

## NEUROPEPTIDE Y AND Y1 RECEPTORS IN KINDLING EPILEPTOGENESIS

**Neuropeptide Y Delays Hippocampal Kindling in the Rat**

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Prolonged intrahippocampal infusion of the neurotrophin brain-derived neurotrophic factor (BDNF) has been shown to delay kindling epileptogenesis in the rat, and several lines of evidence suggest that neuropeptide Y could mediate these inhibitory effects. Long-term infusion of BDNF leads to a sustained overexpression of neuropeptide Y in the hippocampus, which follows a time course similar to that of the suppressive effects of BDNF on kindling. In vivo, immediate applications of neuropeptide Y or agonists of its receptors exert anticonvulsant properties, especially on seizures of hippocampal origin. In this study, we examined how prolonged infusion of this neuropeptide in the hippocampus affected kindling epileptogenesis. A 7-day continuous infusion of neuropeptide Y in the hippocampus delayed the progression of hippocampal kindling in the rat, whereas anti-neuropeptide Y immunoglobulins had an aggravating effect. These results show that neuropeptide Y exerts antiepileptogenic properties on seizures originating within the hippocampus and lend support to the hypothesis that BDNF delays kindling at least in part through upregulation of this neuropeptide. They also suggest that the seizure-induced upregulation of neuropeptide Y constitutes an endogenous mechanism counteracting excessive hippocampal excitability.

**Induced Downregulation of Neuropeptide Y-Y1 Receptors Delays Initiation of Kindling**

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Neuropeptide Y appears to modulate epileptic seizures differentially according to the receptor subtypes in-

involved. In the hippocampus, neuropeptide Y expression and release are enhanced in different models of epileptogenesis. Conversely, the expression of Y1 receptors is decreased, and it has been shown that activation of these receptors has proconvulsant effects. The aim of our study was to investigate the role of Y1 receptors during hippocampal kindling epileptogenesis by using (a) knockout mice lacking Y1 receptors and (b) intrahippocampal infusion of Y1 antisense oligodeoxynucleotide in rats. Y1 knockout mice showed similar susceptibility to seizure induction and presented no difference in kindling development as compared with their control littermates. Conversely, local hippocampal downregulation of Y1 receptors during the first week of hippocampal kindling, induced by a local infusion of a Y1 antisense oligodeoxynucleotide, significantly increased seizure threshold intensity and decreased afterdischarge duration. A reverse effect was observed during the week after the infusion period, which was confirmed by a significant decrease in the number of hippocampal stimulations necessary to evoke generalized seizures. At the end of this second week, an upregulation of Y1 receptors was observed in kindled rats infused with the antisense as compared with the mismatch-treated controls. Our results in the rat suggest that the downregulation of Y1 receptors in the hippocampus participates in the control of the initiation of epileptogenesis. The lack of an effect of the deficiency of Y1 receptors in the control of kindling development in Y1 knockout mice could be due to compensatory mechanisms.

**COMMENTARY**

Neuropeptide Y (NPY) is a 36-amino acid residue polypeptide widely distributed in the central and peripheral nervous systems, which acts through at least six receptor subtypes belonging to the G protein-coupled receptor superfamily (1). The peptide has powerful anticonvulsant effects, especially on epileptic activity originating in the hippocampus, as shown in various in vitro and in vivo models of seizures (2–4). Its anticonvulsant actions appear to be mediated by Y2- and Y5-receptor subtypes and involve inhibition of

glutamate release, which is due to suppression of voltage-dependent  $\text{Ca}^{+2}$  influx in presynaptic nerve terminals (5,6). Conversely, as demonstrated by Benmaamar et al. and others, Y1-receptor subtypes mediate excitatory-like effects of the peptide (7), and they have been recently implicated in the control of neuroproliferation and NPY-mediated hippocampal neurogenesis (8,9).

Changes in NPY-mediated neurotransmission as well as NPY-receptor plasticity have been described in epileptic tissue from experimental models and in human temporal lobe epilepsy patients (2,3,10). In addition to its anticonvulsant properties, recent evidence suggests an involvement of NPY in epileptogenesis. Thus endogenous overexpression of this peptide in the hippocampus of transgenic rats or by viral vector-mediated NPY gene transduction significantly delays the rate of kindling development (11,12). Accordingly, the work by Reibel and colleagues demonstrates that prolonged infusion of NPY in the rat hippocampus, during the initial phase of kindling, delays the progression of epileptogenesis, whereas impairment of endogenous NPY, by using specific immunoglobulins, accelerates this epileptogenic process. In particular, NPY affects the occurrence of generalized behavioral seizures, suggesting a specific inhibitory effect on the spreading of seizures of hippocampal origin.

When investigating in more detail the role of NPY-receptor subtypes in kindling, Benmaamar et al. found that Y1 receptors mediate an increase in hippocampal excitability. Thus by inducing a downregulation of Y1 receptors in the hippocampus with an antisense technology, they found that the intensity of current needed to bring about an afterdischarge in the electrically stimulated hippocampus was increased, and that the afterdischarge duration was reduced. When the antisense Y1-receptor oligonucleotide was discontinued, the authors observed a compensatory upregulation of Y1 receptors in the hippocampus and a concomitant acceleration of kindling.

Previous evidence has shown that blockade of hippocampal Y1 receptors, by using a specific antagonist, provides protection against kainate-induced seizures, thus supporting a permissive role of Y1 receptors on seizures (7). In the article by Benmaamar and co-workers, Y1-receptor knockout mice did not show any alteration in the EEG and behavioral sequelae of kindling, suggesting that some compensatory changes in other neurotransmitter systems might have occurred. If Y1 receptors play a facilitating role in seizures and epileptogenesis, then the reduction in Y1 receptors reported both in experimental epilepsy models (2,3) and in brain from human patients with epilepsy (10) may represent an endogenous protective mechanism against hyperexcitability.

The mechanisms whereby Y1 receptors mediate the proconvulsant effects of NPY are still elusive. One possibility

is that activation of these receptors results in inhibition of the release of NPY (13), and possibly  $\gamma$ -aminobutyric acid (GABA), which is colocalized with NPY in the hippocampus. Thus Y1 receptors have been described both on dendrites of granule cells (2) and in hilar interneurons containing NPY (13).

The NPY receptors mediating the antiepileptogenic effects of NPY remain to be established. Unpublished data by Vezzani and colleagues point to a significant role of Y5 receptors. The development of pharmacologic strategies to suppress seizures and delay epileptogenesis by targeting the NPY system should take into account that Y1-receptor stimulation may facilitate seizures; thus drugs should be selectively targeted to Y2 and Y5 receptors.

by Annamaria Vezzani, Ph.D.

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