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Neuropeptides in epilepsy

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ABSTRACT

Neuropeptides play an important role in modulating seizures and epilepsy. Unlike neurotransmitters which operate on a millisecond time-scale, neuropeptides have longer half lives; this leads to modulation of neuronal and network activity over prolonged periods, so contributing to setting the seizure threshold. Most neuropeptides are stored in large dense vesicles and co-localize with inhibitory interneurons. They are released upon high frequency stimulation making them attractive targets for modulation of seizures, during which high frequency discharges occur. Numerous neuropeptides have been implicated in epilepsy; one, ACTH, is already used in clinical practice to suppress seizures. Here, we concentrate on neuropeptides that have a direct effect on seizures, and for which therapeutic interventions are being developed. We have thus reviewed the abundant reports that support a role for neuropeptide Y (NPY), galanin, ghrelin, somatostatin and dynorphin in suppressing seizures and epileptogenesis, and for tachykinins having pro-epileptic effects. Most in vitro and in vivo studies are performed in hippocampal tissue in which receptor expression is usually high, making translation to other brain areas less clear. We highlight recent therapeutic strategies to treat epilepsy with neuropeptides, which are based on viral vector technology, and outline how such interventions need to be refined in order to address human disease.

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1. Introduction

Epilepsy is one of the commonest chronic brain diseases, affecting over 50 million people worldwide. It is characterised by recurrent, unprovoked seizures. The number of drugs marketed to treat epilepsy has been rapidly growing with most antiepileptic drugs targeting either sodium channels or GABA receptors. Unfortunately, despite the burgeoning of new antiepileptic drugs, one third of patients with epilepsy continues to have seizures and their epilepsies are resistant to all current available treatments (Duncan et al., 2006). In addition, the classic antiepileptic drugs which typically target ion channels or ionotropic receptors have substantial side effects which are causally linked to their mechanism of action. Neuromodulators have been explored as potential alternatives to classic antiepileptic drugs (Casillas-Espinosa et al., 2012). Unlike classical neurotransmitters, neuromodulators act through indirect modulation of neurotransmitter release or ion channel/receptor function. Their physiological function is believed to be fine-tuning of neurotransmission, thereby controlling the balance between excitation and inhibition in the CNS (Baraban and Tallent, 2004). Some of the neuromodulators, such as neuropeptide Y, share

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Table 1
Neuropeptides with anticonvulsive/antiepileptogenic properties.

Neuropeptide	Number of amino acids	Structurally similar peptides	Predominant receptors
Neuropeptide Y (NPY)	36	Pancreatic polypeptide (PP), peptide YY (PYY)	Y1, Y2, Y4, Y5, (Y6)
Galanin	30	Galanin message-associated protein (GMAP), galanin-like peptide (GALP), alarin	GALR 1-3
Somatostatin	14/28	Cortistatin	SSTR 1-5
Ghrelin	28	N/A	GHS-R1a
Dynorphin	32	Opoid peptides	κ-opioid receptor (KOR), μ-opioid receptor (MOR), δ-opioid receptor (DOR), (NMDAR)
Substance P	11	Tachykinin peptides, Neurokinin A	NK1-receptor, (NK2, NK3 receptor)

similarities in molecular structure with hormones regulating feeding (Kageyama et al., 2012). It is therefore unsurprising that whereas classical neurotransmitters operate on a millisecond scale, neuropeptides usually act over periods that are orders of magnitude longer. Neuropeptides are stored in large dense vesicles in interneurons and are released upon high frequency firing. Neuropeptides exert both pre- and postsynaptic actions on excitatory and inhibitory transmission (Baraban and Tallent, 2004). A long list of neuropeptides has been explored for the treatment of epilepsy. Of those the most promising candidates with multiple reports corroborating their direct antiepileptic and antiepileptogenic action include neuropeptide Y (NPY), galanin, dynorphin, somatostatin and ghrelin. In contrast, substance P and the tachykinens seem to have a pro-epileptic effect. These are all small peptides with several aminoacids which lack a complex protein structure (Table 1). Most of the neuropeptides act at G-protein coupled receptors thereby modulating release of neurotransmitters or modifying effects of postsynaptic receptor activation. Receptor distribution of the peptidic neuromodulators within the brain varies; however, unsurprisingly, given their importance in also regulating feeding behavior, most of the peptidic neuromodulators show high expression within the hypothalamus and hippocampal structures (Allen et al., 1983; Mitsukawa et al., 2008). Limbic, archecortical, structures have a strong impact on feeding regulation (Mogenson et al., 1980). The distribution of their target receptors renders the neuromodulators an attractive target for the treatment of epilepsy. Hippocampal sclerosis and limbic structure dysfunction is one of the most common pathologies underlying pharmacoresistant epilepsy and therefore constitutes the largest cohort in surgical series (de Tisi et al., 2011). In addition, epilepsy in patients with hippocampal sclerosis is more likely to be pharmacoresistant than epilepsy due to other lesions within the brain (Stephen et al., 2001).

Neuromodulation to treat epilepsy harbours great translational potential as neuropeptide structure, such as the structure of NPY, is highly conserved among species (Larhammar, 1996). Moreover, as endogenous substances, neuropeptides are less likely substrates of multi drug transporters. Multi drug transporters are abundantly expressed at the blood brain barrier and can prevent drugs from reaching sufficient concentrations within the brain parenchyma, thereby contributing to pharmacoresistant epilepsy (Lazarowski et al., 2007).

One pharmacokinetic difficulty that needs to be overcome is the poor bioavailability of neuropeptides, which are prone to cleavage by peptidases and show poor blood brain barrier penetration. This can be overcome by non-peptide analogues such as galnon, a synthetic galanin receptor agonist (Saar et al., 2002). An alternative to this approach is local neuromodulator delivery. This can be achieved via polymers or with viral vector based technologies which are increasingly recognized as a technique that has translational potential in treating pharmacoresistant epilepsy (Szybala et al., 2009; Wykes et al., 2012).

Numerous neuropetides have been proposed to have direct and indirect effects on epilepsy and seizures. One, ACTH, has a long history of use in childhood epilepsies, in particular West syndrome, although its mode of action in epilepsy is unclear. We have concentrated on the direct antiepileptogenic and anticonvulsive effect of NPY, galanin, somatostatin, dynorphin and ghrelin, and the pro-epileptic effects of substance P. We will review their mechanism of action and receptor function with regards to their effects on epilepsy. Finally, we will highlight the translational research that has been done in the past few years aimed at treating seizures with neuropeptide delivery focussing on reports of viral vector mediated delivery of neuropeptides.

2. Npy

NPY is probably the most studied neuropeptide in epilepsy. NPY is structurally related to two gut peptides, peptideYY and pancreatic polypeptide (Tatemoto, 1982; Tatemoto et al., 1982) and similarly plays a pivotal role in regulating food intake (Chee and Colmers, 2008; Kageyama et al., 2012). Since its discovery, the range of functions identified for NPY has expanded considerably. NPY's effects on the brain include regulation of anxiety, pain, depression, drug addiction and regulation of excessive hyperexcitability such as occurs during seizure activity (Benarroch, 2009). More recently a role for NPY in both hippocampal and subventricular neurogenesis has been discovered, which likely play a critical role in neurodegenerative disease and in remodelling during epileptogenesis (Cheung et al., 2012; Decressac and Barker, 2012, 2011, 2009, 2010; Laskowski et al., 2007; Rodrigo et al., 2010).

Five receptors have been identified – Y1, Y2, Y4, Y5 and the Y6 receptor (Michel et al., 1998, p. 199). NPY receptors are G-protein coupled receptors with a widespread distribution in the brain reflecting the large range of physiological systems in which NPY plays a role. There seems to be a regional difference in NPY receptor distribution with each receptor showing a specific distribution within the brain (Dumont et al., 1998a). Whereas Y2 receptors are abundantly expressed in the hippocampus their expression is low in the neocortex. The reverse holds true for the Y1 receptor, which is seen in high concentrations in the neocortex but at low concentration in the hippocampus (Dumont et al., 1998b). Most of the effects mediated by NPY are postsynaptic except for Y2- mediated presynaptic inhibition (Colmers et al., 1987, p. 199; Stanić et al., 2011).

NPY acts as an endogenous anticonvulsant. The highest concentrations of the neuropeptide have been measured in the hypothalamus and limbic structures thus linking this peptide to temporal lobe epilepsy (de Quidt and Emson, 1986). NPY's anticonvulsant actions have been mainly studied in the hippocampus (Baraban, 2004; El Bahh et al., 2005). In keeping with the peptide's distribution, NPY-receptor expression is high in brain areas involved in the