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STUDY OF GABAERGIC AGONISTS

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Abstract-

GABA (gaba amino butyric acid) is an inhibitory neurotransmitter in the mammalian cell which occurs in brain tissue, except in trace amounts. It produces hyperpolarizing response on neurons which is blocked competitively by the alkaloid biculline. The hyperpolarizing response is due to increase in the chloride conductance of the neuronal membrane allowing the chloride ions to flow down the electrochemical gradient into the cell.¹ It is abundantly present in the brain, and serves as a balancer between excitation and inhibition. As a neurotransmitter in the central nervous system, GABA is essential for brain metabolism, aiding in balanced brain function, especially during episodes of anxiety, stress.²

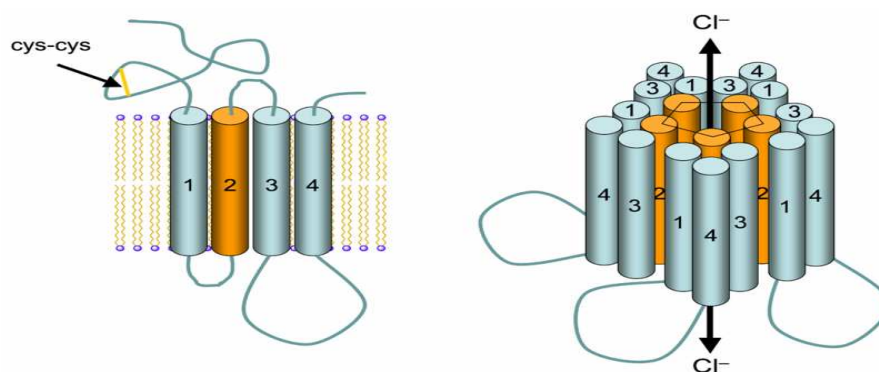
Keywords- GABA, neurotransmitters, conductance, electrochemical gradient

Introduction

The **GABA_A receptor (GABA_AR)** is an ionotropic receptor and ligand-gated ion channel. Its endogenous ligand is γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Upon activation, the GABA_A receptor selectively conducts Cl⁻ through its pore, resulting in hyperpolarization of the neuron. This causes an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurring. The active site of the GABA_A receptor is the binding site for GABA and several drugs such as muscimol, gaboxadol, and bicuculline. The protein also contains a number of different allosteric binding sites which modulate the activity of the receptor indirectly. These allosteric sites are the targets of various other drugs, including the benzodiazepines, nonbenzodiazepines, barbiturates, ethanol,

neuroactive steroids, inhaled anaesthetics, and picrotoxin, among others. Mild Inhibition of neuronal firing by drugs acting at the GABA_A receptor causes a reduction of anxiety in the patient (an anxiolytic effect) while more pronounced inhibition induces sleep (sedation) and in extreme cases of overdose, may result in death.³

Schematic structure of the GABA_A receptor

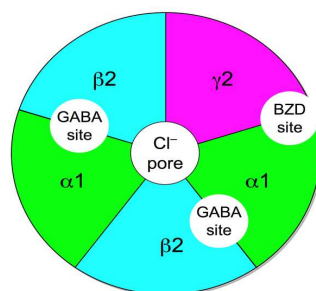


Schematic structure of the GABA_A receptor. **Left:** GABA_A monomeric subunit imbedded in a lipid bilayer (yellow lines connected to blue spheres). The four transmembrane α -helices (1-4) are depicted as cylinders. The disulfide bond in the C-terminal extracellular domain which is characteristic of the family of cys-loop receptors (which includes the GABA_A receptor) is depicted as a yellow line. **Right:** Five subunits symmetrically arranged about the central chloride anion conduction pore.⁴

Structure and function

The receptor is a multimeric transmembrane receptor that consists of five subunits arranged around a central pore. The receptor sits in the membrane of its neuron, usually localized at a synapse. However, some isoforms may be found extrasynaptically. The ligand GABA is the endogenous compound that causes this receptor to open; once bound to GABA, the protein receptor changes conformation within the membrane, opening the pore in order to allow chloride anions (Cl^-) to pass down an electrochemical gradient. Because the reversal potential for chloride in most neurons is close to or more negative than the resting membrane potential, activation of GABA_A receptors tends to stabilize the

resting potential, and can make it more difficult for excitatory neurotransmitters to depolarize the neuron and generate an action potential. The net effect is typically inhibitory, reducing the activity of the neuron. The GABA_A channel opens quickly and thus contributes to the early part of the inhibitory post-synaptic potential (IPSP). The endogenous ligand that binds to the benzodiazepine receptor is inosine.⁵



Subunits

GABA_A receptors are members of the large "Cys-loop" super-family of evolutionarily related and structurally similar ligand-gated ion channels that also includes nicotinic acetylcholine receptors, glycine receptors, and the 5HT₃ receptor. There are numerous subunit isoforms for the GABA_A receptor, which determine the receptor's agonist affinity, chance of opening, conductance, and other properties.

In humans, the units are as follows:

six types of α subunits (GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6)

- three β 's (GABRB1, GABRB2, GABRB3)
- three γ 's (GABRG1, GABRG2, GABRG3)
- as well as a δ (GABRD), an ϵ (GABRE), a π (GABRP), and a θ (GABRQ)

There are three ρ units (GABRR1, GABRR2, GABRR3), however these do not coassemble with the classical GABA_A units listed above, but rather homooligomerize to form GABA_A- ρ receptors (formerly designated as GABA_C receptors). Five subunits can combine in different ways to form GABA_A channels. The minimal requirement to produce a GABA-gated ion channel is the inclusion of both α and β subunits but the most common type in the brain is a pentamer comprising two α 's, two β 's, and a γ ($\alpha_2\beta_2\gamma$).

The receptor binds two GABA molecules,^[20] at the interface between an α and a β subunit.⁶

BIOSYNTHESIS AND METABOLISM OF GABA

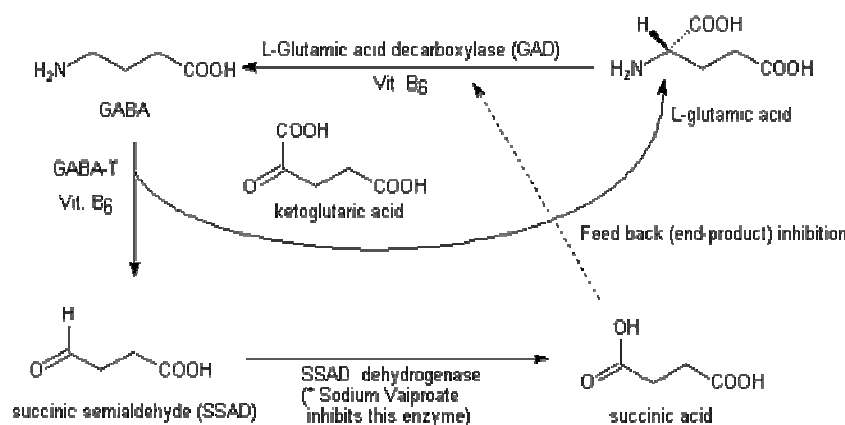


Figure 1. Biosynthetic Pathway and Metabolism of GABA

GABA is formed in neurons by the decarboxylation of the amino acid L-glutamic acid. The rate-determining enzyme which catalyzes this step is L-glutamic acid decarboxylase (GAD). The essential cofactor of the enzyme is pyridoxal phosphate (Vitamin B₆). The enzyme responsible for eliminating GABA is GABA transaminase (GABA-T). This enzyme also depends on pyridoxal phosphate as its cofactor. The resulting product, succinic semialdehyde (SSAD) is converted to succinic acid, which has negative feedback inhibition on the enzyme GAD, thereby decreasing the conversion of N- glutamic acid to GABA. Therefore if insufficient quantities of GABA are present, GAD is activated due to lack of end-product inhibition resulting from a lower concentration of the end product, succinic acid.⁷

CRYSTALLOGRAPHIC STRUCTURE OF GABA-A RECEPTOR

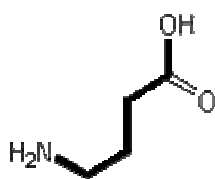
The GABA_A-receptor-associated protein (GABARAP) is a member of a growing family of intracellular membrane trafficking and/or fusion proteins and has been implicated in plasma membrane targeting and/or recycling of GABA_A receptors. GABARAP is localized on intracellular membranes such as the trans-Golgi network, binds to the $\gamma 2$ subunit of GABA_A receptors and interacts with microtubules and the N-ethylmaleimide-sensitive factor. The X-ray crystal structure of mammalian GABARAP at 2.0 Å

resolution consists of an N-terminal basic helical region, which has been implicated in tubulin binding, and a core structure with a conserved ubiquitin-like fold. Consistent with the high extent of sequence conservation among GABARAP homologues from plants to mammals, one face of the core structure is absolutely conserved while the opposite face shows considerable divergence. These features are in agreement with the conserved surface mediating protein-protein interactions shared by all members of the family, whereas the non-conserved surface region may play specific roles, such as docking to particular membrane receptors.⁸

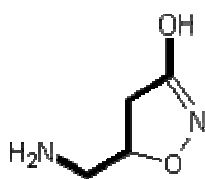
Examples

- **Agonists:** GABA, Gaboxadol, Ibotenic Acid, Muscimol, Progabide.
- **Antagonists:** Bicuculline, Gabazine.
- **Positive Allosteric Modulators:** Barbiturates, Benzodiazepines, Carisoprodol, Ethanol (Alcohol), Etomidate, Glutethimide, Kavalactones,^[21] Meprobamate, Methaqualone, Neuroactive Steroids,^[22] Niacin/Niacinamide, Nonbenzodiazepines, Propofol, Theanine, Valerenic Acid, Volatile/Inhaled Anesthetics.
- **Negative Allosteric Modulators:** Flumazenil, Ro15-4513, Sarmazenil.
- **Non-competitive Channel Blockers:** Cicutoxin, Oenanthotoxin, Pentylentetrazol, Picrotoxin, Thujone, Lindane⁹

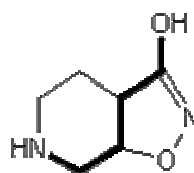
GABA-A AGONISTS



GABA



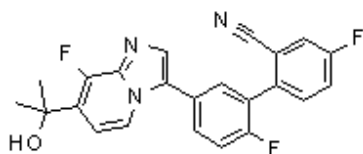
Muscimol



THIP

NEW GABA-A AGONISTS

1. TP-003 - TP003

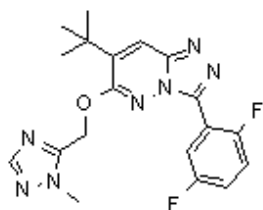


Chemical Name: 4,2'-Difluoro-5'-[8-fluoro-7-(1-hydroxy-1-methylethyl)imidazo[1,2-a]pyridin-3-yl]biphenyl-2-carbonitrile

Biological Activity:

Subtype selective partial agonist at GABAA receptor, showing significant efficacy at $\alpha 3$; nonbenzodiazepine anxiolytic
Significant Role of $\alpha 3$ -Containing GABAA Receptors in Mediating the Anxiolytic Effects of Benzodiazepines. J.

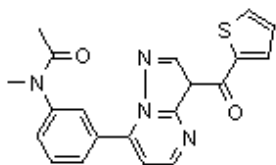
2. L-838,417 - L 838417



Biological Activity:

Partial agonist at non- $\alpha 1$ GABAA and antagonist at GABAA- $\alpha 1$ receptor
Chemical Name: 7-tert-Butyl-3-(2,5-difluoro-phenyl)-6-(2-methyl-2H-[1,2,4]triazol-3-ylmethoxy)-[1,2,4]triazolo[4,3-b]pyridazine

3. NBI 34060 - Indiplon

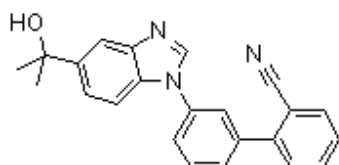


Biological Activity:

A high-affinity positive allosteric modulator with selectivity for $\alpha 1$ subunit-containing GABAA receptors; NBI 34060 modulates specific GABAA receptor subtypes at the benzodiazepine site; nonbenzodiazepine hypnotic.

Chemical Name: N-Methyl-N-{3-[3-(thiophene-2-carbonyl)-3H-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-acetamide

4.NS 11394- NS11394

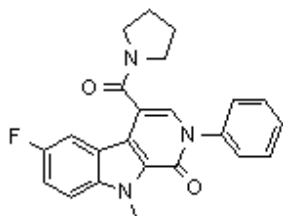


Chemical Name: 3'-[5-(1-Hydroxy-1-methyl-ethyl)-benzimidazol-1-yl]-biphenyl-2-carbonitrile

Biological Activity:

A unique subtype-selective GABAA receptor positive allosteric modulator (PAM); with a subtype selectivity profile at GABAA receptors of $\alpha 5 > \alpha 3 > \alpha 2 > \alpha 1$. Compared with other subtype-selective ligands, NS11394 is unique in having superior efficacy at GABAA- $\alpha 3$ receptors while maintaining low efficacy at GABAA- $\alpha 1$ receptors, which might be attributed for its significantly reduced side effect profile in rat.

5. SL 651498



Biological Activity:

GABAA agonist subtype $\alpha 2$ selective

Chemical Name: 6-Fluoro-9-methyl-2-phenyl-4-(pyrrolidine-1-carbonyl)-2,9-dihydro-beta-carboline-1-one

Novel drugs

A useful property of the many benzodiazepine site allosteric modulators is that they may display selective binding to particular subsets of receptors comprising specific subunits. This allows one to determine which GABA_A receptor subunit combinations are prevalent in particular brain areas and provides a clue as to which subunit combinations may be

responsible for behavioral effects of drugs acting at GABA_A receptors. These selective ligands may have pharmacological advantages in that they may allow dissociation of desired therapeutic effects from undesirable side effects. Few subtype selective ligands have gone into clinical use as yet, with the exception of zolpidem which is reasonably selective for α_1 , but several more selective compounds are in development such as the α_3 -selective drug adiplon. There are many examples of subtype-selective compounds which are widely used in scientific research, including:

- CL-218,872 (highly α_1 -selective agonist)
- bretazenil (subtype-selective partial agonist)
- imidazenil and L-838,417 (both partial agonists at some subtypes, but weak antagonists at others)
- QH-ii-066 (full agonist highly selective for α_5 subtype)
- $\alpha 51A$ (selective inverse agonist for α_5 subtype)
- 3-acyl-4-quinolones: selective for α_1 over $\alpha_{3/5}$

Ligand binding to the GABA A receptor

GABA binding (to the “GABA site”) activates the GABA A receptor, allowing chloride ions to flow through the central pore and hyperpolarize the neuron, decreasing the probability that it will propagate an action potential. In this activity, the GABA A receptor does not differ from any other ligand-gated ion channels. However, among neurotransmitter receptors, GABA A receptors are unique in the number of ligands that allosterically modulate receptor function.

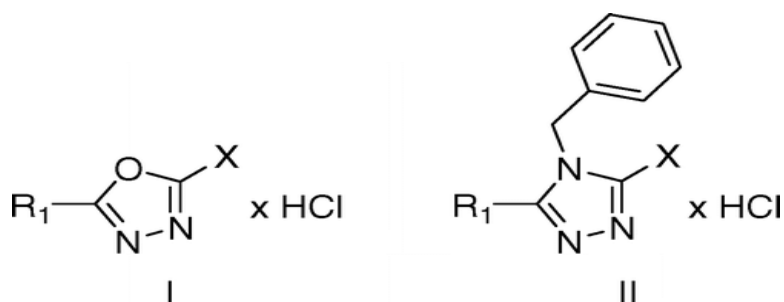
GABA A receptors can exist in at least three different conformations: open, closed, and desensitized. Up to 14 different ligand binding sites have been proposed to account for the modulation of GABA. Binding to the receptor can alter the conformation in such a way as to enhance or diminish the chloride flux in response to GABA binding. Some anesthetics (etomidate, pentobarbitone) both enhance chloride flow in response to GABA binding as well as activating it directly in the absence of GABA. Other ligands, cage convulsants of the picrotoxin type, bind within the central pore, occluding the channel and preventing chloride flow no matter what (other) ligand subsequently binds. Some of these compounds have seen commercial use as pesticides.

Possession of a γ subunit and a particular type of α subunit (1, 2, 3, or 5) is required to confer sensitivity to the class of compounds known as benzodiazepines (an example of

which is diazepam—brand name Valium®). Of course, GABA A receptors of these subtypes are overwhelmingly numerically dominant in the CNS. Classical benzodiazepines do not directly open the ion channel, rather they allosterically modify the GABA A receptor upon binding, potentiating the effect of GABA binding when there is a submaximal concentration of GABA present and thereby increasing hyperpolarizing responses and neuronal inhibition. Benzodiazepines produce systemic effects that include sedation, amnesia, muscle relaxation, and anxiolysis (Krogsgaard-Larsen et al., 2002). They were the most widely prescribed class of drugs during the 1970s and, as a group, have one of the largest therapeutic indexes. Although the site is called the benzodiazepine site, drugs of other types can also bind and allosterically modify the receptor at that site. These include drugs with β -carboline, imidazopyridine, and triazolopyridazine structures

11.

Synthesis of GABA_A Receptor Agonists and Evaluation of their α -Subunit Selectivity and Orientation in the GABA Binding Site



Drugs used to treat various disorders target GABA_A receptors. To develop α subunit selective compounds, 5-(4-piperidyl)-3-isoxazolol (4-PIOL) derivatives are synthesized. The 3-isoxazolol moiety was substituted by 1,3,5-oxadiazol-2-one, 1,3,5-oxadiazol-2-thione, and substituted 1,2,4-triazol-3-ol heterocycles with modifications to the basic piperidine substituent as well as substituents without basic nitrogen. Compounds were screened by [³H]muscimol binding and in patch-clamp experiments with heterologously expressed GABA_A $\alpha_1\beta_3\gamma_2$ receptors. The effects of 5-aminomethyl-3H-[1,3,4]oxadiazol-2-one were comparable to GABA for all α subunit isoforms. 5-piperidin-4-yl-3H-[1,3,4]oxadiazol-2-one

and 5-piperidin-4-yl-3*H*-[1,3,4]oxadiazol-2-thione were weak agonists at α_2 -, α_3 -, and α_5 -containing receptors. The effects of 5-aminomethyl-3*H*-[1,3,4]oxadiazol-2-one were comparable to GABA for all α subunit isoforms. 5-piperidin-4-yl-3*H*-[1,3,4]oxadiazol-2-one and 5-piperidin-4-yl-3*H*-[1,3,4]oxadiazol-2-thione were weak agonists at α_2 -, α_3 -, and α_5 -containing receptors. When coapplied with GABA, they were antagonistic in α_2 -, α_4 -, and α_6 -containing receptors and protected GABA binding site cysteine-substitution mutants α_1 F64C and α_1 S68C from reacting with methanethiosulfonate-ethylsulfonate. **6a** specifically covalently modified the α_1 R66C thiol, in the GABA binding site, through its oxadiazolethione sulfur. These results demonstrate the feasibility of synthesizing α subtype selective GABA mimetic drugs.

APPLICATIONS OF GABA-A RECEPTOR AGONISTS

1. Indiplon: A short-acting GABA-A receptor agonist sedative hypnotic for the treatment of insomnia

Insomnia is a common disorder characterized by difficulty falling asleep, problems staying asleep, and/or prematurely waking in the presence of adequate opportunity and circumstance for sleep. A number of clinical approaches are utilized in managing insomnia. Indiplon (Pfizer) is a selective non-benzodiazepine sedative hypnotic under consideration by FDA for the treatment of insomnia. Like other agents in its class, indiplon binds selectively to the GABA-A receptors in the brain, promoting sleep. Clinical studies have demonstrated improved efficacy in the treatment of sleep initiation and sleep maintenance with indiplon therapy in patients with acute and chronic insomnia¹²

2. SL651498, a GABA_A Receptor Agonist with Subtype-Selective Efficacy, as a Potential Treatment for Generalized Anxiety Disorder and Muscle Spasms

SL651498 (6-fluoro-9-methyl-2-phenyl-4-(pyrrolidin-1-yl-carbonyl)-2, 9-dihydro-1*H*-pyrido[3,4-*b*]indol-1-one) was identified as a drug development candidate from a research program designed to discover subtype-selective GABA_A receptor agonists for the treatment of generalized anxiety disorder and muscle spasms. The drug displays high affinity for rat native GABA_A receptors containing α_1 and α_2 subunits, and weaker affinity for α_5 -containing GABA_A receptors. Studies on recombinant rat GABA_A receptors confirm these findings and indicate intermediate affinity for the $\alpha_3\beta_2\gamma_2$ subtype. SL651498 behaves as a full agonist at recombinant rat GABA_A receptors containing α_2 and α_3 subunits, and as a partial agonist at recombinant GABA_A receptors expressing α_1 and α_5 subunits. SL651498 produced anxiolytic-like and skeletal muscle relaxant effects qualitatively similar to those of benzodiazepines (BZs). However, unlike these latter

drugs, SL651498 induced muscle weakness, ataxia or sedation at doses much higher than those having anxiolytic-like activity. Moreover, in contrast to BZs, SL651498 did not produce tolerance to its anticonvulsant activity or physical dependence. It was much less active than BZs in potentiating the depressant effects of ethanol or impairing cognitive processes in rodents. The differential profile of SL651498 as compared to BZs may be related to its selective efficacy at the α_2 and α_3 -containing GABA_A receptors. This suggests that selectively targeting GABA_A receptor subtypes can lead to drugs with increased clinical specificity. SL651498 represents a promising alternative to agents currently used for the treatment of anxiety disorders and muscle spasms without the major side effects seen with classical BZs.¹³

3.USE OF GABAA RECEPTOR AGONISTS FOR THE TREATMENT OF HEARING, VESTIBULAR AND ATTENTION DISORDERS, INTENTION TREMOR AND RESTLESS LEG SYNDROME

GABA (γ -Aminobutyric acid) is the major inhibitory neurotransmitter in the mammalian central nervous system. Its primary action is through the GABAA receptor, which is composed of a family of functionally diverse subunits that assemble into a pentameric structure. To date there are 17 different subunits identified ($\alpha 1-6$, $\beta 1-3$, $\gamma 1-3$, $\rho 1-2$, δ , ϵ , θ). These subunits have discrete locations within the brain, but the most abundant receptor subtypes have been found to express α , β and γ subunits. The GABAA receptor can be modulated by a number of therapeutic agents, including benzodiazepines, barbiturates, anaesthetics, ethanol and neuroactive steroids. The extent of this modulation is subunit specific. Recombinant studies have shown the α and γ subunits are responsible for benzodiazepine and zinc sensitivity, and β subunits control loreclezole and etomidate sensitivity. $\alpha 4$ subunits comprise only a small percentage of neuronal subunits, concentrated in hippocampus, striatum, cerebral cortex, thalamus, and basal ganglia. They assemble with $\beta 2/3$ and $\gamma 2$ subunits in most areas of the brain but also with $\rho 2/3$ and δ subunits in olfactory bulb, dentate gyrus, and thalamus. Of the 20-27% of thalamic GABAA receptors that contain $\alpha 4$ subunits, approximately one-third contain $\gamma 2$ subunits, and two-thirds contain δ subunits.¹⁴

3.The GABA_A receptor agonist THIP is neuroprotective in organotypic hippocampal slice cultures

The potential neuroprotective effects of the GABA_A receptor agonists THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) and muscimol, and the selective GluR5 kainate

receptor agonist ATPA ((*RS*)-2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propanoic acid), which activates GABAergic interneurons, were examined in hippocampal slice cultures exposed to *N*-methyl-D-aspartate (NMDA). The NMDA-induced excitotoxicity was quantified by densitometric measurements of propidium iodide (PI) uptake. THIP (100–1000 μ M) was neuroprotective in slice cultures co-exposed to NMDA (10 μ M) for 48 h, while muscimol (100–1000 μ M) and ATPA (1–3 μ M) were without effect. The results demonstrate that direct GABA_A agonism can mediate neuroprotection in the hippocampus *in vitro* as previously suggested *in vivo*.¹⁵

4.GAMA Aminobutyric Acid (A) Receptor Agonists Accelerate Cutaneous Barrier Recovery and Prevent Epidermal Hyperplasia Induced by Barrier Disruption

Gama Aminobutyric acid, is an amino acid transmitter, which mediates rapid inhibition in the central nervous system. γ -Aminobutyric acid (A) receptor is a ligand-gated chloride ion channel playing an important part in polarizing the cell membrane and reducing neuronal excitability in the neuron. In this study, demonstrated the effects of γ -aminobutyric acid (A) receptor agonists on the cutaneous barrier repair process after the barrier disruption of hairless mice. Topical application of γ -aminobutyric acid and γ -aminobutyric acid (A) receptor-specific agonists, muscimol and isoguvacine, after barrier disruption accelerated the barrier recovery. The γ -aminobutyric acid (B)-specific agonist, baclofen, did not affect the barrier recovery rate. The effect of γ -aminobutyric acid on the barrier recovery was blocked by the γ -aminobutyric acid (A)-receptor antagonist, bicuculline methobromide, but γ -aminobutyric acid (B) receptor antagonist, saclofen, did not affect the effect of γ -aminobutyric acid. Topical application of γ -aminobutyric acid also prevented epidermal hyperplasia, which was induced by the barrier insults under low environmental humidity and bicuculline methobromide blocked the effect of γ -aminobutyric acid on the epidermal hyperplasia. Immunoreactivity against γ -aminobutyric acid (A) polyclonal antibody was observed in hairless mouse epidermis. The fluorescent probe of γ -aminobutyric acid (A) receptor, TXR-muscimol showed the localization of γ -aminobutyric acid (A) receptor in the epidermis of the hairless mice. Elevation of intracellular chloride ion was induced by γ -aminobutyric acid in cultured human keratinocytes and it was blocked by bicuculline methobromide. These results suggest that the γ -aminobutyric acid (A)-like receptor is associated with skin barrier homeostasis and regulation of the receptor clinically effective for barrier dysfunctional or epidermal hyperproliferative diseases.¹⁶

REFERENCES

1. Clayton T, Chen JL, Ernst M, Richter L, Cromer BA, Morton CJ, Ng H, Kaczorowski CC, Helmstetter FJ, Furtmüller R, Ecker G, Parker MW, Sieghart W, Cook JM (2007). "An updated unified pharmacophore model of the benzodiazepine binding site on gamma-aminobutyric acid(a) receptors: correlation with comparative models". *Curr. Med. Chem.* **14** (26): 2755–75
2. Campagna-Slater V, Weaver DF (January 2007). "Molecular modelling of the GABAA ion channel protein". *J. Mol. Graph. Model.* **25** (5): 721–30..
3. [^] Sancar F, Ericksen SS, Kucken AM, Teissère JA, Czajkowski C (January 2007). "Structural determinants for high-affinity zolpidem binding to GABA-A receptors". *Mol. Pharmacol.* **71** (1): 38–46. Santhakumar V, Wallner M, Otis TS (May 2007). "Ethanol acts directly on extrasynaptic subtypes of GABAA receptors to increase tonic inhibition". *Alcohol* **41** (3): 211–21.
4. [^] Johnston GAR (1996). "GABA_A Receptor Pharmacology". *Pharmacology and Therapeutics* **69** (3): 173–198. [^] Sigel E (August 2002). "Mapping of the benzodiazepine recognition site on GABA_A receptors". *Curr Top Med Chem* **2** (8): 833–9.
5. Akabas MH (2004). "GABA_A receptor structure-function studies: a reexamination in light of[^] Johnston GAR (1996).
6. "GABA_A Receptor Pharmacology". *Pharmacology and Therapeutics* **69** (3): 173–198. Sigel E (August 2002). "Mapping of the benzodiazepine recognition site on GABA_A receptors". *Curr Top Med Chem* **2** (8): 833–9..
7. [^] Akabas MH (2004). "GABA_A receptor structure-function studies: a reexamination in light of new acetylcholine receptor structures".
8. *Int. Rev. Neurobiol.* **62**: 1–43 new acetylcholine receptor structures". *Int. Rev. Neurobiol.* **62**: 1–43.
9. Bateson AN (2004) The benzodiazepine site of the GABA A receptor: an old target with new potential? *Sleep Med* 5 Suppl 1: S9-15
10. Chou KC (2004) Modelling extracellular domains of GABA-A receptors: subtypes 1, 2, 3, and 5 *Biochem Biophys Res Commun* 316: 636-642.
11. Cromer BA, CJ Morton, MW Parker (2002) Anxiety over GABA(A) receptor structure relieved by AChBP *Trends Biochem Sci* 27: 280-287.
12. Hanson SM, Czajkowski C (March 2008). "Structural mechanisms underlying benzodiazepine modulation of the GABA(A) receptor". *J. Neurosci.* **28** (13): 3490–9. doi:10.1523/JNEUROSCI.5727-07.2008. PMID 18367615.
13. Twyman RE, Rogers CJ, Macdonald RL (March 1989). "Differential regulation of gamma-aminobutyric acid receptor channels by diazepam and phenobarbital". *Ann. Neurol.* **25** (3): 213–20. doi:10.1002/ana.410250302. PMID 2471436.
14. Wei W, Zhang N, Peng Z, Houser CR, Mody I (November 2003). "Perisynaptic localization of delta subunit-containing GABA(A) receptors and their activation by GABA spillover in the mouse dentate gyrus". *J. Neurosci.* **23** (33): 10650–61. PMID 14627650.

International Standard Serial Number: 0976-139X

14. EMBO reports **3**, 2, 183–189 (2002) doi:10.1093/embo-reports/kvf026, February 2002

15. Brain Research volume 973, Issue2, 30 May 2003, Pages 303-306.

16. *Journal of Investigative Dermatology* (2002) **119**, 1041–1047; doi:10.1046/j.1523-1747.2002.19504.x