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Stress and seizures: space, time and hippocampal circuits

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Abstract

Stress is a major trigger of seizures in people with epilepsy. Exposure to stress results in the release of several stress mediators throughout the brain including the hippocampus, a region sensitive to stress and prone to seizures. Stress mediators interact with their respective receptors to produce distinct effects on the excitability of hippocampal neurons and networks. Crucially, these stress mediators and their actions exhibit unique spatio-temporal profiles, generating a complex combinatorial output with time- and space- dependent effects on hippocampal network excitability and seizure generation.

Keywords

Stress; hippocampus; network; epilepsy; seizure; cortisol; corticosterone; neurosteroid; CRH

Why stress and seizures?

Stress is a phenomenon common in everyday life and requires the orchestrated interaction between neuronal and hormonal systems to produce the appropriate behavioral and physiological responses. Interestingly, stress is the most common self-reported precipitant of seizures in patients with epilepsy [1–6]. Indeed, a number of stress mediators contribute to the regulation of neuronal excitability and of seizure generation [7–9]. The severity, duration of a stress, and the developmental time point (e.g. childhood vs adulthood) of stressor exposure can not only influence the susceptibility to seizures and their frequency [7, 10–12], but can also increase the actual risk of epileptogenesis [13, 14].

The epilepsies are a group of disorders characterized by the generation of spontaneous seizures. One of the most common and often severe forms of adult epilepsy, temporal lobe epilepsy (TLE), involves the hippocampal network, a circuit underlying spatial learning and memory processes. Animal models of TLE have shed light upon molecular, cellular and network level-changes within the hippocampus which may underlie the pathogenesis of

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TLE, i.e. the susceptibility of the network to generate spontaneous seizures [15]. The multiple changes identified in the epileptic hippocampal circuit render the network hyper-excitable. Thus, the hippocampus in an epileptic individual is more likely to generate a seizure in response to the enhanced excitability that occurs during stress. In addition, specific alterations of neurotransmitter and receptor systems within the epileptic hippocampus may render it more sensitive to the pro-excitant effects of specific stress mediators including glucocorticoids, peptides and neurosteroids, as discussed below.

There are multiple alterations in the epileptic hippocampus: sprouting of dentate gyrus mossy fiber (axons of granule cells), abnormal granule cell neurogenesis and maturation as well as loss of inhibitory interneurons have been postulated to influence the ability of this structure to filter afferent input from the entorhinal cortex (EC) [15–17]. Dysfunction of the CA1 temporoammonic pathway has been reported in animal models, as have alterations in the associated EC [15]. Changes in hippocampal interneuron number, connectivity or function may also contribute to hyperexcitability of the network [15, 18].

Further subtle alterations in hippocampal neurons may predispose the epileptic hippocampus to the pro-excitant effects of stress, by influencing both inhibitory and excitatory neurotransmission. For example, changes in the composition of $GABA_A$ receptors ($GABA_ARs$) may influence the subcellular location of these receptors (i.e. synaptic or extra-synaptic sites), and their sensitivity to neurosteroid-induced potentiation [19, 20]. The resulting changes in inhibitory transmission (i.e. phasic or tonic) may affect a neuron's capacity to attenuate excessive excitability and to compute afferent inputs correctly, particularly when concomitant changes in excitatory transmission occur [21–23]. The aberrant neurotransmission at the single cell level then influences network processes. Here we discuss how the multiple alterations within the epileptic hippocampus interact with the divergent and complex actions of individual stress-mediators and their combinatorial interactions to produce space- and time-dependent effects on network excitability and the probability of seizures.

The temporal aspects of the functions of stress-mediators in hippocampus

The hippocampus is highly sensitive to stress and plays a prominent role in mediating many of the behavioral/functional and neuroendocrine responses to stress [24, 25]. Following stress, the hippocampus is bathed in a number of peripherally derived and centrally released stress mediators, which bind to their respective receptors. Crucially, there are distinct temporal profiles of release (i.e. rapid or slow) of these stress mediators as well as of their actions. The receptor targets of the distinct stress mediators are located on specific types of neurons and at discrete subcellular domains on these cells. These distinctive spatio-temporal properties of each stress mediator result in the activation of distinct downstream signaling pathways and consequent effects on neuronal and network function.

Corticosteroids

The brain levels of glucocorticoids are rapidly and transiently elevated following stress [26, 27], typically peaking around 30 minutes after the onset of stress [28]. Glucocorticoids signal through mineralocorticoid and glucocorticoid receptors (MR and GR respectively),

which are broadly expressed throughout the hippocampal formation [29]. Each of these receptors is expressed in two variants: the classical nuclear receptor that modulates gene expression and a membrane-associated receptor that mediates rapid, non-genomic effects [30]. The high affinity of nuclear MRs to its ligand results in these receptors being almost completely occupied even at low steroid levels. In contrast, nuclear and membrane-associated GRs as well as membrane-associated MRs are of lower affinity; thus, they are only activated when levels of corticosteroids are high such as following stress or at the circadian steroid peak [31, 32].

Rapid effects—In general, rapid pro-excitatory stress hormone effects are mediated by membrane MRs, which increase neuronal excitability via pre- and postsynaptic mechanisms. The activation of presynaptic membrane MRs by corticosterone (100 nM; CORT; see Glossary) increases the frequency of miniature excitatory postsynaptic currents (mEPSCs) in CA1 pyramidal cells [33], and this effects takes place within minutes. Similar finding are reported in dentate gyrus granule cells [34]. In addition, activation of membrane MRs by CORT reduces the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) in CA1 pyramidal cells in ventral, but not dorsal CA1 [35]. Postsynaptic effects of CORT include a rapid MR-mediated increase in the lateral diffusion of GluR2 AMPA receptor subunit [36] and a reduction in the A-type K^+-channel conductance [37] at postsynaptic sites in CA1 pyramidal cells. Notably, membrane bound GRs expressed in hippocampal CA1 mediate nitric oxide-induced increase in inhibitory transmission onto pyramidal cells [38]. Thus, the combinatorial rapid effects of stress hormones are a function of how these two opposing effects interact during stress.

Slow (genomic) effects: the slow actions of stress steroids, mediated by nuclear GRs are thought to normalize hippocampal function via a number of mechanisms [26]. These include an increase in the amplitude of spontaneous and miniature IPSCs (mIPSCs) [35], as well as the delayed increase in the expression of L-type Ca^{2+} channels in CA1 pyramidal cells [39]. The latter results in a GR-induced enhancement of the after-hyperpolarization current (I_{AHP}) mediated by Ca^{2+}-dependent K^+ channels [40, 41], which provides a potential negative feedback mechanism to normalize the increased pyramidal cell spiking that follows stress onset [30, 42].

CRH and other neuropeptides

CRH is rapidly released in the hippocampus following stress from a subpopulation of GABAergic interneurons that reside throughout the hippocampal formation (Box 1). The receptors for this peptide, CRH receptor 1 and 2 (CRHR1 and CRHR2) are located at discrete subcellular domains of pyramidal cells [43–45]. CRH has been implicated in mediating some of the stress-induced effects on hippocampus-dependent memory functions [46–49].

Box 1

CRH in the hippocampus

Within the mature hippocampal formation, CRH is expressed in a heterogeneous population of GABAergic interneurons that target the perisomatic and axo-axonic regions of pyramidal cells [77, 78, 113]. CRH is rapidly released within the pyramidal cell layer following stress [113] and the presumed concentration during stress is in the 100nM range [79, 114].

Upon its release, CRH binds to two, class B, seven transmembrane G Protein coupled receptors (GPCRs) termed CRH receptor 1 and 2 (CRHR1 and CRHR2). Within hippocampus, CRHR1 is the receptor mediating most of the established actions of the peptide, such as the rapid stress-induced reduction of dendritic spines [56]. CRHR1 receptor resides on the proximal dendrites of pyramidal cells [43, 45, 55] as well as at other subcellular locations. In contrast, CRHR2 is reported to be confined to the axon initial segment of principal cells [44]. Though CRH receptors can signal via multiple pathways [96,97], in hippocampus they preferentially couple to $G_s\alpha$, promoting cAMP production and subsequent PKA activation [115].

Experiments using organotypic hippocampal slice cultures provided the first evidence for a functional role for endogenous, hippocampus-derived CRH: Blocking CRHR1 with the selective antagonist NBI 30775 led to significant increase in dendritic arborization and a similar hyper-arborization was cultures derived from mice lacking the CRHR1 ($CRHR1^{0/0}$) [116]. Furthermore, the number of dendritic spines on the apical dendrites of CA3 pyramidal cells was significantly reduced in $CRHR1^{0/0}$ mice. Recently, electrophysiological studies have revealed the presence of a CRH “tone” within the hippocampus CA3 that modulates excitatory transmission and thereby influences hippocampal network-level excitability [55].

The effects of CRH on neuronal transmission within the hippocampus are highly dependent upon the duration of the stress. Application of CRH results in a rapid dose-dependent increase in the excitability of CA1 and CA3 pyramidal cells [50–52], most likely through a reduction in the I_{AHP} that occurs following action potentials [50, 53] and, at least in CA1, the inhibition of A-type K^+ channel function [54]. Consistent with these effects of exogenous peptide, endogenous CRH increased action potential firing and excitatory transmission onto CA3 pyramidal cells in the acute hippocampal slice. This effect resulted, at least in part, through the shortening of I_{AHP} [55] (Box 1).

In contrast to clear actions of CRH over seconds-to minutes, more prolonged exposure to the peptide results in more complex effects. Application of exogenous CRH for 1 hour or less selectively reduced the number of thin dendritic spines located on apical dendrites of CA1 and CA3 pyramidal cells [46, 56] whereas longer application influenced both thin (silent) and mushroom spines (rich in AMPA receptors), promoting a reduction in fast excitatory transmission [57]. These CRH effects contribute to the effects of stress of this duration: stress lasting hours resulted in impaired long term potentiation (LTP) at CA3 commissural-associational synapses that was associated with the selective reduction in dendritic spines on

segments of apical dendrites located within the stratum radiatum [46], and was prevented by the application of CRH blockers into the brain.

In addition to CRH, a number of other neuropeptides expressed within hippocampus may contribute to hyper-excitability and the generation of seizures (reviewed in [58, 59]). Of these, vasopressin and dynorphin are involved in the stress response, and their effects are summarized in Box 2.

Box 2

Other potential stress mediators

While there are a significant number of neuropeptides and neuromodulators expressed and released within the hippocampus, only a few have been implicated in mediating the effects of stress on hippocampal excitability.

Arginine vasopressin (AVP) projections originating in the PVN reach area CA2 and modulate social recognition learning via activation of AV1b receptor [117]. The activation of AV1b results in an increase in the fEPSP amplitude and the amplitude of the AMPA-mediated evoked EPSC (eEPSC) with no effect upon the NMDA-mediated current [118].

The hippocampus receives considerable noradrenergic afferents originating in the locus coeruleus (LC) [119]. Norepinephrine can promote epileptiform activity via β-adrenergic transmission inhibit it via α-adrenergic receptors [120].

Dynorphins are expressed in the axons (mossy fibers) an dendrite of the DG granule cells [121]. Dynorphins suppress seizure activity via activation of the κ-opioid receptor. Consistent with this notion, mice lacking dynorphin exhibited reduced seizure threshold and pro-epileptic phenotype [122]. In contrast, at high concentrations, this opioid may promote seizures through actions at the μ-opioid receptor [122].

Neurosteroids

Neurosteroids, including the progesterone (PROG) metabolite 5α-pregnane-3α-tetrahydro-progesterone (5α3α-THPROG) and the deoxycorticosterone (DOC) metabolite 5α3α-tetrahydrodeoxycorticosterone (5α3α-THDOC), are potent, positive allosteric modulators of $GABA_AR$ function [20, 60]. They are synthesized within the brain from peripherally derived precursors or *de novo* (from cholesterol) [61] (Box 3). Neurosteroid synthesis within the hippocampus is primarily confined to glutamatergic principal cells [62], consistent with the location of these steroids [63].

Box 3

Neurosteroids: synthesis and mechanism of action

Neurosteroids, including the progesterone (PROG) metabolite 5α-pregnane-3α-tetra-hydro-progesterone (5α3α-THPROG) and the deoxycorticosterone metabolite 5α3α-tetrahydro-deoxycorticosterone, are potent positive allosteric modulators of $GABA_AR$

[20, 60]. They are synthesized from peripheral sources or de novo within the brain from cholesterol [61]. Components of the synthetic machinery necessary for neurosteroid synthesis are expressed in a neuron-specific manner. Furthermore, 5α3α-reduced steroids are located in the dendrites and soma of excitatory, and to a lesser extent, inhibitory neurons [63]. Neurosteroids thus contribute to the local regulation of $GABA_AR$-mediated inhibition [20] and, in turn their synthesis is regulated by neuronal activity, e.g., NMDA receptor activation [67].

Neurosteroids act at two distinct sites located within the transmembrane (TM) domain of the $GABA_AR$ that are essential for the GABA-modulatory and GABA-mimetic actions [97]. Highly lipophilic, neurosteroids accumulate within lipid membranes, increasing their local concentration and facilitating lateral diffusion to the TM domain binding sites [123].

Multiple factors, including subunit composition of the receptor, phosphorylation state and local metabolism, contribute to the sensitivity of $GABA_ARs$ to modulation by neurosteroids [20]. For example, extra-synaptic δ-subunit-containing $GABA_ARs$ that mediate tonic inhibition [19] are significantly more sensitive to neurosteroid modulation than γ2-containing receptors in some systems [124] [98], yet synaptic γ2-$GABA_ARs$ may be modulated by similar concentrations of neurosteroids [20, 125].

Following stress onset, brain levels of neurosteroids increase in a region-specific manner. Levels in cortex peak at 20 minutes, whereas hypothalamic levels peak after 60 minutes of stress [64]. There is little information about the temporal course of neurosteroid levels in hippocampus. In accord with their GABA-modulatory effects, stress-induced increase in 5α3α-THDOC levels resulted in an elevated threshold to pentylenetetrazol (PTZ)-induced seizures. This effect required endogenous neurosteroid synthesis within the brain [65]. These and additional reports [66] support the notion that the stress-induced elevation of neurosteroids within hippocampus acts to reduce network excitability and seizures.

Interestingly, seizures themselves might promote neurosteroid synthesis: application of NMDA (1 μM) for 5 minutes on hippocampal slices increased neurosteroids and impaired the induction of LTP in area CA1 [67]. This observation is intriguing because it suggests that the initial effects of stress are to induce neuronal excitation via rapid actions of CORT-MR and CRH, followed by the induction of neurosteroids both by stress and by stress-provoked hyperexcitability. Neurosteroids, in concert with GR, may then function to dampen network excitability. Notably, the ability of neurosteroids to function as anti-convulsants might be constrained by seizure-induced reduction in the surface expression of neurosteroid-sensitive synaptic $GABA_AR$ (i.e. γ2-containing) isoforms. These occur following long seizures and may last for hours [68, 69]. Finally, when stress is prolonged or chronic, brain neurosteroid levels are reduced [70], likely contributing to seizure susceptibility.

The brief paragraphs above provide a snapshot of the temporal profiles of effects of key stress mediators on network excitability, as portrayed in Fig 1. The figure highlights both discrete and overlapping temporal domains of these mediators, as well as their time-dependent actions on the network itself. Importantly, this type of temporal evolution is

difficult to ascertain in human studies, which are typically based on questionnaires [2–6, [71–73]. In the aggregate, human studies implicate both acute and chronic stress, occurring over time-periods ranging from hours to weeks, as a seizure-promoting factor in people with epilepsy [71–76]. Clearly, this clinical observation is a result of complex interactions among numerous factors, and some are described in the section below.

Spatial domains of the actions of individual stress mediators integrate to influence network function and seizure generation

Spatial domains of individual stress mediators derive from sites of their origin, distribution and function

Each stress mediator generally acts within a given spatial domain that is largely governed by the location of its release and the expression profile of its receptors. Corticosteroids arriving from the adrenal, permeate the entire hippocampus and as a result, their actions are constrained by the distribution of MR and GR. Similarly, the peripherally derived neurosteroid precursors, DOC and PROG, diffuse through the entire hippocampus, and their actions are constrained by the distribution of the neurosteroid synthetic machinery [61, 62] and of their $GABA_AR$ targets. The synthetic enzymes, and thus the neurosteroids themselves, are primarily expressed in glutamatergic pyramidal cells [63]. Neurosteroids actions take place on synaptic and extra-synaptic $GABA_ARs$, likely those expressed on the same cell (Box 3).

The peptide CRH is synthesized in hippocampal interneurons and is released from their axon terminals [77, 78]. There is no evidence for the peptide's release from dendrites [79]. In the pyramidal cell layer, basket–type and axo-axonic CRH cells release the peptide peri-somatically or at the axon initial segment respectively. In both cases, the site of release is relatively distant (~100 μm in rat, ~50 μm in mouse) from the location of the CRH type 1 receptors that are located on dendritic spines within stratum radiatum [46, 79], and the peptide is dispersed via volume transmission [79, 80]. Thus, the spatial domain of CRH is constrained by both release and receptor expression profile and likely results in the peptide exerting its effects across multiple synapses on several neurons. Finally, neurotransmitters, such as noradrenaline (Box 2), are typically released pre-synaptically and act on single neurons via modulation of single or multiple synapses. These distinct spatial domains ensure that each stress mediator modulates a distinct module: single or multiple synapses, neurons and neuronal ensembles that underlie larger scale network processes. The combinatorial output of these distinct action domains enables orchestration of multiple levels of hippocampal physiology by stress.

The dentate gyrus: a crucial node strongly influencing hippocampal network excitability

Within the temporal lobe, the hippocampus and entorhinal cortex (EC) are intimately connected via multiple feed forward excitatory loops that are constrained by both feed-forward and feed-back inhibitory mechanisms [15, 81]. The dentate gyrus (DG) is a key node in the hippocampal-EC network, responsible for filtering the excitatory inputs from the EC so that only a small component of these relay to the downstream CA3. This DG gating is not only important for the sparse coding of EC inputs required for the computational role of

the DG in pattern separation, but also for protecting the densely associated CA3 from hypersynchronous EC activity. The mossy fiber (MF) pathway connects DG granule cells with their cellular targets, both excitatory principal cells and inhibitory interneurons residing in area CA3 and the hilus. Although the connectivity between DG granule cells and CA3 pyramidal cells is sparse, these synapses are anatomically large structures possessing a number of unique properties. They contain multiple release sites which results in the generation of large amplitude EPSCs and, unlike many other synapses in the hippocampus, they also exhibit considerable frequency facilitation [82, 83]. Functionally, these MF synapses are integral to the generation of a form of intrinsic network activity, sharp wave ripple complexes (SPWs) within the CA3b region of the hippocampus [84] and these composite events are propagated through the dense associational connections [85]. The mechanisms underlying DG gating are diverse and likely include the intrinsic electrophysiological properties of DG granule cells, the unique properties of their dendrites that underlie integration of afferent inputs, as well as multiple forms GABAergic inhibition (e.g. feedforward and feedback inhibition) [86, 87]. Thus, it seems plausible that the action of stress mediators on DG gate function will greatly influence the probability of seizure generation within the hippocampus. For example, pharmacologically-induced epileptiform activity in the EC does not propagate through the DG to CA3 under normal conditions, but does so following inhibition of $GABA_AR$ function or in the kindled hippocampus [88]. Consistent with this notion, evidence from animal models indicates dysfunction of the DG gate during epileptogenesis, including alterations in the expression of specific $GABA_AR$ isoforms, impaired Cl^- homeostasis and loss of hilar GABAergic interneurons [15]. Therefore, in the following section we focus on the effects of stress mediators on DG and its direct influences on the hippocampal network.

Stress Corticosteroids—Within the DG-CA3 node the effects of CORT varies in DG granule cells and CA3 pyramidal neurons. Membrane MR mediates a rapid increase in excitatory transmission in DG granule cells [34]. Despite high levels of GR expression, these cells do not respond to GR activation [89]. The effects of acute CORT treatment upon excitatory transmission onto CA3 pyramidal cells are unknown. However, activation of MRs and GRs results in an enhancement and suppression of LTP respectively at the associational/commissural synapse in CA3, with no effect on MF synapses [90]. Whereas the genomic effects of CORT, mediated by the nuclear receptors, have not been extensively studied in CA3 pyramidal cells, exogenous CORT enhances the amplitude of Ca^{2+} currents and increases the slow I_{AHP} [91].

CRH—The effects of CRH on synaptic transmission and DG granule cell firing have not been extensively studied. Intra-DG injection of CRH produces a gradual and persistent increase in the amplitude of DG population spikes as well as potentiating field excitatory postsynaptic potentials (fEPSPs) *in vivo* [92]. Consistent with an increase in DG excitability, bath application of this peptide produces large synchronized polysynaptic action potential discharges in CA3 pyramidal cells following MF stimulation [51]. CRH may thus enhance excitatory transmission between the DG and CA3, act at the spatial domain of multiple synapses and perhaps multiple neuronal populations. CRHR1 is expressed within DG granule cells [43] providing the anatomical framework for modulation of action potential

driven release of glutamate from mossy fibers. Within area CA3, CRH increases the frequency of excitatory transmission onto pyramidal cells, an effect that is mediated in part via inhibition of I_{AHP} [50, 55]. The excitatory effects of the peptide are apparent both by application of exogenous peptide as well as from blocking the actions of intrinsic, hippocampus-released CRH [38, 43]. the effects of endogenous CRH on phasic transmission modulate the activity of the whole hippocampal networks, by influencing the frequency of sharp-waves [55] (Figure 2). Accordingly, the peptide rapidly enhances neuronal activity propagation throughout the hippocampal formation in a CRHR1-dependent manner [55], likely underlying the observed pro-convulsant actions of this peptide [7, 10, 93–96].

Neurosteroids—Neurosteroids are highly expressed within DG granule cells [63], and bind to trans-membrane regions of $GABA_AR$ within the same cells [97], though effects on neighboring inhibitory cells or pre-synaptic afferents cannot be excluded [20]. As mentioned, neurosteroids act on both synaptic and extra/perisynaptic forms of $GABA_ARs$ on DG granule cells. Their actions on the latter influence tonic GABAergic currents, thus significantly modulating network excitability [98]. Interestingly in DG the sensitivity of $GABA_ARs$, both synaptic and extrasynaptic, to neurosteroid potentiation appears to be dependent upon the phosphorylation state of the receptor, which, in turn, depends on the subunit composition of the receptor, the kinase involved and the specific site of phosphorylation [99–101]. Synaptic $GABA_AR$-mediated IPSCs are relatively insensitive to neurosteroid potentiation, partially governed by levels of PKC-mediated phosphorylation of the receptor [102]. Local metabolism is another mechanism by which the sensitivity of DG granule cells to neurosteroid-induced inhibition may be regulated [103]. In summary, the sensitivity of synaptic and extrasynaptic $GABA_ARs$ in the DG to potentiation by neurosteroids, and its functional implications are highly complex and multifactorial [20, 99, 104].

In area CA3, neurosteroids are expressed within pyramidal cells [63]. Exogenous 5α3α-THPROG prolongs the decay time and increases the frequency of $GABA_AR$-mediated sIPSCs and enhances tonic currents recorded from acutely dissociated CA3 pyramidal cells [105]. Neurosteroids enhance the amplitude and frequency of sEPSCs [106], and potentiate presynaptic δ-$GABA_ARs$ to increase glutamate release from mossy fiber boutons [107]. Thus neurosteroids increase both excitatory and inhibitory transmission. Beyond acting on the cells in which they are produced, neurosteroids cause a reduction in the levels of δ-$GABA_AR$ expressed in parvalbumin expressing interneurons, associated with an increase in the frequency of kainic acid-induced γ-oscillations in CA3 [108]. These effects may result from decreased tonic current in these interneurons [109]. In vivo, neurosteroids have been reported to reduce hippocampal excitability and elevate seizure threshold [65, 66].

The effects of the stress mediators (described above) on the different synapses of the DG-CA3 node are summarized in Figure 2.

Interactions among steroid neuropeptide and neurotransmitter stress mediators

When considering the different stress mediators, it seems that their spatial and temporal domains often overlap, raising the intriguing possibility that these stress-mediators interact with one another. Here we discuss examples of interactions among stress mediators within the hippocampal formation.

CORT and CRH

Exposing hippocampal acute slices concomitantly to presumed stress levels of CORT and CRH for one hour or longer recapitulates the physiological, structural and behavioral effects of stress [110]. These two neuromodulators act synergistically to prevent activation and promote degradation of the actin regulator RhoA and consequently destabilize dendritic spines [110]. These observations highlight the complex interaction that likely occurs during multiple concurrent short stresses or prolonged stress, reducing functional synapse integrity and dampening excitation within the network.

CORT and norepinephrine

Within the hippocampus, CORT enhances norepinephrine function via increased β1-adrenoceptor activation [111]. The consequences of interactions between these two stress mediators on neuronal excitability remain unclear. Interestingly, in the basolateral amygdala, CORT and norepinephrine summate to produce a large increase in mEPSC frequency following their concomitant application [112].

Concluding remarks

This review commenced with the clinical observation that the overall effects of stress are to promote hyper-excitability and seizures generation, especially in people prone to seizures. Elucidating the effects of stress and stress-mediators on hippocampal excitability mandates a full knowledge of the principles governing the excitability of this complex network. These principles are currently only partially understood, and rely on the integration of molecular, synaptic cellular, and network processes, as well as on the use of animal models (Box 4). The review clarified that stress mediators influence every level of this complex system, affecting both inhibitory and excitatory neurotransmission. In addition, time, space, interactions of several stress mediators and complex homeostatic forces come into play in governing hippocampal network excitability [44].

Box 4

Effects of stress on seizure generation in animal models

In people with epilepsy, stress of various types and durations promotes seizures. In the laboratory, effects of individual stress-mediators and of stress have been studied in both naïve and epileptic animals.

In adult rodents, stress has been reported to exert variable effects [9]. Chronic stress promoted seizures [126, 127], whereas swimming produced anti-convulsant effects and

increased seizure threshold [65, 128–130]. Chronic early life stress provoked seizures and epilepsy [11, 12, 131]. For individual stress mediators, CORT was found to increase the rate of kindling and seizure susceptibility [8, 132]. CRH consistently provoked seizures in adult and developing naïve rodents [7, 93–95], whereas DOC increased seizure threshold in epileptic rodents [65, 133–135].

The temporal and spatial effects of individual stress mediators on neuronal excitability are becoming better understood. However, missing in the quest to solve the enigma of the pro-excitant actions of stress is an improved understanding of the concerted actions of all of the stress-activated neuromodulators on the dynamic outputs of the hippocampal network. Specifically, elucidating how individual stress mediators interact mechanistically (e.g. interactions between receptor signaling pathways) in the context of both space and time to modulate function at the synapse and neuron level, and how such effects translate to changes in network-level phenomena will be crucial.

We have highlighted that simple arithmetic summation of the effects of multiple stress mediators - whether through their individual excitatory actions or the impairment of inhibitory mechanisms - are likely insufficient to account for stress-induced increases of seizure probability. Therefore, it seems likely that enhanced seizure susceptibility may result from shifts in network excitability stemming from non-linear interactions between stress-mediators. These may derive from the temporal integration of stress-induced alterations in intrinsic neuronal properties, their influence on the network as a whole, and the balance between excitatory and inhibitory transmission at specific hippocampal nodes [22, 23]. The development of realistic, biophysical models, in conjunction with electrophysiological recordings, should prove crucial in bridging this gap in our knowledge.

Additional important questions for future research, highly relevant to the clinical problem of stress-induced seizure probability in people with epilepsy, include addressing the roles of the age and sex of the individual involved. These factors influence the diverse effects of individual stress mediators upon hippocampal excitability (see Outstanding Questions).

Outstanding questions box

- How do individual stress mediators interact, both at the phenomenological level (spatial and temporal integration) and at the mechanistic level (e.g. interactions among receptor-activated pathways)?
- How do the effects of stress mediators--at the receptor, synapses and neuron level--translate into network-level changes? The development of comprehensive, biophysically relevant modeling is required to address this knowledge gap.
- How do the multiple changes taking place within the epileptic hippocampus influence the effects of stress mediators at the receptor, synapses and neuron level? At the network-level? Modeling is required here as well.

- What are the relative contributions of the specific hippocampal network nodes to the overall network excitability in response to stress? Do these contributions evolve with the duration of the stress?
- Do the age-dependent effects of stress govern the consequences of stress on hippocampal excitability and seizure generation? During development? In the aging hippocampus?
- What are the sex-specific mechanisms for stress-induced modulation of hippocampal excitability and seizure generation?

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Glossary

After-hyperpolarization current (I_{AHP})
a hyperpolarizing current mediated by Ca^{2+}-dependent K^+ channels that follows individual, bursts or trains of action potentials.

Corticosterone (CORT)
a steroid hormone that is synthesized and released from the adrenal cortex in response to stress. This steroid rapidly enters the brain and mediates rapid and slow effects upon neuron function.

Corticotropin-releasing hormone (CRH)
a 44 amino acid peptide that is expressed throughout a number of brain regions and is involved in mediating many of the behavioral and endocrine responses to stress.

Dentate Gyrus (DG)
a region of the hippocampus comprised primarily of granule cells that project to hippocampal area CA3. The DG receives afferent projections from the entorhinal cortex via the perforant path and plays a crucial role in memory processes.

Entorhinal cortex (EC)
an area of the temporal lobe that transfers sensory information from the neocortex to the hippocampus. The EC constitutes the major input to the hippocampal formation via the perforant path and temporoammonic pathways. Neurons in the ventral subiculum project back to layer V/VI pyramidal cells (EC) to complete a feedforward loop between the hippocampus and EC.

Excitatory postsynaptic current (EPSC)
the postsynaptic current resulting from the activation of synaptic receptors by neurotransmitters (e.g. glutamate) that are usually released from a single (miniature [mEPSC]) or multiple vesicles (spontaneous [sEPSC]).

$GABA_A$ receptor ($GABA_AR$)
the γ-aminobutyric acid (GABA) type A receptor is a member of the cys-loop ligand gated ion channel super family that mediates the majority of fast inhibitory neurotransmission. Within the CNS there are ~20–30 $GABA_AR$ isoforms, possessing distinct physiological and pharmacological properties.

Inhibitory postsynaptic current (IPSC)
the postsynaptic current resulting from the activation of synaptic receptors by neurotransmitters (e.g. GABA, glycine) that are usually released from a single (miniature [mIPSC]) or multiple vesicles (spontaneous [sIPSC]).

Mossy Fiber pathway (MF)
mossy fiber axons arise from DG granule cells and travel through the hilus and CA3, in a narrowband termed the stratum lucidium. MF axons form synapses with excitatory and inhibitory cells in the hilus and CA3.

Temporal lobe epilepsy (TLE)
is a prominent form of epilepsy, where seizures originate in the temporal lobe and is prevalent in children, adolescents and adults. This condition is typically associated with hippocampal damage, such as atrophy and gliosis, in humans and animal models of TLE.

Temporammonic pathway
a modest direct projection from the EC to the apical dendrites of CA1 pyramidal cells residing in stratum lacunosum.

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Trends box

- Clinically, stress is the most common predictor of a seizure in people prone to seizures, i.e., people with epilepsy.
- The biological basis of the pro-convulsant actions of stress is unclear.
- The effects of stress evolve over time and at different spatial nodes of the interconnected hippocampal network.
- The effects of stress on hippocampal network excitability are a complex interplay of the individual and concerted actions of several molecules unleashed by stress.

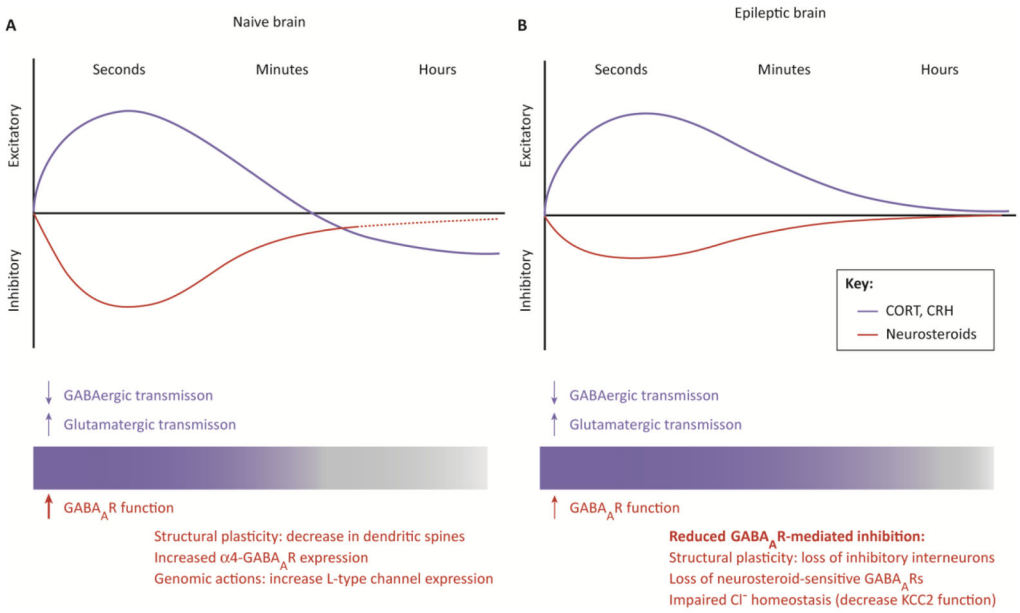

Figure 1. The temporal profile of the excitatory and inhibitory actions of stress mediators: plasticity in the epileptic brain

CORT and CRH rapidly increase excitatory transmission within the hippocampus following stress. These actions are mediated by increasing excitatory transmission, and to a lesser extent reducing inhibitory inputs. Over time (hours) the effects of CORT and CRH become inhibitory, through modulation of gene expression and structural plasticity. Neurosteroids act to rapidly curtail some of the pro-excitatory effects of stress (i.e. CORT, CRH) by enhancing $GABA_AR$-mediated inhibition shortly after stress onset. Under normal conditions such inhibitory mechanisms prevent excessive hippocampal excitability and reduce the risk of seizures (A). However, in the epileptic brain (B), the loss of inhibitory interneurons, alterations in $GABA_AR$ subtype expression and impaired Cl^- homeostasis, results in reduced stress-induced inhibition of the hippocampus and increases the risk of seizures.

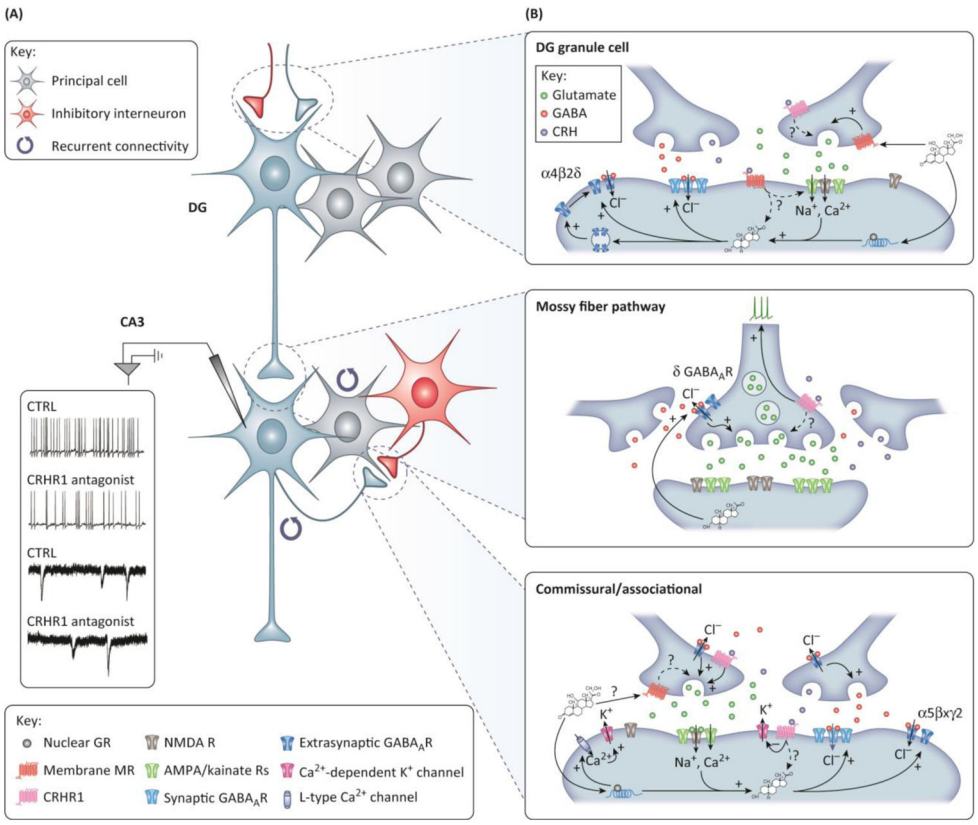

Figure 2. Stress mediators exert synapse-specific effects upon excitatory and inhibitory transmission at the DG-CA3 node

A. Simplified schematic representation of the DG-CA3 node comprised of principal cells (grey) and inhibitory interneurons (red). Inset illustrating the effects of endogenous CRH upon CA3 pyramidal spiking and the generation of sharp waves demonstrates how subtle alteration sin neurotransmission at the single cell level can influence network processes (adapted from [55]). **B.** The effects of stress mediators upon excitatory and inhibitory transmission at specific synapses within the DG-CA3 node. Note that unknown or postulated effects are additionally highlighted.