



## Editorial

## Inhibition, oscillations and focal seizures: An overview inspired by some historical notes



## A B S T R A C T

GABA (*i.e.*,  $\gamma$ -amino-butyric acid) is the main inhibitory neurotransmitter in the adult mammalian brain. Once released from inhibitory cells, it activates pre- and post-synaptic GABA receptors that have been categorized into type A and type B. GABA<sub>A</sub> receptors open ionotropic anionic channels while GABA<sub>B</sub> receptors are metabotropic, acting through second messengers. In the 1980s, decreased GABA receptor signaling was considered an appealing factor in making cortical neurons generate synchronous epileptiform oscillations and thus a good, perhaps obvious, candidate for causing focal epileptic disorders. However, studies published during the last four decades have demonstrated that interneuron firing - which causes GABA release and thus GABA<sub>A</sub> receptor activation - can lead to the generation of both physiological (*e.g.*, theta and gamma oscillations or sharp wave-ripples) and pathological oscillations including focal interictal spikes, high frequency oscillations and seizures. Taken together, the reviews published in this special issue of *Neurobiology of Disease* highlight the key role of inhibition, and in particular of GABA<sub>A</sub> receptor signaling, in neuronal network functions under physiological and pathological conditions that include epilepsy and Alzheimer's disease.

Paraphrasing the first lines of the Beatles' song "It was forty years ago today, Dr. Gloor taught the band to play...", may be - with a zest of pop culture - an approach to this overview for the Special Issue of *Neurobiology of Disease* titled *Inhibition, Oscillations and Focal Seizures*. Indeed, in March 1979, I was surprised to hear Pierre Gloor saying that a decrease in inhibition should not to be considered the only cause of seizure generation and thus, presumably, of epileptic disorders. Even though we must wait 10 years to have this concept put, at least partially, in writing (Gloor, 1989), and take into account that his opinion mainly stemmed from experiments performed in a feline model of absence seizures (Gloor and Fariello, 1988), yet in the late 1970s/early 1980s such notion was contrary to current, accepted belief.

The firm characterization of GABA<sub>A</sub> and GABA<sub>B</sub> receptors was still a few years to come (*cf.*, Bowery *et al.*, 1980; Dutar and Nicoll, 1988; Olsen and Tobin, 1990). However, several papers which were published around that time, reported that the generation of focal interictal spikes (Dingledine and Gjerstad, 1980; Schwartzkroin and Prince, 1980; Traub and Wong, 1982) as well as of secondarily generalized tonic-clonic limbic (Ben-Ari *et al.*, 1979) or neocortical seizures (Kostopoulos *et al.*, 1983) were accompanied by progressive weakening of GABAergic inhibition. This point of view changed in the late 1980s when several studies demonstrated that GABA<sub>A</sub> receptor-mediated inhibition could actively contribute to epileptiform interictal oscillations that were induced by applying K<sup>+</sup> channel blockers as well as medium containing low Mg<sup>2+</sup> or high K<sup>+</sup>; these findings have been previously reviewed by Avoli and de Curtis (2011) but it is noteworthy to emphasize here the seminal contributions made in Daniel Johnston's laboratory (*e.g.*, Rutecki *et al.*, 1987).

Later, experiments performed by applying the K<sup>+</sup> channel blocker 4-aminopyridine, revealed that hippocampal neuronal networks were prone to generate "slow" interictal oscillations that (i) continued to occur and to propagate in the presence of ionotropic glutamatergic receptor blockers, and (ii) were abolished by GABA<sub>A</sub> receptor antagonists (Perreault and Avoli, 1992; Michelson and Wong, 1994). In the

following three decades, several Investigators also reported that synchronous activation of GABA<sub>A</sub> receptor resulting from interneuron firing can play a an unexpected and paradoxical role in initiating and maintaining focal seizure-like activity (Avoli, 1990; Avoli *et al.*, 1996; Velazquez and Carlen, 1999; Köhling *et al.*, 2000; Timofeev *et al.*, 2002; Dzhala and Staley, 2003; Ziburkus *et al.*, 2006; Gnatkovsky *et al.*, 2008; Lévesque *et al.*, 2016; Khoshkhoo *et al.*, 2017). Such role of GABA<sub>A</sub> receptor signaling in ictogenesis was recently confirmed by employing optogenetic activation of parvalbumin- or somatostatin-positive interneurons; these experimental procedures can trigger ictal events similar to those occurring spontaneously during specific pharmacological manipulations (Shiri *et al.*, 2015; Yekhelef *et al.*, 2015; Chang *et al.*, 2018). Many aspects that relate to this experimental evidence - which highlights the role of GABA<sub>A</sub> receptor in synchronizing limbic neuronal networks and thus in producing epileptorm activity - will be addressed in the reviews contributed in this *Neurobiology of Disease* Special issue by de Curtis *et al.* (2019) and by Menendez de la Prida and Huberfeld (2019).

Moreover, during the last few years, several *in vivo* studies employing single-unit recordings in hippocampal or para-hippocampal structures have shown that enhanced interneuron activity - causing a concomitant decreased firing or silencing of principal glutamatergic cells - occurs at the onset of focal seizures in pilocarpine-treated epileptic rodents (Grasse *et al.*, 2013; Fujita *et al.*, 2014; Toyoda *et al.*, 2015; Karunakaran *et al.*, 2016). Moreover, it has been established that the firing of fast spiking interneurons predominates in hippocampal and neocortical circuits during ictal discharges in two additional chronic rodent models of epilepsy (Neumann *et al.*, 2017). In line with this experimental evidence, intracranial pre-surgical recordings obtained with microelectrodes from patients with focal epilepsy have shown at seizure onset a reduction of firing in a large population of neurons (Truccolo *et al.*, 2011; Schevon *et al.*, 2012; Elahian *et al.*, 2018); in addition, presumptive inhibitory interneurons recorded in the seizure onset zone of epileptic patients increase their firing rate at the start of

<https://doi.org/10.1016/j.nbd.2019.104478>

Available online 22 May 2019

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focal seizure activity (Elahian et al., 2018). Therefore, the onset of focal seizures in chronic animal models and in epileptic patients is hallmarked by enhanced inhibition even though this mechanism has also been interpreted as a restraining process aimed at preventing seizure spread (Schevon et al., 2012); such concept is in keeping with early evidence suggesting that the “epileptic neuronal aggregate” is bordered by a population of neurons which receive a powerful inhibitory drive during interictal activity” even when the cortical focus was experimentally induced by topical application of the weak GABA<sub>A</sub> receptor antagonist penicillin (Prince and Wilder, 1967). Data, which were obtained from epileptic patients analyzed *in vivo* will be reviewed in this Special Issue in the papers contributed by Weiss et al. (2019) and by Schevon et al. (2019).

The propensity of human cortical networks to generate spontaneous, synchronous IPSPs - which should mirror interneuron firing - is in line with findings obtained by several investigators in *in vitro* preparations that were performed in post-surgical human tissue obtained from patients with pharmacoresistant epilepsies (Schwartzkroin and Haglund, 1986; Köhling et al., 1998; Cohen et al., 2002; Huberfeld et al., 2007). The basic oscillatory modes recorded from human brain slices and how these activities are contributed by activation of GABA<sub>A</sub> receptors will be reviewed here by Menendez de la Prida and Huberfeld (2019). Moreover, as highlighted in this Special Issue by Peyrache and Destexhe (2019), technological advances are making possible to monitor the activity of inhibitory cells in several mammalian species, from rodents to humans, in both *in vitro* and *in vivo* preparations.

Up to now, I have addressed how evidence obtained during the last 40 years, has changed our view on the role played by interneurons and GABA<sub>A</sub> signaling in the generation of focal interictal oscillations and seizures. However, an updated picture of GABA<sub>A</sub> receptor function in the brain, cannot be complete unless taking into account its role in the generation of physiological EEG rhythms such as theta and gamma oscillations (Traub et al., 1998; Buzsáki, 2002; Amilhon et al., 2015; Buzsáki and Schomburg, 2015) or sharp-wave ripples (Buzsáki, 2015; Buzsáki and Lopes da Silva, 2012). These studies have shown that GABA<sub>A</sub> receptor signaling provides an active contribution to neuronal network oscillations that are fundamental in processing information as well as in memory consolidation. Relevant to the topic of this overview (*i.e.*, focal seizure generation), experiments performed in pilocarpine-treated epileptic rats have identified enhanced theta oscillatory activity before seizure occurrence (Fujita et al., 2014; Grasse et al., 2013; Karunakaran et al., 2016; Toyoda et al., 2015). As proposed in the review contributed here by Moxon et al. (2019), theta oscillations may vary their *tempo* from slow rhythms, which predominate during the interictal phase, to faster and more rhythmic oscillations that occur during the so-called pre-ictal period; these transformations in theta frequency may indeed reflect changes in interneuron function that influence the ability of inhibitory cells to control seizure and transform them in seizure promoters. Moreover, these pathological alterations may play a role in cognitive processing. This last aspect is specifically addressed in the review by Vico Varela et al. (2019) in which dysregulation of neuronal network activity is considered in the context of Alzheimer's disease, a severe cognitive disorder that may be associated with an elevated occurrence of epileptic seizures.

During the last decade, high-pass filtering (> 80 Hz) of EEG signals has enabled neuroscientists to identify the occurrence of high frequency oscillations (HFOs) - which have been often categorized as *ripples* (80–200 Hz) and *fast ripples* (250–500 Hz) – in both epileptic patients (Jacobs et al., 2012) and in animal models (Jefferys et al., 2012; Jiruska et al., 2017). As reviewed in this Special Issue by Lévesque and Avoli (2019) and by Li et al. (2019), HFOs reflect pathological neuronal network activity, occur during interictal and ictal discharges, and are involved in ictogenesis and epileptogenesis. Moreover, as originally reported by Lévesque et al. (2012), a selective increase ripples or fast ripple rates may be associated with the onset of specific types of seizure in temporal lobe regions of epileptic animals thus pinpointing to the

mechanisms of seizure generation, which in turn should lead to the development of mechanistically targeted anti-epileptic strategies to be implemented after pathological events such as *status epilepticus* or traumatic brain injury. These topics are addressed here in the reviews contributed by Lévesque and Avoli (2019) and by Li et al. (2019).

The involvement of brain oscillations in the occurrence of seizure activity has also been analyzed by employing *in silico* models. In this Special Issue, González et al. (2019) review computational studies that have analyzed the roles played by synaptic homeostasis and ionic concentration dynamics in the generation of spontaneous seizures while Kalitzin et al. (2019) explore the concept that a focal epileptic condition represents a pathological manifestation of a multistate network composed of coupled oscillatory units. Evidence presented by these Investigators also pinpoint to the role played by glial cells in modulating hyperexcitability within brain neuroglial networks.

Finally, Frauscher and Gotman (2019) review evidence on the influence of sleep on human focal epilepsy by considering both sleep microstructure and the information provided by new epileptogenic markers such as the HFOs that are obtained during invasive intracranial EEG recordings in humans. These studies, while underscoring the role of sleep slow waves in enhancing epileptic activity, indicate that sleep is useful to better identify the epileptogenic zone in pharmacoresistant epileptic patients, who are candidates for neurosurgical resection.

In conclusion, there is no doubt that GABA - and in particular the GABA<sub>A</sub> receptor - represents the main inhibitory transmitter in the brain, that its function can be enhanced by drugs with anticonvulsant properties as well as that when GABAergic transmission is decreased or blocked, seizure activity occurs. However, the role of GABA in seizure generation and epileptogenesis is more complex than just that of being the mere controller of neuronal excitability whose action must be diminished to have abnormal neuronal network synchronization, and thus epileptic (or epileptiform) discharges. The papers published in this Special Issue explore further these issues, extending the focus of inhibitory cell function to both physiological and pathological synchronizing oscillations.

## Acknowledgements

I apologize to a number of colleagues for not having mentioned here some of their own studies. This was not an intentional overlook but the result of the need of being concise in addressing a series of topics that have attracted the attention of many neuroscientists.

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