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Alterations of Neuropeptides and Neutrotrophic Factors in Kindled Seizures

점적(漸積) 발작에서 신경펩타이드와 신경친화성 인자의 변화

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Kindling ; Experimental Model of Chronic Epilepsy

Kindling is the process of repeated, intermittent administration of subconvulsant electrical stimulation, which eventually induces generalized seizure. Amygdala kindling is typically achieved by using once daily electrical stimulation with 60 Hz for 1 second. This stimulation initially evokes little behavioral reaction, but does evoke afterdischarges from the amygdala that, over days, spread in duration, complexity, and anatomic distribution. The process acquires such neuronal strength that a fulll-blown seizure eventually occurs in response to the same 1 second (previously subthreshold) stimulation.

Finally, the animal remains in the 'kindled state' where a single kindling stimulation can elicit a generalized seizure even after months without stimulation or seizures. If continued sufficiently, seizures cease to require triggering by electrical stimulation and begin to occur spontaneously. Thus, the kindling process provides an interesting model for conceptualization of growth of neural memorylike mechanisms as a progression from minor to major and from reactive to spontaneous changes in behavior and physiological processes. This experimental model has been used to understand epileptogenesis and neural plasticity until recently.[1]

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Molecular Mechanisms Involved in Kindling Evolution

Many of the neurobiological mechanisms of kindling evolution are beginning to be clarified. There is increasing recognition that brain stimulation leads not only to shot-term adaptations but also to long-term modifications of synaptic strength by the induction of immediate early genes(IEG) such as c-fos, c-jun, and NGFI-A, and their subsequent down stream effects on late effector genes(LEG) encoding neurotransmitter and its receptor machinery, such as benzodiazepine-gamma aminobutyric acid(GABA)-chloride channel complex and NMDA or non-NMDA glutamatergic receptors, ion channels responsible for excitability, enzymes, neuropeptides, neurotrophic factors, neural cell adhesion molecules(N-CAMS) and other regulatory factors.

Sutula *et al.*[2] observed a loss of hilar cells, supposed to contribute disinhibition of GABAergic interneurons, in direct propotion to the number of amygdala-kindled stimulations. Recently, Zhang *et al.*[3], in our laboratory, demonstrated that bax and other genes such as bcl-2, P 53 involved in programmed cell death or apoptotic programs are also induced with kindled seizures. Some of microstructural alterations may be involved in synaptic reorganization of the dentate granule cells for dendritic or axonal sprouting into the supragranular layer and CA3 pyramidal neurons and neosynaptogenesis.

Recently, Esclapez *et al.*[4] reported an extensive axonal sprouting of CA1 pyramidal neurons, output of perforant path, with many axonal branches entering the pyramidal cell layer and stratum radiatum. Concurrently with this anatomical reorganization, a large increase of

the spontaneous glutamatergic drive were observed in the dendrites and somata of CA1 pyramidal cells. Furthermore, electrical activation of the reorganized CA1 associated pathway evokes epileptiform bursts in CA1 pyramidal cells. In addition to axonal sprouting of glutamatergic neurons, granule cell migration and neurogenesis were observed.[5]

This plasticity of excitatory pathways may contribute an imbalance between excitation and inhibition, responsible for abnormal hyperexcitability. Taken together, these data emphasize the remarkable synaptic plasticity of this one region of the hippocampus in response to repeated stimulation of the brain. Not only is there dramatic change and reprogramming of the cellular biochemistry but also a change in the structure of the brain itself, perhaps mediated by neurotrophic factors involving both sprouting(readily observed microscopically with Timm's staining) and cell loss.

Induction of Neuropeptides by Kindling : The Functional Implication in a Modulatory Role in Developing Seizure

We previously demonstrated using *in situ* hybridization that thyrotropin-releasing hormmone(TRH), neuropeptide Y(NPY), dynorphin(DYN), enkephalin(ENK), corticotropin factor(CRF), corticotropin factor-binding protein(CRF-BP) and cholecystokin(CCK) mRNAs are differentially expressed following amygdala kindling with distinct spatiotemporal pattern, particularly in regions known to be important in kindling and epilepsy, such as dentate gyrus granular layer, pyriform and entorhinal cortices and the dentate hilus.[6-9]

The differences in the spatial and temporal changes in mRNA expression need to adressed when defining the role of neuropeptides in the neuroatomical and chemical network associated with seizures. There may be a dual set of processes occurring with amygdala-kindled seizures : 1) the longer-lasting primary pathologic process that conveys seizure susceptibility and progression, and 2) a set of more transient, endogenous, adaptive changes represents attempts to reinstate homeostasis and exert endogenous anticonvulsant effects.

This is particularly important for understanding the anti- or pro-convulsant effects of peptides and how they may function as transient and long lasting modulators of seizure disorders. Understanding of the functional role of different peptide systems in the evolution and maintenance of kindling may assist in the elucidation of the role of neuropeptides in human epilepsy.

Alterations in m-RNA Expression of Neurotrophic Factors Underlying Structural Remodeling

We demonstrated the alterations of neurotrophic factor expression(i.e.,brain-derived neurotrophic factor(BDNF), neurotrophin-3 (NT-3), nerve growth factor(NGF)) following amygdala kindling and hormonal manipulation in specific limbic regions.[10] BDNF and NGF are increased and NT-3 is decreased following amygdala kindling while immobilization stress affect the endogenous level in the opposite direction. The kindling-induced decrease in NT-3 mRNA expression in the dentate gyrus granule cell layer was significantly attenuated by thyroid hormone depletion. The expression pattern of receptors for the neurotrphic factors (tyrosine receptor kinase A(trkA), trkB and trkC) were observed to be altered following kindlimg, similarily to the neurotrophic factors.[11]

Neurotrophic factors are important in neuronal survival and differentiation and axonal outgrowth. Kindling-induced plasticity of glutamatergic excitatory neurons may be partly related with the enhancement of neurotrophin expression. It has previously reported that intrventricular administration of antibodies to NGF or trkB receptor body retarded and blocked mossy fiber sprouting in adult rat, suggesting the important roles of neurotrophic factors in structural plasticity.[12][13]

We hope the large amount of information from 'kindling', as the excellant experimental model, provide the understanding the epileptogenesis and therapeutic strategy with anticonvulsant agents in the human epilepsy.

중심 단어 : Kindling · Neuropeptide · Neurotophic factor.

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