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LINEAR AND NON-LINEAR DOSE-RESPONSE FUNCTIONS REVEAL A HORMETIC RELATIONSHIP BETWEEN STRESS AND LEARNING

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□ Over a century of behavioral research has shown that stress can enhance or impair learning and memory. In the present review, we have explored the complex effects of stress on cognition and propose that they are characterized by linear and non-linear dose-response functions, which together reveal a hormetic relationship between stress and learning. We suggest that stress initially enhances hippocampal function, resulting from amygdala-induced excitation of hippocampal synaptic plasticity, as well as the excitatory effects of several neuromodulators, including corticosteroids, norepinephrine, corticotropin-releasing hormone, acetylcholine and dopamine. We propose that this rapid activation of the amygdala-hippocampus brain memory system results in a linear dose-response relation between emotional strength and memory formation. More prolonged stress, however, leads to an inhibition of hippocampal function, which can be attributed to compensatory cellular responses that protect hippocampal neurons from excitotoxicity. This inhibition of hippocampal functioning in response to prolonged stress is potentially relevant to the well-described curvilinear dose-response relationship between arousal and memory. Our emphasis on the temporal features of stress-brain interactions addresses how stress can activate, as well as impair, hippocampal functioning to produce a hormetic relationship between stress and learning.

Keywords: hippocampus, amygdala, corticosterone, dose-response, stress, memory

INTRODUCTION

Extensive work has shown that, depending on several factors, stress can enhance or impair learning and memory. A major challenge that faces investigators in the field of stress-memory interactions is to explain the cellular and molecular mechanisms by which such a complex relationship between stress and memory exists. One possible explanation is that the effects of stress on brain memory systems follow a hormetic, biphasic dose-response pattern, where low levels or brief periods of stress stimulate and enhance memory mechanisms, while high levels or pro-

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longed periods of stress inhibit these mechanisms (Calabrese and Baldwin 2002). Hormetic dose-response functions have been well documented in toxicology research, where a number of chemical substances that have harmful, toxic effects at high doses (e.g., arsenic, alcohol) can produce decidedly non-toxic, and even beneficial, effects at low doses (Calabrese *et al.* 1999). In the current review, we will discuss how stress interacts with learning to either enhance or impair memory and how the relationship between the amount of stress and its effects on cognitive processes depends on the interactions of factors related to the stressor, the learning experience and the brain memory systems activated by the learning experience.

PHYSIOLOGICAL SYSTEMS ACTIVATED BY STRESS

It is essential for stressors to rapidly activate physiological systems which enable an individual to survive a threat to its survival. To accomplish this goal, stressors activate two primary physiological systems, the sympathetic-adrenomedullary system and the hypothalamus-pituitary-adrenal (HPA) axis. Activation of the sympathetic-adrenomedullary system leads to a rapid release of epinephrine (EPI) and norepinephrine (NE) from the adrenal medulla, which mobilizes metabolic resources that are necessary for the fight-or-flight response (Gunnar and Quevedo 2007). Activation of the HPA axis, on the other hand, is a slower response that eventually leads to the release of corticosteroids from the adrenal cortex (de Kloet *et al.* 1999; Joels 2001). An important function of corticosteroids is to act as a homeostatic mechanism and regulate the stress response by exerting negative feedback inhibition on brain structures involved in the HPA axis and by inhibiting sympathetic nervous system (SNS) activity (Kvetnansky *et al.* 1993; Brown and Fisher 1986; Komesaroff and Funder 1994).

The hippocampus is a medial temporal lobe structure that plays a significant role in declarative memory in humans (Squire *et al.* 2004; Eichenbaum 2004; Eichenbaum 2006) and spatial working memory in rodents (Moser and Moser 1998; Kaut and Bunsey 2001; Broadbent *et al.* 2004; Moses *et al.* 2005; Winocur *et al.* 2005; Broadbent *et al.* 2006). Bruce McEwen and colleagues first reported that the hippocampus contains more corticosteroid receptors than any other brain region, making it highly susceptible to the effects of stress (McEwen *et al.* 1968; McEwen *et al.* 1969; McEwen and Weiss 1970). There are two types of corticosteroid receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), both of which are widely distributed throughout the hippocampus (McEwen *et al.* 1994; de Kloet *et al.* 1999; Joels 2001). The MR has a very high affinity for corticosteroids and is thus almost fully saturated under baseline physiological conditions, while the GR has one-tenth the affinity for corticosteroids as the MR and thus only becomes exten-

sively occupied when there is an increase in circulating levels of corticosteroids, such as that which occurs during stress. Most MRs and GRs are located in the intracellular space and, when bound by corticosteroids, act as nuclear transcription factors to alter gene expression. However, recent work has indicated that corticosteroids can also bind to membrane-bound receptors and exert nongenomic effects on cellular activity (Karst *et al.* 2005; Wiegert *et al.* 2006). These nongenomic effects have become increasingly important in our understanding of the cellular and molecular mechanisms by which stress affects learning and memory.

THE DOSE-RESPONSE FUNCTIONS BETWEEN STRESS AND LEARNING

Research has shown that, as Yerkes and Dodson originally described (Yerkes and Dodson 1908), the effects of stress on learning depend upon the interaction of factors related to the stressor, the learning experience and the subject under investigation (Joels *et al.* 2006; Kim *et al.* 2006; Sandi and Pinelo-Nava 2007; Lupien *et al.* 2007). For example, acute periods of stress or elevations of corticosteroids may enhance or impair hippocampus-dependent learning and memory, while leaving hippocampus-independent learning and memory, such as reference (long-term) memory, unaffected (Diamond *et al.* 1996; Kirschbaum *et al.* 1996; Diamond *et al.* 1999; Woodson *et al.* 2003). With regards to hippocampus-dependent tasks, investigators have often reported an inverted U-shaped relationship between stress and learning. In human and rodent work, acute stress or corticosteroid administration dose-dependently influences declarative and spatial memory, with short periods of stress or low doses of corticosteroids enhancing (Lupien and McEwen 1997; Cahill *et al.* 2003; Diamond *et al.* 2007) and longer periods of stress or high doses of corticosteroids impairing (Healy and Drugan 1996; Kirschbaum *et al.* 1996; Lupien and McEwen 1997; Richter-Levin 1998; Klenerova, V *et al.* 2002; Elzinga *et al.* 2005; Diamond *et al.* 2006) these processes. Studies in humans and rodents have shown that exposure to laboratory stressors of a prolonged duration (typically longer than 20 minutes) before or after learning can impair the recall of information. On the other hand, brief periods of stress (typically less than 5 minutes) before or after learning can enhance the recall of information. Importantly, this enhancement of memory is dependent on the temporal proximity of the stressor to the learning experience. Brief periods of stress can enhance the consolidation of hippocampus-dependent memories if they are administered *immediately* prior to or after learning. But stress may have no effect on, and in some cases impair, long-term memory if there is a substantial delay between the initiation of the stressor and learning. These findings are consistent with the suggestion by Joels and colleagues (Joels *et al.* 2006) that the stressor and learning experience must converge in time for memory to be enhanced by stress.

Joels and coworkers proposed that, to enhance learning, the stressor must not only occur around the time of the learning experience, but also within the context of the learning experience (Joels *et al.* 2006). The ability of stress to facilitate learning when it occurs in the context of the learning experience is clearly evident by the existence of flashbulb memories, which are characterized by an unexpected and evocative event enhancing the storage of neutral, otherwise forgettable, information (Brown and Kulik 1977). These memories, such as those regarding the terrorist attacks on September 11, 2001, are so strong that they can last a lifetime and, in some cases, become pathological (e.g., post-traumatic stress disorder). In the case of flashbulb memories, the stressor fulfills both of the criteria set forth by Joels and colleagues (Joels *et al.* 2006)—that is, the stressor occurs closely in time and in the same context as the explicit learning experience.

Researchers studying stress-memory interactions have differentiated between the effects of extrinsic stressors and intrinsic stressors on learning (Joels *et al.* 2006; Sandi and Pinelo-Nava 2007). Extrinsic stressors are stressors that are outside the context of the learning experience, while intrinsic stressors are a component of the explicit learning experience. Although intrinsic stress is typically beneficial to learning and enhances long-term memory, it can also have deleterious effects on cognition if present for a long enough duration and at a large enough magnitude (Sandi and Pinelo-Nava 2007). For instance, although people who experience trauma, such as rape or wartime combat, often have vivid, detailed memories for various aspects of the event, there are some cases in which these individuals develop traumatic amnesia for certain parts of, or even the entire, traumatic incident (Joseph 1998; Joseph 1999). In rodent work, investigators have manipulated the water temperature in the water maze to examine the influence of intrinsic stress on spatial learning. The results of these manipulations have shown that rats trained in relatively cold (i.e., 19°C) water exhibited greater corticosteroid levels (suggestive of a greater stress response) and better memory than rats trained in warmer (i.e., 25°C) water (Sandi *et al.* 1997). However, rats trained in *extremely* cold water (12°C) demonstrated impaired memory, suggesting an overall inverted U-shaped relationship between the intrinsic stressfulness of the task and spatial memory (Selden *et al.* 1990). Thus, although intrinsic stress can be beneficial to learning, it can have adverse effects on these processes as well.

Joels and colleagues proposed that stressors which are outside the context of another learning experience (i.e., extrinsic stressors) can enhance learning and memory as long as the stressor is in close temporal and spatial proximity to the learning experience. But is it necessary for both space and time to overlap for an animal to generate a flashbulb memory? Can stress occurring in one environment enhance memory for

events occurring in another environment? We tested this possibility in recent work in which rats were stressed in one environment (exposed to a cat—predator stress) and were then given water maze training in another environment (Diamond *et al.* 2007). We found that brief (2-minute) cat exposure administered just prior to water maze training (which occurred in another environment) enhanced long-term (24-hour) spatial memory in the water maze. The enhancement of long-term spatial memory was evident only when cat exposure occurred immediately before training and not when 2 minutes of cat exposure occurred 30 minutes before water maze training. This finding indicated that the brief stress experience had to occur close in time with the learning experience to enhance memory consolidation, but it did not need to occur in the same environment as the explicit learning experience to enhance long-term spatial memory.

We would suggest that the stress-induced enhancement of memory, as is found in flashbulb memories or in the cat stress-induced enhancement of spatial memory, follows a linear dose-response function. Thus, the magnitude of the stress-induced enhancement of a simple learning experience increases linearly as the stressor intensity and corticosteroid levels increase. For more complex learning tasks, especially those that involve great cognitive demands which require prefrontal cortex activity, high levels of stress would interfere with performance. In this case, the true hormetic relationship between stress and learning would occur, where low levels of stress stimulate and high levels of stress impair cognitive processes. That is, subjects under a minimal amount of stress (or motivation) would exhibit relatively weak levels of performance. From this low motivational level, increasing levels of stress would facilitate performance, and importantly, high levels of stress would actually produce performance that is significantly impaired.

The three different dose-response functions (i.e., linear, curvilinear or simple hormetic, true hormetic) describing the relation between arousal and performance may be related to the model of stress-hippocampus interactions which we described recently. In this model, we suggested that stress has an initial stimulatory effect on memory-related functioning of the hippocampus. This rapid and short-lived activation of the hippocampus may underlie the linear dose-response relationship between stress and memory. That is, for rapid memory processing, increases in arousal or stress may produce corresponding increases in memory functions of the hippocampus. However, within minutes of the stress onset, the enhancement of hippocampal functioning would be followed by an inhibitory effect on hippocampal functioning. New learning occurring during this inhibitory, or refractory, phase of hippocampal functioning would be impaired. This hypothesis is consistent with the finding that brief periods of stress enhance the acquisition and consoli-

dation of hippocampus-dependent memories, but only if they are administered *immediately* prior to or after learning. If there is a substantial delay between the stress and learning, then long-term memory is not enhanced and, in some cases, is actually impaired. Additionally, this model suggests that even a brief stressor of a large enough magnitude could, after some delay, lead to an inhibition of hippocampal function. Overall, exposure to a brief, intense stressor immediately prior to or following training can initially produce a facilitation of the consolidation of information, while exposure to a prolonged stressor immediately prior to training can impair the consolidation of information.

EFFECTS OF STRESS ON HIPPOCAMPAL SYNAPTIC PLASTICITY

Extensive work has shown that acute stress and the administration of corticosteroids impair the induction of long-term potentiation (LTP) in the hippocampus (Kim and Diamond 2002; Diamond *et al.* 2004; Diamond *et al.* 2005; Kim *et al.* 2006; Diamond *et al.* 2007; Joels and Krugers 2007). Thompson and colleagues were the first to show that exposing rats to 30 minutes of restraint or restraint combined with tailshock blocked the induction of LTP in CA1 *in vitro* (Foy *et al.* 1987). Diamond and colleagues extended these findings by showing that acute stress (exposure to a novel environment) blocked the induction of primed burst potentiation (PBP), a low threshold form of LTP, in the behaving rat (Diamond *et al.* 1990). Since then, investigators have reported that exposing rodents to a variety of stressors, including predators, predator scent, restraint, tailshock, elevated platform stress and a novel environment, impair the induction of hippocampal LTP and PBP *in vitro* and *in vivo* (Kim and Diamond 2002; Diamond *et al.* 2004; Diamond *et al.* 2005; Kim *et al.* 2006; Diamond *et al.* 2007). Importantly, the effects of stress on synaptic plasticity are not short-lived, as the stress-induced impairment of hippocampal LTP has been observed up to 48 hours post-stress (Shors *et al.* 1997). In contrast to their effects on hippocampal LTP, acute episodes of stress have been shown to facilitate the induction of hippocampal long-term depression (LTD) (Kim *et al.* 1996; Xu *et al.* 1997; Xu *et al.* 1998; Yang *et al.* 2004; Yang *et al.* 2005; Chaouloff *et al.* 2007), a long-lasting reduction of synaptic efficacy that is involved in the stress-induced impairment of hippocampus-dependent memory (Wong *et al.* 2007). Researchers have theorized that acute stress activates mechanisms in common with hippocampal LTP (Diamond *et al.* 2004; Huang *et al.* 2005), which then causes subsequent synaptic changes to favor depression (i.e., LTD) rather than potentiation (Kim and Yoon 1998).

Importantly, in studies reporting a stress-induced impairment of hippocampal LTP and a stress-induced enhancement of hippocampal LTD, the animals were exposed to a relatively long (at least 30 minutes) stress experience before electrical stimulation was applied to the hippocampus.

Our temporal dynamics model (Diamond *et al.* 2007), which states that the hippocampus is initially activated and then suppressed by stress, predicts that when an emotionally arousing experience occurs in close proximity to the delivery of high-frequency stimulation, the duration of hippocampal LTP should be *enhanced*. This prediction has been supported by the findings of numerous studies over the past decade.

HORMETIC RELATIONSHIP BETWEEN ADRENAL HORMONES AND HIPPOCAMPAL FUNCTION

The mechanisms involved in the stress-induced modulation of memory and LTP involve the rapid release of epinephrine and norepinephrine from the adrenal medulla, which facilitates the mobilization of metabolic resources that are necessary for the fight-or-flight response. Numerous studies have reported that the administration of epinephrine before or after learning enhances hippocampus-dependent memory (Gold and Van Buskirk 1975; Gold *et al.* 1975; Gold *et al.* 1977; Izquierdo *et al.* 1988; Introini-Collison *et al.* 1992; Alkire and Cahill 1999; Cahill and Alkire 2003; Halonen *et al.* 2007). Similar to the stress-induced enhancement of learning, this effect is temporally-restricted, and as the delay between epinephrine administration and learning increases, the epinephrine-induced enhancement of learning decreases (Gold and Van Buskirk 1975). In addition, epinephrine enhances hippocampal LTP (Korol and Gold 2007), while adrenal demedullation impairs hippocampal LTP (Shors *et al.* 1990). Research has suggested that the enhancing effects of epinephrine are due to β-adrenergic receptor activity, as the administration of β-adrenergic receptor antagonists blocks the epinephrine-induced enhancement of hippocampal function (Sternberg *et al.* 1985; Introini-Collison *et al.* 1992), and the administration of β-adrenergic receptor agonists facilitates hippocampal function (Gray and Johnston 1987; Introini-Collison *et al.* 1994; Gelinas and Nguyen 2005).

When Thompson and colleagues first reported that acute stress impaired hippocampal synaptic plasticity, they also noted a significant negative relationship between corticosteroid levels and inducible LTP (Foy *et al.* 1987). Since then, several studies have reported that the administration of corticosteroids can impair hippocampus-dependent learning and memory and hippocampal LTP *in vivo* and *in vitro* (Lupien and Lepage 2001; Joels 2001; Lupien *et al.* 2007). However, a complete removal (via adrenalectomy) or significant reduction (via metyrapone, a pharmacological inhibitor of corticosteroid synthesis) of circulating corticosteroids also leads to impairments of hippocampus-dependent learning and memory, as well as hippocampal synaptic plasticity, suggesting an inverted U-shaped dose-response relationship (i.e., simple hormetic) between corticosteroids and hippocampal function (Lupien and Lepage 2001; Joels 2001; Lupien *et al.* 2007). Diamond and colleagues found that

at low levels of circulating corticosteroids (i.e., 0-20 μg/dL), there was a positive relationship between corticosteroids and hippocampal PBP, while at elevated levels (i.e. stress levels, or > 20 μg/dL), this relationship was negative (Diamond *et al.* 1992). The investigators also reported that extremely high levels of corticosteroids (i.e., > 60 μg/dL) promoted synaptic depression. Such findings suggested that there was a true hormetic, rather than a simple inverted U-shaped, dose-response relationship between corticosteroids and hippocampal synaptic plasticity. Although adrenalectomy, which resulted in almost a complete absence of circulating corticosteroids, impaired synaptic potentiation, it did not result in the facilitation of synaptic depression. Such a response was only observed in the presence of extremely high circulating levels of corticosteroids. This work therefore suggested that moderate levels of corticosteroids facilitate hippocampal synaptic plasticity, while extremely high levels of corticosteroids have deleterious effects on hippocampal synaptic plasticity. These findings coincide with research in humans examining the effects of corticosteroid administration on learning. For instance, hydrocortisone impaired learning when it was administered prior to learning in the morning hours (when cortisol levels are at their peak in humans) (Lupien *et al.* 1999), but enhanced learning when it was administered prior to learning in the afternoon hours (when cortisol levels are relatively low in humans) (Lupien *et al.* 2002). Collectively, the human and rodent literature suggests that the hormetic relationship between stress and hippocampus-dependent learning and memory may be a result of corticosteroid activity.

The initial, simplistic view of corticosteroid receptor involvement in the modulation of hippocampal function was that activation of MRs enhanced hippocampal synaptic plasticity, while the activation of GRs impaired hippocampal synaptic plasticity (Conrad *et al.* 1999). Further research, however, has revealed that some GR occupancy is necessary for optimal hippocampal function. In a series of experiments, Conrad and colleagues found that when GRs were either completely blocked or highly occupied, rats exhibited impaired spatial memory in the Y-maze, an effect that was independent of the level of MR activation (Conrad *et al.* 1999). That is, only when there was a moderate level of GR occupancy did rats exhibit intact spatial memory. These findings support the notion that during low levels of stress, when there are moderate increases in corticosteroid levels which occupy few GRs, hippocampal synaptic plasticity and hippocampus-dependent learning and memory are enhanced, while during high levels of stress, when there are significant elevations of corticosteroid levels and almost a complete saturation of GRs, hippocampal synaptic plasticity and hippocampus-dependent learning and memory are impaired.

Recent work has indicated that, in addition to their genomic effects, corticosteroids can also bind to membrane-bound receptors and exert rapid, nongenomic effects on neuronal transmission. For instance, in rats, peripheral administration of corticosterone leads to a rapid (less than 15-minute) increase in extracellular levels of glutamate and aspartate in the CA1 region of the hippocampus, an effect that is still observed following the administration of selective intracellular corticosteroid receptor antagonists (Venero and Borrell 1999). In addition, bath application of corticosteroids enhances the frequency of miniature excitatory postsynaptic currents (mEPSCs) in CA1 hippocampal neurons within 5-10 minutes (Karst *et al.* 2005). This effect was shown to be mediated by an MR-dependent increase in glutamate transmission. Interestingly, the threshold corticosteroid concentration for these rapid nongenomic effects was 10- to 20-fold greater than the *in vitro* effects observed on intracellular MRs and could explain how stress can have an immediate excitatory effect on hippocampal synaptic plasticity and, consequentially, learning and memory (Karst *et al.* 2005).

The nongenomic effect of corticosteroids on hippocampal function could explain how an intense episode of brief stress rapidly facilitates hippocampus-dependent learning and memory and aids in the formation of flashbulb memories. As indicated above, the corticosteroids rapidly increase glutamate transmission in the hippocampus, which would foster optimal conditions for synaptic plasticity and learning to occur. However, this corticosteroid-induced enhancement of glutamatergic transmission in the hippocampus would eventually trigger NMDA receptor desensitization in order to protect the cells from excitotoxicity (Zorumski and Thio 1992; Rosenmund and Westbrook 1993; Rosenmund *et al.* 1995; Price *et al.* 1999; Nakamichi and Yoneda 2005). Although this is an advantageous mechanism to shelter the cells from damage, it would lead to impaired synaptic plasticity and learning.

THE AMYGDALA MEDIATES THE HORMETIC RELATIONSHIP BETWEEN STRESS AND LEARNING

Although elevations of corticosteroids have been extensively implicated in the stress-induced modulation of learning, it turns out that increases in corticosteroids, alone, are not necessary or sufficient for stress to significantly affect hippocampus-dependent learning and memory. For instance, Diamond and colleagues reported that acute predator stress impaired within-day memory in the radial arm water maze in adrenalectomized rats that could not manifest stress-induced increases in corticosteroids (Campbell *et al.* 2003). Even greater, numerous studies have reported that manipulations which block the effects of acute stress

on hippocampus-dependent learning and memory often leave the stress-induced increase in corticosteroids unaffected (Campbell *et al.* 2008). What appears to be a major factor determining the effects of corticosteroids on memory is the emotional context in which the elevated corticosteroid levels occur. Studies in both humans and rodents have recently shown that elevated corticosteroid levels only enhance or impair (direction of effect is dose- and time-dependent) learning and memory if the subjects are placed in a fear-provoking (i.e., amygdala-activating) situation (Okuda *et al.* 2004; Park *et al.* 2006; Kuhlmann and Wolf 2006).

The amygdala is a medial temporal lobe structure that is important for processing arousing, fearful stimuli and storing emotional memories (LeDoux 2000; McGaugh 2004). Reciprocal connections between the amygdala and hippocampus allow for dynamic interactions between these two brain regions (Pitkanen *et al.* 2000), and researchers have shown that an intact amygdala, specifically the basolateral amygdala (BLA), is essential for the stress- and corticosteroid-induced modulation of hippocampus-dependent learning and memory (McGaugh 2004). For instance, lesions or inactivation of the BLA blocks the stress-induced impairment of hippocampus-dependent memory and synaptic plasticity (Kim *et al.* 2001; Kim *et al.* 2005). Furthermore, amygdala lesions or pharmacological blockade of β-adrenergic receptors or GRs in the amygdala blocks the effects of corticosteroid administration on learning and memory (Roozendaal and McGaugh 1997; Roozendaal *et al.* 1999; Roozendaal 2003; Roozendaal *et al.* 2006). Together, these findings indicate that the effects of stress and corticosteroids on hippocampus-dependent learning and memory are dependent on amygdala-induced modulation of hippocampal function.

Researchers have shown that activation of the amygdala directly affects hippocampal synaptic plasticity (Abe 2001). For example, Akirav and Richter-Levin reported a biphasic, temporally-restricted relationship between amygdala activation and hippocampal LTP (Akirav and Richter-Levin 1999). These investigators showed that stimulation of the BLA immediately prior to high-frequency stimulation of the hippocampal perforant pathway led to enhanced LTP in the dentate gyrus, while stimulation of the BLA one hour before high-frequency stimulation of the hippocampal perforant pathway impaired LTP in the dentate gyrus. Subsequent work by these investigators showed that the administration of metyrapone or N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride blocked the excitatory and inhibitory effects of BLA stimulation on hippocampal plasticity, indicating that both effects were dependent on corticosteroid and noradrenergic receptor activity (Akirav and Richter-Levin 2002). Thus, these findings suggest that the amygdala has an immediate excitatory, but a longer-lasting inhibitory, effect on hippocampal plasticity, which is dependent upon a synergistic interaction

between corticosteroids and norepinephrine and may play an important role in mediating the hormetic relationship between stress and learning.

INTEGRATIVE APPROACH TO HORMESIS BETWEEN STRESS AND LEARNING

Acute stress promotes a massive release of neuromodulators (glutamate, acetylcholine, dopamine, corticotropin-releasing hormone, norepinephrine), which ultimately leads to enhanced learning and memory and activates endogenous forms of neuroplasticity in the hippocampus (Gray and Johnston 1987; Hopkins and Johnston 1988; Katsuki *et al.* 1997; Adamec *et al.* 1998; Wang *et al.* 1998; Izumi and Zorumski 1999; Wang *et al.* 2000; Ye *et al.* 2001; Blank *et al.* 2002; Li *et al.* 2003; Chen *et al.* 2004; Ovsepian *et al.* 2004; Lisman and Grace 2005; Ahmed *et al.* 2006; Lemon and Manahan-Vaughan 2006). Corticosteroid-mediated effects on the hippocampus would not be observed immediately following the onset of stress, as there is a substantial delay from the onset of stress and the release of corticosteroids from the adrenal cortex. When the corticosteroids did reach the hippocampus, they would exert an immediate nongenomic, MR-dependent excitatory effect on learning and memory mechanisms. This excitatory effect would result from increased glutamatergic transmission and activate intracellular calcium-dependent signaling cascades. At the same time, stress would activate cellular processes within the amygdala, which would also lead to a direct enhancement of hippocampal synaptic plasticity. Collectively, all of these stimulatory mechanisms would facilitate the storage of information occurring at the time of stress onset, thus enabling the formation of flashbulb memories. However, as the stressor continued and corticosteroid levels steadily rose, a massive buildup of postsynaptic glutamate and calcium, as well as extensive GR activation, would ensue, promoting the desensitization of NMDA receptors and impaired hippocampal function. This stress-induced refractory period would lead to impaired synaptic plasticity within the hippocampus and, consequently, impaired learning and memory.

It is important to note that the hormetic relationship between stress and learning undoubtedly varies depending on the context in which the stress and learning occur. For instance, the type and duration of stressor, as well as several characteristics of the task itself (e.g., difficulty, aversiveness), would likely modulate the height and width of the peak and nadir of the hormetic curve. In addition, although prolonged periods of acute stress may lead to impaired hippocampal function, they do not completely incapacitate the subject's ability to learn. Indeed, some tasks, such as contextual fear conditioning, are likely to remain unaffected following prolonged periods of stress, especially when these tasks retain important survival information. The cognitive abilities that remain unaffected in

such periods of stress are likely to be explained by the fact that some forms of synaptic plasticity are not impaired, and may actually be enhanced, by prolonged stress (e.g., voltage-gated calcium channel-dependent LTP) (Joels and Krugers 2007).

SUMMARY

Stress may enhance, impair or have no effect on learning and memory. In the present review, we have discussed the behavioral and neurobiological basis of these findings in a format which represents stress-memory interactions as conforming to linear, U-shaped (i.e., simple hormetic) or true hormetic dose-response functions. We have also discussed how the expression of stress-memory interactions is influenced by brain structures (prefrontal cortex, hippocampus and amygdala) involved in processing information and how these structures interact with aspects of the stress to modulate memory storage. Our approach to integrate multiple dose-response functions with synaptic plasticity underlying memory storage may provide a structure with which to improve our understanding of how strong emotionality exerts such powerful positive, as well as negative, effects on memory.

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