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Stress, Hippocampal Plasticity, and Spatial Learning

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ABSTRACT During the last two decades numerous studies have been conducted in an attempt to correlate the mechanisms of long-term potentiation (LTP) of hippocampal synaptic transmission with those required for spatial memory formation in the hippocampus. Because stressful events block the induction of hippocampal LTP, it has been suggested that deficits in spatial learning following stress may be related to suppression of LTP-like phenomena in the hippocampus. Here I review these studies and discuss them in light of the emerging view that stress may induce changes in thresholds for synaptic plasticity necessary for both LTP induction and spatial memory formation. This phenomenon, known as metaplasticity, may involve a glucocorticoid modulation of calcium homeostasis. **Synapse 40:180–183, 2001.** © 2001 Wiley-Liss, Inc.

INTRODUCTION

The hippocampus is considered an important brain structure for the treatment of spatial information (O'Keefe and Nadel, 1978). For example, lesion studies have shown that damage to the hippocampus in rats impairs the acquisition and retrieval of information required to navigate in spatial mazes (Jarrard, 1978; Morris et al., 1982). Electrophysiological studies in rats have indicated that neurons in the hippocampus fire in a location-specific manner during spatial exploration (O'Keefe and Nadel, 1978; Muller et al., 1987). Studies in humans suggest that the hippocampus participates in the formation of a spatial representation of the environment (Maguire et al., 2000). In this context, recent studies indicate that the role of the hippocampus in long-term memory storage is transient (Bontempi et al., 1999; Ramos, 2000; Teng and Squire, 1999). However, the mechanisms by which hippocampal circuits enable memory trace formation and transient storage remain to be elucidated.

Memory storage is widely believed to involve long-term changes in synaptic strength (Hebb, 1949). In the hippocampus, a long-lasting enhancement of synaptic efficacy, following a brief tetanic stimulation of afferent fibers, was reported almost 30 years ago (Bliss and Lomo, 1973; Bliss and Gardner-Medwin, 1973). This phenomenon, LTP, has been widely proposed to serve as a mechanism by which synapses are strengthened in the course of hippocampal-dependent (spatial) learning tasks. Various experimental approaches have been used to investigate whether the mechanisms underlying hippocampal LTP are also activated during spatial learning. A number of these studies were designed to study the effects of stress on hippocampal plasticity.

Conclusions drawn from these studies in rats support the notion that stressful events impair both LTP induction in the hippocampus (Diamond et al., 1990, 1992; Foy et al., 1987; Mesches et al., 1999; Shors et al., 1989) and spatial memory formation (Diamond et al., 1996; Healy and Drugan, 1996; Krugers et al., 1997; Stillman et al., 1998; Thomas et al., 1991).

In this review, I first describe the effects of physical and psychological stress on hippocampal LTP induction, then describe the effects of stress on spatial learning, and finally comment on potential cellular mechanisms by which stress may regulate hippocampal synaptic plasticity.

STRESS-INDUCED SUPPRESSION OF LTP INDUCTION

LTP induction

LTP is a persistent increase in synaptic efficacy that can be induced following specific stimulation of afferent fibers. In most studies, conventional LTP stimulation consists of a train of 100 pulses delivered in 1 sec. In other studies, the tetanus is patterned after the theta rhythm in a manner also known as theta-burst stimulation (Larson et al., 1986; Pavlides et al., 1988). A third paradigm is primed-burst stimulation, which consists of five pulses presented in a pattern that mimics features of hippocampal physiology (Diamond et al., 1988). The primed-burst potentiation is also considered a low-threshold form of hippocampal LTP.

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LTP impairment

An impairment in LTP induction has been observed following either exposure to physical stressors, such as restraint and intermittent tailshock, or behavioral manipulations inducing psychological stress, such as exposure to novelty and being placed in close proximity to a predator.

Foy et al. (1987) reported an early finding of stress-induced alteration of hippocampal plasticity. Specifically, marked impairment of LTP induction was observed in hippocampal slices prepared from rats exposed to physical stress. Other authors later confirmed these data both in rats (Kim et al., 1996; Shors et al., 1989) and mice (Garcia et al., 1997). In mice, LTP induction was impaired in slices prepared both at 1 h after acute stress as well as 24 h later (Garcia et al., 1997). From this study, it was shown that there is a long-term effect of physical stress on hippocampal CA1 synaptic transmission. Complete recovery of LTP induction was observed 48 h after stress exposure (Garcia et al., 1997). However, in a similar study using rats LTP still remained impaired 48 h after cessation of stressors (Shors et al., 1997). In this latter case, 4 days were necessary to obtain complete recovery of LTP induction. Physical stress might therefore interfere with mechanisms required for hippocampal LTP induction.

A closer analysis of stress-induced impairment in hippocampal functioning has been provided by studies designed to analyze the effects of psychological stress on primed-burst stimulation that induces the low-threshold form of hippocampal LTP. Primed-burst potentiation was suppressed in freely moving rats exposed to natural stressors, such as an unfamiliar environment (Diamond et al., 1990, 1994). The same form of LTP was blocked in hippocampal slices prepared from rats exposed to a cat (Mesches et al., 1999). In conjunction with studies on primed-burst potentiation, other research indicates that psychological stress resulting from an unfamiliar environment blocked the development of conventional LTP (Xu et al., 1997), while psychological stress induced by instinctual fear of a predator had no effect on the same form of LTP (Mesches et al., 1999). When these studies are evaluated together, they indicate that LTP resulting from stimulation that better mimics hippocampal physiology is more sensitive to psychological stress than LTP elicited by conventional stimulation.

STRESS-INDUCED IMPAIRMENT OF SPATIAL LEARNING

Hippocampal-dependent spatial learning tasks

One of the behavioral tasks used to demonstrate a spatial deficit in rodents is the "place" version of the open-field water maze. In this task, rats or mice learn to locate a hidden platform (place) by swimming to it from several different starting points around the perimeter of a circular pool. Animals with hippocampal lesions perform poorly in this task (Morris et al., 1982). Spatial learning can also be examined by means of delayed recognition radial maze task in which an arm choice is considered correct if the animal enters a target arm in which it receives a food pellet as a reward. In this type of spatial working memory task, which is dependent on the hippocampus (for review, see Barnes, 1988), the animal is required to remember which of the arms had been previously visited within a session.

Spatial learning impairment

Recently, the degree to which stress caused by exposure to novel situations can interfere with learning a spatial water maze task was investigated. It was found that nonhandled rats learned the water maze task more slowly than handled ones (Hölscher, 1999). In another study, in which the rats were exposed to a 6-month period of social stress and then subjected to the water maze task, a transient impairment of spatial learning ability was observed (Bodnoff et al., 1995).

Stress also affects radial maze learning performance. For example, Diamond et al. (1996) demonstrated that placing rats in an unfamiliar and stress-provoking environment impaired spatial working memory in a radial maze. With repeated daily exposure to this environment, their memory impairment abated. Nishimura et al. (1999) showed that chronic stress exposure (immersion up to the neck in cold water for 15 min daily over 12 weeks) also impaired radial maze learning performance in rats. In addition, impairment of learning performance could be observed even after a 4-week recovery period following a long-term stress exposure (Nishimura et al., 1999). Based on these behavioral studies, the long-term effects of stressful events on spatial learning performance are clearly demonstrated.

CELLULAR MECHANISMS

Stress is known to result from stimuli that disrupts the homeostasis of the organism. Stressful signals, which reach the brain following transduction (sensorial or endocrine-neural) into neural signals and psychological components of stress, can alter the strength of synaptic transmission in the hippocampus in a long-lasting manner. The cellular mechanism by which stress impairs synaptic functions is not fully understood. However, glucocorticoids are thought to mediate the mechanisms by which stress might impair synaptic transmission properties required for both LTP in CA1 area and hippocampal-dependent (spatial) learning tasks.

First, glucocorticoids (principally corticosterone in rodents) are released from the hypothalamic pituitary-adrenal system during stress. The release of glucocorticoids represents one of the central adaptive mechanisms under conditions that threaten homeostasis.

However, continued exposure to elevated circulating glucocorticoid levels can constitute a serious risk for the organism. Thus, following stressful conditions it is in the animal's best interest to terminate the release of adrenal glucocorticoids. Hence, circulating glucocorticoids exert negative feedback onto specific brain regions in order to inhibit further release (McEwen, 1982; Plotsky et al., 1986). Most important among these regions is the hippocampus. It is known that hippocampal lesions are associated with elevated corticosterone levels in response to stress (Sapolsky et al., 1984). Since the hippocampus is rich in corticosteroid receptors, it is assumed that this structure is involved in the inhibitory influence of glucocorticoids over adrenocortical activity (Meaney et al., 1991).

Second, one of the effects of a prolonged elevation of glucocorticoid levels is disruption of hippocampal function. For example, morphological studies have shown that elevation of glucocorticoid levels causes selective atrophy of apical dendrites from CA3 pyramidal neurons (Magarinos and McEwen, 1995; Watanabe et al., 1992). Joëls and de Kloet (1989) carried out electrophysiological studies and demonstrated that glucocorticoids produce a reduction in hippocampal excitability. These data support, in part, the idea that stress-induced impairment of hippocampal LTP induction is related to stress-induced depression in hippocampal excitability (Garcia et al., 1998). This concept is also supported by direct studies of the effects of glucocorticoids on hippocampal LTP which showed that both acute and chronic administration of glucocorticoids resulted in a reduction of the expression of hippocampal LTP (Bennett et al., 1991; Diamond et al., 1992; Pavlides et al., 1993). Behavioral studies using a hippocampal-dependent task also provided convincing support for the negative effects of corticosterone on spatial learning. Specifically, Bodnoff et al. (1995) reported that in middle-aged rats (12 months of age) a 3-month treatment period of exposure to levels of corticosterone, which are routinely observed in stress, profoundly impaired spatial memory performance in the Morris water maze.

Changes in calcium homeostasis may also potentially contribute to the glucocorticoid-induced impairment of hippocampal synaptic functions. Induction of synaptic plasticity involves a rise in intracellular Ca^{++} concentration. At the hippocampal CA3–CA1 synapses, Ca^{++} ions enter the postsynaptic cell by two types of channels, one being the *N*-methyl-D-aspartate (NDMA) receptor-associated channel. At resting potential or during low-frequency stimulation of the Schaffer collaterals, the NMDA receptor channels are blocked by Mg^{++} ions (present extracellularly). However, during high-frequency stimulation the Mg^{++} block of the NMDA channels is reduced by depolarization, enabling Ca^{++} ions to permeate these channels. The other type of calcium channel is the voltage-dependent Ca^{++} channel (VDCC). However, activation of VDCC is followed by a K^{+}-mediated hyperpolarization, which participates in afterhyperpolarization (AHP). It is known that glucocorticoids increase Ca^{++}-dependent AHP in hippocampal neurons (Joëls and de Kloet, 1989). In addition, a large AHP has profound effects on voltage-dependent events that are required for LTP induction (Sah and Bekkers, 1996).

Consequently, stress may block LTP induction by altering Ca^{++} regulation. More specifically, prior activation of hippocampal glucocorticoid receptors by stress can alter the capacity of hippocampal synapses to undergo plastic changes in response to later stimuli. This phenomenon has been termed metaplasticity (Abraham and Bear, 1996). According to the original theory, also known as the Bienenstock-Cooper-Munro model or BCM theory (Bienenstock et al., 1982), presynaptic activity associated with low levels of postsynaptic activity results in long-term depression (LTD), while presynaptic activity associated with high levels of postsynaptic activity results in LTP. Stress may induce an increase in VDCC activity, which in turn may produce a shift in the thresholds for synaptic modifiability with a reduced threshold for LTD induction and an increased threshold for LTP induction. This hypothesis readily explains why LTD induction is facilitated by stressful events (see Kim et al., 1996; Xu et al., 1997), whereas LTP induction is impaired (Diamond et al., 1990, 1992; Foy et al., 1987; Garcia et al., 1997, 1998; Shors et al., 1989, 1997). The metaplasticity effect of stress has also been widely discussed in a recent review by Kim and Yoon (1998). The authors postulate that an extreme shift in the threshold for synaptic modifiability, in the direction of LTD facilitation, may aggravate neuronal death in the hippocampus by affecting Ca^{++} buffering.

CONCLUSION

The electrophysiological data described here demonstrate that hippocampal LTP and spatial memory formation may share certain cellular mechanisms that are impaired by stress. Specifically, following a stressful situation the magnitude and direction of changes in hippocampal synaptic functions required for both LTP and spatial learning can be influenced by the amplitude of the effects induced by Ca^{++} regulation.

Even if the cellular mechanisms involved in stress-induced regulation of hippocampal synaptic plasticity (possibly through the cellular effects of glucocorticoids) are not yet clearly understood, the BCM theory provides future directions for investigating the relationships between the LTP phenomenon and spatial memory formation. Although several lines of evidence support the glucocorticoid hypothesis of stress effects on learning and hippocampal plasticity, Foy et al. (1987) also suggest that there are many other neurochemical and endocrine responses to stress that may be

responsible for impairment of long-term neuronal plasticity in the hippocampus.

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