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

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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 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 synapse 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 depends 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-
characterized by a much smaller but long-lasting elevation of quantal release rate following the rapid synchronous release. 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. 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 epileptic brain and pilocarpine-treated rats. 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-FS synapse 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.

1. Atluri PP, Regehr WG. Delayed release of neurotransmitter from cerebellar granule cells. J Neurosci 1998; 18: 8214–27.
2. Lu T, Trussell LO. Inhibitory transmission mediated by asynchronous transmitter release. Neuron 2000; 26: 683–94.
3. Goda Y, Stevens CF. Two components of transmitter release at a central synapse. Proc Natl Acad Sci U S A 1994; 91: 12942–6.
4. Jiang M, Zhu J, Liu Y, Yang M, Tian C, Jiang S, et al. Enhancement of asynchronous release from fast-spiking interneuron in human and rat epileptic neocortex. PLoS Biol 2012; 10: e1001324.
5. Haider B, Duque A, Hasenstaub AR, McCormick DA. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. J Neurosci 2006; 26: 4535–45.
6. Marco P, Sola RG, Pulido P, Alijarde MT, Sanchez A, Ramon y Cajal S, et al. Inhibitory neurons in the human epileptogenic temporal neocortex. An immunocytochemical study. Brain 1996; 119: 1327–47.
7. Hefft S, Jonas P. Asynchronous GABA release generates long-lasting inhibition at a hippocampal interneuron-principal neuron synapse. Nat Neurosci 2005; 8: 1319–26.
8. Rahamimoff R, Yaari Y. Delayed release of transmitter at the frog neuromuscular junction. J Physiol 1973; 228: 241–57.
9. Barrett EF, Stevens CF. The kinetics of transmitter release at the frog neuromuscular junction. J Physiol 1972; 227: 691–708.
10. Yao J, Gaffaney JD, Kwon SE, Chapman ER. Doc2 is a Ca\(^{2+}\) sensor required for asynchronous neurotransmitter release. Cell 2011; 147: 666–77.