Pathophysiology of Status Epilepticus

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Summary

Status epilepticus is refractory to initial intravenous anticonvulsants in every third patient and at least the generalised convulsive form is commonly associated with neuronal long-term consequences. The understanding of pathophysiological mechanisms underlying development and maintenance of status epilepticus and its sequelae is therefore of uttermost importance. Spontaneous seizure termination seems to be an active energy-demanding inhibitory process aiming at restoration of impaired Na^+-K^+-pump function. Lack of sufficient energy supply by mitochondrial ATP synthesis may result in ongoing seizure activity and the development of status epilepticus. Continuing epileptic activity itself induces a cascade of pathological alterations in the brain that contribute to maintenance of the condition. Decrease of inhibitory $GABA_A$ receptors and increase of excitatory NMDA receptors at the postsynaptic membrane facilitate sustained epileptic activity. Furthermore, these key adaptions impact pharmacology of status epilepticus with progressive pharmacoresistance to GABAergic anticonvulsants and an increased anticonvulsant effect of NMDA receptor antagonists in advanced stages of status epilepticus. Long-term consequences such as development of chronic epilepsy have been studied extensively in experimental animals but in patients status epilepticus is epileptogenic as well. Neuronal circuit modifications such as mossy fiber sprouting and loss of GABAergic interneurons may contribute to epileptogenesis, other mechanisms comprise long-term changes in gene expression and disruption of the blood-brain-barrier. The proper identification of molecular targets is the prerequisite todevelop effective antiepileptogenic treatment strategies in conditions such as status epilepticus and other severe brain injuries.

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Key words: epileptogenesis, GABA receptor, loss of inhibition, mitochondrial energy failure, neuronal loss, NMDA receptor

Pathophysiologie des Status epilepticus

Ein Status epilepticus ist bei jedem dritten Patienten refraktär gegenüber den initial applizierten intravenösen Antikonvulsiva und ist zumindest in seiner generalisiert konvulsiven Form häufig mit neuronalen Langzeit-Schädigungen assoziiert. Ein vertieftes Verständnis der pathophysiologischen Mechanismen, die der Entstehung und Aufrechterhaltung des Status epilepticus und dessen Folgeschäden zugrunde liegen, ist daher von entscheidender Bedeutung. Die spontane Beendigung von epileptischen Anfällen scheint ein energieabhängiger inhibitorischer Prozess zu sein, der letztendlich die Wiederherstellung der zuvor eingeschränkten Na^+-K^+-Pumpfunktion zum Ziel hat. Ein Mangel an ausreichender Energieversorgung durch mitochondriale ATP-Synthese kann zu anhaltender Anfallsaktivität und zur Entwicklung eines Status epilepticus führen. Die kontinuierliche epileptische Aktivität selbst induziert eine Kaskade an pathologischen Änderungen im Gehirn, die zur Aufrechterhaltung des Status epilepticus beitragen. Eine Abnahme der inhibitorischen $GABA_A$-Rezeptoren und eine Zunahme der exzitatorischen NMDA-Rezeptoren an der postsynaptischen Membran ermöglichen und fördern das Anhalten der epileptischen Aktivität. Darüber hinaus haben diese Adaptationsvorgänge Einfluss auf die Pharmakologie des Status epilepticus, einerseits hinsichtlich der progredienten Pharmakoresistenz gegenüber GABAerg wirkenden Antikonvulsiva und andererseits hinsichtlich eines mit der Dauer des Status epilepticus zunehmenden Wirkeffekts von NMDA-Rezeptor-Antagonisten. Langzeit-Schäden wie die Entwicklung einer chronischen Epilepsie sind ausführlich in Tiermodellen aufgezeigt worden, aber bei Menschen ist ein Status epilepticus ebenfalls epileptogen. Modifikationen neuronaler Netzwerke wie die aberrante Moosfasersprossung und ein Verlust GABAerger Interneurone tragen wahrscheinlich zur Epileptogenese bei, andere Mechanismen beinhalten langfristige Änderungen der Genexpression und die Ruptur der Blut-Hirn-Schranke. Die eindeutige Identifikation von molekularen Zielstrukturen ist die Grundvoraussetzung für die Entwicklung effizienter antiepileptogener Therapiestrategien beim Status epilepticus oder anderen schweren Hirnschädigungen.

Schlüsselwörter: Epileptogenese, GABA-Rezeptoren, Inhibitionsverlust, mitochondrialer Energieverlust, Neuronenverlust, NMDA-Rezeptoren

Pathophysiologie du statut épileptique

Chez une personne sur trois, un statut épileptique (status epilepticus) est réfractaire aux administrations initiales d'anticonvulsifs intraveineux ; et en tout cas dans sa forme convulsive généralisée, il est fréquem-

ment associé à des lésions sur le long cours. D'où l'importance capitale d'une compréhension approfondie des mécanismes pathophysiologiques qui régissent l'apparition et la persistance du statut épileptique et de ses séquelles. La terminaison spontanée de crises épileptiques semble être un processus inhibiteur énergético-dépendant ayant pour objectif le rétablissement de la fonction de pompage de Na^+-K^+ précédemment restreinte. Un approvisionnement énergétique déficient par synthèse ATP mitochondriale peut conduire à une activité de crise durable et au développement d'un statut épileptique. L'activité épileptique, lorsqu'elle est continue, induit elle-même une cascade d'altérations pathologiques dans le cerveau qui contribuent au maintien du statut épileptique. Une diminution des récepteurs $GABA_A$ et une augmentation des récepteurs excitateurs NMDA sur la membrane post-synaptique permettent et favorisent la persistance de l'activité épileptique. Ces processus d'adaptation ont en outre une influence sur la pharmacologie du statut épileptique sous forme d'une pharmacorésistance progrédiente aux anticonvulsifs à action GABAergique et d'un impact grandissant des antagonistes de récepteurs NMDA à mesure que la durée du statut épileptique se prolonge. Les lésions en résultant sur le long terme, par exemple le développement d'une épilepsie chronique, ont été montrées en détail par modélisation animale, mais un statut épileptique est également épileptogène chez l'homme. Les modifications de réseaux neuronaux tels que la prolifération aberrante d'axones et une perte d'interneurones GABAergiques contribuent probablement à l'épileptogenèse, d'autres mécanismes entraînent à long terme des modifications de l'expression génique et la rupture de la barrière sang-cerveau. L'identification claire de structures moléculaires cibles est un prérequis pour le développement de stratégies thérapeutiques anti-épileptogènes efficaces dans la lutte contre le statut épileptique ou d'autres lésions cérébrales graves.

Mots clés : Epileptogenèse, récepteurs GABA, perte d'inhibition, perte d'énergie mitochondriale, perte de neurones, récepteurs NMDA

Some 150 years ago, Armand Trousseau from Paris recognised that during "status epilepticus, something happens [in the brain] that requires an explanation" [1]. Though we have seen some progress in our understanding of what is happening, we are far from being at the end of the road. Treatment success is still limited, more than one in three patients develops refractory status epilepticus (SE). Neuronal and clinical sequelae are commonly seen. Therefore, a better understanding of pathophysiological mechanisms underlying the development, maintenance and consequences of status epilepticus is urgently required.

Animal models resembling status epilepticus

Though EEG and MRI (functional and structural) may offer the chance to get insight into some pathophysiological aspects of SE in patients in vivo, the vast majority of work in this field has been performed on animals. However, experimental findings from animal model systems of SE have to be discussed critically regarding their translational relevance.

There are two commonly used approaches to induce SE in living animals, one is local or systemic administration of a proconvulsant drug, the other is electrical stimulation of susceptible brain structures. One of the most frequently used chemoconvulsants is pilocarpine that is a cholinergic substance acting on muscarinic acetylcholine receptors. Eventually, secondary release of the excitatory neurotransmitter glutamate acts proconvulsantly [2]. Turski was one of the first to develop this model system and he described a stereotypical sequence of electro-clinical alterations [3]. Twenty to 30 min following intraperitoneal administration of pilocarpine, intracranial recordings demonstrate isolated high voltage spikes in the hippocampal region that after another 20 min occur in neocortical structures as well. These electrophysiological alterations are accompanied by behavioural changes such as initial oral automatisms and eye blinking. After 30 min, the rats exhibit first partial motor seizures that progress to frequent generalised motor activity. After approximately 90 to 120 min, convulsions cease, and the rat is in a state termed limbic SE. This condition is characterised by staring, chewing and other stereotypical subtle movements, the EEG demonstrates continuous ictal discharges that occur predominantly in limbic structures. The electro-clinical features of experimental limbic SE resemble complex partial SE in patients. The main difference is the extent of continuous excitatory seizure activity, that is less severe and more fluctuating in patients compared to the animal models. This issue is of particular relevance in regard of consequences of SE such as neuronal loss and the development of chronic epilepsy and is discussed in more detail below.

The other frequently used chemoconvulsant is kainic acid that binds to a subtype of the ionotropic excita-

tory glutamate receptor which is termed kainate receptor [4, 5]. Nowadays less commonly used substances include picrotoxine, bicuculline, and penicilline [6]. Besides systemic administration, chemoconvulsants can be given intrahippocampally or intraventricularly.

Electrical stimulation of limbic structures such as the amygdala, the ventral hippocampus and the perforant path results in high-amplitude spontaneous discharges that occur continuously for hours even after the end of stimulation [7-10]. Therefore, in this model system, SE persisting beyond electrical stimulation is clearly *self-sustaining*. Behavioural changes are similar to those in the pilocarpine model, SE is predominantly limbic but motor features may be seen.

Most animal studies do not focus on pathophysiology of SE itself, but employ SE to induce brain injury subsequently resulting in the development of chronic epilepsy. The behavioural, electrophysiological and neuropathological features of this form of experimental epilepsy resemble temporal lobe epilepsy in patients [11]. The research interest is to elucidate the pathophysiological alterations underlying epileptogenesis, to identify possible molecular targets and to develop antiepileptogenic treatment strategies [12]. SE is the most commonly used model system to study subsequent epileptogenesis, and – depending on the specific model used – 70 to 100 % of rats develop chronic epilepsy within 2 to 8 weeks [10, 13-15].

Advantageous and disadvantageous features of chemoconvulsant SE animal models are contrasted with those of electrical stimulation models in **table 1**.

Development and maintenance of status epilepticus

Status epilepticus is the consequence of failure of spontaneous seizure termination. While seizure initiation has widely been studied, the underlying mechanisms of seizure termination still have to be elucidated. One hypothesis currently discussed is based on failure and restoration of mitochondrial energy supply. Following a stimulus, mitochondrial ATP synthesis is diminished and subsequently the energy-dependent Na^+-K^+-pump function is impaired. Increased extracellular K^+ concentration facilitates neuronal excitability [16, 17]. The clinical response may be an epileptic seizure. This evokes marked cerebral vasodilatation, allowing increased cerebral perfusion that renews the access to oxygen. Mitochondrial ATP synthesis and Na^+-K^+-pump function are restored, neuronal excitability is reduced and the epileptic seizure may terminate. This model suggests that epileptic seizures should inherently be self-limiting [18]. However, if seizure-associated hyperperfusion is unable to override the hypoxic stimulus, mitochondrial ATP synthesis can not be restored and ictal discharges persist. Clinically, the patient may develop SE. Other mechanisms contributing to seizure termination that – if impaired – may explain its failure are discussed in detail in an excellent recent review by Lado and Moshé [19].

Epileptic activity itself induces a cascade of pathophysiological alterations in the brain that contribute to the development and eventually maintenance of SE. Within the frame of milliseconds to seconds, neurotransmitters and modulators are released, ion channels become activated and inactivated, and receptors are phosphorylated and desensitised. In the range of seconds to minutes, receptor trafficking affecting GABA and glutamate receptors is responsible for some key adaptation. In the framework of minutes to hours, inhibitory peptides such as dynorphin, galanin and somatostatin are depleted, and the expression of the proconvulsant tachykinins substance P and neurokinin B is increased [20]. In the following, the focus is on receptor trafficking that may have direct implications for treatment approaches tailored to the specific stage of SE.

Following the current "receptor trafficking" hypothesis, ongoing epileptic activity results in gradual reduction in the number of inhibitory $GABA_A$ receptors at the synaptic membrane following receptor internalisation into endocytic vesicles and subsequent degradation. Experimental in vitro findings have demonstrated that pilocarpine-induced SE of 1 h duration significantly diminishes the number of $GABA_A$ receptors compared to control rats [21]. This process results in erosion of endogenous GABAergic inhibition that on the one hand majorly contributes to sustained epileptic activity and thus facilitates and maintains SE. On the other hand, loss of postsynaptic $GABA_A$ receptors constitutes the pathophysiological basis for progressive pharmacoresistance of GABAergic drugs such as benzodiazepines, barbiturates and propofol with ongoing seizure activity. In an experimental in vivo model, the diazepam dose required to terminate SE was 10fold increased when administered 45 min compared to 10 min after onset of epileptic activity [22]. Analogously, clinical data indicate that treatment success of SE is dramatically reduced from 80% when initiated 30 min after seizure onset to 40% after 120 min [23].

While with ongoing seizure activity the number of $GABA_A$ receptors is significantly reduced, AMPA and NMDA receptors are progressively transported to the synaptic membrane [24]. This facilitates neuronal excitability and sustained SE. However, the enhanced expression of glutamate receptors may be useful in the therapeutic management of advanced stages of SE. In the electrical stimulation model of SE, the NMDA receptor antagonist ketamine did not have any effect when administered 15 min after onset of seizure activity while SE was terminated in all four rats when given after 60 min [25].

Furthermore, experimental data suggest that NMDA receptor activation regulates SE refractoriness to benzodiazepines, as receptor blockade reverses GABAergic pharmacoresistance [26]. This interrelation may

Table 1

Characteristics of chemoconvulsant and electrical stimulation animal models of status epilepticus

	chemoconvulsants	electrical stimulation of limbic structures
technical requirements to induce SE	(+)	++
acute fatality during SE	++*	(+) [27]
rate of successful SE (%)	40 – 100 [3, 28]	70 – 90 [10, 29]
self-sustaining character of SE	Δ	+++
neurotoxicity of the SE inducing methodological approach	++	Δ
rate of animals developing chronic epilepsy (%)	60 – 100 [13, 14]	50 – 100 [30, 31]

SE, status epilepticus; * fatality following systemic administration of pilocarpine was significantly reduced by coadministration of methylscopolamine [32]

have therapeutic relevance. Ketamine coadministered with diazepam in rats has recently been demonstrated to have strong synergistic anticonvulsant effects while each substance given alone did not have any effect at all [33]. In a patient with difficult-to-treat SE refractory to barbiturates and propofol, ketamine coadministered to midazolam eventually was successful [34].

Consequences of status epilepticus

Generalised convulsive SE is accompanied and complicated by a plethora of systemic alterations that manifest early in the course and that significantly contribute to morbidity and mortality. Generalised continuous epileptic activity results in excitation of hypothalamic and subsequently brain stem structures that eventually lead to massive release of endogeneous catecholamines. The clinical consequences are – occasionally massive – arterial hypertension, tachycardia and potentially lethal tachyarrhythmia. In addition, severe hyperthermia up to 41°C that is due to ongoing convulsions is commonly observed. Furthermore, acid-base-dysbalance due to metabolic and respiratory acidosis and pulmonary oedema often occur [35]. Beyond any discussion on long-term neuronal consequences, these severe systemic complications of generalised convulsive SE require an early and aggressive anticonvulsant treatment approach. In non-convulsive forms of SE such as complex partial SE, these systemic consequences do not occur at all or at most subtly. Therefore, the aggressiveness of anticonvulsant treatment has to be balanced against the risk of neuronal consequences and corresponding clinical sequelae [36].

In landmark experiments by Meldrum and colleagues, generalised convulsive SE induced by bicuculline in baboons lasting 1.5 to 5 h caused neuronal damage in cerebellar, hippocampal and neocortical structures [37]. If convulsions were avoided by complete muscle relaxation, neuronal cell loss was less severe but not completely prevented indicating the deleterious effects of continuing epileptic activity itself [38]. This argues to treat subtle SE (late stage of previously overt generalised convulsive SE [39]) as aggressively as the overt convulsive form [40]. Self-sustaining SE induced by electrical stimulation of limbic structures in rats results in a phenomenological spectrum ranging from continuous limbic, partial motor to generalised convulsive SE [41]. Comparing animals with partial motor SE to those with generalised convulsive SE, neuronal damage and development of chronic epilepsy were significantly less severe but still present. In summary, animal data on SE indicate that the severity of brain structural consequences depends on the extent of convulsive activity. However, non-convulsive epileptic activity has the potential to damage neurons as well. Translation of these experimental findings to human forms of non-convulsive SE should be made with caution for the following reasons. SE in animal models is often associated with extensive continuous excitatory seizure activity while – most no-

tably complex partial – SE in humans generally is interrupted by periods of less severe activity. Duration and frequency of epileptic activity have been shown to correlate with the extent of neuronal damage [42], and therefore experimental SE can not indiscriminately be compared with the human condition.

Neuronal consequences of non-convulsive forms of SE in humans may be assessed methodologically in postmortem autopsies or in vivo by neuroimaging. Commonly, non-convulsive SE is a condition that does not result in patients' death unless the underlying causative medical condition is lethal. Since in such cases allocation of the origin of neuronal cell loss can not be made with certainty, there are no reliable reports on structural consequences of non-convulsive SE as shown by histology, as yet.

Structural neuroimaging has also been used to search for cerebral consequences of status epilepticus. Indeed, a single case with temporal lobe epilepsy was reported who developed hippocampal atrophy after complex partial SE [43]. This report contrasts to another MRI volumetry study that assessed nine patients up to 12 months after generalised convulsive status epilepticus and did not reveal atrophy in limbic structures [44].

Non-convulsive SE occurring in patients with pre-existing epilepsy allows to clearly assess isolated clinical effects of continuing epileptic activity. Outcome is reported to be good to excellent for complex partial SE [45-47]. Advanced analysis of neuropsychological functions in patients with pre-existing epilepsy and at least one episode of complex partial SE showed an excellent intellectual prognosis in adults [48].

As mentioned above, 70 - 100% of animals develop chronic epilepsy with spontaneous recurrent seizures within 2 - 8 weeks after SE [10, 13-15]. The exact pathophysiological mechanisms underlying epileptogenesis still have to be elucidated. In mesial temporal lobe structures, mossy fiber sprouting [49] and transient impairment of inhibition possibly due to loss of GABAergic interneurons [10, 15] currently are discussed to facilitate the development of chronic epilepsy. Both alterations are NMDA receptor regulated [50, 51] that may display a molecular target for antiepileptogenic treatment strategies [12]. In patients, it may be difficult to discern whether epileptogenesis is the consequence of SE or of the underlying brain disease. The 10-year risk of developing epilepsy after acute symptomatic SE has been reported to be 41% and thus 3.3 fold higher than after a single epileptic seizure with comparable aetiology [52], giving evidence for the major impact of SE itself on epileptogenesis in humans. Perspectively, clinical research on consequences of SE and on prevention strategies should be further emphasised. This requires follow-up studies for years or even better for decades.

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