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Molecular Determinants Mediating Effects of Acute Stress on Hippocampus-Dependent Synaptic Plasticity and Learning

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Abstract

The understanding of the molecular events underlying the neuroendocrine and behavioral sequelae of the response to stress has advanced rapidly over recent years. The hippocampus is a target of stress hormones, and we are beginning to dissect the molecular players in the modulation of synaptic plasticity and learning and memory involving this region of the brain. Given the wealth of data obtained from electrophysiological and behavioral experiments and in view of the importance to use identical experimental protocols in order to correlate the results obtained under both experimental conditions, this review focuses primarily on those contributions, which combine both approaches. From these studies it is evident that a single stressful event elicits responses in the hippocampus with different time-spans ranging from rapid changes in glutamatergic neurotransmission (i.e., *N*-methyl-D-aspartate receptor signaling), activation of second messenger cascades by corticotropin-releasing factor to long-lasting transcriptional changes of acetylcholinesterase. The relative contribution of these molecular targets to the stress response, the relation to hippocampal synaptic plasticity and memory formation, and the possible interaction of the underlying processes are discussed.

Index Entries: Hippocampus; stress; LTP; CRF; glutamate; AChE; learning; memory; priming; NMDA.

Introduction

Exposure to threatening conditions results in a series of coordinated responses organized to enhance the probability of survival. These coordinated responses, often referred to as "stress responses," are composed of alterations in behavior, autonomic function, and the secretion of multiple hormones *(1)*. Activation of the hypothalamic-pituitary-adrenal (HPA) axis is the main defining feature of the stress response. In the present review, we concentrate on the

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hippocampus, a critical component of the neuroanatomical stress circuit *(2)* which is also involved in forming episodic, spatial, and contextual memories *(3–7).* A general conclusion from many observations is that acute stress can affect hippocampus-dependent memory in entirely opposite directions, depending on experimental conditions such as type and duration of the stressor, learning task, and animal species *(8).* For example, stressed rats show impaired spatial working memory in the radial arm water maze *(9,10)* and deficits in object recognition memory *(11).* These learning paradigms both depend on intact hippocampus *(12,13).* On the other hand, acute stress was found to improve context-dependent fear conditioning in BALB/c mice *(14,15)* and trace eyeblink conditioning in rats *(16).* In parallel to these behavioral findings, it was observed that stress impairs long-term potentiation (LTP), a long-lasting, use-dependent modification of synaptic strength, induced by high-frequency stimulation *(17,18).* LTP may be a cellular substrate of learning and memory *(19,20).* Stress also impairs primed burst potentiation (PBP), a low-threshold form of synaptic plasticity, in the hippocampus in vitro *(21).* Numerous studies demonstrate that stress consistently favors the induction of long-term depression (LTD) which is characterized by a decrease in synaptic efficacy following low-frequency stimulation of afferent fibers *(22,23).* Interestingly, LTP elicited by theta-burst stimulation (TBS) in hippocampal brain slices from stressed mice is facilitated whereas LTP induced by high-frequency stimulation (HFS) is impaired *(14).* While different conditions of behavioral experiments resulted in controversial data about the impact of stress on learning and memory, a great part of the reported contradictory data on changes in synaptic plasticity after stress may be due to different stimulation protocols used to elicit LTP.

The following review describes in more detail some of the molecular components, which mediate the complex neurobiological response to stress, especially the effect of acute stress in contrast to chronic stress, with functional significance for the hippocampus. In particular, excitatory amino acids and *N*-methyl-D-aspartate (NMDA) receptors, as well as corticotropin-releasing factor (CRF) and acetylcholinesterase (AChE) have been identified to interfere with hippocampus-dependent synaptic plasticity, learning, and memory after an acute stressful experience as reported in studies combining behavioral with electrophysiological approaches.

N-Methyl-D-Aspartate (NMDA) Receptors

The *N*-methyl-D-aspartate (NMDA) receptor, which represents a subtype of the glutamate receptor family, is thought to be involved in multiple physiological processes including the stress response. Activation of glutamatergic neurotransmission during acute stress exposure was demonstrated by microdialysis studies showing a rise in extracellular levels of glutamate mainly in the hippocampus and prefrontal cortex *(24,25).* However, the role of NMDA receptors in stress-induced effects on hippocampal plasticity and learning and memory is still under debate.

Immobilization induces significant changes in specific NMDA receptor subunit mRNA 24 h after stress exposure. This may be involved in the altered hippocampal responsiveness to glutamate *(26).* Kim and colleagues *(27)* reported that their stress paradigm consisting of restraint combined with multiple tailshocks impairs HFS-LTP and enhances LTD in the CA1 area of the adult rat hippocampus. These effects on HFS-LTP and LTD are prevented by CGP39551, a competitive NMDA receptor antagonist, injected before the stress session *(27).* The same stress paradigm also markedly impairs hippocampal-dependent object-recognition memory, as tested on the visual paired comparison task (VPC) in rats *(11).* VPC is an object-recognition task that utilizes the rat's natural tendency to explore novel stimuli *(28).* This task is nonspatial in nature and is viewed as an object-recognition task without aversive association *(29).* Similar to

stress, microinfusions of DL-2-amino-5-phosphonovaleric acid (APV), a competitive NMDA receptor antagonist which blocks HFS-LTP, into the dorsal hippocampus selectively impairs object-recognition memory *(11).* From these studies, it might be concluded that stress affects recognition memory by influencing synaptic plasticity in the hippocampus, and this appears to be mediated by the activation of the NMDA receptor subtype of the glutamate receptor.

Corticotropin-Releasing Factor

An early signal in the response to stress is corticotropin-releasing factor (CRF), a 41-residue peptide acknowledged as the principal hypophysiotropic factor driving stress-induced adrenocorticotropic hormone (ACTH) secretion and subsequent elevation of circulating glucocorticoids *(30).* During exposure to stress, CRF production is preferentially elevated in CRF-producing neurons of the parvicellular hypothalamic paraventricular nucleus *(31),* but large CRF-immunoreactive neurons have also been found in the hippocampal CA1 and CA3 region *(32,33).* Application of human/ratCRF (h/rCRF) to hippocampal slices has been shown to reduce the slow afterhyperpolarization and spike frequency accommodation *(34–36)* and to enhance the amplitude of CA1 population spikes evoked by stimulation of the Schaffer collateral pathway in rats *(37)* and mice *(14).* In vivo h/rCRF produces a long-lasting enhancement of synaptic strength in rat hippocampus *(38,39).* h/rCRF application-like exposure to an acute stressor facilitates (primes) persistence of TBS-induced LTP in brain slices from the hippocampus of the BALB/c mouse *(14)* and enhances context-dependent fear conditioning of this strain *(14,15).* Both the priming of LTP and the improvement of context-dependent fear conditioning are prevented by the CRF receptor antagonist [$Glu^{11,16}$] astressin and by the protein kinase C inhibitor bisindolylmaleimide I *(14).* It is consistent with the enhancement of hippocampal-specific learning upon CRF receptor activation that CRF_1-null mutant mice are deficient in spatial recognition memory *(40).* Interestingly, the effect of CRF appears to be highly dependent on the difficulty of the learning task. Under difficult learning conditions (massed trials), intracerebroventricular (icv) injection of h/rCRF or rat urocortin (rUcn), a CRF homolog *(41),* facilitates the acquisition of spatial navigation in the Morris water maze. In contrast, both peptides impair water maze performance under less difficult learning conditions (spaced trials) *(42).* The effect of CRF on hippocampus-dependent forms of learning and memory does not only depend on the learning task difficulty, but also on the transductional pathway activated by the CRF receptor *(36).* While h/rCRF increases neuronal activity of pyramidal cells of the CA1 region in slices from BALB/c and C57BL/6N mice, inhibition of protein kinase C (PKC) prevents the h/rCRF effect only in slices from BALB/c, but not C57BL/6N mice. On the other hand, inhibition of cAMP-dependent protein kinase (PKA) abolishes the h/rCRF effect in pyramidal neurons from C57BL/6N mice with no effect in slices from BALB/c mice. Accordingly, h/rCRF elevates PKA but not PKC activity in hippocampal slices from C57BL/6N mice. In the hippocampus of BALB/c mice, PKC activity is increased, whereas PKA activity is decreased. In hippocampal membrane suspensions from BALB/c mice, CRF receptors couple to $G_{q/11}$ upon stimulation by h/rCRF, whereas hippocampal CRF receptors couple to G_s, $G_{q/11}$ and G_i in C57BL/6N mice. The differences in G protein coupling are also reflected on the behavioral level as indicated by the observation that intrahippocampal injection of h/rCRF improves context-dependent fear conditioning in BALB/c mice, but has no effect in C57BL/6N mice *(36).*

Acetylcholinesterase

In the hippocampus, stress initially induces cholinergic activation *(43)* followed by a feedback response retrieving neural activity through acetylcholinesterase (AChE) overproduction *(44).* Thus, cholinergic elements are

involved in the response to stress. Of the key cholinergic regulation elements, AChE possesses both catalytic and neuronal plasticity activities *(45).* The AChE gene produces several types of coding sequences differing in an alternative choice of splice acceptor sites in the 3′ region of the primary transcript. This process generates catalytic subunits, which contain the same catalytic domain, associated with distinct C-terminal peptides *(46).* Soreq and colleagues observed hippocampal overproduction of the normally rare type R ("readthrough") AChE variant following multiple forms of stress (e.g., anticholinesterase exposure, confined swim, head injury, circadian switch or a single intraperitoneal injection) *(44,47–49).* At extracellular sites, AChE-R reduces the stress-induced acetylcholine levels *(44).* However, AChE-R also accumulates in neuronal cell bodies where the presence of acetylcholine is unlikely. Therefore, AChE-R may be involved in functions other than the classical hydrolysis of acetylcholine. The increase of hippocampal AChE-R protein following immobilization of mice is accompanied by intensified contextual fear conditioning and facilitated TBS-LTP in the hippocampal CA1 area *(50).* These stress effects are prevented by the prior treatment of mice with antisense probes directed against AChE-R. Further evidence supporting a role of AChE in hippocampus-dependent learning and memory is provided by studies with transgenic mice overexpressing synaptic human AChE. These mice show a rapid age-dependent decline of learning in the hidden platform water maze *(51,52),* a spatial learning task that requires an intact hippocampus *(53,54).* The memory deterioration of these mice suggests that old animals are no longer able to fully compensate for a cholinergic imbalance *(55).* Untreated transgenic mice further present variable intense neuronal overexpression of mouse AChE-R mRNA in several areas including the hippocampus *(56).* It can be hypothesized that at appropriate levels AChE-R accumulation in response to stress restores normal cholinergic activity but when AChE-R levels increase beyond a certain level the cholinergic system might not be able anymore to respond, and pathological states may be reached. In mice the stress-induced splice variant AChE-R interacts neuronally with the scaffold protein RACKI and through it, with its target, protein kinase CβII *(47).* Since PKCβII is known to be essential for fear conditioning *(57),* the signaling cascade AChE-R/RACKI/PKCβII is thus a possible pathway to be involved in the stress-induced changes in hippocampus-dependent learning and memory *(14).*

Conclusion

Exposure to stress has been shown to alter synaptic plasticity in the hippocampus and to interfere with hippocampal-dependent memory. Can we speculate then that stress affects hippocampal memory via impacting hippocampal plasticity?

As mentioned above, acute stress impairs spatial memory *(22)* and long-delay object-recognition memory *(11)* but has been observed to facilitate trace eyeblink conditioning *(16,58)* and contextual fear conditioning *(14,15).* While stress exerts differential effects on different kinds of hippocampal learning and memory, the experience of stress consistently impairs HFS-LTP in the hippocampus. We have confirmed that acute stress impairs hippocampal HFS-LTP but demonstrated that it facilitates LTP elicited by weak TBS *(14).* This priming effect is similar to the facilitation of TBS-LTP persistence observed after activation of group I metabotropic glutamate receptors (mGluRs) or muscarinic receptors *(59–64).* To date, no relation has been found between NMDA-receptor activation and TBS-LTP facilitation. Activation of mGluR enhances NMDA receptor function, which persists only during mGluR activation *(65–67).* In view of the finding that facilitated TBS-LTP outlasts the enhancement of NMDA receptor-mediated responses, Cohen and Abraham (1996) propose that this form of metaplasticity is NMDA-receptor independent. Again, the LTP stimulation protocol is crucial since LTP priming is

absent when high-frequency stimulation is applied *(60).* However, during stress exposure NMDA receptor-dependent changes occur, which result in impaired HFS-LTP in the hippocampal CA1 region *(27).* It appears conceivable that stress induces LTP or LTP-like phenomena in the hippocampus and thereby impairs further LTP induction *(27).* In support of this assumption, it has been observed that CRF injected into the hippocampus of rats produces a dose-dependent and long-lasting enhancement in synaptic efficacy *(39).* This effect of CRF is partially blocked by the NMDA receptor antagonist MK-801. During a stressful event CRF receptor signaling and the stress-related AChE-R variant both seem to converge at the activation of PKC in the hippocampus *(36,47).* The two mechanisms differ in the duration of their impact. Whereas the impact of CRF diminishes within hours *(14),* the elevated levels of AChE-R can be detected even weeks after the stress experience *(48).*

It is concluded that the modulation of different forms of LTP by stress might provide a cellular substrate for the stress-mediated modulation of specific hippocampal-dependent forms of memory. Indeed, our data show a significant correlation between stress-mediated improvement of contextual fear conditioning and facilitation of TBS-induced LTP. Both phenomena appear to depend on activation of the CRF receptor and PKC *(14),* as well as on the production of AChE-R *(50).*

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