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Research Highlight

Increased asynchronous GABA release causes more inhibition in human epileptic brain?

Qi FANG, Zhong CHEN*

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When an action potential (AP) propagates to the presynaptic terminals, Ca^{2+} influx through voltage-gated Ca^{2+} channels triggers rapid synchronous transmitter release within milliseconds, which is then followed by a so-called asynchronous release with a prolonged time course of tens or hundreds of milliseconds at both excitatory and inhibitory synapses[1–3]. Fast synchronous release is well-known as the foundation of precise neuronal communication, whereas the characteristics and functions of asynchronous release in central nervous system, especially in human brain, are largely unexplored. Jiang *et al*[4] now report that asynchronous release occurs in all GABAergic synapses of fast-spiking (FS) interneurons, and the strength of asynchronous GABA release increases in human epileptic neocortex, which may contribute to the regulation of epileptiform activities.

In central nervous system, individual neurons receive both excitatory and inhibitory synaptic transmission. Proper and dynamic balance between the excitatory and inhibitory inputs are essential for precise information coding in complex neuronal network[5], whereas disruption of this balance may cause severe neurological diseases, such as epilepsy[6]. GABA is the predominant inhibitory neurotransmitter which is released from GABAergic axon terminals and consequently activates postsynaptic and extrasynaptic GABA receptors. Besides fast synchronous GABA release tightly coupled with AP, asynchronous GABA release has been recently demonstrated in the avian nucleus magnocellularis neurons and rat hippocampal interneuron–principal neuron synapse, which generates long-lasting inhibition and may contribute to the control of postsynaptic target neurons[2, 7]. Therefore, it will be interesting to study the functional role of this asynchronous GABA release in both physiological and pathological conditions.

In this report, Jiang *et al* performed simultaneous recordings from inhibitory FS neurons and excitatory pyramidal neurons (PC) in human epileptic or non-epileptic cortical slices. They demonstrate for the first time that single AP- or AP train-evoked asynchronous GABA release from FS interneuron occur at all GABAergic synapses, including FS autapses (synapses formed by the axon of the FS interneuron on its own dendrites), FS-FS and FS-PC synapses in human brain, among which FS autapses show the strongest asynchronous release. Moreover, the duration and total number of asynchronous release increase when enhancing the frequency or the number of presynaptic APs, demonstrating the dependence of asynchronous release strength on the intensity of presynaptic stimulation. Most interestingly, elevated asynchronous release from FS autapses was found in human epileptic cortical slices as compared with that in non-epileptic peri-tumor tissue. To confirm this phenomenon, authors examined the asynchronous release from FS autapses and FS-PC synapese in the rat pilocarpine model of status epilepsy, which mimics human temporal-lobe epilepsy. Consistent with what is observed in human brain, AP train induces asynchronous release both at FS autapses and FS-PC synapses, with its strength depending on the intensity of presynaptic stimulation. Meanwhile, FS autapses exhibited significantly stronger asynchronous release than FS-PC synapse in both control and pilocarpine-treated rats, which showing that the strength of asynchronous release tightly depend on the type of synaptic connection. Notably, asynchronous GABA release at both FS autapses and FS-PC synapse in pilocarpine-treated rats were remarkably increased as compared with those in control rats. The enhanced asynchronous GABA release at FS neuron synapses in both epileptic human brain and epileptic animal model provide scientific insight that the long-lasting inhibition mediated by increased asynchronous GABA release may contribute to the regulation of epileptiform activities.

Decades ago, asynchronous release was found as a "delayed" phase char-

Department of Pharmacology, Key Laboratory of Medical Neurobiology of Ministry of Health of China, Zhejiang Province Key Laboratory of Neurobiology, College of Pharmaceutical Sciences, School of Medicine, Zhejiang University, Hangzhou 310058, China
Correspondence to: Prof Zhong CHEN
(chenzhong@zju.edu.cn)

acterized by a much smaller but long-lasting elevation of quantal release rate following the rapid synchronous release[8, 9]. Similar to fast synchronous release, asynchronous release also depends on presynaptic Ca^{2+}. Different Ca^{2+} sensor and the distance between the Ca^{2+} source and the sensor of exocytosis have been considered as the mechanism underlying the distinct properties of these two types of transmitter release[10]. According to this report, blocking background Ca^{2+} by EGTA-AM, a membrane-permeable Ca^{2+} chelator, almost completely abolishes the asynchronous release at FS autapses, FS-FS and FS-PC synapses. This result confirms the Ca^{2+} dependence of asynchronous GABA release from FS neurons in human brain. Does the enhanced asynchronous GABA release in epileptic human brain or pilocarpine-treated animal model relate to the presynaptic Ca^{2+}? In pilocarpine-treated rats, the authors found that the train stimulus-induced APs in presynaptic neuron exhibited larger peak amplitude and integrated area than those in control rats. Meanwhile, proper reduction of presynaptic AP amplitude by a low concentration of TTX (100 nmol/L) significantly decreased the strength of asynchronous release from FS neurons. Therefore, Jiang *et al* hypothesized that increased AP amplitude may cause more Ca^{2+} entry and consequently enhance asynchronous GABA release from FS synapses. Although more evidence should be provided, it's still worth to examine the related channels and Ca^{2+} sensors that may be involved in the underlying mechanism.

This study by Jiang *et al* is important because it confirms the existence of asynchronous release in human brain, and reveals the enhanced asynchronous GABA release from FS interneuron in human epileptic brain and pilocarpine-treated rats. Consider the fact that asynchronous GABA release in FS autapses is significantly stronger than that in FS-PC synapse, it is noticeable that asynchronous GABA release in FS autapses can actually lead to self-inhibition and consequently excites its target neurons. Therefore, further works are needed to test whether or not the increased asynchronous GABA release really causes more inhibition in the epileptic brain. Except asynchronous GABA release, the properties and functional role of excitatory asynchronous release in the epileptic brain are also attractive. At last, it's would be anticipated, yet interesting, to uncover the regulation effect of asynchronous release on the neurological diseases, such as epilepsy.

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