EBioMedicine 42 (2019) 14–15

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

An enigmatic role of tonic inhibition in gabapentin therapy

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Gabapentin (*Neurontin®)* is a second-generation antiepileptic drug widely used for treatment of neuropathic pain. It is also used to treat anxiety, insomnia, bipolar disorder, and restless leg syndrome. Although first introduced as an adjunct therapy for epilepsy, gabapentin became a *blockbuster* drug for the management of chronic pain from many nerve conditions [8]. Side effects are usually mild, but include somnolence, fatigue, ataxia, and dizziness. These neurological effects may affect the quality of life of patients, especially during chronic use. However, the mechanisms underlying gabapentin's clinical efficacy or side effects are poorly understood.

Although gabapentin is a GABA analogue, it does not bind to and modulate the GABA receptors nor does it affect GABA transport or metabolism. Gabapentin is a gabapentinoid, which acts as an inhibitor of the α2δ subunit-containing voltage-dependent calcium channels (VDCCs) that are linked to neurotransmitter release. Gabapentin binds with high affinity to the $\alpha_2\delta$ VDCCs [6], which is considered the primary target of the drug. Yu and colleagues published a study in this issue of *EBioMedicine* that uncovered the hitherto hidden GABAergic mechanism for gabapentin [10]. They identified δGABA-A receptors as targets of gabapentin for eliciting anxiolysis and motor side effects (Fig. 1). This seminal study defies the current notion about gabapentin as a VDCC inhibitor.

GABA-A receptors (GABA-ARs) play a critical role in regulating inhibition and are prime targets for many clinical drugs including benzodiazepines, barbiturates, and neurosteroids [9]. GABA-ARs are stratified into synaptic and extrasynaptic receptors according to their localization (Fig. 1). The δ-containing receptors are mostly extrasynaptic with high GABA affinity but low efficacy and low desensitization rate as compared with γ-containing synaptic receptors. Activation of δGABA-ARs produces tonic current inhibition, a form of persistent hyperpolarizing current in neurons in specific brain areas such as the hippocampus, amygdala, neocortex, thalamus, hypothalamus, and cerebellum [1,5]. Therefore, these receptors are strategically located to regulate neuronal excitability by controlling the basal tone through shunting and tonic inhibition in neurons [2,7]. The δGABA-AR subtypes have a relative abundance of 5% and are mostly insensitive to modulation by benzodiazepines [3]. However, δGABA-ARs are not static but undergo rapid changes in their number or composition in response to the neuroendocrine milieu and pharmacological treatments [2,5].

Yu and coworkers' paper addresses this issue: Using specific cell-surface biotinylation and immunoblot analysis, they demonstrated an enhanced abundance of δ-subunit protein expression after acute and long-term gabapentin treatment [10]. This approach allowed them to delineate the membrane levels δGABA-ARs from the total cellular levels. Taking clues from their previous in vitro study, in which an increased tonic conductance was noted in hippocampal neurons incubated with gabapentin [4], the current study now provides the first evidence of a strikingly enhanced expression of δGABA-ARs and tonic currents in cerebellar neurons of the mice treated with gabapentin. Treatment of mice with gabapentin resulted in an increase in surface, but not total, expression in cerebellum and hippocampus. There was no change in expression of α1- or α5-subunits. Treatment of mice with gabapentin did not increase GABA, taurine, or alanine levels, or neurosteroids in the brain. They further demonstrated the physiological significance of these alterations in a behavioral assay for motor incoordination and anxiety behavior. As expected, gabapentin produced ataxic (cerebellar-mediated) and anxiolytic (amygdala-mediated) actions in wild-type mice but not in mice with a targeted ablation of δGABA-ARs in the brain. Surprisingly, the antinociceptive (spinal-mediated) effect of gabapentin was undiminished in δ-subunit knockout mice, confirming that tonic inhibition is not contributing to its analgesic actions. These results are not directly relevant to gabapentin's common indication to treat neuropathic pain; however, they are pertinent to its adverse effects and for its use in anxiety therapy. Thus, the study has key implications in brain conditions, in which the gabapentin-induced increase in δGABA-AR expression could be exploited to augment the therapeutics of neurosteroids, tiagabine, and many other drugs (Fig. 1).

There are many potential genetic and molecular regulatory pathways that control the expression, trafficking, and function of extrasynaptic receptors [5]. The authors provided a new light on such a possibility but have not specified any regulatory pathway underlying the gabapentin actions. There are many key questions to be addressed in the future, such as how gabapentin increases surface expression of δGABA-ARs, how such changes cause ataxia and anxiolysis, and whether this property is unique to gabapentin compared to other gabapentinoids such as pregabalin (*Lyrica®)*. It would be useful to know how fast these changes occur and reach a steady state as well as whether they actually alter the pharmacology of these receptors (e.g. neurosteroids), which might be an indication of altered subunit composition. Overall, drug-induced rapid changes in the abundance or distribution of δGABA-ARs may revolutionize the GABAergic physiology and thereby open new frontiers for gabapentin.

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.03.008.

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https://doi.org/10.1016/j.ebiom.2019.03.047

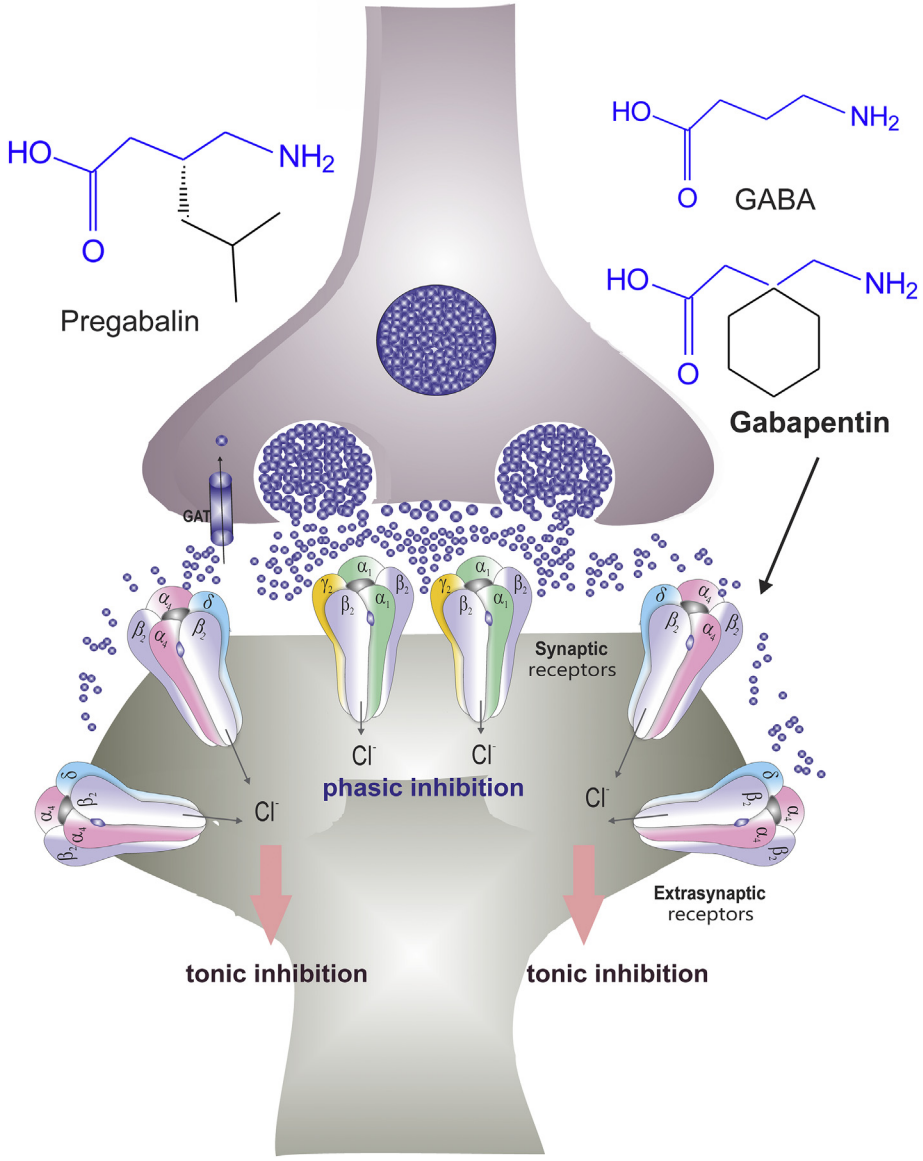

Fig. 1. Extrasynaptic GABA-A receptors and their potential modulation by gabapentin. GABA-A receptors, which are GABA-gated chloride channels, are pentameric channels composed of various subunits (α1–6, β1–4, γ1–3, δ, ε, θ, ρ1–3). They are localized at synaptic and extrasynaptic sites. Synaptic (γ-containing) receptors, present ubiquitously within the brain, produce phasic currents in response to the vesicular release of GABA. Extrasynaptic (δ-containing) receptors, which are strategically localized in specific brain regions including the hippocampus, thalamus, amygdala, and cerebellum, generate non-desensitizing tonic currents that are continuously gated by extracellular GABA. Gabapentin (3-cyclohexyl-GABA) is designed as a lipophilic analogue of GABA for blood-brain barrier penetration and closely resembles pregabalin. Although gabapentin does not directly modify GABA-A receptor function, it may indirectly increase tonic inhibition via enhanced expression of extrasynaptic receptors in specific brain regions including the cerebellum and hippocampus.

Author disclosure

The author declares no conflicts of interest.

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