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Neuronal plasticity in animal models and the epileptic human hippocampus

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Prolonged status epilepticus in humans as in experimental animals can initiate the development of temporal lobe epilepsy (TLE) (Kapur, 1999). Therefore, application of potent convulsant substances such as kainic acid or pilocarpine in rats induces acute status epilepticus that, after a silent period of 1–2 weeks, is followed by spontaneous convulsions. The status epilepticus is characterized by severe limbic seizures and sequelae of neuropathologic signs including opening of the blood–brain barrier, local brain edema, bleeding into the brain, and activation of microglia and astrocytes followed by neurodegeneration in the hippocampus, amygdala, entorhinal cortex, and other brain areas (Sperk et al., 1983; Du et al., 1993; Rizzi et al., 2003). Induced by the seizure activity, neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, or amine transmitters are released from their stores and mechanisms of their resynthesis are strongly activated (Sperk et al., 1983). In addition, pronounced changes in the expression of multiple functionally important proteins have been found in brains of experimental animals and humans (Herdegen et al., 1993; Sperk, 1994; McNamara, 1999; Morimoto et al., 2004).

Some of these dynamic neurochemical changes persist also in the chronically epileptic state or may be altered or substituted by other changes. They are accompanied by progressing rearrangement of neuronal circuitries, characterized by continuing neurodegeneration and by axonal outgrowth. The best-characterized example of such plastic changes is the sprouting of mossy fibers to the inner molecular layer of the dentate gyrus, where they seem to substitute the loss of associational/commissural fibers arising from dentate mossy cells (Houser et al., 1990).

Herein we review some of our findings and the findings of others on neurochemical and morphologic changes related to GABAergic and peptidergic neurotransmission (Table 1; Pirker et al., 2001).

There are clear indications for a loss of excitatory as well as of inhibitory GABAergic neurons early after induction of the status epilepticus. At the same time, expression of immediate early genes and of many proteins becomes severely altered, mostly activated presumably leading to an altered functioning of neuronal circuitries (Herdegen et al., 1993; Sperk, 1994; Morimoto et al., 2004). Expression of the GABA-synthesizing enzymes glutamate decarboxylases GAD65 and GAD67 and of an embryonic form of GAD67 becomes enhanced (Sperk et al., 1983, 2003; Esclapez & Houser, 1999; Szabo et al., 2000), indicating enhanced GABA synthesis in the surviving neurons. Also at the receptor level,

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GABAergic transmission appears to be markedly altered. In human TLE, as in animal models, $GABA_A$ and $GABA_B$ receptors undergo dynamic changes in their expression. Whereas expression of $GABA_B$ receptors is decreased initially after status epilepticus (perhaps resulting in enhanced release of glutamate), it is increased in patients with chronic TLE (Furtinger et al., 2003a,b). Changes in the expression of $GABA_A$ receptor subunits are complex. In animal models, typically expression of the β-subunits (β2 and β3) containing the binding site for GABA, and of α2 and γ2, contributing to the binding of the anticonvulsant benzodiazepines is increased. On the other hand, levels of subunits presumably comprising extrasynaptic receptors involved in tonic GABA-mediated inhibition, such as δ and α5 (in mice), become decreased in the dentate gyrus after status epilepticus. Interestingly in human TLE most subunits expressed in the hippocampus seem to be upregulated (notably subunits α2, α3, α5, β1-3, γ2, and δ), indicating little functional changes but consistent upregulation of the receptors presumably leading to generally enhanced GABAergic transmission. (Table 1; Loup et al., 2000; Pirker et al., 2001).

Neuropeptides are cotransmitters of classical neurotransmitters. They are rapidly released during status epilepticus but are considerably slower resynthesized than classical neurotransmitters (Vezzani et al., 1996). It has been well documented that synthesis of neuropeptides is dynamically regulated by seizures and that neuropeptides may potently influence later epileptic events in different ways. Therefore, the peptides thyrotropin-releasing hormone (TRH) and neurokinin B exert proconvulsive actions, and neuropeptide Y (NPY), galanin, and dynorphin exert potent anticonvulsive actions (Vezzani et al., 1999; Mazarati & Wasterlain, 2002). Expression of all of these peptides is altered by the status epilepticus. NPY exerts its anticonvulsive effects through presynaptic Y2 receptors located presynaptically on glutamate neurons and by mediating inhibition of the release of the excitatory transmitter (Vezzani et al., 1999; Furtinger et al., 2001). Seizures not only cause marked upregulation of NPY but also of Y2 receptors in mossy fibers of rats and patients with TLE (Furtinger et al., 2001). Interestingly, whereas NPY is expressed ectopically in principal neurons of epileptic rats and may act there on presynaptic receptors, it becomes overexpressed in GABA/NPY neurons that prominently sprout in human TLE. In contrast to the rat, in human TLE, the peptide may be released from interneurons upon nerve endings of excitatory neurons and may result in impaired glutamate release (Furtinger et al., 2001).

Other than for NPY, expression of dynorphin becomes decreased in the hippocampus of epileptic rats (Douglass et al., 1991). Consequently, its endogenous action may be limited in epileptic rats. In contrast, in patients with TLE, expression of dynorphin is markedly upregulated in mossy fibers. mRNA levels are especially high in patients that experienced seizures within 48 h prior to epilepsy surgery, indicating a confounding effect of seizures on dynorphin expression (Pirker et al., 2009). Because dynorphin exerts anticonvulsive actions (mediated by κ-opioid receptors) in experimental animals, it may act as an endogenous anticonvulsant peptide in human TLE, upregulated by a previous seizure episode. The anticonvulsant potency of various neuropeptides, notably of NPY and galanin, has recently led to the concept of using viral vectors overexpressing the neuropeptides, which then may be selectively released during epileptic seizures and may exert anticonvulsive action.

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Table 1

Parameters of GABAergic and peptidergic neurotransmission altered after kainic acid–induced status epilepticus and in temporal lobe epilepsy

	Kainic acid model (rat)		TLE (humans)	References
	Acute (status)	Chronic (epilepsy)		
Parameters of GABAergic transmission				
Glutamate decarboxylase				
(GAD67, GAD65)				
Enzyme activity	↓	↑	nd	Sperk et al., 1983
mRNA	↑	↑		Esclapez & Houser, 1999; Sperk et al., 2003
Histochemistry	sprouting	sprouting		Furtinger et al., 2001
Ectopic expression in mossy fibers	+	+	+	Schwarzer & Sperk, 1995
Vesicular GABA transporter	−	−		Sperk et al., 2003
GAT-1 (molecular layer)	↑	↑	↑	Sperk et al., 2003; Mathern et al., 1999
$GABA_A$ receptor in dentate gyrus				
Subunit $\alpha 1$	↑	↑	↓	Sperk, 2007; Pirker et al., 2003; Loup et al., 2000
Subunit $\alpha 2$	↓	↑	↑	Sperk, 2007; Loup et al., 2000
Subunit $\alpha 3$	−	−	↑	Sperk, 2007; Pirker et al., 2003; Loup et al., 2000
Subunit $\alpha 4$	−	↑	(↑)	Sperk, 2007
Subunit $\alpha 5$	↓	−	↑	Sperk, 2007
Subunit $\beta 2$	↑	↑	↑↑	Sperk, 2007; Pirker et al., 2003
Subunit $\beta 3$	−	↑	↑↑	Sperk, 2007; Pirker et al., 2003
Subunit $\gamma 2$	−	↑	↑	Sperk, 2007; Pirker et al., 2003; Loup et al., 2000
Subunit δ	↓↓	↓↓	↑	Sperk, 2007
$GABA_B$ receptors in dentate gyrus				
$GABA_BR$. 1 and $GABA_BR$-2	↓	(↑)	↑	Furtinger et al., 2003a; Furtinger et al., 2003b
Parameters of peptidergic transmission				
Dynorphin				
Dentate gyrus (granule cells)	↓	↓	↑↑	Douglass et al., 1991; Houser et al., 1990; Pirker et al., 2001
Neuropeptide Y (mRNA/peptide)				
Dentate gyrus				
Interneurons	↑/↓	↑/↑	↑/↑ (cell loss)	Sperk, 1994; Furtinger et al., 2001

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	Kainic acid model (rat)		TLE (humans)	References
	Acute (status)	Chronic (epilepsy)		
Mossy fiber	↑/−	↑/↑	−/−	Furtinger et al., 2001; Sperk et al., 1992; Vezzani et al., 1999
CA1/Subiculum	↑/−	↑/↑ (pyramidal neurons)	↑/↑ (interneurons)	Furtinger et al., 2001; Vezzani & Sperk, 2004
Y2 receptors (mossy fibers)	↑	↑	↑/↑	Furtinger et al., 2001; Sperk et al., 1992
Somatostatin				
Dentate gyrus	↑/↓	↑/↑	↑/↑ (cell loss)	Furtinger et al., 2001; Marksteiner et al., 1992
CA1/Subiculum	↑/−	↑/↑ (interneurons and pyr. neurons)	↑ (interneurons, sprouting	Drexel, in preparation
SSR-2 receptors	↓	↓	↑	Moneta et al., 2002; Csaba et al., 2005
Neurokinin B (dentate granule cells)	↑	↑	nd	Marksteiner et al., 1992
Galanin (dentate granule cells)	↑		nd	Mazarati et al., 1998; Mazarati et al., 2004

↑, increased ↑↑, markedly increased; (↑), not significantly increased; ↓, decreased; ↓↓, markedly decreased; not altered; ↑/↓, ↑/−, different results, depending on the study cited.

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