No. 4](#) > [Original Papers](#)

Yoga Asana Sessions Increase Brain GABA Levels: A Pilot Study

Chris C. Streeter, J. Eric Jensen, Ruth M. Perlmutter, Howard J. Cabral, Hua Tian, Devin B. Terhune, Domenic A. Ciraulo, and Perry F. Renshaw

Published Online: 28 May 2007 | <https://doi.org/10.1089/acm.2007.6338>

GABA Correction of Metabolites

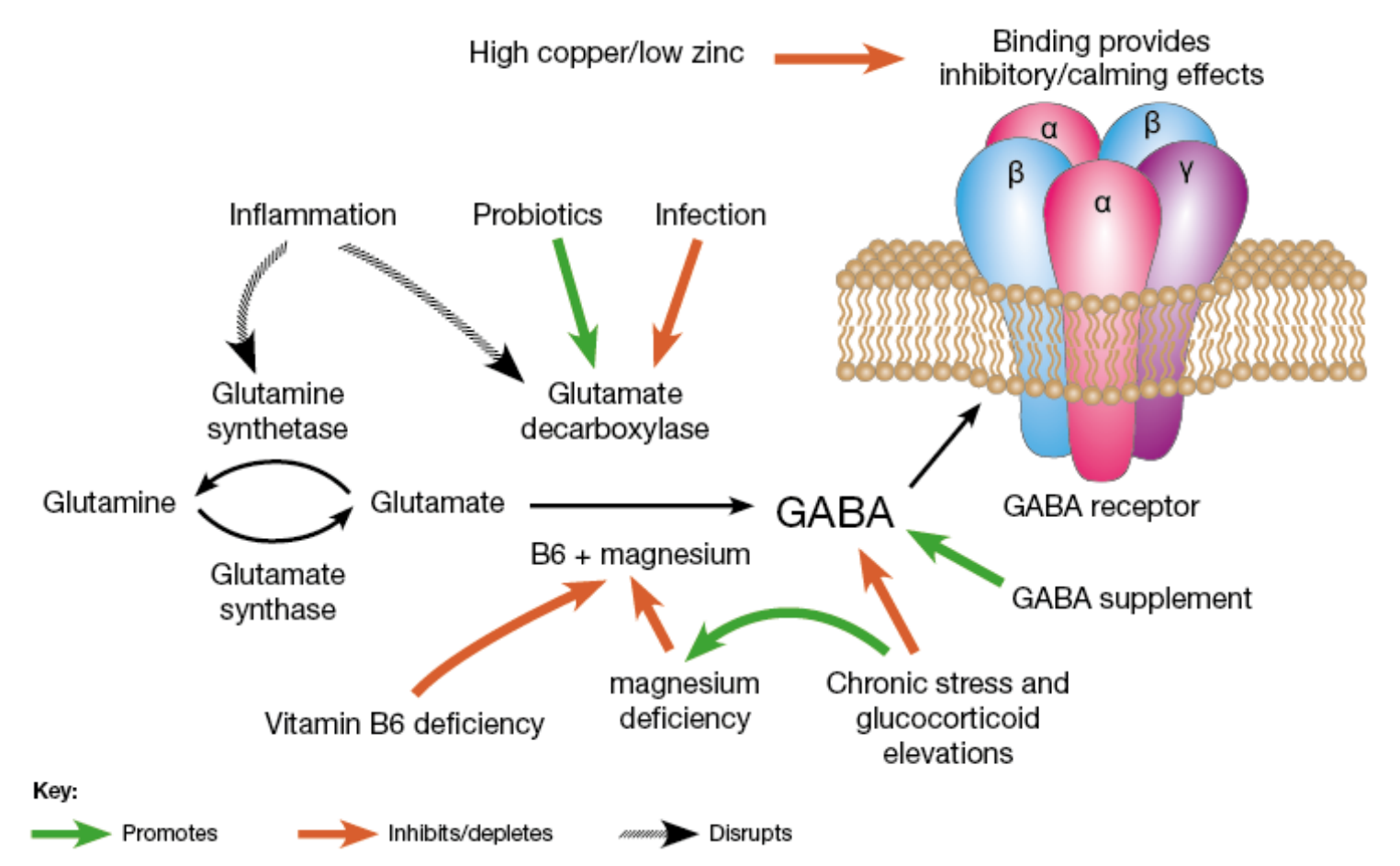


Metabolite Repletion

B6, Magnesium, Minerals, AA
levels

Fix a leaky gut

Factors Affecting GABA Synthesis



Neurotransmitter Metabolites

Kynurenine Markers	Vitamin B6	Reference Range
Kynurenic Acid	3.2	<= 7.1
Quinolinic Acid	6.8	<= 9.1
Kynurenic / Quinolinic Ratio	0.47	>= 0.44
Xanthurenic Acid	0.34	<= 0.96

Nonessential Protein Amino Acids

Amino Acid	Reference Range
Alanine	19-45
Asparagine	3.5-8.3
Aspartic Acid	<= 0.40
Cyst(e)ine	5.7-14.1
γ-Aminobutyric Acid	<= 0.04
Glutamic Acid	1.7-17.8
Glutamine	37-88
Proline	16-50
Tyrosine	6.5-16.5

Nutrient Elements

Element	Reference Range
Copper (plasma)	75.3-192.0 mcg/dL
Magnesium (RBC)	30.1-56.5 mcg/g
Manganese (whole blood)	3.0-16.5 mcg/L
Potassium (RBC)	2,220-3,626 mcg/g
Selenium (whole blood)	109-330 mcg/L
Zinc (plasma)	64.3-159.4 mcg/dL

Functional Imbalance Scores

Key < 2 : Low Need for Support 2-3 : Optional Need for Support 4-6 : Moderate Need for Support 7-10 : High Need for Support

Need for Digestive Support	Need for Inflammation Modulation	Need for Microbiome Support	Need for Prebiotic Support	Need for Antimicrobial Support
MALDIGESTION	INFLAMMATION	DYSBIOSIS	METABOLIC IMBALANCE	INFECTION
3	0	10	2	10
Fecal Fats ▲ Pancreatic Elastase ● Products of Protein Breakdown ●	Calprotectin ● Eosinophil Protein X ● Secretory IgA ● Occult Blood ●	Reference Variance ▲ Total Abundance ▲ IAD/Methane Score ▲ PP Bacteria/Yeast ●	Total SCFA's ▼ n-Butyrate Conc. ▼ SCFA (%) ● Beta-glucuronidase ●	Parasitic Infection ▲ Total Abundance ▲ Pathogenic Bacteria ● PP Bacteria/Yeast ●
<ul style="list-style-type: none"> • Digestive Enzymes • Betaine HCl • Bile Salts • Apple Cider Vinegar • Mindful Eating Habits • Digestive Bitters 	<ul style="list-style-type: none"> • Elimination Diet/ Food Sensitivity Testing • Mucosa Support: Slippery Elm, Althea, Aloe, DGL, etc. • Zinc Carnosine • L-Glutamine • Quercetin • Turmeric • Omega-3's • GI Referral (If Calpro is Elevated) 	<ul style="list-style-type: none"> • Pre-/Probiotics • Increase Dietary Fiber Intake • Consider SIBO Testing • Increase Resistant Starches • Increase Fermented Foods • Meal Timing 	<ul style="list-style-type: none"> • Pre-/Probiotics • Increased Dietary Fiber Intake • Increase Resistant Starches • Increase Fermented Foods • Calcium D-Glucarate (for high beta-glucuronidase) 	<ul style="list-style-type: none"> • Antibiotics (if warranted) • Antimicrobial Herbal Therapy • Antiparasitic Herbal Therapy (if warranted) • <i>Saccharomyces boulardii</i>

How to dim GABA switches (no prescription required)



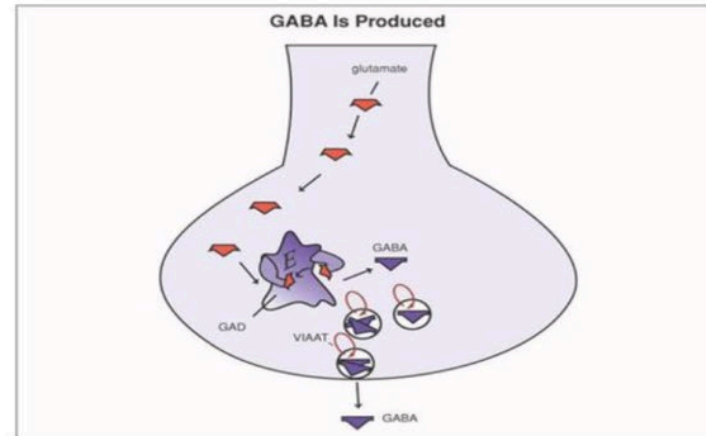
Supplementation

Does GABA get across the BBB?

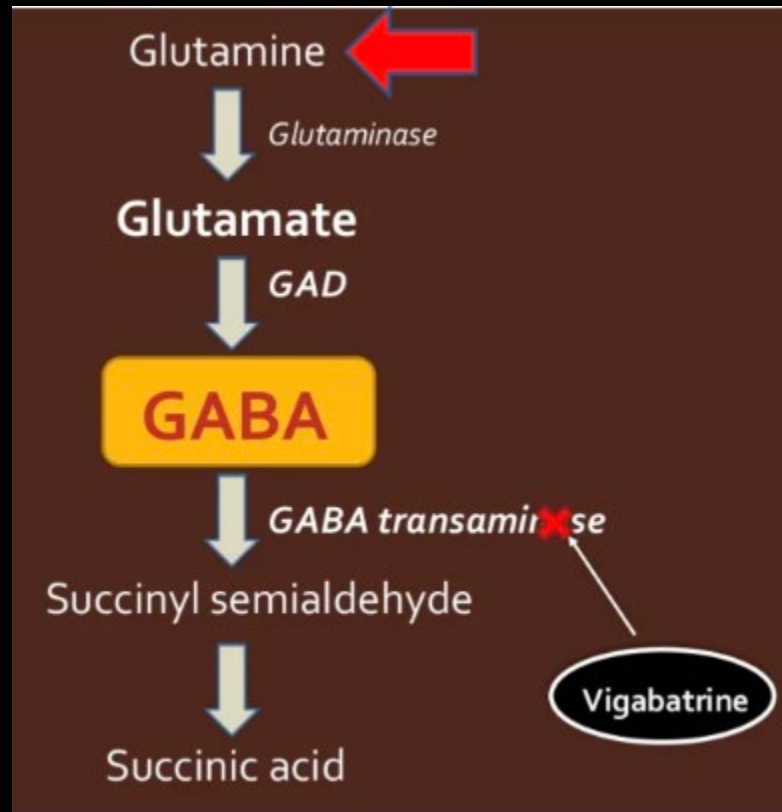
Do NOT take GABA supplements

Exogenous GABA Does Not Cross the Blood Brain Barrier(BBB)

- GABA is produced in GABA-ergic neurons from the excitatory neurotransmitter Glutamate by the enzyme GAD (glutamic acid decarboxilase)



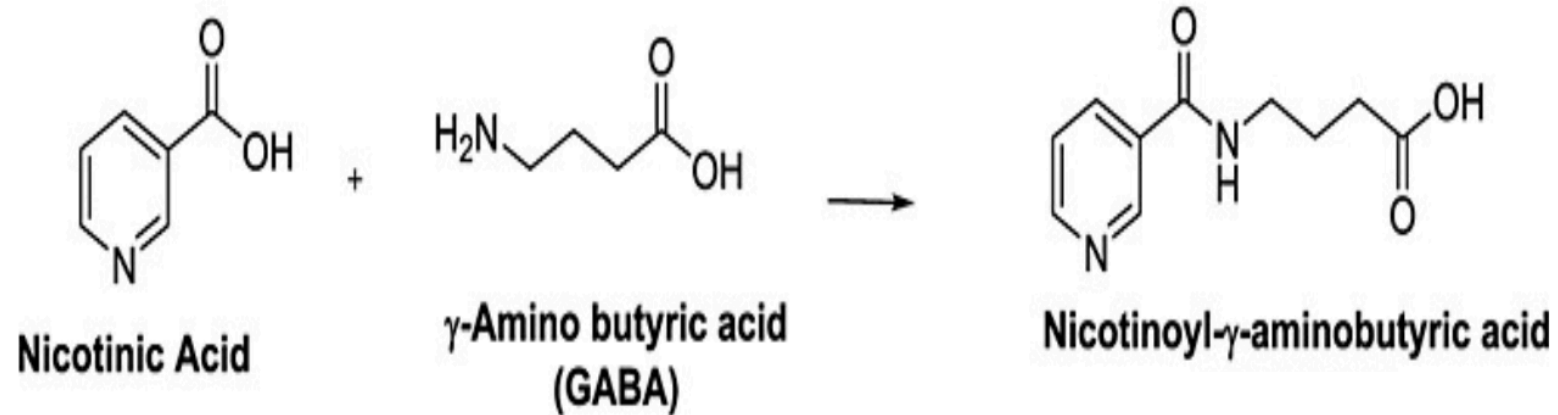
Glutamine & (not) Glutamate Supplementation



Nonessential Protein Amino Acids		
Amino Acid	Reference Range	
Alanine	32	19-45
Asparagine	7.7	3.5-7.8
Aspartic Acid	<dl	<= 0.40
Cyst(e)ine	9.5	5.7-14.1
γ-Aminobutyric Acid	<dl	<= 0.04
Glutamic Acid (indicated by a blue arrow)	14.4	1.7-17.8
Glutamine (indicated by a red arrow)	48	37-88
Proline	25	16-50
Tyrosine	10.0	6.5-16.5

Orthosteric Ligand: Nicotinoyl GABA

- is a molecule formed by a combination of [niacin \(Vitamin B3\)](#) and [γ-aminobutyric acid \(GABA\)](#)
- permeates the blood–brain barrier and then is hydrolyzed into GABA and niacin (a vasodilator)





Orthosteric Ligand: Agaricin

- GABAA receptor Agonist
- Easily crosses the BBB
- High Potency
- Long acting
- Naturally occurring or synthetic
- Low doses safe, effective, low risk of tolerance and withdrawal
- High doses hallucinogenic

GABAA PAM: Valerian Root

> [Planta Med.](#) 2008 Jan;74(1):19-24. doi: 10.1055/s-2007-993761. Epub 2007 Dec 19.

Modulation of GABAA receptors by valerian extracts is related to the content of valerenic acid

Gabriele Trauner¹, Sophia Khom, Igor Baburin, Birgit Benedek, Steffen Hering, Brigitte Kopp

Affiliations + expand

PMID: 18095218 DOI: [10.1055/s-2007-993761](#)

GABAA PAM: Kavain

PLOS ONE



[PLoS One](#). 2016; 11(6): e0157700.

Published online 2016 Jun 22. doi: [10.1371/journal.pone.0157700](https://doi.org/10.1371/journal.pone.0157700)

PMCID: PMC4917254

PMID: [27332705](https://pubmed.ncbi.nlm.nih.gov/27332705/)

Kavain, the Major Constituent of the Anxiolytic Kava Extract, Potentiates GABA_A Receptors: Functional Characteristics and Molecular Mechanism

[Han Chow Chua](#),¹ [Emilie T. H. Christensen](#),^{1,2} [Kirsten Hoestgaard-Jensen](#),² [Leonny Y. Hartiadi](#),¹ [Iqbal Ramzan](#),¹ [Anders A. Jensen](#),² [Nathan L. Absalom](#),¹ and [Mary Chebib](#)^{1,*}

Steven Barnes, Editor

GABAA PAM: Honokiol

MINI REVIEW article

Front. Neurol., 11 September 2013

Sec. Neuropharmacology

Volume 4 - 2013 | <https://doi.org/10.3389/fneur.2013.00130>

Neuro-modulating effects of honokiol: a review

Anna Woodbury^{1*}, Shan Ping Yu^{1,2}, Ling Wei¹ and Paul García^{1,2}

¹ Department of Anesthesiology, Emory University, Atlanta, GA, USA

² Department of Anesthesiology, Veteran Affairs Medical Center, Atlanta, GA, USA

Drugs and Supplements that Decrease GABA Activity

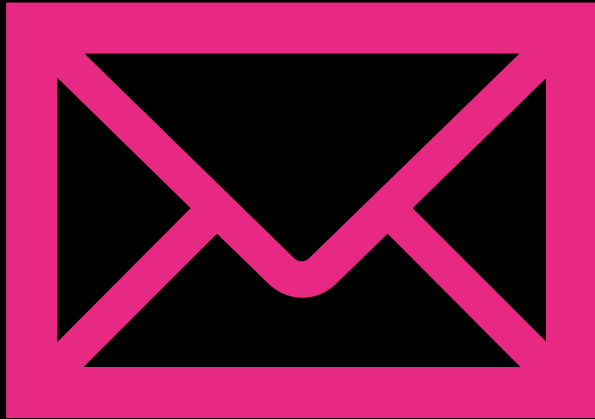
- Stimulants: decrease GABA receptor sensitivity
- Opioids:
 - Mu-opioid receptor agonists like morphine and heroin and inhibit the release of GABA by binding to opioid receptors located on GABAergic neurons
 - Opioids also affect GABAergic neurotransmission in regions of the brain and spinal cord involved in pain perception
- THC inhibits GABA release
- DHEA
- Beta Carbolines
- Anxiety drugs

Detect and Correct GABA Deficiency

- Keep it on your clinical radar
- Implement dietary and lifestyle measure to boost GABA production
- Test for levels of nutrients (magnesium, B6, etc.) to ensure optimized GABA production
- Consider herbal or fungal GABAA Agonists or PAMs to support GABA production / release
- Avoid Benzos and other GABAergic drugs associated w/dependence, withdrawal, and tolerance

Thank you!

scott@snhlife.com



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