

## Editorial

### GABAergic Modulation as Treatment Strategy: Consideration of Several Diseases

$\gamma$ -aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the mammalian central nervous system and as such regulates neuronal excitability. The regulation of the neurotransmitter itself is achieved by several specialized molecular mechanisms mediating its transport, sequestration, synthesis, and degradation, but also is influenced by several other regulatory mechanisms (e.g. receptors). Namely, GABA neurotransmission is regulated at the pre-synaptic site by synthesis, vesicular release and by reuptake mechanisms and also at the post-synaptic site at the level of interactions with GABA receptors. In the recent years Prof Wu's group has been studied regulation of GABA neurotransmission at the pre-synaptic site with a special emphasis on glutamic acid decarboxylase (GAD), the rate-limiting enzyme for GABA synthesis. In this Thematic issue authors discuss the regulation of GABA transmission by GAD activity, thus describing mechanisms underlying regulation of GABA neurotransmission at the pre-synaptic site which are known to include regulation of GAD expression at the transcriptional level and regulation of GAD enzyme activity at post-translational levels [1].



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Since GABA exerts its effects via ionotropic (GABA<sub>A</sub>) and metabotropic (GABA<sub>B</sub>) receptors both types of receptors are targeted by many clinically important drugs that affect GABAergic function and are widely used in the treatment of various disorders. Drugs that modulate GABA<sub>A</sub> receptor complex, such as benzodiazepines, barbiturates, neuroactive steroids, intravenous and inhalational anesthetics, and ethanol, interact with receptors. The pharmacological effects produced are rather complex due to structural heterogeneity of receptors and existence of allosterically interconnected binding sites. Therefore, there is a growing interest in the development and application of subtype-selective drugs that will achieve specific therapeutic goals without side effects. Jazvinščak Jembrek and Vlanić in their review describe the recent progress in research of GABA<sub>A</sub> receptors including known ligand binding sites and their allosteric interactions. Moreover, the key pharmacological properties of GABA receptors are summarized along with novel findings with the potential to open new perspectives in the development of more effective therapeutic strategies [2].

Although GABA was classified as neurotransmitter back in 1970s and the literature has brought many advances in our understanding of the GABA system since then there are still large gaps in our knowledge on its functions and involvement in physiology/pathophysiology of the organism. Thus, dysregulation of GABAergic transmission could lead to various neurological and psychiatric disorders (epilepsy, insomnia, anxiety, panic disorders, depression, schizophrenia, dementia, Alzheimer disease), but also other diseases recently identified as, at least partially, GABA mediated. The GABAergic system is therefore gaining attention as a potential target for therapeutic interventions being effective in the reversal of the impaired excitatory/inhibitory imbalance at various diseases and syndromes.

In this thematic issue the prominent authors bring novel knowledge on GABAergic system functions and give the overview of several GABA-related therapeutic options. The authors review evidence-based therapeutic potential and the rationale of novel GABAergic treatment of several disorders only recently connected, among others, to the abnormal function of GABAergic neurotransmission. Namely, the early clinical studies or pre-clinical evidences suggest that a promising GABAergic strategy could be developed since GABA targeting could reduce the symptoms associated with the several diseases whose symptoms were recently attributed to the imbalanced inhibitory/excitatory GABA signal.

It has been shown that dysfunction of the GABAergic system may contribute to cognitive impairment in humans. Ramirez and colleagues wrote a timely review on the relatively neglected role of GABAergic system in Alzheimer's disease (AD) which could be underlying the behavioral and psychological symptoms of AD, discussing the potential neuroprotective effects of GABA<sub>A</sub> agonists, along with potential interactions between these receptors and APP processing [3].

Dr. Hagerman has years of experience in the field of neurodevelopmental disorders and is an internationally respected leader in fragile X research including fragile X syndrome. Her research team conducts clinical research on individuals with fragile X-associated disorders with a main goal on targeted treatments for neurodevelopmental disorders. In this review main advances in the understanding of the GABAergic neurobiology of fragile X spectrum disorders along with clinical GABA- directed treatments are discussed [4].

Evidences from preclinical and clinical studies suggest that GABA plays a role in the pathophysiology of the diabetic encephalopathy-related depression. Dr. Wayhs and his colleagues in their review discuss GABAergic modulation in diabetic encephalopathy-related depression, thus pointing GABAergic system as potential target for treating diabetes, depression and related comorbidities [5].

Dr Gazulla and his research group aimed at identifying effective therapies to treat cerebellar ataxias and other motor disorders of the central nervous system performing therapeutic tests with GABAergic drugs. In the present paper they review therapeutic trials undertaken using GABA agonist drugs (e.g. gabapentin, pregabalin, tiagabine, baclofen and zolpidem), for the treatment of various types of cerebellar ataxia and other motor disorders of the central nervous system, such as progressive encephalomyelitis with rigidity, diaphragmatic myoclonus, cervical dystonia, Parkinson's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis [6].

GABA is involved in the circuitry of the enteric nervous system, controlling GI secretion and motility, as well as in the GI endocrine system, possibly acting as a autocrine/paracrine or hormonal agent and potential powerful modulator of GI visceral pain processing, enteric immune system and carcinogenesis. In an attempt to propel novel scientific efforts addressing the detailed characterization of the GABAergic signaling in the GI tract, and consequently the development of novel strategies for the treatment of different GI disorders, Dr. Serio and her research team reviewed and discussed the current evidence about GABA actions in the enteric environment, with a particular focus on possible therapeutic implications [7].

This issue provides current knowledge but is also provocative for the research community in conducting research aimed at identifying effective therapies, as well as to clinicians to perform therapeutic tests with GABAergic drugs when treating certain conditions related to the GABAergic neurotransmission dysfunction in order to improve patient care.

Editing this Thematic Issue for *Current Pharmaceutical Design* has been a great honor for me and I kindly thank to all contributing authors dedicated to publish novel ideas. I also appreciate reviewers who kindly reviewed the articles and contributed to the excellence of the issue by their constructive remarks. I am grateful to Editorial Director Mr. Kazim Baig and the staff members of the Bentham Science Publishers for their kind support and assistance in coordinating the publication of this special issue.

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