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Commentary

High Times for Low-Frequency Stimulation as Endocannabinoids Engage in Hippocampal Long-Term Depression

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Long-term changes in synaptic efficacy are key neural substrates of learning and memory (Kandel, 2009). This is especially true within the hippocampus, which has been used as a model system for studying the cellular and molecular mediators of synaptic plasticity for almost half a century. Despite this long legacy, new and important cellular mechanisms contributing to synaptic plasticity continue to emerge. In the current issue of *Neuropsychopharmacology*, Izumi and Zorumski (2011) describe a novel role for endogenous cannabinoid (eCB) signaling in hippocampal long-term depression (LTD), providing new insight into the molecular mechanisms regulating long-term changes in synaptic strength at excitatory synapses in the hippocampus.

While repetitive high-frequency stimulation of hippocampal glutamatergic synapses generally results in long-term potentiation (LTP), longer duration low-frequency stimulation (LFS; 1HZ for 15 min) of this pathway results in LTD (Albensi *et al*, 2007). As summarized and confirmed by Izumi and Zorumski (2011), LFS–LTD at these synapses involves group-1 metabotropic (mGluR1/5) and *N*-methyl D-aspartate (NMDA) glutamate receptor activation. They also found a selective role for the mGluR5 subtype in LFS–LTD. Given the presynaptic expression of LFS–LTD and the tight link between mGluR5 activation and eCB mobilization (Kano *et al*, 2009), these authors tested the hypothesis that LFS–LTD may involve a retrograde eCB signaling component. eCBs are lipid neuromodulators synthesized by neurons and glia that activate central cannabinoid receptors (CB1 and CB2). Activation of CB1 receptors localized to glutamatergic and GABAergic (see below) synapses results in a reduction in presynaptic neurotransmitter release (Heifets and Castillo, 2009). Within the hippocampus, and elsewhere, activation of mGluR5 results in mobilization of the eCB 2-arachidonoylglycerol (2-AG) and results in both short- and long-term retrograde synaptic suppression (Alger, 2002; Chevaleyre *et al*, 2006). Izumi and Zorumski (2011) showed that mGluR5-LTD and LFS–LTD were mutually occlusive, suggesting a common molecular mechanism subserving these two types of LTD. That both mGluR5-LTD and LFS–LTD were blocked by a CB1 receptor antagonist suggests that eCB signaling is the final common molecular pathway linking these forms of plasticity. Importantly, activation of CB1 alone also causes LTD, which was not dependent upon either mGluR5 or NMDA activity, but occluded further induction of mGluR5-LTD or LFS–LTD. The putative sequence of events leading to LTD in response to LFS was suggested by the authors to include initial activation of postsynaptic mGluR5 and NMDA receptors, followed by eCB release downstream of mGluR5, and finally activation of CB1 to cause a presynaptically expressed LTD (Figure 1a).

Several other important findings were reported in the current manuscript. First, dual activation of mGluR1 and mGluR5 with the nonselective agonist dihydroxyphenylglycine causes a robust LTD that is independent of CB1 receptors, suggesting that divergent downstream signaling of mGluR1 and mGluR5 can regulate glutamatergic signaling via eCB-dependent and -independent mechanisms. Second, the authors exogenously applied several eCB molecules to hippocampal slices to determine which one most closely mimicked the high-potency synthetic CB1 agonist Win 55212-2. Intriguingly, noladin ether was the most potent ligand at depressing excitatory transmission and producing LTD. In contrast, the two most well-studied eCBs anandamide and 2-AG had only minimal effects. It is possible that rapid degradation of anandamide and 2-AG by hydrolytic enzymes in the brain slice limited the apparent efficacy of these compounds, however, at least for the case of anandamide, blocking degradation did not increase efficacy (Izumi and Zorumski, 2011). Further studies aimed at determining the

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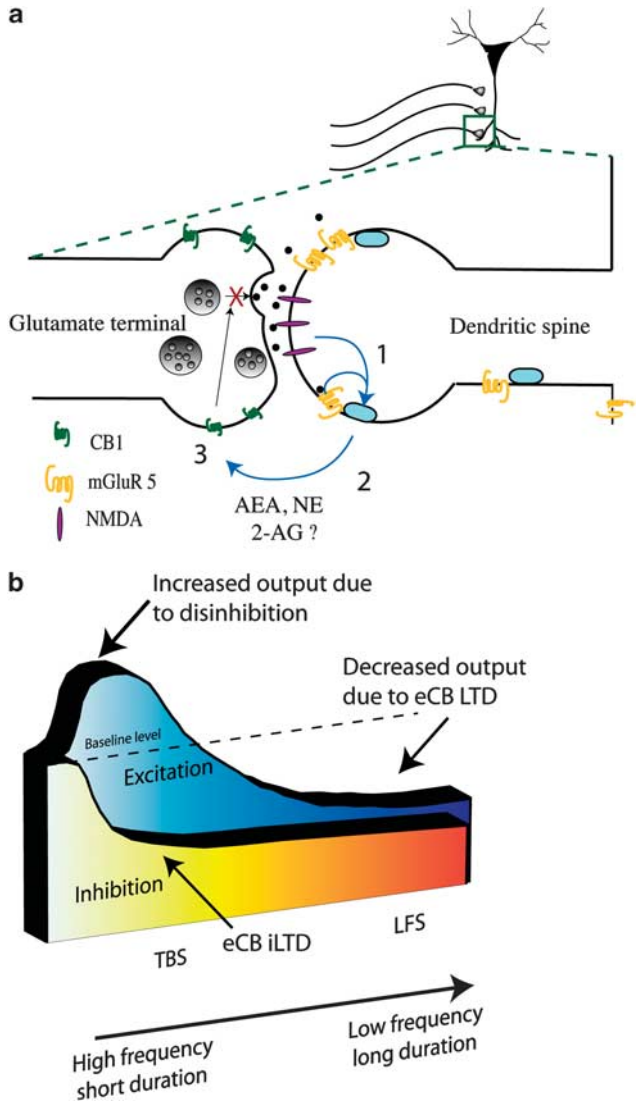

Figure 1 (a) Schematic diagram of the main findings described in Izumi and Zorumski (2011). At glutamatergic inputs to hippocampal pyramidal neurons, LFS results in the activation of both NMDA and mGluR5 receptors (1). Activation of these receptors mobilizes eCB synthesis and release, although the identity of the specific eCB ligand remains to be determined (2). Finally, eCBs biding to CB1 receptors located on presynaptic axon terminals results in LTD at these synapses (3). (b) Hypothetical model depicting differential effects of TBS and LFS on GABAergic inhibition and glutamatergic excitation in the hippocampus. During TBS, eCB signaling depresses GABAergic transmission, induces iLTD, causes disinhibition of pyramidal neurons and facilitation of TBS–LTP; the net result is increased hippocampal output. During LFS, eCB iLTD continues to be induced; however, now eCB signaling also contributes to LTD, with the net result being decreased excitation of pyramidal neurons and decreased hippocampal output. Therefore, depending on the type/duration of afferent activity, eCB signaling will be differentially recruited at excitatory and inhibitory synapses and can have opposing effects on hippocampal output.

eCB ligand-mediated LFS–LTD will require the use of additional pharmacological and genetic approaches.

Taken together with previous data demonstrating a role for eCB signaling in LTD of GABAergic transmission (iLTD) at hippocampal interneuron-pyramidal neuron synapses (Chevaleyre *et al*, 2006), these data indicate eCBs can participate in long-term modulation of both excitatory and inhibitory afferent neurotransmission onto hippocampal pyramidal neurons. These data raise several critical questions regarding the mechanisms regulating the synaptic specificity of eCB signaling at these two types of synapses. First, are there specific patterns of afferent activity that preferentially induce eCB signaling at GABAergic *vs* glutamatergic synapses? Second, what are the net effects of eCB signaling induced by different afferent activity patterns on hippocampal pyramidal cell output, and third, are the eCB messengers subserving retrograde depression different at different synapse types? With regard to the first two points, Chevaleyre and Castillo (2004) have provided evidence that theta burst stimulation (TBS) induces production of 2-AG, which depresses afferent GABAergic transmission and facilitates subsequent LTP induction at excitatory synapses onto hippocampal pyramidal neurons. Thus, TBS may preferentially mobilize eCB signaling at hippocampal GABAergic synapses, causing a net disinhibition of pyramidal neuron activity (Figure 1b). In contrast, the work of Izumi and Zorumski (2011) suggest prolonged LFS recruits eCB signaling at glutamatergic synapses. It is known that LFS, as brief as a few minutes, can induce eCB-mediated depression of GABAergic transmission in other brain regions (Kano *et al*, 2009), suggesting this pattern of activity may recruit eCB signaling at both glutamatergic and GABAergic synapses. Taken together, these data suggest a scenario whereby postsynaptic eCB mobilization at GABAegic synapses is fairly promiscuous, and can be induced by a variety of afferent activity patterns, and when induced alone facilitates LTP and perhaps hippocampal output (Figure 1b). In contrast, prolonged LFS, in addition to inducing eCB suppression of GABAergic transmission, begins to recruit eCB signaling at glutamatergic synapses serving to dampen hippocampal output. Thus, eCB signaling may be an important mechanism by which different patterns and durations of afferent activity can differentially modulate GABAergic and glutamatergic efficacy that ultimately determined hippocampal output. Determining the functional consequences of eCB modulation of excitatory and inhibitory inputs to hippocampal pyramidal neurons remains a critical open question for future investigation.

DISCLOSURE

The author declares no conflict of interest.

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