ENDOCANNABINOID EFFECTS ON FEBRILE SEIZURES: NOT JUST A TOKE(N) MECHANISM

Long-term Plasticity of Endocannabinoid Signaling Induced by Developmental Febrile Seizures

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Febrile (fever-induced) seizures are the most common form of childhood seizures, affecting 3% to 5% of infants and young children. Here we show that the activity-dependent, retrograde inhibition of γ-aminobutyric acid (GABA) release by endogenous cannabinoids is persistently enhanced in the rat hippocampus after a single episode of experimental prolonged febrile seizures during early postnatal development. The potentiation of endocannabinoid signaling results from an increase in the number of presynaptic cannabinoid type 1 receptors associated with cholecystokinin-containing perisomatic inhibitory inputs, without an effect on the endocannabinoid-mediated inhibition of glutamate release. These results demonstrate a selective, long-term increase in the gain of endocannabinoid-mediated retrograde signaling at GABAergic synapses in a model of a human neurologic disease.

COMMENTARY

Endogenous cannabis compounds, or endocannabinoids (CBs), are becoming increasingly recognized as an important, novel form of interneuronal communication (1). CBs are endogenous fatty acids that are synthesized when principal neurons are depolarized, especially by their prolonged activation. CBs are then released rapidly into the synaptic cleft, diffuse in a retrograde fashion across the cleft, and bind to cannabinoid type 1 (CB1) receptors on the presynaptic membrane. The consequence of CB1-receptor activation is that neurotransmitter release from the presynaptic terminal is decreased. CBs have been shown to decrease both inhibitory and excitatory neurotransmitter release. These phenomena, physiologically characterized by depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE), respectively, represent novel mechanisms by which neuronal excitability can be modulated, by using a non-synaptic signaling mechanism (2,3).

CBs may play numerous roles in neuronal signaling and may be important in mediating pathologic processes, such as neuropathic pain, anxiety, and movement disorders (4,5). Recently, seizures have joined this ever-growing list. For instance, Wallace and colleagues have shown a protective effect of endogenous CBs in maximal electroshock seizures (6) and an anticonvulsant effect of CBs in the pilocarpine model of temporal lobe epilepsy (7). One proposed manner in which CBs might protect against seizure-induced damage is that the excessive neuronal activity of a seizure engenders "on-demand" (i.e., as needed) CB synthesis and release; CBs then protect against excitotoxic damage by reducing presynaptic glutamate release (8).

The present report by Chen and colleagues describes an important modification of that concept in experimental febrile seizures in rats. The authors found that a single febrile seizure (average duration, 22 minutes), on postnatal day 10, induced CB formation and release. Acting on presynaptic CB1 receptors, CBs reduced the release of presynaptic γ-aminobutyric acid (GABA) but not glutamate, as determined by a reduction in DSI but not DSE in rats that had febrile seizures. Therefore in this system, a dissociation occurs between CB effects on inhibitory and excitatory neurotransmission. The effect is mediated by an upregulation of CB1 receptor number on cholecystokinin-containing inhibitory interneurons but not on parvalbumin-containing interneurons. The suppression of DSI is replicated by either endogenous or exogenous CBs. It is not mediated by metabotropic receptors or axonal sprouting. Finally, the effect is persistent, lasting for more than 1 week. Therefore limbic network excitability appears to be altered on a long-term basis after a single febrile seizure.

These results have several important implications. First, endogenous CBs act selectively to decrease GABA release, depriving the postsynaptic neurons of important inhibitory neuronal input and facilitating the hyperexcitable state. Second, this finding is an additional pathophysiologic consequence of febrile seizures. In experimental febrile seizures, evidence now exists for (a) a persistent increase in presynaptic GABAergic drive (9); (b) long-term postsynaptic limitation of GABA

action via an increase in the hyperpolarization-activated I_h conductance (10); and now, (c) a retrograde signal from an endogenous lipid that selectively targets GABAergic inhibitory transmission by CB1-receptor upregulation. The report does not establish the specific identity of the CB (e.g., anadamide or 2-arachidonylglycerol), which would be critical to know for design of a therapeutic intervention. The developmental regulation of this effect also should be examined, in light of the tight age-specificity of febrile seizures. It would be interesting to know whether multiple febrile seizures would give results that are even more robust. These exciting findings open new avenues for investigation of this common, and perhaps not so benign, childhood epilepsy.

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