Title:
The transition to status epilepticus: how the brain meets the demands of perpetual seizure activity

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Abstract

The pathophysiology leading to the development of status epilepticus (SE) remains a topic of significant scientific interest and clinical relevance. The use of multiple experimental and computational models has shown that SE relies on a complex interaction between mechanisms that operate at both a cellular and network level. In this review, we will summarise the current knowledge on the factors that play a key role in allowing SE to develop and persist. These include pathological adaptations to changing ion dynamics, neuroenergetics, receptor expression and neurotransmission, which enable the brain to meet the extensive demands required to maintain ongoing synchronous hyperexcitability. We will examine how these processes converge to enable synapses to support seizure perpetuation. Lastly, we will use the concept of a perpetuating network to highlight how connections between brain regions can provide positive feedback loops that can serve to propagate seizure activity. We hope this review will collate the findings of previous research and help fuel further studies into studying the mechanisms that underlie how the brain can make the transition to SE.

Introduction

Status epilepticus (SE) is a state of 'fixed' and 'enduring' seizure activity that reflects significant disruption to brain activity [1, 2]. If a seizure does not self-terminate within 5-15 minutes it is unlikely to do so without additional pharmacological intervention – a factor which has significantly informed the most recent clinical guidelines [3]. This implies that the brain of a patient in SE has obtained the capacity to recruit self-propagating mechanisms, which allow seizure activity to circumvent otherwise robust endogenous anticonvulsant systems. While it is appealing to view SE as a 'seizure that never ends' (as previously proposed in a review by Lado and Moshé [4]), it may be more useful to consider SE as a separate, but related, entity to seizures. SE is a steady-state of hypersynchronous hyperexcitability, which arises following an insult to the brain and is maintained by various activity-driven changes at both a synaptic and a network level. Currently there is little consensus on what the underlying gatekeeping factors are that enable the transition into SE. This is an area of continued interest and a greater understanding of the pathophysiology underlying SE would help to optimise approaches for treating this condition.

There have been several previous reviews that have summarised the pathophysiology of SE [5-8]. However, the explanations put forward have largely been based on changes to neurophysiology that have been observed before and after SE has occurred. Therefore, these reviews focus more on the consequences of prolonged excitability, but provide less insight into the factors that allow for such activity to develop and or persist. In this review, we will propose the idea that SE emerges from activity-dependent changes at both a synaptic and network level that allow for perpetuation of hypersynchronous hyperexcitability. We first briefly introduce the experimental and computational models that have been used to recreate SE-like activity. We will then focus on key systems that we believe play a pivotal role in the generating and maintaining persistent seizure-activity. These include exploring the ionic milieu that may be necessary for ongoing hyperexcitability, changes to neurometabolism that are needed to meet the increased energy demands of persistent seizure activity, as well as adaptations to neurotransmission that favour excitation. Lastly, we will highlight how interactions between the seizure focus and other, in some cases distant, parts of brain may support continued seizure propagation.

Models of SE: exploring the old and the new

Our current understanding of SE is based on a series of *in vitro*, *in vivo* and, most recently, *in silico* models. Whilst it is understood that these models will not be able to completely recapitulate the complex clinical phenotype of SE, they do offer a platform to discover what mechanisms may be implicated. Previous reviews have summarised different models of SE [9, 10]. In **Table 1** we have collated the key findings of this previous work, by detailing the various models of SE and their mechanisms of action. It is clear from experimental models, that an effective strategy to elicit prolonged seizure activity is to cause a significant imbalance between excitation and inhibition. This can be achieved by either receptor agonism (glutamatergic or cholinergic), receptor antagonism ($GABA_A$) or disruption of ion-mediated control mechanisms (namely potassium channel activity and magnesium blockade of NMDA receptors). Furthermore, this overview reveals the hippocampus as a favoured region to target, presumably due to its vulnerability to insult and the predisposition of its intrinsic circuitry to produce and propagate network hyperexcitability. However, it is important to note that these experimental models have largely been

used to study the consequences of SE, rather than the development of SE. To achieve the latter, it seems likely that more refined models will be required, namely ones that afford access to the transitions between baseline, seizures that self-terminate, and seizures that self-perpetuate.

Recently, there has been an increasing trend to use animal and human seizure data to guide computational and theoretical models [11, 12]. This has largely been inspired by the consistency of the electrographic phenotype of seizures across multiple species which has allowed researchers to identify universal contributing factors that may be relevant to different seizure states and are therefore amenable to theoretical modelling [13]. However, a major limitation of the modelling approach has been the compromise between biological realism and model simplification [14]. Encouragingly, there is a steady development towards producing more accurate models of seizures that also include SE (see review by Wendling and collegeaues [12]). A notable example, is Jirsa and colleagues' 'Epileptor' model, which is able to incorporate a multitude of different physiological variables and reproduce activity that resemble seizures that have been observed within *in vitro* and *in vivo* preparations [13]. Indeed, the application of this model has been extended to show that it can reliably simulate SE [15, 16].

Table 1: Animal models of status epilepticus

Model	Mechanism of action	References
Electrical stimulation		
Perforant pathway stimulation[#]	30 minutes of stimulation of main excitatory pathway into hippocampus	[17, 18]
Continuous hippocampal stimulation[$]	90 minutes of continuous stimulation of hippocampus recruits limbic circuits	[19]
Ionic perturbations		
0 Mg^{2+}	Remove voltage-dependent Mg^{2+} block from NMDA receptors	
High $[K^+]_e$	Prevent passive K^+ efflux causing persistent membrane depolarisation	[20]
4-aminopyridine	Potentiation of synaptic transmission through blockade of Kv channels causing wide spread depolarisation	[21, 22]
Hyperthermia	Raised body temperature causes hyperventilation leading to a prolonged alkalosis that promotes network hyperexcitability	[23, 24]
$GABA_A$ antagonism		
Bicuculline	Block $GABA_A$ receptors thereby decreasing synaptic inhibition	[25]
Pentylenetetrazol		[26, 27]
Glutamatergic agonism		
DL-Homocysteine	Activate glutamate receptors thereby increasing synaptic excitation	[28-30]
Kainate acid		[31, 32]
Cholinergic agonism		
Pilocarpine	Activate muscarinic receptors causing increased synaptic excitation	[33]
Organophosphates (including paraoxon and DFP)	Increase synaptic ACh by blocking ACh esterase	[34]

Soman		[35]

'ACh', acetylcholine; 'DFP', Diisopropylfluorophosphate; '$[K^+]_e$', extracellular concentration of potassium; 'Mg^{2+}', magnesium

[#]Perforant pathway stimulation protocol: 10s of 20Hz (20V) 0.1msec square pulse trains delivered every minute with 2 Hz continuous stimulation for 30min total

[$]Continuous hippocampal stimulation protocol: 10s of 50Hz (400uA) 1msec biphasic square pulse repeated in 9min on / 1min off intervals continuously for 90min.

Creating an ionic milieu conducive for ongoing seizure activity

One of the key mechanistic insights that has emerged from experimental models is how the intra- and extracellular ionic environment changes during seizures. In a previous review, we summarised the various changes in ion dynamics that may contribute to the initiation, maintenance and termination of a single seizure event [36]. Here we will extend this discussion by exploring what ionic milieu may facilitate the development and propagation of SE.

One of the first ions to be studied in the context of seizures was potassium (K^+). During a seizure, the extracellular concentration of K^+ ($[K^+]_e$) is significantly elevated [37], which is generally associated with neuronal hyperexcitability. At the same time, rises in $[K^+]_e$ could also contribute towards seizure termination by facilitating 'depolarisation block' - a positive shift in membrane potential at which voltage-gated sodium (Na^+) channels become inactivated and neuronal action potential firing is impeded [38]. Previous work by Dreier and Heinemann had shown that during *in vitro* SE-like activity induced by 0 Mg^{2+}, $[K^+]_e$ appears to vary dynamically between 4mM – 9mM [39]. Such fluctuations in $[K^+]_e$ may be well-suited to maintaining ongoing seizure activity, whilst avoiding the threshold required to impose either widespread depolarisation block or spreading depression-like states that could terminate seizure activity [40]. To understand the mechanisms that may maintain $[K^+]_e$ within a range that sustains synchronous network excitability, one needs to also consider the complex neuronal and glial systems that are involved in regulating $[K^+]_e$ (see review by Kofuji and Newman [41]) and how these are engaged during seizures (see review by de Curtis and colleagues [42]).

Closely accompanying the observed increase in $[K^+]_e$ are corresponding changes in $[Na^+]_i$. Specifically, the intense membrane depolarisation that occurs during seizure-like activity is largely due to significant Na^+ influx through voltage-gated and ligand-gated channels. This leads to a steady elevation in the intracellular concentration of Na^+ ($[Na^+]_i$) [43]. Interestingly, the peak $[Na^+]_i$ is typically reached immediately prior to seizure termination suggesting that rising $[Na^+]_i$ might contribute to a seizure ceasing. The inhibitory effects of raised $[Na^+]_i$ could be explained by a reduction in the inward driving force for depolarizing Na^+ conductances [44]. Therefore, in order for seizure activity to persist neurons would need to maintain relatively low $[Na^+]_i$.

The chief regulator of $[Na]_i$ and $[K^+]_e$ is the Na^+/K^+ ATPase and therefore it is logical to assume that its function is critical for sustaining ongoing hyperexcitability in neurons. Raised $[Na]_i$ is known to enhance the activity of the Na^+/K^+ ATPase [45, 46] and has been shown to support ongoing seizure activity in computational models [44]. At the same time, both animal and human data suggest that pharmacological blockade or loss-of-function mutations in Na^+/K^+ ATPase are associated with the development of seizures [47, 48]. This in turn implies that whilst perturbed function of the Na^+/K^+ ATPase might allow $[Na^+]_i$ and $[K^+]_o$ to reach levels that are high enough to promote large-scale excitation and seizures, sufficient activity must remain in order to allow ongoing neuronal excitability to be maintained in the context of SE.

Chloride (Cl^-) has been implicated in many developmental and disease processes [49]. During seizures there is a significant elevation in the intracellular concentration of chloride ($[Cl^-]_i$) [50-53]. This is thought to be caused by increased Cl^- influx through intense GABA A receptor ($GABA_AR$) activation, accompanied by a decrease in K^+-mediated Cl^- extrusion via the K^+-Cl^--cation cotransporter (KCC2) [54]. In this state of elevated $[Cl^-]_i$, $GABA_AR$ signalling can become excitatory, as evidenced by the activation of the GABAergic interneurons triggering action potentials in pyramidal cells [50, 52, 53]. Once $[Cl^-]_i$ has returned to baseline, interneurons resume their normal inhibitory function. The influence of manipulating $[Cl^-]_i$ in the generation of seizure activity has been demonstrated by the work of Alfonsa and colleagues [55, 56]. Recently, we have also studied the role of this excitatory shift in GABAergic signalling in SE [57]. Using the 0 Mg^{2+} *in vitro* model, we have demonstrated that during SE-like activity, $[Cl^-]_i$ remains persistently elevated and that activation of interneurons can trigger continuous bursting in the network. A key contributor to maintaining a high $[Cl^-]_i$, and thereby facilitating entry and propagation of SE, may be impaired function of KCC2 be caused by activity-driven phosphorylation and or protein-protein interactions [58-61]. By contrast, boosting KCC2 function appears to block entry into SE-like activity [21, 62]. In addition, the Cl^- importer, Na-K-Cl-Co-transporter (NKCC1) may also be implicated, for example ongoing seizure activity has been shown to increase the activity of NKCC1 [63], which would enhance intracellular Cl^- accumulation. During SE there is an increase in extracellular ammonia, a product of protein catabolism [25], which has been shown to enhance NKCC1 function, leading to an increase in $[Cl^-]_I$ [64]. Taken together, the activity-dependent increase in $[Cl^-]_I$ via $GABA_ARs$, impaired

KCC2 function and upregulation of NKCC1, may work in combination. As $GABA_AR$s are the predominant mechanism for fast synaptic inhibition in the brain, their subversion into driving excitatory activity during SE likely constitutes a powerful means for sustaining hyperexcitability.

Calcium (Ca^{2+}) is another ion that changes significantly during different activity states. Seizures have been shown to be associated with large negative shifts in the extracellular concentration of Ca^{2+} ($[Ca^{2+}]_e$), largely as a result of a widespread Ca^{2+} influx into the intracellular compartments [65-67]. Low $[Ca^{2+}]_e$ can favour non-synaptic transmission via ephaptic coupling and increased synchronisation between neurons [68, 69]. The increased neuronal $[Ca^{2+}]_i$ is thought to trigger a cascade of second-messenger systems that promote activity-dependent synaptic changes in favour of excitation (to be discussed further in the following sections). However, a low $[Ca^{2+}]_e$ also inhibits presynaptic neurotransmitter release which would inevitably prevent further synaptic activity. Therefore, in order for seizure activity to be sustained, the Ca^{2+} gradient, similar to the K gradient, would need to be would need to be maintained within range that allows for continued seizure activity.

Changes in pH are also known to occur during seizure activity. The intraneuronal pH becomes more acidic during seizures and appears to correlate with seizure duration [70-72]. This negative shift in pH initiates a cascade of anticonvulsant effects (as discussed in the review by Raimondo and colleagues [36]). The extracellular pH however, appears to exhibit a biphasic response, initially becoming more alkalotic at the start of a seizure, followed by a period in which it becomes progressively more acidic [73]. The initial alkalotic response may be due to increased bicarbonate (HCO_3) efflux caused by intense $GABA_AR$ activation [74], while the extracellular acidosis that follows is likely caused by the recovery from intracellular acidosis caused by increased CO_2 and lactic acid production as by-products of neuronal oxidative metabolism [75]. Interestingly, alkalosis appears to promote network excitability and can even precipitate the onset of seizures [24]. Therefore, in order for seizure activity to persist, the intraneuronal and extracellular compartments would need to maintain a state of sufficient alkalosis and/or be able to mitigate anticonvulsant effects of the activity-driven acidosis. The former is suggested by previous work by Howse and colleagues, who showed that during a seizure the acidic shift in extracellular pH is brief and followed by a steady alkalosis [76]. Those authors proposed that the increase in perfusion to the area causes enhanced clearance of the acidic metabolic waste products, namely CO_2. In addition, Laxer and colleagues have shown that in patients with refractory epilepsy, the extracellular pH is more alkaline at the seizure focus [77]. Astrocytes appear to demonstrate an alkaline shift during seizures that correlates with a significant depolarisation in their membrane potential as well as a widespread increase in network activity [78]. This alkalotic shift within astrocytes is thought to be a key element in the process by which glia shuttle more energy substrates, in the form of lactate, to neurons during periods of increased network activity [79]. Taken together these ideas suggest that 'compartment specific' pH dynamics are critical for how a network can maintain the ionic and energy demands of SE.

Meeting the energy demands of prolonged network hyperexcitability

The majority of energy consumption within the brain takes place at the postsynaptic membrane where membrane pumps actively restore the required ion gradients to permit neural transmission (see review by Harris and colleagues [80]). Excitation is an 'expensive' energy process, mainly owing to the requirement of using the Na^+/K^+ ATPase to maintain the necessary Na^+ and K^+ gradients. By contrast, inhibition appears to be more efficient, as the systems that maintain inhibitory ionic gradients, namely Cl^-, are less reliant on active transport mechanisms [81]. Seizures are well-known to represent hypermetabolic periods, as evidenced by neurovascular coupling to the seizure focus and increased consumption of glucose and oxygen [82, 83]. This enhanced energy demand is likely caused by hyperexcitability [84].

In order for seizures to persist, they require an ongoing supply of energy substrates. Experimental work performed in the 1970s provided important insights into the changes in metabolism that occur during prolonged seizures [25, 29, 85, 86]. During the early phase of SE, there is significant glucose oxidation as evidenced by a decrease in the concentration of cerebral glucose accompanied by an increase in oxygen consumption and increase in NADH oxidation. Coincident with this decline in glucose is an increase in concentration of lactic acid. This is consistent with Pellerin and Magistretti's hypothesis that increased synaptic excitation and glutamate release stimulate astrocytes to produce lactate that is then fed to the neurons via the so-called 'lactate shuttle' [87-89]. Lactic acid is converted back into pyruvate (via lactate dehydrogenase), which is then used by the tricyclic acid cycle to produce metabolites for

oxidative phosphorylation. This pathway demonstrates the brain's ability to utilise the by-products of glucose oxidation to further its energy production capacity during periods of increased network activity.

However, there is much debate as to the validity of this hypothesis. Firstly, there is uncertainty as to whether lactate can be used by the brain as an energy substrate [80]. Notably, Hall and colleagues have demonstrated that blocking the conversion of intraneuronal lactate dehydrogenase does not affect a neuron's metabolic capacity [90]. Secondly, the elevated levels of cerebral lactate may also be caused by systemic factors, such as respiratory arrest or convulsions [91]. In addition, glucose's role in neural metabolism during seizures is also not clear. While hypoglycaemia is a well-known cause of seizures [92, 93]; Kirchner and colleagues have presented *in vitro* data that suggest removal of glucose can prevent seizure onset [94]. However, these proposed changes in neuronal metabolism are not universally accepted. Schuchmann and colleagues have suggested that the entry into continuous seizure-like activity is caused by a reduction in oxidative phosphorylation and a failure to produce the required ATP to maintain Na^+/K^+ ATPase function [22]. This hypothesis would be consistent with the predictions made by Krishnan and colleagues, who have suggested that entry into SE is caused by reduced Na^+/K^+ ATPase activity [95]. Whilst it remains unclear how exactly the brain adapts its metabolism to meet the immense energy demands posed by ongoing seizure activity, it is likely to be a combination of these complex interacting mechanisms.

Adapting the synaptic environment to promote ongoing excitation

Prolonged seizures are known to cause significant changes to neurotransmission, through alterations in the spatiotemporal kinetics of neurotransmitter release and neurotransmitter receptors [96]. These changes typically favour a shift towards excitation over inhibition and are therefore in agreement with the idea that synaptic changes may adapt to facilitate ongoing network activity. Work by Smolders and colleagues has shown that following seizure onset, there is a significant increase in extracellular levels of glutamate and GABA [97]. The observed increase in glutamate is likely a 'spill-over' from the increased presynaptic release of glutamate combined with a failure of the surrounding astrocytes to buffer the excess glutamate through their excitatory amino acid transporters (EAATs) [98]. Tian and colleagues, have also shown that astrocytes are capable of releasing glutamate and can therefore contribute to extracellular glutamate levels [99]. A similar process is thought to underlie the sustained elevation of extracellular GABA during seizure states, which may initially be due to the increased recruitment of inhibitory circuits through feedforward inhibition [67], but may also reflect a key contribution by astrocytes. Specifically, the ability for astrocytes to resorb GABA through their GABA transporters (GATs) may be overwhelmed, and/or there may be an increase in the direct release of GABA from astrocytes [100, 101]. In the context of a high $[Cl^-]_i$, presence of excess amounts of GABA could further promote excitatory GABAergic signalling that would further perpetuate seizure activity,

With regards to the receptor targets of these ligands, it is widely accepted that persistent seizure activity induces changes to receptor proteins in the postsynaptic membrane. Notably, there is an increased expression of the excitatory NMDA receptors [102, 103] and AMPA receptors [104, 105]. In addition, there is a loss of synaptic $GABA_A$ receptors, which become internalised [106-108]. Changes in the AMPA and $GABA_A$ receptors that occur during SE have pertinent therapeutic implications. Specifically, the internalisation of $GABA_A$ receptors could explain the failure of benzodiazepines as SE becomes more prolonged, whilst the upregulation of AMPA receptors would advocate the use of ketamine in refractory SE.
Significant changes in purinergic receptors on both astrocytes and neurons also seem to contribute to ongoing excitation (see review by Henshall and colleagues [109]). SE has also been shown to significantly alter neuropeptide signalling at synapses. Wasterlain and colleagues showed a decrease in anticonvulsant neuropeptides including galanin, dynorphin, neuropeptide Y and somatostatin [110]. This was accompanied by an increase in proconvulsant neuropeptides such as substance P and neurokinin B. In addition, entry into SE activity appears to correlate with a loss of anticonvulsant adenosine receptors on the postsynaptic membrane [111]. It is also interesting to note that many of the above-mentioned processes are also associated with the changes that mediate forms of synaptic plasticity, such as those which occur during long-term potentiation (LTP). This suggests that, under pathological conditions, seizures may harness positive feedback mechanisms at the synapse to promote their continued propagation.

The importance of regional interactions in the emergence of SE

We have focussed primarily on self-propagating mechanisms that operate at the level of single neurons and their immediate cellular environment. It is important to recognise, however, that the sustainability of seizure activity also depends upon large scale network interactions throughout the nervous system. In perhaps its most extreme form, seizures originating centrally can result in substantial sympathetic activation of the heart [112] and disruption of respiration, including both central and peripheral apnoeas that can be fatal [113]. These systemic symptoms are most likely due to the effects of status epilepticus upon brainstem networks, which can lead to inactivation or "spreading depolarisation" during prolonged seizures [114]. This highlights the fact that the extent by which wider networks are recruited, can have important implications for the clinical consequences of status epilepticus *in vivo*.

At the level of the cortex, seizures appear to involve the recruitment of neighbouring cortical networks, as the seizure propagates "contagiously" into other areas [115, 116]. Recruitment of subcortical structures can also engage powerful positive feedback circuits, which provide an effective strategy for establishing continuous seizure drive. For example, Hamani and colleagues have implicated the thalamus as a key subcortical structure and shown that by preventing cortico-thalamic interactions, it is possible to limit a seizure's sustainability and thereby prevent the development of SE [117, 118]. A similar relationship seems to exist between the cortex and the hippocampus with a recent *in vitro* study by Codadu and colleagues showing how seizures originating in the neocortex then transition into SE-like activity once the hippocampus is recruited [119]. While in this state, the hippocampus can serve as a 'pacemaker' and is able to feedback to the cortex through non-synaptic mechanisms. While these studies demonstrate that the recruitment of remote brain regions, such as the thalamus and hippocampus, play a key role in the transition to continuous seizure activity, future work will need to provide insights into what defines particular circuits as gate keepers for the emergence of SE and whether-local changes are more, or less, likely to lead to the active recruitment of distant circuits.

Concluding remarks

In order to be maintained, SE relies on the brain's ability to adapt to meet the profound demands of sustained synchronous neuronal activity. While it is difficult to simplify this complex pathological process, we have identified four key mechanisms that are likely to play central roles. The first is the Na^+/K^+ ATPase, whose function influences all of the transmembrane gradients, whilst also representing the largest consumer of energy within the brain. The second is the shift towards sustained excitatory GABAergic signalling, as the switching of fast synaptic inhibition into excitation represents a powerful and energy efficient way of maintaining hyperexcitability within the network. Thirdly, astrocytes appear to play a pivotal role in sustaining network hyperexcitability by providing neurons with necessary ionic gradients, metabolic substrates and neurotransmitters. Fourthly, changes in receptor expression, most notably $GABA_A$ receptor internalisation, change the synaptic landscape which will both affect synaptic transmission and influence therapeutic intervention. Finally, by effectively hijacking the brains connectivity pathways to establish positive feedback loops, a seizure is able to further promote its perpetuation.

What remains less well defined, are the processes that cause some seizures to stop and others to develop into SE. Kramer and colleagues Halgren [120] have proposed that the boundary of a self-terminating seizure and SE is demarcated by a 'critical transition' between the ictal and post ictal states. This transition is thought to represent the endogenous anticonvulsant mechanisms that usually are sufficient in stopping seizures. However, during SE the seizure appears to "retreat away" from entering into this transitionary period and instead is "attracted" to a state that favours continued hyperexcitability. The complex interactions between local cellular mechanisms as well as positive feedback loops formed with distant brain areas may be the required 'attractors' that are involved in sustaining seizure activity. Therefore, the defining feature of seizures that persist may be their ability to establish these mechanisms before the endogenous anticonvulsant system is initiated.

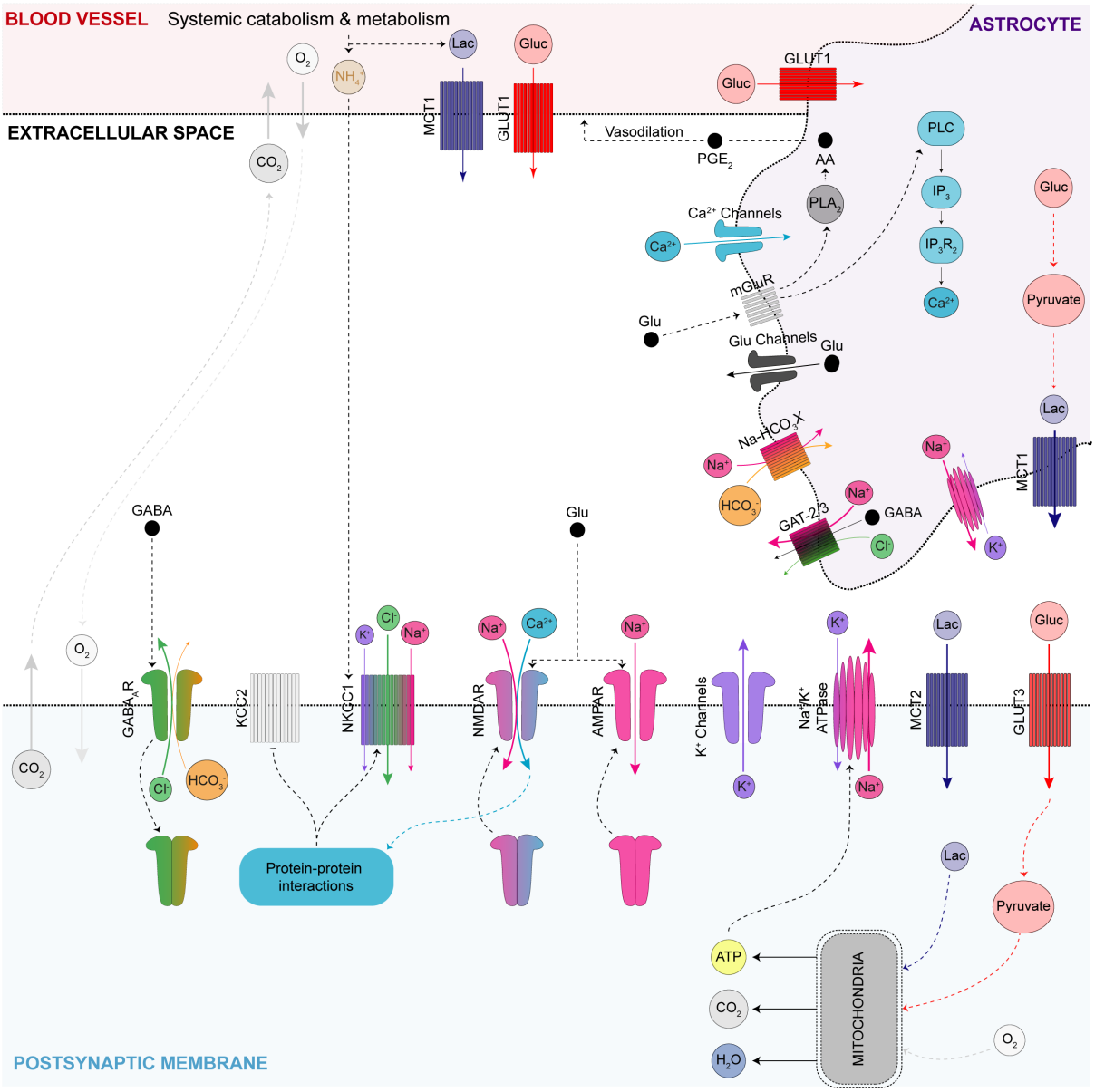
The mechanisms underlying the transition into SE are undoubtedly complex, but appear to capitalise on intrinsic features within the brain that favour excitation over inhibition. Future efforts should aim to consolidate what has previously been described across different experimental models, and to use these data as a springboard to understand how different local and large-scale network changes may interact in order to allow SE to emerge. There are clearly many challenges ahead, but there is pressing clinical need to ensure that there are ongoing improvements in understanding the pathophysiology of SE.

Figure captions

Figure 1: The self-perpetuating synapse. A schematic illustrating the activity-dependent interactions that are thought to occur between the postsynaptic membrane (blue), a surrounding astrocytic process (purple) and blood vessel (red). The complex interactions between the neuro-glia, glia-blood and neuro-blood compartments demonstrate the myriad of processes at the level of the synapse thought to sustain seizure activity. Specifically, the continuous shuttling of ions and energy substrates between compartments as well as changes in various receptors, creates a synaptic environment that promotes the ongoing excitation associated with SE. 'AA', arachidonic acid; 'AMPAR', α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; '$GABA_AR$', gamma-Aminobutyric acid A receptor; GAT', GABA transporter; 'Glu', glutamate; 'Gluc', glucose; 'GLUT', glucose transporter'; 'Lac', lactic acid'; 'mGluR5', metabotropic glutamate receptor 5; 'MCT', monocarboxylate transporter; 'Na-HCO_3X', Na^+-HCO_3^- exchanger; 'NMDAR', N-Methyl-D-aspartate receptor; 'PGE_2', prostaglandin E_2; 'PLA_2', phospholipase A_2; 'PLC', protein lipase C; 'IP_3', inositol triphosphate; 'IP_3R_2', IP_3 receptor 2.

Figure 2: Regional interactions are important in the development of self-perpetuating seizures. **A**, Simplified schematic illustrating how self-terminating cortical seizures spread contagiously from the focus to neighbouring cortical areas. **B**, If a cortical seizure propagates along cortico-thalamic and cortico-hippocampal pathways, it may be able to establish powerful positive feedback loops with the thalamus and or the hippocampus which can then perpetuate seizure activity.

Figures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mGluR
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GAT-2/3
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Pyruvate
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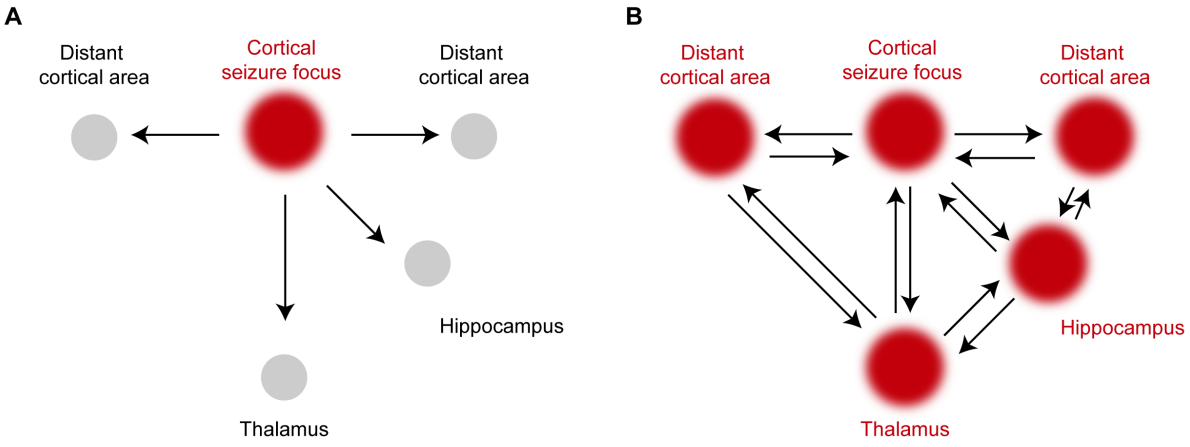
A
Distant cortical area
Cortical seizure focus
Distant cortical area
Hippocampus
Thalamus
B
Distant cortical area
Cortical seizure focus
Distant cortical area
Hippocampus
Thalamus

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