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Neuropeptide Y: potential role in recurrent developmental seizures

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Abstract

Seizures induce profound plastic changes in the brain, including altered expression of neuropeptide Y (NPY) and its receptors. Here I discuss a potential role of NPY plasticity in the developmental brain: In a rat model of febrile seizures (FS), the most common type of seizures in infants and young children, NPY expression was up-regulated in hippocampus after experimentally-induced FS. Interestingly, NPY up-regulation was associated with an increased seizure threshold for additional (recurrent) FS, and this effect was abolished when an antagonist against NPY receptor type 2 was applied. These findings suggest that inhibitory actions of NPY, released after seizures, exert a protective effect that reduces the risk of seizure recurrence in the developing brain.

Keywords

neuropeptide Y; NPY; febrile seizures; rat; hyperthermia; epilepsy; hippocampus

1. Introduction

Neuropeptide Y (NPY) is an important modulator of hippocampal synaptic transmission[27, 49,50,58,79,81]. Increasing attention has therefore been devoted to assessing whether seizures induce changes in NPY-mediated neurotransmission, and whether these changes are involved in the underlying pathophysiology of seizure disorders or compensatory mechanisms. Indeed, elevated NPY release after seizures and in epileptic tissue has been reported in brain regions that are crucial for the initiation and propagation of epileptic discharges, such as the amygdala, hippocampus, piriform and entorhinal cortices [13,54,61,65,67,74,75,77]. In these limbic regions, up-regulation of NPY may be part of an adaptive response aimed at counteracting hyperexcitability and thus recurrence of seizures [78]. Recent findings in an animal model of developmental febrile seizures, which I shall review here, suggest that such an adaptive role of NPY release may also be critical in the developing brain, and may protect the highly plastic, immature brain from undergoing recurrent seizures.

2. Febrile seizures and epileptogenesis

A frequent hallmark in the histories of patients with temporal lobe epilepsy (TLE), particularly if associated with hippocampal sclerosis (mesial TLE), is the occurrence of prolonged febrile seizures (FS) early in life [21,38,44,72], prompting suggestions that the FS are a causal factor

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in the etiology of this epileptic disorder [6,52]. However, most FS (affecting 2–14% of all children worldwide; [46, 71 for review]) do not lead to epilepsy, and certain risk factors have been distinguished. These include: 1) FS that are prolonged, i.e., >10 to 15 min [3,16,56], 2) FS that are recurrent, i.e., several seizures within a 24h period [3,55], and 3) FS that are focal. A seizure that has one or more of the previous features is referred to as complex FS [28].

In order to study the consequences of complex FS, and thus to gain a better understanding of their potential contribution to human epilepsy, an animal model of FS was established in our laboratory [10,18,19,32,33,73]. In this model, experimental FS are induced in rat pups on postnatal days 10 or 11, an age that corresponds to the hippocampal developmental stage at which human infants are most susceptible to febrile seizures (see comparison of developmental milestones in humans and rodent hippocampus in [4]). The majority of FS in humans occur between 6 months and 5 years of age with a peak of incidence at 18 months [46,57].

Experimental FS are induced by hyperthermia [30] which triggers processes in the brain that are similar to those evoked by fever (e.g., release of cytokines, [34,41,63,64]). For seizure generation, rat pups are placed in a glass jar and exposed to a constant stream of mildly heated air [32,73]. Seizures reliably occur when core and brain temperatures reach a threshold temperature of ~40.8°C. The threshold temperatures generating experimental FS are close to those required for FS in normal children [14]. As indicated by seizure behavior and confirmed with electrophysiological recordings from multiple brain sites, these seizures are limbic and the behavior during the seizures is reproducible and stereotyped [10,18,32]. Seizure duration can be tightly controlled in the model. In addition, mortality (<1%) and morbidity after seizures are low. Taken together, the similarities to the human situation and the controllability of seizure conditions render this animal model suitable for studying the impact of developmental “febrile” seizures on the immature brain.

We first used this model to generate experimental FS of prolonged duration, the type of complex FS most frequently associated with mesial TLE [22, 69 for review]. For this purpose, seizure duration was controlled to last ~24 minutes (i.e., not status epilepticus). Rats were then returned to their mothers and further investigated weeks or months later. The major findings of these studies are that prolonged FS do not lead to cell death nor to other neuroanatomical abnormalities, although transient neuronal injury occurs [10,11,33,35,73]. Nevertheless, rats that had experienced prolonged FS early in life have a reduced seizure threshold later in life and ~35% develop spontaneous seizures, i.e. limbic (temporal lobe) epilepsy, as adults [32, 33]. This may be due in part to profound and long-lasting changes in the expression of the hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel genes after FS [12,18,19,66]. These data together suggest that prolonged experimental FS induce plastic processes in the brain that render the neuronal network hyperexcitable [18,19,23,24,32,33].

3. The problem of seizure recurrence

We used this animal model to study recurrent “FS”, i.e., those occurring during the subsequent 24 hours. The rationale for these studies derives from observations on human FS. Thus, most FS remain single events [2], and repeated seizures are uncommon (occurring only in ~14% of FS; [15]), although core temperatures may remain elevated in children for several hours during a febrile episode. What protects these children from having recurrent febrile seizures?

To study this question, we induced experimental FS once, twice or three times at 3–4 hour intervals to approximate the clinical situation [15]. We found that threshold temperatures for the second seizure were significantly higher compared with the first, and were even further increased for the third seizure [31]. This suggests that seizure occurrence triggers mechanisms that reduce network excitability and thus render a recurrent seizure less likely.

Our search for potential mechanisms led us to neuropeptides because: 1) Initial in vitro hippocampal slice experiments, carried out 10 to 30 minutes after experimental FS, suggested that altered inhibition through $GABA_A$ receptors was less likely to be involved within several hours after FS (Eghbal-Ahmadi et al., unpublished) and 2) In general terms, peptides induce a response of longer duration than classic neurotransmitters [47,48]. We first considered corticotropin releasing hormone (CRH) as a potential candidate for mediating the increased threshold for a second and third experimental FS. CRH is abundantly expressed in neurons of the developing hippocampus [25]. Its release excites hippocampal neurons [1,49] and evokes seizures in immature rodents [7,8]. Thus, a first FS may reduce CRH levels in hippocampal synapses, leading to a decrease of the excitatory drive. However, quantitative analyses of CRH mRNA expression in the hippocampus demonstrated an increase after experimental FS, suggesting an enhanced rather than a reduced release of the endogenous peptide [45]. Down-regulation of CRH expression is therefore unlikely to provide "protection" from generating another FS.

Our next logical candidate was NPY. NPY is, like CRH, abundantly expressed in the hippocampal formation [39,60], and, in contrast to CRH, reduces excitatory synaptic neurotransmission in the hippocampus after release, mainly through its actions on Y2-receptors [26, 27, 42, 50, 51, 58, 67, 79, 81 but see 80]. This effect has been attributed to the reduction of Ca^{2+} influx into presynaptic nerve terminals through several types of Ca^{2+} channels [26, 59,70].

To determine whether endogenous NPY was released after a FS, and acts on its receptor(s) to reduce excitability of the hippocampal network, we used selective inhibitors of NPY receptors, Y2- (BIIE0246, 100nm/kg, 2.5 nm/μl, administered into the lateral ventricle using a semistereotaxic freehand infusion; [20,29,36,37]) and Y5 (GW459633B, 30 mg/kg, injected intraperitoneally). The antagonists were infused 4 hours after a first FS at 10 (Y2) and 3 (Y5) minutes before the induction of a second experimental FS. Both antagonists abrogated the progressive increase in seizure threshold as shown in Fig. 1 [31]. These data suggest that native NPY is released after the first seizure and acts to increase threshold (i.e., reduce excitability) for a second one.

For neuropeptides, the increased release typically leads to enhanced synthesis [47,48]. Indeed, increased NPY mRNA expression was detected in dentate gyrus (DG) granule cell layer of FS-experiencing rats already by 4 hours, and in DG, CA1 and CA3 hippocampal areas 24 hours after a seizure (Fig. 2), suggesting seizure-induced enhancement of endogenous NPY release [31]. Thus these findings strongly suggest that seizure-induced release of endogenous NPY is involved in endowing limbic circuits with resistance to a second experimental FS.

4. Relevance to human studies

These findings in the FS animal model are consistent with findings in other experimental epilepsy models and with the presumed roles of NPY in human limbic epilepsy. Thus, NPY expression increases after various types of seizures, including kindling [61,68,77] and kainic acid-induced seizures [9,43,76]. NPY expression is also increased in dentate gyrus granule cells of human epileptic hippocampus [54]. In addition, NPY expression changes are accompanied by altered receptor expression both in seizure models [17,62,67], and in tissue from epileptic patients [40]. In all these situations, altered NPY function is assumed to increase inhibition and thus reduces hyperexcitability of the epileptic network. Our findings in an animal model of developmental seizures are novel in that they show for the first time that tight regulation of NPY expression and release is already employed early in life as a mechanism to balance network excitability, and thus to counter changes that could promote epileptogenesis.

The detection of remarkably high levels of NPY relatively early in developing human brain [53], and particularly in hippocampus [5], is consistent with this hypothesized regulatory role.

In conclusion, a single FS leads to enhanced inhibitory processes in the normal hippocampal circuit, that protect it from ensuing hyperthermia-provoked seizures within hours of the original ictus . These processes most likely involve the actions of NPY. These findings may provide a molecular and mechanistic basis for the “single-seizure-per-febrile-episode” phenomenon occurring in most children that experience FS. In contrast, recurrence of FS during a febrile episode may be indicative of an underlying brain dysfunction that potentially involves or affects the NPY system. Importantly, improved knowledge about the role of NPY and the signaling cascade triggered by the peptide could provide targets for therapeutic intervention.

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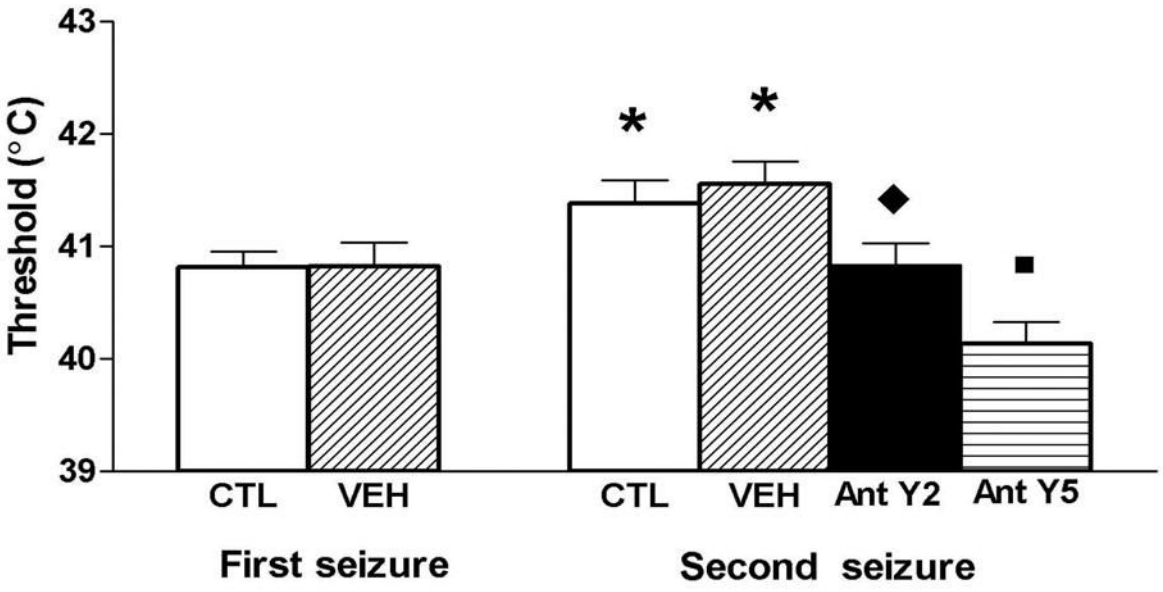

Fig. 1.

The progressive increase of threshold temperature for a second experimental febrile seizure (4 hours after the first) is abolished by selective neuropeptide Y (NPY), NPY-Y2 and NPY-Y5 receptor antagonists administered to 10 day old rats. Core threshold temperatures are significantly higher for the second seizure compared with the first for both, untreated control rats (CTL) and infused rats with vehicle (VEH). Vehicle administration does not modify the increased threshold temperature for a second febrile seizure. Asterisk denotes a significant difference from the first seizure threshold. Administration of the Y2 (BIIE0246) and Y5 (GW459633B) NPY receptor antagonists reduce the threshold temperature for the second seizure compared with animals treated with the vehicle. The diamond and square indicate significantly lower threshold compared with the threshold for the second seizure in the vehicle-infused group. Modified from Dubé C, Brunson KL, Eghbal-Ahmadi M, Gonzalez-Vega R, Baram. TZ. Endogenous neuropeptide Y prevents recurrence of experimental febrile seizures by increasing seizure threshold. J Mol Neurosci 2005;25:275–84, with permission.

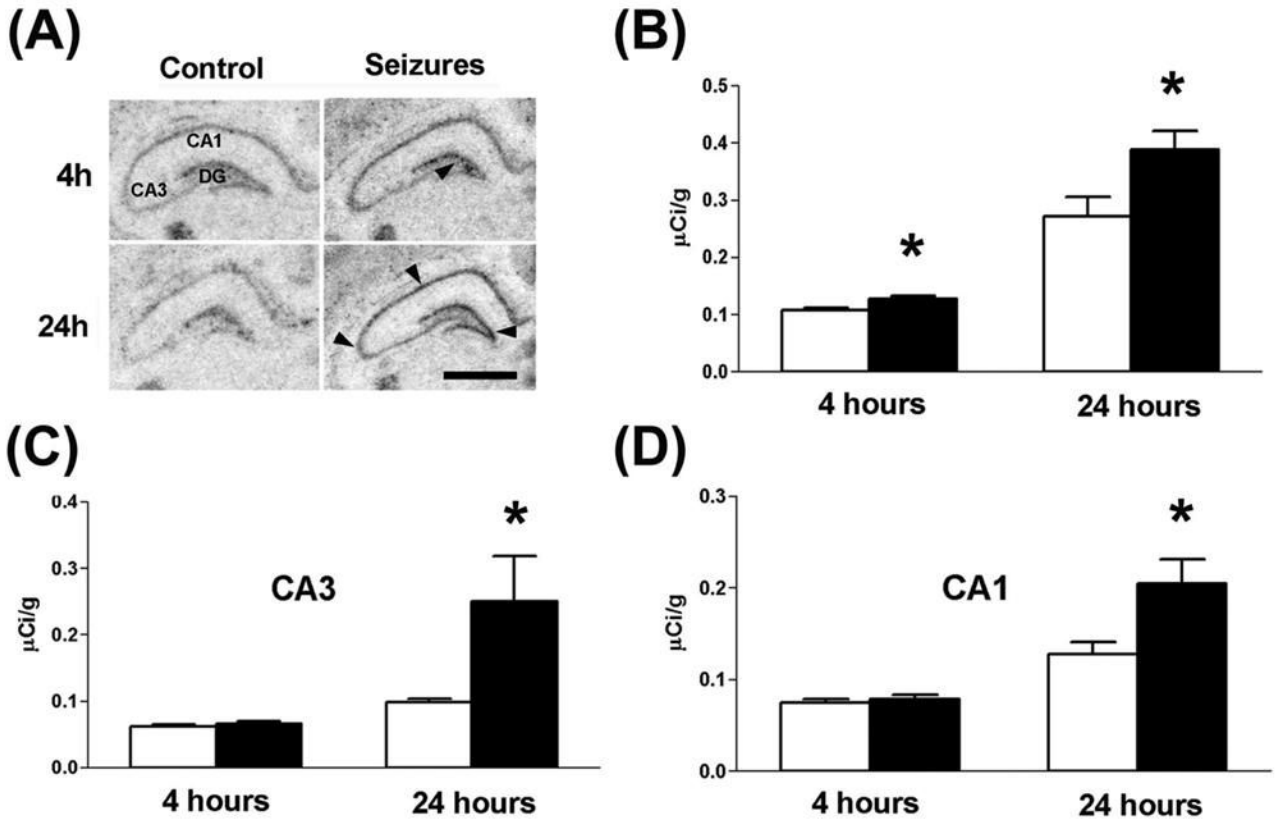

Fig. 2.

Experimental febrile seizures lead to an enhancement of NPY mRNA expression in hippocampus. In situ hybridization (ISH) histochemistry was performed on brain coronal sections (20 μm) from animals sacrificed 4 or 24 hours after experimental febrile seizure induction (n = 6 per group). (A) Example of sections illustrating the increased NPY signal after febrile seizures in the hippocampus compared with untreated rats. NPY mRNA expression is already enhanced 4 hours after seizures in the dentate gyrus (B) and 24 hours later in the dentate gyrus, CA3 (C) and CA1 (D) hippocampal areas. Reprinted with permission from Dubé C, Brunson KL, Eghbal-Ahmadi M, Gonzalez-Vega R, Baram. TZ. Endogenous neuropeptide Y prevents recurrence of experimental febrile seizures by increasing seizure threshold. J Mol Neurosci 2005;25:275–84.