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Prolonged seizures: what are the mechanisms that predispose or cease to be protective? A review of animal data

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ABSTRACT – There is no doubt that seizures change processes in neuronal networks which themselves impact on seizure susceptibility, and reports on such changes probably account for the majority of studies in experimental epileptology. As much as there is no doubt about this general fact, there is, to date, quite some disagreement on whether such changes are pro-epileptic, anti-epileptic, or both, and which are crucial and which are less so. While it is not possible to provide a general answer to this, this review attempts to categorise and highlight some of these findings, and relate them to specific ontogenetic or pathophysiological conditions. Data from studies of animal models (nearly exclusively) is presented, with a focus on two main aspects: ontogenetic particularities and pathophysiological conditions, supporting evidence of susceptibility and seizure termination mechanisms in adult animal models.

Key words: prolonged seizures, predisposition, seizure termination, ontogenesis, modeling, adenosine, GABA, metabolism, neuromodulators, ion channels, ionic currents

Seizures occur upon changes in the brain and its function; this is a generally accepted fact. It is also widely accepted that some, if not most, of these changes impact on seizure susceptibility, or even on the mechanisms which determine seizure duration and termination. These changes have been the subject of a number of reviews on the mechanisms of seizure generation, particularly in the ontogenetically-immature brain (Holmes and Ben-Ari, 2001; Holmes *et al.*, 2002; Heinemann *et al.*, 2002; Avanzini and Franceschetti, 2003; Avoli *et al.*, 2005; Brooks-Kayal, 2005; Löscher and Köhling, 2010); these cited reviews only represent a small sample. Apart from the general problem of differentiating between the chicken and the egg (*i.e.* causative changes and epilepsy, or vice versa), these changes may act in homeostatic or even protective ways. This review will focus on two main issues,

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ontogenetic particularities and pathophysiological conditions supporting evidence of susceptibility and seizure termination mechanisms in adult animal models, while only briefly touching on protective mechanisms and status epilepticus (SE)-associated functional alterations as predisposing factors to subsequent seizures.

Seizure-induced changes

There is a plethora of functional and structural changes associated with seizures, ranging from neuronal loss (from location- and neuron type-specific, to general), sprouting and network reorganisation, to alterations of voltage-gated or ligand-gated ion channels and receptors. Arguably, for many of these, it is difficult to differentiate whether they are a consequence or primary cause of seizures (other than those that are genetically determined), as many are considered to be detrimental by increasing seizure propensity or inflicting further functional damage (Sutula *et al.,* 2003; Löscher and Brandt, 2010). In contrast, some may actually limit seizures or act in a neuroprotective fashion (Lado and Moshé, 2008). Below, the mechanisms involved in seizure predisposition or prevention will be reviewed.

Mechanisms that prevent seizures

In adult animal brain tissue, after single or prolonged seizures, a number of changes have been reported which either specifically affect changes in seizure threshold or more broadly result in preconditioning and neuroprotective actions.

Seizure threshold changes

While prolonged seizures, in particular SE, in tissues of adult animals, generally result in subsequent development of spontaneous recurrent seizures (as in pilocarpine- or kainate-induced SE), as first described by (Turski *et al.,* 1983) and (Ben-Ari and Lagowska, 1978; Ben-Ari *et al.*, 1979), single and brief seizures may have opposite effects, at least transiently. Increases in seizure threshold after previous seizures, known since the 1940s (Toman *et al.,* 1946), have systematically been analysed by the group of Nutt *et al.* (1981); for an overview see Löscher and Köhling (2010). To summarise these reports briefly, in different models (kindling, maximal electroshock, and others), a previous, usually single seizure, or a series of mild seizures will at least transiently increase seizure-induction threshold for subsequent seizures, lasting from minutes to several hours, whereas this is not the case for subconvulsive attacks. As also reviewed by Löscher and Köhling (2010), changes in GABA transmission may play a role, albeit resulting in both up- (receptor density) and down-regulation (presynaptic release) (Tuff *et al.,* 1983; Löscher and Frey, 1987; Swijsen *et al.,* 2012). In the case of early-life seizures, these effects may even be long-lasting (Swijsen *et al.,* 2012). Furthermore, evidence from transcriptome analyses demonstrate down-regulation of calcium signalling, including subunits of voltage-gated calcium channels, and neuronal excitability components, including NMDA- and AMPA-receptor subunits (Jimenez-Mateos *et al.,* 2008), which could also account for an increase in seizure threshold. At least in immature animals, there are also conflicting reports suggesting an increase in excitability and a reduction in seizure threshold (Gashi *et al.,* 2007). Summarising these findings, in mature tissue, *single or mild seizures* appear to have short- (hours) to longer-term (days) effects, resulting in transiently reduced excitability which is likely due to changes in inhibitory, as well as excitatory, transmission and voltage-gated channels. In immature tissue, some evidence points to increased excitability, an issue which will further be discussed below.

Neuroprotection

It is highly conceivable that a reduction in excitability, as discussed above, can also lead to a protection from cell death, *i.e.* neuroprotection, as calcium signalling is also linked to excitotoxicity. This injury protection (coined "epileptic tolerance") was proven in a variety of models, as reviewed by Jimenez-Mateos and Henshall (2013), including the kindling model (Kelly and McIntyre, 1994; Andre *et al.*, 2000; Penner *et al.*, 2001) and electroshock (Kondratyev *et al.*, 2001) and kainic acid-induced seizures (Blondeau *et al.,* 2000). Again, these findings are not undisputed; anti-apoptotic protection may be provided, however, it may also fail, even after single seizures, and induce damage (Bengzon *et al.,* 1997; Andre *et al.,* 2000). It remains to be tested whether distinct models (electroshock *vs.* amygdala kindling; *i.e.* deleterious *vs.* beneficial; [Andre *et al.*, 2000]) or kindling positions (amygdala *vs.* hippocampal; *i.e.* beneficial *vs.* deleterious; [Bengzon *et al.,* 1997; Andre *et al.,* 2000 respectively]) actually account for these disparate results.

Predisposing mechanisms

In contrast to the main tenor of the previous section, the consequences of seizures may also result in increased seizure predisposition and excitability, in particular, as long-term (days and months) rather than short-term effects of initial, and severe, insults on the

one hand, and under specific circumstances in juvenile tissue on the other. These findings will briefly be summarised.

During ontogenesis

Most findings in neonatal and infant tissue (in rats this age ranges from postnatal day 0 to 17 [P0-P17]) suggest that early-life seizures, or more specifically SE, have little impact on subsequent seizure susceptibility, or even neuronal injury or network changes (as reviewed by Scantlebury *et al*. [2007]), even though SE can be more severe than in adults. In prepubescent rodents (P18-P30), this relative protection against subsequent damage declines, and full vulnerability is reached in adults (Scantlebury *et al.,* 2007). Under certain circumstances, however, subsequent increases in seizure susceptibility have also been reported in immature animals. Whether increased excitability is induced or not may either depend on the epilepsy model used or an underlying pathology. Regarding underlying pathologies, the conversion of relatively resistant tissue to tissue that becomes more seizure-susceptible, and more excitable, appears to result from both artificially induced migration disorders or cortical dysplasia and neonatal hypoxia, possibly due to interference with GABAergic inhibition or voltage-gated currents, such as I_h, a hyperpolarisation-activated inward current which is down-regulated after early-life hypoxia (Jensen *et al.,* 1992; Germano and Sperber, 1997; Germano *et al.,* 1998; Jensen *et al.,* 1998; Scantlebury *et al.,* 2004; Zhang *et al.,* 2006). Regarding the epilepsy model, febrile seizures appear to be another exception: If rodents experience these early in life (P8-P11), they will develop increased hippocampal excitability, again due to increased I_h (Chen *et al.*, 2001; Brewster *et al.,* 2002), possibly mediated *via* hyperthermia-induced hyperventilation and associated alkalinisation, as well as cannabinoid receptor up-regulation (Chen *et al.,* 2001; Brewster *et al.,* 2002; Schuchmann *et al.,* 2006). In addition, a reduction of GABA-mediated inhibition (Liebregts *et al.,* 2002; Swijsen *et al.,* 2012) may be involved. The effect is dependent on duration of the febrile condition; more severe effects are observed if the temperature rise lasts for more than an hour, compared to around 25-30 minutes. Under prolonged febrile conditions, inflammation, as evidenced by increases in interleukin-1ß, may also play a role (Dube *et al.,* 2010). Even at later developmental stages, *i.e*. at P21, a febrile seizure episode increases responsiveness to epileptogenic agents, as well as induced cognitive dysfunction (Wilhelm *et al.,* 2012).

Importantly, although SE early in life does not increase sensitivity to convulsants (Nehlig *et al.*, 2002), other models of infantile epilepsy (at age P6-13; PTZ-induced recurrent seizures, kainate SE) do induce changes in receptor expression and function later in life. Such changes can be interpreted as increases in net excitability induced by early-in-life seizures. Thus, adult up-regulation of NMDA-receptors (Gashi *et al.*, 2007), down-regulation of the GluR2 subunit (which would convey a reduced calcium permeability to the AMPA receptor if present in the receptor molecule) (Zhang *et al.,* 2004), and even gender-specific effects on GABAergic signalling (GABA-reversal potential) (Galanopoulou, 2008) were observed.

During the adult state

While there appears to be some consensus that in juvenile epilepsies at least two conditions, a second underlying pathology and febrile seizures, predispose to subsequent seizures in adulthood, it is much less clear which of the manifold changes associated with chronic epilepsy are actually causal for subsequent seizures (and therefore support the disease and its progression), and which are perhaps even homeostatic reactions to the seizures.

Obviously, based on genetic models of epilepsy, we can deduce that some functional changes cause subsequent seizures, with the general cautionary note that usually the whole transcriptome of such animals is not known, and consequently it remains uncertain whether compensatory processes might play pivotal roles in addition. Such defects (and their relation to human "mutants") have been extensively reviewed by Noebels (2003) and Lerche *et al*. (2013). In short, they include mutations in: voltage-gated sodium channels (prolonged opening, reduced inactivation, but also exclusive down-regulation in inter-neuronal populations), voltage-gated potassium channels (again with channel defects in principal or interneurones, or ontogenetically bound), voltage-gated calcium channel compartments (pre-synaptic down-regulation resulting in selective transmitter release changes, favouring rhythmic discharges and increases in thalamic currents), transmitter release machinery (reduction of inhibitory transmitter release, sustained release, or even alterations of co-release of *e.g*. Zn^{2+}), GABAergic function (GABA synthesis, receptor down-regulation or changes in deactivation kinetics, reduction in late GABA responses, and alterations in chloride distribution leading to depolarising GABA), glutamatergic function (increased calcium permeability, impaired glutamate reuptake), cholinergic and serotonin receptors, and finally proteins controlling proliferation or migration *etc*. (all reviewed in Noebels [2003], Lerche *et al*. [2013], and Lerche *et al*. [2001]). Not all of the mutations generated in animals that result in epileptic phenotypes, however, are applicable to humans.

Reports on transcriptional or post-translational changes that play a role in disease progression in

animal models usually focus on two conditions: febrile seizures early in life and post-SE mesial temporal lobe epilepsy (TLE) (Lerche *et al.,* 2013), which can therefore be considered as the two main factors favouring the emergence of increased seizure susceptibility and disease progression, as reported in animal models (McCloskey and Scharfman, 2011) and TLE patients (Walker *et al.,* 2002). Since febrile seizures have already been discussed in the previous section, in the following, the focus will be on post-SE TLE models.

In post-SE models, long-term changes in expression and post-transcriptional changes of a variety of genes have been described, among them up-regulation of juvenile forms of NMDA-receptor subunits, differential expression and splicing of AMPA-receptor subunits, down-regulation of GABA-receptors or differential $GABA_A$-receptor subunit expression, dysregulation of chloride transporters and GABA-synthesizing enzymes (glutamate decarboxylase), down-regulation of calcium-activated potassium (SK) channels, up-regulation of I_h, down-regulation of sodium channel subunits, up-regulation of calcium channels mediating T-type currents, up-regulation of synaptotagmin subtypes, nitric oxide (NO)-synthase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and DNA methylation changes, which either influence net excitability (*e.g.* neuronal bursting, synaptic synchronisation) or promote cell death (Babity *et al.,* 1997; DeLorenzo and Morris, 1999; Gilby *et al.,* 2005; Porter *et al.,* 2006; Becker *et al.,* 2008; Chuang *et al.,* 2010; Barmashenko *et al.,* 2011; Schulz *et al.,* 2012; Müller *et al.,* 2013; Ryley *et al.,* 2013). The cited papers (ibid) and other studies (Macdonald and Kapur, 1999; Shao and Dudek, 2004; Shao and Dudek, 2006; Chen *et al.,* 2011) also generally provide evidence of functional sequelae of these genetic changes, such as: faster desensitization, depolarisation, or reduction in the frequency of GABA currents (regarding mini IPSC); reduced SK-mediated after-hyperpolarisations; and increased sodium-channel, I_h and T-type calcium channel-dependent bursting, *etc*. Beyond this, there is a discussion as to whether cell death (Andre *et al.,* 2000) and stem cell proliferation (Parent *et al.,* 1997; Parent *et al.,* 2006) are major consequences. Moreover, these may also be epileptogenic factors at least for TLE, and further give rise to deafferentation of interneurons (dormant basket cells; a controversial subject) (Sloviter, 1991; Bernard *et al.,* 1998), a reorganisation of interneuronal wiring (Andre *et al.,* 2001), and, importantly, a reduction of intrinsic antiepileptic mechanisms such as control of adenosine-mediated excitability *via* increased adenosine degradation (Fedele *et al.,* 2005) or receptor desensitization (Hamil *et al.,* 2012).

A causal relationship between disease progression and these changes is epistemologically impossible, but it is tempting to speculate that such prolonged changes are somehow involved in progression of seizure severity in animal models (McCloskey and Scharfman, 2011). Even beyond the discussion of the chicken and the egg, it is, however, improbable that any single mechanism is key to chronification of the epileptic condition, especially since studies so far have identified a large number of divergent mechanisms.

Seizure termination mechanisms

When addressing the question of predisposing mechanisms to prolonged seizures, rather than looking at processes which aggravate seizures (as in the previous section B), one may also ask which factors lead to seizure termination, and consequently fail once a seizure does not stop but continues to develop into SE. Studies focusing specifically on seizure termination mechanisms, interestingly, are rare, and hence most of the hints from animal studies are indirect. Nevertheless, numerous hypotheses have been put forward, which will be discussed in this section, and an overview of which is given in *table 1*.

Theoretical considerations are perhaps useful in setting the scene. In one study in which the question of why some seizures stop and others evolve into SE was decidedly addressed, human EEG, electrocorticogram (ECoG), and local field potential and multi-unit recordings were actually used (Kramer *et al.,* 2012). In this study, three distinctive features were used to characterise the phases of seizure termination: a decrease in power (and frequency), an increase in temporal correlation as well as spatial correlation, and flickering (alternating high or low variances of spectral power). The authors concluded that all seizures terminated as a result of a discontinuous critical transition from one attractor to another, *i.e.* ictal to post-ictal state. All data from SE, in turn, displayed repetitive periods of strong correlation and anti-correlation of spectral power and temporal correlation measures; in other words, with SE, the system approaches but fails to cross the boundary condition repetitively (Kramer *et al.*, 2012). This suggests that seizure termination is a sudden, and likely time-dependent, and perhaps even deterministic, rather than gradual process, as already corroborated by other modelling studies using animal absence model data (Suffczynski *et al.,* 2006). The studies also suggest that it is unlikely that a single mechanism, such as intracellular calcium accumulation, is responsible, as speculated in another modelling study (Kudela *et al.,* 2003). Rather, the theoretical considerations suggest that different mechanisms can converge into the same transition border state (Kramer *et al.*, 2012).

Table 1. Overview of possible endogenous mechanisms of seizure termination reported in the literature, indicating: whether parameters related to these mechanisms have been reported to change during or after seizures/epileptiform activity (functionally significant activity-dependent changes); the role in the generation of seizures/epileptiform activity determined by exogenous application or blockade of endogenous action (role in seizure initiation or maintenance); an assessment on their likely role in seizure termination. Antiepileptic actions are given in italics and proepileptic actions in bold italics.

Possible mechanism	Functionally significant activity-dependent change	Role in seizure initiation or maintenance	Likely role in seizure termination
Metabolic compromise			
Glucose deprivation	No	Yes[1] blocks epileptiform activity with artificial strong reduction (not in vivo)	No
Hypoxia, ATP deprivation	No	Yes[2,3] induces seizures in ATP-sensitive K+-channel KO model	No
Synaptic mechanisms			
Glutamatergic failure	Yes *Transient vesicular depletion*	Yes[4,5] *Determines inter-burst intervals/duration*	Uncertain
GABAergic up-regulation	Yes *Increase of recurrent inhibition (after few seizures)* ***Induction of high-frequency oscillations and epileptogenesis*** ***Synchronisation of network activity*** ***Depolarising actions (in chronic models / epilepsy)***	Yes[6-14] ?[6] ***Induces mirror foci*** ***Generates rhythmic activity*** ***Drives bursting neurons***	Uncertain
Loss in neuronal gap junction coupling	? Loss of coupling during seizures uncertain	Yes[15-18] Blockade usually leads to reduction of discharges (not in all models)	Uncertain
Cellular excitability			
Potassium current activation (Ca^{2+}-activated/voltage-gated)	Yes *Neuronal hyperpolarisation: Reduction of burst frequency*	Yes[19,20] *Determines inter-burst intervals and neuronal firing rates* Changes are only short-lived and transient	***Likely***
Reduction of input resistance	Yes Persistent reduction of resistance in chronic epilepsy + dynamic reduction with K^+-current activation: *reduction of synaptic efficacy* Decrease in time constant: ***Increase in maximal firing rate***	Possible[20-23]	***Likely***

Table 1. *(Continued).*

Possible mechanism	Functionally significant activity-dependent change	Role in seizure initiation or maintenance	Likely role in seizure termination
Ionic environment			
↑extracellular K^+	Yes *Neuronal depolarisation block: Reduction in neuronal firing and synaptic transmission*	Yes[21,24,25] ***Medium levels induce seizures*** *High levels block neuronal activity* Depolarisation block insufficient to stop network activity Extracellular K^+ levels lower in chronically epileptic tissue than in normal one	***Likely***
↓extracellular Ca^{2+}	Yes *Modulates transmitter release* ***Depolarises neurons (surface charge effect)***	Yes[25-27] ***Initiates epileptiform activity at very low levels***	Uncertain
Glial function			
Disturbed astrocytic K^+ regulation (see also Ionic microenvironment)	Yes ***Loss of Ba2+ sensitivity of $[K^*]_o$ due to astrocytic K_{ir} down-regulation*** ***Reduced connexin expression (in blood-brain-barrier dysfunction)***	Possible[51]	***Likely***
pH			
↓pH	Yes *Intra- and extracellular acidification: reduces glutamatergic transmission, gates acid-sensing channels*	Yes 28-32 ↑ *CO_2 blocks seizures*	***Yes***
Neuromodulators			
↑Adenosine	Yes *Activates K^+ and inhibits Ca^{2+} channels via A1 receptors*	Yes[33-36] Endogenous release controls seizure initiation and duration	***Yes***
↑NPY	Yes *Receptors up-regulated;* *Reduced glutamatergic synaptic transmission via Y2 receptors*	Yes[37-39] *Endogenous release controls recurrent excitation and epileptiform activity*	***Yes***
↑Cytokines	Yes *Interleukin-1Ra (endogenous receptor antagonist) reduces excitability* ***Interleukins (1ß, 6): increase neuronal excitability***	Yes[40] ***Induces seizures*** *Blocks seizures*	Uncertain
↑Opioids	Yes Receptors up-regulated. *μ-receptor-mediated reduction of neuronal excitability* ***μ-receptor- and BDNF mediated increase in excitability***	Yes[41-45] *Application blocks seizures;* *Endogenous dynorphin expression controls seizure threshold, duration* ***Induce seizures***	Uncertain

Table 1. *(Continued).*

Possible mechanism	Functionally significant activity-dependent change	Role in seizure initiation or maintenance	Likely role in seizure termination
Endocannabinoid Release	? Release during seizures uncertain	Yes[46-50] *Exogenous endocannabinoids block seizures* ***Endogenous endocannabinoids regulate GABA-release*** ***Exogenous endocannabinoids activate glutamate release* via *TRPV1 receptor***	Uncertain

[1]Kirchner *et al*. (2006); [2]Namba *et al*. (1989); [3]Yamada *et al*. (2001); [4]Staley *et al*. (1998); [5]Jones *et al*. (2007); [6]Tuff *et al*. (1983); [7]Khalilov *et al*. (2003); [8]Köhling *et al*. (2000); [9]Köhling *et al*. (1998); [10]Khazipov and Holmes (2003); [11]Cohen *et al*. (2002); [12]Barmashenko *et al*. (2011); [13]Bragin *et al*. (2009); [14]Pathak *et al*. (2007); [15]Gigout *et al*. (2006); [16]Roopun *et al*. (2010); [17]Köhling *et al*. (2001); [18]Wallraff *et al*. (2006); [19]Schulz *et al*. (2012);[20]Timofeev *et al*. (2004); [21]Bikson *et al*. (2003a); [22]Stegen *et al*. (2009); [23]Isokawa (1996); [24]Pinto *et al*. (2005); [25]Lux *et al*. (1986); [26]Bikson *et al*. (2003b); [27]Cohen and Fields (2004); [28]Somjen (1984); [29]Xiong *et al*. (2000); [30]Velisek *et al*. (1994); [31]Caspers and Speckmann (1972); [32]Schuchmann *et al*. (2006); [33]Lewin and Bleck (1981); [34]During and Spencer (1992); [35]Young and Dragunow, (1994);.[36]Dunwiddie and Masino (2001); [37]Vezzani *et al*. (1999); [38]Marksteiner *et al*. (1989); [39]Tu *et al*. (2005); [40]Vezzani *et al*. (2002); [41]Koepp *et al*. (1998); [42]Hammers *et al*. (2007); [43]Loacker *et al*. (2007); [44]Avoli *et al*. (1996b); [45]Zhang and Ko (2009); [46]Karler *et al*. (1986); [47]Wada *et al*. (1973); [48]Wada *et al*. (1975); [49]Isokawa and Alger (2005); [50]Bhaskaran and Smith (2010);[51]Heinemann *et al*. (2012).

One tempting hypothesis to explain seizure arrest is a proposed depletion of resources, under the presumption that *e.g*. oxygen and/or glucose supply would drop under continued seizure activity, and hence also intracellular ATP (Doman and Pelligra, 2004). Indeed, in both chronically epileptic human tissue, as well as tissue from post-SE rats, induced seizure-like activity results in reduced NAD(P)H recovery, suggesting mitochondrial respiratory chain or glycolysis failure (Kann *et al*., 2005). While this explains ictal hypometabolism, it is unlikely, however, that it actually is instrumental in stopping seizures, precisely because, in these models, seizure-like activity actually progresses. Indeed, the authors speculate that the reduction of NADH production could be instrumental in developing pharmacoresistance (Heinemann *et al*., 2002). Furthermore, although hypoxia (and particularly re-oxygenation after hypoxia) can induce seizures, and likewise severe hypoglycaemic conditions (while moderate reductions are actually pro-convulsant) (Kirchner *et al*., 2006), local cerebral glucose utilisation is generally reduced immediately postictally in kindled rats, which suggests a lowered rather than increased glucose demand at the end of a seizure (Namba *et al*., 1989).

Loss of neuronal synchronisation *via* loss of excitatory drive or increasing impact of inhibitory mechanisms or differential function of electrical coupling is another attractive hypothesis to explain seizure termination. At first sight, experiments using an *in vitro* model of status-like activity (high K^+), suggesting a progressive exhaustion of presynaptic glutamate release during epileptic bursts, favour this hypothesis (Staley *et al*., 1998). However, again, in this model, inter-burst intervals successively increase due to this mechanism, but the activity, as such, persists, and burst duration actually increases with reduced and desynchronized glutamate release (Jones *et al*., 2007). The role of glutamatergic failure in seizure termination is thus uncertain. Increasing inhibitory restraint might also play a role in seizure arrest.

The concept of surround inhibition playing a role in spatial containment of seizures was already put forward by David Prince and Joe Wilder in the 1960s (Prince and Wilder, 1967). Direct recordings from interneurones from such foci demonstrate inhibitory cells to be very active during discharges (Domann *et al*., 1991). Irrespective of this initial restraint (Trevelyan *et al*., 2006; Trevelyan *et al*., 2007; Schevon *et al*., 2012), however, there are strong indications that, with the progression of seizures, or more precisely with the spatial spread of activity, the inhibitory restraint fails, as reviewed by Trevelyan and Schevon (2013).

There may be several reasons for this, including a depolarising block, presynaptic inhibition of GABA release, GABAergic vesicular depletion or postsynaptic desensitisation, and in fact also development of a depolarising drive for GABA as chloride accumulates (Dzhala *et al*., 2010); reviewed by Trevelyan and Schevon (2013). Hence, at least in acute models of epilepsy, the role of inhibition is probably a restraining one at first, but then changes to one which likely merely shapes the structure of an ictal event (*i.e*. support of tonic-like phases *vs*. clonic-like ones) without,

however, playing a role in determining their duration (Swartzwelder *et al.,* 1988). Indeed, GABA, by being rhythmically released during seizure-like activity, may actually subserve network synchronisation by pacing bursts, both in acute *in vivo* animal models (Khazipov and Holmes, 2003), as well as in human epileptic tissue (Köhling *et al.,* 1998). Beyond this, in chronically epileptic tissue, the aforementioned chloride accumulation may chronify as well, as GABAergic activity, at least in the hippocampus in TLE models and in human tissue, is often depolarising, likely due to a dysregulation in chloride transporter expression (Köhling *et al.,* 2000; Cohen *et al.,* 2002; Pathak *et al.,* 2007; Bragin *et al.,* 2009; Barmashenko *et al.,* 2011). In the worst case, GABAergic activity can finally also contribute to the expansion and chronification of the epileptic condition itself, since GABAergic fast oscillations are apparently able to establish mirror foci under certain conditions (Khalilov *et al.,* 2003; Le Van Quyen *et al.,* 2006). Phasic $GABA_A$ transmission is hence not a realistic candidate mechanism limiting seizure duration.

The case is less clear for tonic GABAergic activity, which is stable or even increased in chronically epileptic tissue (Walker and Kullmann, 2013). Whether this up-regulation of tonic current is mediated *via* neurosteroids, as in non-epileptic tissue (Stell *et al.,* 2003), remains to be elucidated, but can be disputed on the grounds that neurosteroid-sensitivity in epileptic animals *in vivo* is reduced (Lawrence *et al.,* 2010). At any rate, a reduction in the inhibitory action of phasic GABA release, combined with an up-regulation of a tonic action, is actually likely to increase the gain of neurons, and hence their responsiveness to excitatory input (Walker and Kullmann, 2013).

With respect to neuronal and/or glial gap junctions, the studies so far favour the notion that inter-neuron coupling supports synchronisation, while inter-glia coupling reduces it. The evidence comes from experiments using pharmacological or genetic blockade, which either leads to increased activity in the case of glial gap junction knockout (due to loss of spatial potassium buffering and increased extracellular potassium) (Wallraff *et al.,* 2006) or to a decrease in activity when gap junctions are pharmacologically blocked (putatively then also, or even mainly, neuronal ones) (de Curtis *et al.,* 1998; Köhling *et al.,* 2001; Gigout *et al.,* 2006; Roopun *et al.,* 2010). It would be critical to demonstrate an activity-dependent loss of neuronal gap junctional coupling or increase of glial coupling to support gap-junction involvement in shaping seizure duration. Although changes in the level of intracellular pH and calcium are activity-dependent (de Curtis *et al.,* 1998) and could well induce functional changes in gap junctions, a direct demonstration of these effects remains to be confirmed. Hence, the impact of gap-junctional coupling in seizure termination remains uncertain. Regarding ephaptic interactions, *i.e.* transmembranous currents induced by extracellular currents due to resistance changes in extracellular vs. membrane compartments, these could also possibly influence synchronisation (Köhling *et al.,* 2000). However, as there is cell swelling during seizures (Lux *et al.,* 1986), it is likely to increase, rather than to decrease at the end of seizures, and hence can probably be ruled out as a termination mechanism.

A possible seizure termination mechanism could also be a dynamic change in intrinsic neuronal excitability or transmembranous currents. The main class of transmembranous currents which reduce neuronal excitability consists of various potassium currents. Of the multitude of these, those currents which show activity-dependent activation would be particularly interesting in this context. Indeed, at least in an *in vivo* model of spike-and-wave discharges, in particular, calcium-activated potassium currents appear to limit activity duration (Timofeev *et al.,* 2004). As calcium is known to accumulate intracellularly during seizures, this mechanism could be a plausible one. Interestingly, in chronically epileptic tissue (post-SE TLE), this current appears to be critically reduced, both regarding function and expression. This predisposes the tissue to prolonged discharges (Schulz *et al.,* 2012). Input-resistance changes have been implicated in determining epileptogenicity, as they decrease in animal models and human epileptic tissue (Isokawa, 1996; Stegen *et al.,* 2009). In effect, this means that synaptic currents need to be much larger to change neuronal membrane potential, and hence, excitatory drive will be less efficient. In turn, however, this also means that firing frequency will be increased as a consequence of a decrease in time constant (remember that τ=RC) (Bikson *et al.,* 2003a). More importantly, input resistance often dynamically decreases rather than increases in the course of a seizure, since further channels open and the cells become leaky, making this too a possible mechanism to stop the seizure (Timofeev *et al.,* 2004).

Among the different dynamic changes during seizures and epileptiform activity, alterations in ionic microenvironment, including pH, are well documented. A comprehensive review by Hans-Dieter Lux, Uwe Heinemann and Irmgard Dietzel summarises these phenomena (Lux *et al.,* 1986). During activity, in the focus, extracellular potassium rises to a ceiling of 12-14 mM; further increase is prevented by glia buffering. This trans-glial potassium flux is compensated, albeit not fully, by sodium, resulting in focal extracellular sodium increases, but a decrease in osmolarity,

and hence cell swelling. Calcium is reduced focally to 0.6 mM due to influx into neurons, while chloride follows the potassium buffering flux and is hence reduced in the focus. What does this mean for excitability? In particular, the increase in potassium will lead to a depolarisation of all cells within the focal area by an estimated 15-20 mV, which could actually lead to a depolarisation block (inactivation of sodium currents), and is speculated to support activity termination at least in acute *in vitro* models (Lux *et al.,* 1986; Bikson *et al.,* 2003a; Pinto *et al*., 2005). Although in chronically epileptic tissue, such potassium increases are generally lower than in healthy tissue (Köhling *et al.,* 1995) and potassium levels are mainly lower at the end of a seizure-like event than at the start (Avoli *et al.,* 1996a), it is likely that these changes do exert some influence on seizure duration, particularly should buffering be compromised. There are indeed indications in this direction. In human tissue from epilepsy patients, induced changes in extracellular potassium are not modified by Ba^{2+}, a blocker of inwardly-rectifying astrocytic potassium-currents (K_{IR}), and the expression of K_{IR}-channels was found to be down-regulated (hence at the first prerequisite for potassium buffering, astrocytic potassium uptake appears to be compromised). Furthermore, in addition, astocytic connexins in rodent brain (the second prerequisite for potassium buffering), challenged with blood-brain-barrier breakdown, are equally down-regulated (Heinemann *et al*., 2012). A critical experiment would now be to show that the duration of seizures actually is inversely correlated to the extent of potassium increases.

In contrast, the decrease in extracellular calcium plays an ambiguous role; it increases excitability by reducing surface charge, leading to neuronal depolarisation (Bikson *et al.,* 2003b) (something which is taken advantage of in the low-calcium epilepsy model), but also decreases epileptogenicity by reducing synaptic transmitter release (Cohen and Fields, 2004). A drop in extracellular chloride, in turn, is likely to increase excitability, since this will shift its equilibrium potential to positive, depolarising values. Having identified potassium as one possible factor of seizure termination, pH is another critical one. Thus, during seizure-like activity, the extracellular space acidifies (Somjen, 1984). Furthermore, activity duration and extracellular (Lux *et al*., 1986), as well as intracellular (Xiong *et al.,* 2000), acidification are related, and artificial acidification (also *via* CO_2-ventilation) stops activity both *in vitro* and *in vivo* (Caspers and Speckmann, 1972; Velisek *et al*., 1994), likely *via* several mechanisms, including activation of acid-sensing channels or interference with glutamatergic synaptic transmission (Velisek, 1998; Ziemann *et al*., 2008). Any condition supporting alkalinisation, such as hyperventilation, in turn, will prolong and exacerbate seizures (Schuchmann *et al.,* 2006). Activity-dependent acidification is hence, together with extracellular potassium accumulation, probably a critical candidate mechanism controlling seizure duration.

Activity-dependent release of neuromodulators, *i.e*. substances released as non-classic transmitters with metabotropic action, which are capable of influencing synaptic transmission, is another candidate group of seizure-terminating mechanisms. Among these, adenosine and neuropeptide Y (NPY) are most interesting. Regarding adenosine, it was shown early on that it is released endogenously in an activity-dependent fashion during seizures in animal models (Lewin and Bleck, 1981) and patients (During and Spencer, 1992). Furthermore, prolonged seizures were speculated to result from loss of adenosine function (Young and Dragunow, 1994), which is generally accepted to be net inhibitory (Dunwiddie and Masino, 2001). It is not surprising that novel therapeutic strategies are being considered on the basis of adenosine delivery (Boison, 2005). Regarding NPY, this molecule is also released during and particularly after seizures (Marksteiner *et al.,* 1989), to inhibit excitatory synaptic transmission (Tu *et al.,* 2005). In chronic epilepsy models, its release and receptor expression are up-regulated, which is interpreted as an intrinsic antiepileptic compensatory reaction (reviewed in Vezzani *et al*. [1999]).

Other potential modulators also include cytokines, endogenous opioids, and cannabinoids, however, the role of these requires further elucidation, suffice to say that cytokines are usually considered to be pro-epileptic. Yet, in chronic models, an endogenous receptor blocker of interleukin 1 receptors was also reported to be up-regulated (Vezzani *et al.,* 2002), thus one might speculate that this may also be activity-dependent. Supporting evidence for this hypothesis, however, is still lacking. Likewise, endogenous dynorphin was shown to control seizures as long as releasing fibres were conserved (Wasterlain *et al.,* 2002), presumably *via* κ receptors (Loacker *et al.,* 2007), a finding which is corroborated also in human tissue (Koepp *et al.,* 1998; Hammers *et al.,* 2007). The ambiguous nature of opioids, however, becomes evident when considering that these negatively control GABA release (Avoli *et al.,* 1996b) *via* μ receptors, and that activation of this receptor eventually leads to induction of seizures (*via* brain-derived neurotrophic factor [BDNF] expression) (Zhang and Ko, 2009). Endogenously-released cannabinoids, likewise, are ambiguous in their action, being both anti- and pro-epileptic (Wada *et al.,* 1973; Wada *et al.,* 1975; Karler *et al.,* 1986). They share with

opioids a negative control of GABA release, and beyond this they enhance glutamate release, since they cross-react also with TRPV1 channels (Isokawa and Alger, 2005; Bhaskaran and Smith, 2010). Again, more investigations are needed to gauge their net role in seizure termination.

A factor clearly supporting sustained SE apparently is Substance P (Wasterlain *et al.,* 2000), which was shown to be released during seizures, and its receptors were up-regulated in the chronic epileptic condition. The unfortunate combination of release and receptor up-regulation may allow for a vicious cycle to be initiated, which is speculated to maintain SE.

Outlook

In an attempt to simplify the interpretation of the findings discussed in this review, which probably reflect a broad consensus, the main factors derived from animal experiments which predispose to prolonged seizures are febrile seizures early in life (and possibly also later), as well as migration disorders/cortical dysplasia, or neonatal hypoxia. This emphasises the point that ontogenetic factors are paramount. The only other factor which apparently also plays an important role in determining seizure susceptibility, and perhaps also prolonged seizures, is a history of SE itself, and perhaps traumatic brain injury (Holmes *et al*., 2002), again, mainly in an ontogenetic context. Of the underlying mechanisms determining seizure duration, extracellular increases in potassium, acidification, adenosine, NPY, and substance P are interesting candidates, and future key experiments should establish whether defects in these mechanisms can be found both in animal models and the clinical context which specifically relates to prolonged seizures.

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References

Andre V, Ferrandon A, Marescaux C, Nehlig A. The lesional and epileptogenic consequences of lithium-pilocarpine-induced status epilepticus are affected by previous exposure to isolated seizures: effects of amygdala kindling and maximal electroshocks. *Neuroscience* 2000; 99: 469-81.

Andre V, Marescaux C, Nehlig A, Fritschy JM. Alterrations of hippocampal GABAergic system contribute to development of spontaneous recurrent seizures in the rat lithium-pilocarpine model of temporal lobe epilepsy. *Hippocampus* 2001: 452-68.

Avanzini G, Franceschetti S. Cellular biology of epileptogenesis. *Lancet Neurol* 2003; 2: 33-42.

Avoli M, Barbarosie M, Lücke A, Nagao T, Lopantsev V, Köhling R. Synchronous GABA-mediated potentials and epileptiform discharges in the rat limbic system in vitro. *J Neurosci* 1996a; 16: 3912-24.

Avoli M, Köhling R, Barbarosie M. Anoxia blocks the presynaptic control of GABA release at inhibitory terminals in the rat hippocampus. *Neuroscience* 1996b; 75: 999-1002.

Avoli M, Louvel J, Pumain R, Köhling R. Cellular and molecular mechanisms of epilepsy in the human brain. *Prog Neurobiol* 2005; 77: 166-200.

Babity JM, Armstrong JN, Plumier JC, Currie RW, Robertson HA. A novel seizure-induced synaptotagmin gene identified by differential display. *PNAS* 1997; 94: 2638-41.

Barmashenko G, Hefft S, Aertsen A, Kirschstein T, Köhling R. Positive shifts of the GABAA receptor reversal potential due to altered chloride homeostasis is widespread after status epilepticus. *Epilepsia* 2011; 52: 1570-8.

Becker AJ, Pitsch J, Sochivko D, *et al*. Transcriptional upregulation of Cav3.2 mediates epileptogenesis in the pilocarpine model of epilepsy. *J Neurosci* 2008; 28: 13341-53.

Ben-Ari Y, Lagowska J. Epileptogenic action of intra-amygdaloid injection of kainic acid. *C R Acad Sci Hebd Seances Acad Sci D* 1978; 287: 813-6.

Ben-Ari Y, Lagowska J, Tremblay E, Le Gal La SG. A new model of focal status epilepticus: intra-amygdaloid application of kainic acid elicits repetitive secondarily generalized convulsive seizures. *Brain Res* 1979; 163: 176-9.

Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M, Lindvall O. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *PNAS* 1997; 94: 10432-7.

Bernard C, Esclapez M, Hirsch JC, Ben Ari Y. Interneurones are not so dormant in temporal lobe epilepsy: a critical reappraisal of the dormant basket cell hypothesis. *Epilepsy Res* 1998; 32: 93-103.

Bhaskaran MD, Smith BN. Effects of TRPV1 activation on synaptic excitation in the dentate gyrus of a mouse model of temporal lobe epilepsy. *Exp Neurol* 2010; 223: 529-36.

Bikson M, Hahn PJ, Fox JE, Jefferys JG. Depolarization block of neurons during maintenance of electrographic seizures. *J Neurophysiol* 2003a; 90: 2402-8.

Bikson M, Fox JE, Jefferys JG. Neuronal aggregate formation underlies spatiotemporal dynamics of nonsynaptic seizure initiation. *J Neurophysiol* 2003b; 89: 2330-3.

Blondeau N, Plamondon H, Richelme C, Heurteaux C, Lazdunski M. K(ATP) channel openers, adenosine agonists and epileptic preconditioning are stress signals inducing hippocampal neuroprotection. *Neuroscience* 2000; 100: 465-74.

Boison D. Adenosine and epilepsy: from therapeutic rationale to new therapeutic strategies. *Neuroscientist* 2005; 11: 25-36.

Bragin DE, Sanderson JL, Peterson S, Connor JA, Muller WS. Development of epileptiform excitability in the deep entorhinal cortex after status epilepticus. *Eur J Neurosci* 2009; 30: 611-24.

Brewster A, Bender RA, Chen Y, Dube C, Eghbal-Ahmadi M, Baram TZ. Developmental febrile seizures modulate hippocampal gene expression of hyperpolarization-activated channels in an isoform- and cell-specific manner. *J Neurosci* 2002; 22: 4591-9.

Brooks-Kayal AR. Rearranging receptors. *Epilepsia* 2005; 46: 29-38.

Caspers H, Speckmann E-J. Cerebral pO_2, pCO_2 and pH: changes during convulsive activity and their significance for spontaneouse arrest of seizures. *Epilepsia* 1972; 13: 699-725.

Chen K, Aradi I, Thon N, Eghbal-Ahmadi M, Baram TZ, Soltesz I. Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. *Nat Med* 2001; 7: 331-7.

Chen S, Su H, Yue C, *et al*. An increase in persistent sodium current contributes to intrinsic neuronal bursting after status epilepticus. *J Neurophysiol* 2011; 105: 117-29.

Chuang YC, Chen SD, Lin TK, *et al*. Transcriptional upregulation of nitric oxide synthase II by nuclear factor-kappa B promotes apoptotic neuronal cell death in the hippocampus following experimental status epilepticus. *J Neurosci Res* 2010; 88: 1898-907.

Cohen JE, Fields RD. Extracellular calcium depletion in synaptic transmission. *Neuroscientist* 2004; 10: 12-7.

Cohen I, Navarro V, Clemenceau S, Baulac M, Miles R. On the origin of interictal activity in human temporal lobe epilepsy in vitro. *Science* 2002; 298: 1418-21.

de Curtis M, Manfridi A, Biella G. Activity-dependent pH shifts and periodic recurrence of spontaneous interictal spikes in a model of focal epileptogenesis. *J Neurosci* 1998; 18: 7543-51.

DeLorenzo RJ, Morris T. Long-term modulation of gene expression in epilepsy. *Neuroscientist* 1999; 5: 86-9.

Doman G, Pelligra R. A unifying concept of seizure onset and termination. *Med Hypotheses* 2004; 62: 740-5.

Domann R, Uhlig S, Dorn T, Witte OW. Participation of interneurons in penicillin-induced epileptic discharges. *Exp Brain Res* 1991; 83: 683-6.

Dube CM, Ravizza T, Hamamura M, *et al*. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. *J Neurosci* 2010; 30: 7484-94.

Dunwiddie TV, Masino SA. The role and regulation of adenosine in the central nervous system. *Ann Rev Neurosci* 2001; 24: 31-55.

During MJ, Spencer DD. Adenosine: a potential mediator of seizure arrest and postictal refractoriness. *Ann Neurol* 1992; 32: 618-24.

Dzhala VI, Kuchibhotla KV, Glykys JC, *et al*. Progressive NKCC1-dependent neuronal chloride accumulation during neonatal seizures. *J Neurosci* 2010; 30: 11745-61.

Fedele DE, Gouder N, Guttinger M, *et al*. Astrogliosis in epilepsy leads to overexpression of adenosine kinase, resulting in seizure aggravation. *Brain* 2005; 128: 2383-95.

Galanopoulou AS. Dissociated gender-specific effects of recurrent seizures on GABA signaling in CA1 pyramidal neurons: role of GABA(A) receptors. *J Neurosci* 2008; 28: 1557-67.

Gashi E, Avallone J, Webster T, Friedman LK. Altered excitability and distribution of NMDA receptor subunit proteins in cortical layers of rat pups following multiple perinatal seizures. *Brain Res* 2007; 1145: 56-65.

Germano IM, Sperber EF. Increased seizure susceptibility in adult rats with neuronal migration disorders. *Brain Res* 1997; 777: 219-22.

Germano IM, Sperber EF, Ahuja S, Moshé SL. Evidence of enhanced kindling and hippocampal neuronal injury in immature rats with neuronal migration disorders. *Epilepsia* 1998; 39: 1253-60.

Gigout S, Louvel J, Kawasaki H, *et al*. Effects of gap junction blockers on human neocortical synchronization. *Neurobiol Dis* 2006; 22: 496-508.

Gilby KL, Da Silva AG, McIntyre DC. Differential GABA(A) subunit expression following status epilepticus in seizure-prone and seizure-resistant rats: a putative mechanism for refractory drug response. *Epilepsia* 2005; 46: 3-9.

Hamil NE, Cock HR, Walker MC. Acute down-regulation of adenosine A(1) receptor activity in status epilepticus. *Epilepsia* 2012; 53: 177-88.

Hammers A, Asselin MC, Hinz R, *et al*. Upregulation of opioid receptor binding following spontaneous epileptic seizures. *Brain* 2007; 130: 1009-16.

Heinemann U, Buchheim K, Gabriel S, Kann O, Kovacs R, Schuchmann S. Cell death and metabolic activity during epileptiform discharges and status epilepticus. *Prog Brain Res* 2002; 135: 197-210.

Heinemann U, Kaufer D, Friedman A. Blood-brain barrier dysfunction, TGFβ signaling, and astrocyte dysfunction in epilepsy. *Glia* 2012; 60: 1251-7.

Holmes GL, Ben-Ari Y. The neurobiology and consequences of epilepsy in the developing brain. *Pediatr Res* 2001; 49: 320-5.

Holmes GL, Khazipov R, Ben Ari Y. Seizure-induced damage in the developing human: relevance of experimental models. *Prog Brain Res* 2002; 135: 321-4.

Isokawa M. Decrement of $GABA_A$ receptor-mediated inhibitory postsynaptic currents in dentate granule cells in epileptic hippocampus. *J Neurophysiol* 1996; 75: 1901-8.

Isokawa M, Alger BE. Retrograde endocannabinoid regulation of GABAergic inhibition in the rat dentate gyrus granule cell. *J Physiol* 2005; 567: 1001-10.

Jensen FE, Holmes GL, Lombroso CT, Blume HK, Firkusny IR. Age-dependent changes in long-term seizure susceptibility and behavior after hypoxia in rats. *Epilepsia* 1992; 33: 971-80.

Jensen FE, Wang C, Stafstrom CE, Liu Z, Geary C, Stevens MC. Acute and chronic increases in excitability in rat hippocampal slices after perinatal hypoxia in vivo. *J Neurophysiol* 1998; 79: 73-81.

Jimenez-Mateos EM, Henshall DC. Seizure preconditioning and epileptic tolrance: models and mechanisms. *Int J Physiol Pathophysiol Phramacol* 2013; 1: 180-91.

Jimenez-Mateos EM, Hatazaki S, Johnson MB, *et al*. Hippocampal transcriptome after status epilepticus in mice rendered seizure damage-tolerant by epileptic preconditioning features suppressed calcium and neuronal excitability pathways. *Neurobiol Dis* 2008; 32: 442-53.

Jones J, Stubblefield EA, Benke TA, Staley KJ. Desynchronization of glutamate release prolongs synchronous CA3 network activity. *J Neurophysiol* 2007; 97: 3812-8.

Kann O, Kovacs R, Njunting M, *et al*. Metabolic dysfunction during neuronal activation in the ex vivo hippocampus from chronic epileptic rats and humans. *Brain* 2005; 128: 2396-407.

Karler R, Calder LD, Turkanis SA. Prolonged CNS hyperexcitability in mice after a single exposure to delta-9-tetrahydrocannabinol. *Neuropharmacology* 1986; 25: 441-6.

Kelly ME, McIntyre DC. Hippocampal kindling protects several structures from the neuronal damage resulting from kainic acid-induced status epilepticus. *Brain Res* 1994; 634: 245-56.

Khalilov I, Holmes GL, Ben-Ari Y. In vitro formation of a secondary epileptogenic mirror focus by interhippocampal propagation of seizures. *Nat Neurosci* 2003; 6: 1079-85.

Khazipov R, Holmes GL. Synchronization of kainate-induced epileptic activity *via* GABAergic inhibition in the superfused rat hippocampus in vivo. *J Neurosci* 2003; 23: 5337-41.

Kirchner A, Veliskova J, Velisek L. Differential effects of low glucose concentrations on seizures and epileptiform activity in vivo and in vitro. *Eur J Neurosci* 2006; 23: 1512-22.

Koepp MJ, Richardson MP, Brooks DJ, Duncan JS. Focal cortical release of endogenous opioids during reading-induced seizures. *Lancet* 1998; 352: 952-5.

Köhling R, Lücke A, Nagao T, Speckmann EJ, Avoli M. Extracellular potassium elevations in the hippocampus of rats with long-term pilocarpine seizures. *Neurosci Lett* 1995; 201: 87-91.

Köhling R, Lücke A, Straub H, *et al*. Spontaneous sharp waves in human neocortical slices excised from epileptic patients. *Brain* 1998; 121: 1073-87.

Köhling R, Vreugdenhil M, Bracci E, Jefferys JG. Ictal epileptiform activity is facilitated by hippocampal GABAA receptor-mediated oscillations. *J Neurosci* 2000; 20: 6820-9.

Köhling R, Gladwell SJ, Bracci E, Vreugdenhil M, Jefferys JG. Prolonged epileptiform bursting induced by 0-Mg(2+) in rat hippocampal slices depends on gap junctional coupling. *Neuroscience* 2001; 105: 579-87.

Kondratyev A, Sahibzada N, Gale K. Electroconvulsive shock exposure prevents neuronal apoptosis after kainic acid-evoked status epilepticus. *Brain Res Mol Brain Res* 2001; 91: 1-13.

Kramer MA, Truccolo W, Eden UT, *et al*. Human seizures self-terminate across spatial scales *via* a critical transition. *PNAS* 2012; 109: 21116-21.

Kudela P, Franaszczuk PJ, Bergey GK. Reduction of intracellular calcium removal rate can explain changes in seizure dynamics: studies in neuronal network models. *Epilepsy Res* 2003; 57: 95-109.

Lado FA, Moshé SL. How do seizures stop? *Epilepsia* 2008; 49: 1651-64.

Lawrence C, Martin BS, Sun C, Williamson J, Kapur J. Endogenous neurosteroid synthesis modulates seizure frequency. *Ann Neurol* 2010; 67: 689-93.

Le Van Quyen M, Khalilov I, Ben Ari Y. The dark side of high-frequency oscillations in the developing brain. *Trends Neurosci* 2006; 29: 419-27.

Lerche H, Jurkat-Rott K, Lehmann-Horn F. Ion channels and epilepsy. *Am J Med Genet* 2001; 106: 146-59.

Lerche H, Shah M, Beck H, Noebels J, Johnston D, Vincent A. Ion channels in genetic and acquired forms of epilepsy. *J Physiol* 2013; 591: 753-64.

Lewin E, Bleck V. Electroshock seizures in mice: effect on brain adenosine and its metabolites. *Epilepsia* 1981; 22: 577-81.

Liebregts MT, McLachlan RS, Leung LS. Hyperthermia induces age-dependent changes in rat hippocampal excitability. *Ann Neurol* 2002; 52: 318-26.

Loacker S, Sayyah M, Wittmann W, Herzog H, Schwarzer C. Endogenous dynorphin in epileptogenesis and epilepsy: anticonvulsant net effect *via* kappa opioid receptors. *Brain* 2007; 130: 1017-28.

Löscher W, Frey JM. Postictal refractoriness associated with reduction of glutamic acid decarboxylase in discrete brain regions in epilepsy-prone gerbils. *Biochem Pharmacol* 1987; 36: 2695-9.

Löscher W, Brandt C. Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. *Pharmacol Rev* 2010; 62: 668-700.

Löscher W, Köhling R. Functional, metabolic and synaptic changes after seizures as potential targets for antiepileptic therap. *y. Epilepsy Behav* 2010; 19: 105-13.

Lux HD, Heinemann U, Dietzel I. Ionic changes and alterations in the size of the extracellular space during epileptic activity. *Adv Neurol* 1986; 44: 619-39.

Macdonald RL, Kapur J. Acute cellular alterations in the hippocampus after status epilepticus. *Epilepsia* 1999; 40: S9-20.

Marksteiner J, Sperk G, Maas D. Differential increases in brain levels of neuropeptide Y and vasoactive intestinal polypeptide after kainic acid-induced seizures in the rat. *Naunyn Schmiedebergs Arch Pharmacol* 1989; 339: 173-7.

McCloskey DP, Scharfman HE. Progressive, potassium-sensitive epileptiform activity in hippocampal area CA3 of pilocarpine-treated rats with recurrent seizures. *Epilepsy Res* 2011; 97: 92-102.

Müller L, Tokay T, Porath K, Köhling R, Kirschstein T. Enhanced NMDA receptor-dependent LTP in the epileptic CA1 area *via* upregulation of NR2B. *Neurobiol Dis* 2013; 54: 183-93.

Namba H, Iwasa H, Kubota M, *et al*. Local cerebral glucose utilization in the postictal phase of amygdaloid kindled rats. *Brain Res* 1989; 486: 221-7.

Nehlig A, Dube C, Koning E. Status epilepticus induced by lithium-pilocarpine in the immature rat does not change the long-term susceptibility to seizures. *Epilepsy Res* 2002; 51: 189-97.

Noebels JL. The biology of epilepsy genes. *Annu Rev Neurosci* 2003; 26: 599-625.

Nutt DJ, Cowen PJ, Green AR. Studies on the post-ictal rise in seizure threshold. *Europ J Pharmacol* 1981; 71: 287-95.

Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 1997; 17: 3727-38.

Parent JM, von dem BN, Lowenstein DH. Prolonged seizures recruit caudal subventricular zone glial progenitors into the injured hippocampus. *Hippocampus* 2006; 16: 321-8.

Pathak HR, Weissinger F, Terunuma M, *et al*. Disrupted dentate granule cell chloride regulation enhances synaptic excitability during development of temporal lobe epilepsy. *J Neurosci* 2007; 27: 14012-22.

Penner MR, Pinaud R, Robertson HA. Rapid kindling of the hippocampus protects against neural damage resulting from status epilepticus. *Neuroreport* 2001; 12: 453-7.

Pinto DJ, Patrick SL, Huang WC, Connors BW. Initiation, propagation, and termination of epileptiform activity in rodent neocortex in vitro involve distinct mechanisms. *J Neurosci* 2005; 25: 8131-40.

Porter BE, Cui XN, Brooks-Kayal AR. Status epilepticus differentially alters AMPA and kainate receptor subunit expression in mature and immature dentate granule neurons. *Eur J Neurosci* 2006; 23: 2857-63.

Prince DA, Wilder BJ. Control mechanisms in cortical epileptogenic foci. *Arch Neurol* 1967; 16: 194-202.

Roopun AK, Simonotto JD, Pierce ML, *et al*. A nonsynaptic mechanism underlying interictal discharges in human epileptic neocortex. *PNAS* 2010; 107: 338-43.

Ryley PR, Albertson AJ, Buckingham SC, *et al*. Status epilepticus triggers early and late alterations in brain-derived neurotrophic factor and NMDA glutamate receptor Grin2b DNA methylation levels in the hippocampus. *Neuroscience* 2013; 248C: 602-19.

Scantlebury MH, Ouellet PL, Psarropoulou C, Carmant L. Freeze lesion-induced focal cortical dysplasia predisposes to atypical hyperthermic seizures in the immature rat. *Epilepsia* 2004; 45: 592-600.

Scantlebury MH, Heida JG, Hasson HJ, *et al*. Age-dependent consequences of status epilepticus: animal models. *Epilepsia* 2007; 48: 75-82.

Schevon CA, Weiss SA, McKhann Jr. G, *et al*. Evidence of an inhibitory restraint of seizure activity in humans. *Nat Commun* 2012; 3: 1060.

Schuchmann S, Schmitz D, Rivera C, *et al*. Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. *Nat Med* 2006; 12: 817-23.

Schulz R, Kirschstein T, Brehme H, Porath K, Mikkat U, Köhling R. Network excitability in a model of chronic temporal lobe epilepsy critically depends on SK channel-mediated AHP currents. *Neurobiol Dis* 2012; 45: 337-47.

Shao LR, Dudek FE. Increased excitatory synaptic activity and local connectivity of hippocampal CA1 pyramidal cells in rats with kainate-induced epilepsy. *J Neurophysiol* 2004; 92: 1366-73.

Shao LR, Dudek FE. Changes in mIPSCs and sIPSCs after kainate treatment: status epilepticus-induced neuronal loss or direct activation of kainate receptors? *J Neurophysiol* 2006; 96: 961-2.

Sloviter RS. Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the "Dormant Basket Cell" hypothesis and its possible relevance to temporal lobe epielepsy. *Hippocampus* 1991; 1: 41-66.

Somjen GG. Acidification of interstitial fluid in hippocampal formation caused by seizures and by spreading depression. *Brain Res* 1984; 311: 186-8.

Staley KJ, Longacher M, Bains JS, Yee A. Presynaptic modulation of CA3 network activity. *Nat Neurosci* 1998; 1: 201-9.

Stegen M, Young CC, Haas CA, Zentner J, Wolfart J. Increased leak conductance in dentate gyrus granule cells of temporal lobe epilepsy patients with Ammon's horn sclerosis. *Epilepsia* 2009; 50: 646-53.

Stell BM, Brickley SG, Tang CY, Farrant M, Mody I. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing GABAA receptors. *PNAS* 2003; 100: 14439-44.

Suffczynski P, Lopes da Silva FH, Parra J, *et al*. Dynamics of epileptic phenomena determined from statistics of ictal transitions. *IEEE Trans Biomed Eng* 2006; 53: 524-32.

Sutula TP, Hagen J, Pitkänen A. Do epileptic seizures damage the brain? *Curr Opin Neurol* 2003; 16: 189-95.

Swartzwelder HS, Anderson WW, Wilson WA. Mechanism of electrographic seizure generation in the hippocampal slice in Mg2+-free medium: the role of GABAa inhibition. *Epilepsy Res* 1988; 2: 239-45.

Swijsen A, Avila A, Brone B, Janssen D, Hoogland G, Rigo JM. Experimental early-life febrile seizures induce changes in GABA(A) R-mediated neurotransmission in the dentate gyrus. *Epilepsia* 2012; 53: 1968-77.

Timofeev I, Grenier F, Steriade M. Contribution of intrinsic neuronal factors in the generation of cortically driven electrographic seizures. *J Neurophysiol* 2004; 92: 1133-43.

Toman JEP, Swinyard EA, Goodman LS. Properties of maximal seizures and their alteration by anticonvulsant drugs and other agents. *J Neurophysiol* 1946; 9: 231-9.

Trevelyan AJ, Schevon CA. How inhibition influences seizure propagation. *Neuropharmacology* 2013; 69: 45-54.

Trevelyan AJ, Sussillo D, Watson BO, Yuste R. Modular propagation of epileptiform activity: evidence for an inhibitory veto in neocortex. *J Neurosci* 2006; 26: 12447-55.

Trevelyan AJ, Sussillo D, Yuste R. Feedforward inhibition contributes to the control of epileptiform propagation speed. *J Neurosci* 2007; 27: 3383-7.

Tu B, Timofeeva O, Jiao Y, Nadler JV. Spontaneous release of neuropeptide Y tonically inhibits recurrent mossy fiber synaptic transmission in epileptic brain. *J Neurosci* 2005; 25: 1718-29.

Tuff LP, Racine RJ, Adamec R. The effects of kindling on GABA-mediated inhibition in the dentate gyrus of the rat. I. Paired-pulse depression. *Brain Res* 1983; 277: 79-90.

Turski WA, Cavalheiro EA, Schwarz M, Czuczwar SJ, Kleinrok Z, Turski L. Limbic seizures produced by pilocarpine in rats: behavioural, electroencephalographic and neuropathological study. *Behav Brain Res* 1983; 9: 315-35.

Velisek L. Extracellular acidosis and high levels of carbon dioxide suppress synaptic transmission and prevent the induction of long-term potentiation in the CA1 region of rat hippocampal slices. *Hippocampus* 1998; 8: 24-32.

Velisek L, Dreier JP, Stanton PK, Heinemann U, Moshé SL. Lowering of extracellular pH suppresses low-Mg(2+)-induces seizures in combined entorhinal cortex-hippocampal slices. *Exp Brain Res* 1994; 101: 44-52.

Vezzani A, Sperk G, Colmers WF. Neuropeptide Y: emerging evidence for a functional role in seizure modulation. *Trends Neurosci* 1999; 22: 25-30.

Vezzani A, Moneta D, Richichi C, *et al*. Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. *Epilepsia* 2002; 43: 30-5.

Wada JA, Sato M, Corcoran ME. Antiepileptic properties of 9-tetrahydrocannabinol. *Exp Neurol* 1973; 39: 157-65.

Wada JA, Wake A, Sato M, Corcoran ME. Antiepileptic and prophylactic effects of tetrahydrocannabinols in amygdaloid kindled cats. *Epilepsia* 1975; 16: 503-10.

Walker MC, Kullmann DM. Tonic GABA(A) receptor-mediated signaling in epilepsy. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds. *Jasper's basic mechanisms of the epilepsies*. Bethesda (MD): National Center for Biotechnology Information (US), 2013: 1-13.

Walker MC, White HS, Sander JWAS. Disease modification in partial epilepsy. *Brain* 2002; 125: 1937-50.

Wallraff A, Köhling R, Heinemann U, Theis M, Willecke K, Steinhauser C. The impact of astrocytic gap junctional coupling on potassium buffering in the hippocampus. *J Neurosci* 2006; 26: 5438-47.

Wasterlain CG, Liu H, Mazarati AM, *et al*. Self-sustaining status epilepticus: a condition maintained by potentiation of glutamate receptors and by plastic changes in substance P and other peptide neuromodulators. *Epilepsia* 2000; 41: S134-43.

Wasterlain CG, Mazarati AM, Naylor D, *et al*. Short-term plasticity of hippocampal neuropeptides and neuronal circuitry in experimental status epilepticus. *Epilepsia* 2002; 43: 20-9.

Wilhelm EA, Souza AC, Gai BM, Chagas PM, Roehrs JA, Nogueira CW. Hyperthermic seizures enhance responsiveness to pentylenetetrazole and induce cognitive dysfunction: protective effect of 3-alkynyl selenophene. *Life Sci* 2012; 90: 666-72.

Xiong ZQ, Saggau P, Stringer JL. Activity-dependent intracellular acidification correlates with the duration of seizure activity. *J Neurosci* 2000; 20: 1290-6.

Yamada K, Ji JJ, Yuan H, *et al*. Protective role of ATP-sensitive potassium channels in hypoxia-induced generalized seizure. *Science* 2001; 292: 1543-6.

Young D, Dragunow M. Status epilepticus may be caused by loss of adenosine anticonvulsant mechanisms. *Neuroscience* 1994; 58: 245-61.

Zhang HN, Ko MC. Seizure activity involved in the up-regulation of BDNF mRNA expression by activation of central mu opioid receptors. *Neuroscience* 2009; 161: 301-10.

Zhang G, Raol YS, Hsu FC, Brooks-Kayal AR. Long-term alterations in glutamate receptor and transporter expression following early-life seizures are associated with increased seizure susceptibility. *J Neurochem* 2004; 88: 91-101.

Zhang K, Peng BW, Sanchez RM. Decreased IH in hippocampal area CA1 pyramidal neurons after perinatal seizure-inducing hypoxia. *Epilepsia* 2006; 47: 1023-8.

Ziemann AE, Schnizler MK, Albert GW, *et al*. Seizure termination by acidosis depends on ASIC1a. *Nat Neurosci* 2008; 11: 816-22.