

VIRUS-INDUCED INJURY OF THE DENTATE GYRUS: DECONSTRUCTING THE GATE IN THE WAY OF SEIZURES

Kappa Opioid Control of Seizures Produced by a Virus in an Animal Model

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Brain 2006;129(Pt 3):642–654

Epilepsy remains a major medical problem of unknown aetiology. Potentially, viruses can be environmental triggers for development of seizures in genetically vulnerable individuals. An estimated half of encephalitis patients experience seizures and 4% develop status epilepticus. Epilepsy vulnerability has been associated with a dynorphin promoter region polymorphism or low dynorphin expression genotype, in man. In animals, the dynorphin system in the hippocampus is known to regulate excitability. The present study was designed to test the hypothesis that reduced dynorphin expression in the dentate gyrus of hippocampus due to periadolescent virus exposure leads to epileptic responses. Encephalitis produced by the neurotropic Borna disease virus in the rat caused epileptic re-

sponses and dynorphin to disappear via dentate granule cell loss, failed neurogenesis and poor survival of new neurons. Kappa opioid (dynorphin) agonists prevented the behavioural and electroencephalographic seizures produced by convulsant compounds, and these effects were associated with an absence of dynorphin from the dentate gyrus granule cell layer and upregulation of enkephalin in CA1 interneurons, thus reproducing a neurochemical marker of epilepsy, namely low dynorphin tone. A key role for kappa opioids in anticonvulsant protection provides a framework for exploration of viral and other insults that increase seizure vulnerability and may provide insights into potential interventions for treatment of epilepsy.

COMMENTARY

The dentate gyrus plays a particularly important role in regulating hippocampal excitability and hence, in the mechanisms of temporal lobe epilepsy (TLE). It serves as a major gateway through which excitation from entorhinal cortex enters the hippocampus and then as a filter that processes information originating in the entorhinal cortex, inhibiting its spread to the rest of the hippocampus (1). The substrate of the dentate gyrus filter is multifaceted, with interactions among GABAergic neurotransmission, glutamatergic neurotransmission, and modulatory neuropeptides, such as dynorphin, neuropeptide Y, somatostatin, galanin, and others. The high complexity of the organization of the dentate gyrus suggests that the dysfunction of even a single component of this fine-tuned system might lead to profound impairment of hippocampal function, including development of TLE.

In TLE, the filtering function of the dentate gyrus is impaired as a result of the selective loss of inhibitory interneurons and because of synaptic reorganization, including the sprouting of dentate granule cell axons (i.e., mossy fibers) that causes the formation of positive-feedback reverberating excitatory circuits. Alternatively, dysfunction of the dentate gyrus filter may result from the disruption of its normal ontogenic development, stemming from either genetic or acquired abnormalities. Indeed, mutations of several proteins important for proliferation and differentiation of dentate granule cells manifest seizure phenotypes (2,3). Similarly, neuronal infection, particularly of viral etiology, is an exogenous factor that can affect normal development of the hippocampus. Several viruses exhibit remarkably high tropism toward neuronal tissue. Solbrig and coworkers studied one such virus, the Borna disease virus. In both humans and animals Borna disease is associated with a variety of neurological disorders, including seizures and hippocampal sclerosis (4).

Solbrig et al. focused their attention on dynorphin as a possible target for the Borna disease virus. Dynorphin is an

endogenous opioid peptide abundant in mature dentate granule cells. By activating kappa opioid receptors, dynorphin acts as a powerful retrograde inhibitor of excitatory transmission between the entorhinal cortex and the dentate gyrus (5). Thus, dynorphin is one of the key determinants that shapes the dentate gyrus gateway. It is conceivable that disruption of normal maturation of the dynorphin pathway could lead to insufficient filtering by the dentate gyrus and contribute to the mechanisms of limbic epilepsy.

Solbrig and coworkers established that Borna disease virus infection in periadolescent rats led to development of spontaneous seizures and enhanced hippocampal excitability. The augmented hippocampal excitability was highly sensitive to pharmacological agents that modulated kappa opioid transmission. Morphological studies revealed profound disruption of the dentate gyrus development, resulting in a decrease in the number of dentate granule cells and their axons. Furthermore, complete disappearance of dynorphin-positive neurons from the surviving dentate granule cell population suggests that the Borna disease virus selectively impairs the dynorphin system. Finally, the virus selectively targeted the proliferation and survival of progenitors of dentate granule cells.

Hence, Borna disease virus, when introduced into the brain during the relatively early stages of its development, strongly interferes with normal maturation of the dentate gyrus. In contrast to classic TLE, which is characterized by restructuring of the dentate gyrus filter in favor of excitation, the Borna disease virus virtually eliminates the dentate gyrus gate altogether. As a result, entorhinal projections to the CA3 and CA1 areas of the hippocampus (which are normally kept in check by dentate gyrus) prevail, thus facilitating the spread of excitation throughout the hippocampus. The epileptogenic process is further reinforced by the loss of dynorphin-mediated inhibition of glutamate release from the entorhinal cortex. Although Solbrig et al. focused their studies on dynorphin, other components of dentate gyrus circuitry most certainly were affected as well. The same study found overexpression of another opioid peptide, enkephalin, in the CA1 area of the hippocampus of infected rats. Furthermore, another study implicated the subthalamic nucleus in Borna-virus-induced epilepsy (6), thus expanding Borna disease virus epileptogenicity beyond the dentate gyrus and hippocampus.

While Borna disease is relatively rare in humans, it possibly underlies some cases of TLE for which there is no clearly identifiable precipitating factor, such as status epilepticus or traumatic brain injury. Importantly, in the immature brain, Borna disease virus does not induce an inflammatory response (4), which may complicate establishing the etiology of its neurological sequelae. From the broader perspective, it is conceivable that virus-associated epilepsies occur rather commonly. For example,

human herpes virus-6 (7) and herpes simplex virus type 1 (8) exhibit a very high affinity for the hippocampus and result in the augmentation of hippocampal excitability and seizures. Feline immunodeficiency virus induces changes in the hippocampus that very much resemble those associated with TLE (i.e., gliosis and mossy fiber sprouting) (9). Inflammation following the infection cannot be discounted as well, as it has been shown that the inflammatory cytokine interleukin-6 inhibits neuronal progenitor proliferation in the dentate gyrus (10). For the basic scientist, Borna disease virus provides yet another valuable tool to study the functional organization of the hippocampus and the role of various components that regulate the excitability of its circuitry as well as providing a means to learn more about the mechanisms of TLE.

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References

1. Heinemann U, Beck H, Dreier JP, Ficker E, Stabel J, Zhang CL. The dentate gyrus as a regulated gate for the propagation of epileptiform activity. *Epilepsy Res Suppl.* 1992;7:273–280.
2. Liu M, Pleasure SJ, Collins AE, Noebels JL, Naya FJ, Tsai MJ, Lowenstein DH. Loss of BETA2/NeuroD leads to malformation of the dentate gyrus and epilepsy. *Proc Natl Acad Sci U S A* 2000;97:865–870.
3. Zhao X, Ueba T, Christie BR, Barkho B, McConnell MJ, Nakashima K, Lein ES, Eadie BD, Willhoite AR, Muotri AR, Summers RG, Chun J, Lee KF, Gage FH. Mice lacking methyl-CpG binding protein 1 have deficits in adult neurogenesis and hippocampal function. *Proc Natl Acad Sci U S A* 2003;100:6777–6782.
4. Gonzalez-Dunia D, Volmer R, Mayer D, Schwemmler M. Borna disease virus interference with neuronal plasticity. *Virus Res* 2005;111:224–234.
5. Drake CT, Terman GW, Simmons ML, Milner TA, Kunkel DD, Schwartzkroin PA, Chavkin C. Dynorphin opioids present in dentate granule cells may function as retrograde inhibitory neurotransmitters. *J Neurosci* 1994;14:3736–3750.
6. Solbrig MV, Adrian R, Baratta J, Piomelli D, Giuffrida A. A role for endocannabinoids in viral-induced dyskinetic and convulsive phenomena. *Exp Neurol* 2005;194:355–362.
7. Yamashita N, Morishima T. HHV-6 and seizures. *Herpes* 2005;12:46–49.
8. Wu HM, Huang CC, Chen SH, Liang YC, Tsai JJ, Hsieh CL, Hsu KS. Herpes simplex virus type 1 inoculation enhances hippocampal excitability and seizure susceptibility in mice. *Eur J Neurosci* 2003;18:3294–3304.
9. Mitchell TW, Buckmaster PS, Hoover EA, Whalen LR, Dudek FE. Axonal sprouting in hippocampus of cats infected with feline immunodeficiency virus (FIV). *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:1–8.
10. Vallieres L, Campbell IL, Gage FH, Sawchenko PE. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. *J Neurosci* 2002;22:486–492.