ROLE OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN CATAMENIAL EPILEPSY

Hippocampal Excitability Increases during the Estrous Cycle in the Rat: A Potential Role for Brain-derived Neurotrophic Factor

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To test the hypothesis that induction of brain-derived neurotrophic factor (BDNF) may contribute to changes in hippocampal excitability occurring during the female reproductive cycle, we examined the distribution of BDNF immunoreactivity and changes in CA1 and CA3 electrophysiology across the estrous cycle in rats. Hippocampal BDNF immunoreactivity increased on the day of proestrus, as well as on the following morning (estrus), relative to metestrus or ovariectomized animals. Changes in immunoreactivity were clearest in mossy fiber axons of dentate gyrus granule cells, which contain the highest concentration of BDNF. Increased immunoreactivity also was apparent in the neuropil-containing dendrites of CA1 and CA3 neurons. Electrophysiological recordings in hippocampal slices showed robust cycle-dependent differences. Evoked responses of CA1 neurons to Schaffer collateral stimulation changed over the cycle, with larger maximal responses at both proestrus and estrus relative to metestrus. In area CA3, repetitive hilar stimuli frequently evoked multiple population spikes at proestrus and estrus but only rarely at other cycle stages, and never in slices of ovariectomized rats. Hyperexcitability in area CA3 at proestrus was blocked by exposure to the high-affinity neurotrophin receptor antagonist K252a, or an antagonist of the α7 nicotinic cholinergic receptor, whereas it was induced at metestrus by the addition of BDNF to hippocampal slices.

These studies suggest that hippocampal BDNF levels change across the estrous cycle, accompanied by neurophysiologic responses that resemble the effects of BDNF treatment. An estrogen-induced interaction of BDNF and α7 nicotinic receptors on mossy fibers seems responsible for estrous cycle changes in area CA3. Periovulatory changes in hippocampal function may thus involve estrogen-induced increases in BDNF expression.

COMMENTARY

Women with epilepsy exhibit menstrual cycle–dependent changes in seizure incidence, commonly referred to as catamenial epilepsy. One hormone that plays an important role in catamenial exacerbation of seizures is estrogen. Estrogen influences seizure susceptibility during the menstrual cycle as well as during puberty, pregnancy, and menopause. Estrogen increases neuronal excitability through alterations in neuronal structure, such as increased number of dendritic spines (1,2) and increased number of spine synapses (3). However, the molecular mechanism of estrogen-induced alterations in neuronal excitability remains unknown. One likely candidate is brain-derived neurotrophic factor (BDNF). In addition to its previously known role in the growth, survival, and differentiation of neurons, BDNF regulates synaptic transmission in various ways. First, BDNF enhances excitatory synaptic transmission (4–6) and plays an important role in maintaining long-term potentiation (7). Second, BDNF expression is activity dependent. BDNF messenger RNA (mRNA) levels increase after neuronal depolarization and decrease after neuronal inhibition (8,9). Seizure activity also induces a rapid increase in BDNF mRNA levels in the hippocampus and cortex (10). Finally, BDNF expression can be regulated by estrogen, as BDNF contains an estrogen response element in its promoter (11).

Scharfman et al. tested the hypothesis that BDNF mediates estrogen modulation of hippocampal excitability. BDNF expression in hippocampal slices correlated with circulating levels of estrogen, with immunoreactivity being stronger in cycling rats than in ovariectomized or male rats and greater during proestrus and estrus than during metestrus. Excitability of CA1 and CA3 neurons in hippocampal slices correlated with circulating levels of estrogen. Interestingly, k252a—an antagonist to the TrkB receptor (the high-affinity receptor for BDNF)—eliminated the multiple population spikes typically evoked in proestrus rat slices, further supporting a role for endogenous BDNF in hyperexcitability. Overall, the patterns of BDNF

immunoreactivity and hyperexcitability suggest that estrogen release before ovulation induces BDNF synthesis in granule cells' somata, from where BDNF is transported to axons in the hilus to be released on stimulation of presynaptic mossy fibers.

These results provide critical evidence that estrogen-mediated increases in BDNF synthesis may contribute to hippocampal excitability. It is possible that new treatments for catamenial epilepsy could be developed, involving the administration of BDNF antagonists during the periovulatory period. However, other factors, such as a simultaneous decrease in levels of progesterone and its metabolites, neuroactive steroids, may contribute to catamenial exacerbation of seizures. A comprehensive treatment for catamenial epilepsy should address both possibilities.

Questions arising from this study include the mechanism of BDNF action. How does BDNF increase hippocampal excitability? Numerous mechanisms could be involved, such as increasing phosphorylation of synaptic receptors, modulating the flow of Na^+ and Ca^{2+} ions through glutamate receptors, increasing the number of glutamate receptors at synapses, increasing the number of dendritic spines, or inducing formation of new glutamatergic synapses. Future experiments may tease out the mechanism of BDNF-induced excitability.

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