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Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain

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McEwen BS. Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain. *Physiol Rev* 87: 873–904, 2007; doi:10.1152/physrev.00041.2006.—The brain is the key organ of the response to stress because it determines what is threatening and, therefore, potentially stressful, as well as the physiological and behavioral responses which can be either adaptive or damaging. Stress involves two-way communication between the brain and the cardiovascular, immune, and other systems via neural and endocrine mechanisms. Beyond the "flight-or-fight" response to acute stress, there are events in daily life that produce a type of chronic stress and lead over time to wear and tear on the body ("allostatic load"). Yet, hormones associated with stress protect the body in the short-run and promote adaptation ("allostasis"). The brain is a target of stress, and the hippocampus was the first brain region, besides the hypothalamus, to be recognized as a target of glucocorticoids. Stress and stress hormones produce both adaptive and maladaptive effects on this brain region throughout the life course. Early life events influence life-long patterns of emotionality and stress responsiveness and alter the rate of brain and body aging. The hippocampus, amygdala, and prefrontal cortex undergo stress-induced structural remodeling, which alters behavioral and physi-

ological responses. As an adjunct to pharmaceutical therapy, social and behavioral interventions such as regular physical activity and social support reduce the chronic stress burden and benefit brain and body health and resilience.

I. INTRODUCTION

Stress is a word used to describe experiences that are challenging emotionally and physiologically. "Good stress," in popular jargon, generally refers to those experiences that are of limited duration and that a person can master and which leave a sense of exhilaration and accomplishment, whereas "bad stress" or "being stressed out," in the vernacular, refers to experiences where a sense of control and mastery is lacking and which are often prolonged or recurrent, irritating, emotionally draining, and physically exhausting or dangerous. A hallmark of the stress response is the activation of the autonomic nervous system and hypothalamo-pituitary-adrenal (HPA) axis, and the "fight-or-flight" response is the classical way of envisioning the behavioral and physiological response to a threat from a dangerous situation, be it a predator, a mugger, an accident, or natural disaster. The organism needs the normal stress hormone response to survive such situations, and inadequate or excessive adrenocortical and autonomic function is deleterious for health and survival. Yet, unlike zebras, who don't get ulcers because they do not worry, according to Robert Sapolsky's book *Why Zebras Don't Get Ulcers* (312), human beings are prone to prolonged periods of elevated activity of the same systems which help us survive more acute challenges. This prolonged elevation may be due to anxiety; to constant exposure to adverse environments involving such irritants as noise, pollution, and interpersonal conflict; and to changes in life-style and health-related behaviors that result from being under chronic stress.

The importance of acknowledging the protective, as well as the potentially damaging effects of the mediators of stress and adaptation, has led to the introduction of two terms: "allostasis," meaning the process of maintaining stability (homeostasis) by active means, namely, by putting out stress hormones and other mediators; and "allostatic load or overload," meaning the wear and tear on the body and brain caused by use of allostasis, particularly when the mediators are dysregulated, i.e., not turned off when stress is over or not turned on adequately when they are needed.

The brain is the organ of the body that interprets experiences as threatening or nonthreatening and which determines the behavioral and physiological responses to each situation. Besides the hypothalamus and brain stem, which are essential for autonomic and neuroendocrine responses to stressors, higher cognitive areas of the brain play a key role in memory, anxiety, and decision making. These brain areas are targets of stress and stress hormones, and the acute and chronic effects of stressful experiences influence how they respond. This is particularly evident over the life course, where early life experiences, combined with genetic factors, exert an important influence on adult stress responsiveness and the aging process.

This review summarizes a number of the major themes that have emerged with particular clarity over the past two decades since a previous review in this journal (214). Five themes are described that emphasize both the short-term and the long-term effects of the physiological mediators of the stress response and the central role of the brain as a target of stress and controller of the responses to stressors. The focus on the brain underlies all five themes of this review, including the types of behavioral and social interventions, besides pharmaceutical agents, that can reduce the chronic stress burden. The intent of this review is not only to summarize salient facts but also to provide a conceptual framework for future studies that will introduce more physiology and neuroscience into developing a better mechanistic understanding of vexing stress-related social and medical problems and their solution via biological, behavioral, and sociological means.

II. PHYSIOLOGICAL AND BEHAVIORAL FACTORS IN BRAIN AND BODY AGING ACROSS THE LIFE SPAN

It is not uncommon to hear discussion about how hardships have "aged" a person, and indeed, the "weathering hypothesis" (117) proposed that stressful life experiences accelerate aging. Some of the ways that this can happen have become apparent with subsequent research on animal models (see below), as well as epidemiological studies in human populations (e.g., Ref. 188). The central focus of this review is the role of the brain, which is the key organ of the stress response because it determines what is threatening and, therefore, stressful and also controls the behavioral and physiological responses to potentially stressful experiences (Fig. 1).

The involvement of my laboratory in this topic began with our finding in the late 1960s of receptors for adrenal steroids in the hippocampal formation (116, 217) (Fig. 2), a brain region that is important for spatial, episodic, and contextual memory formation (96, 336). This has led to a wide variety of studies of the functional consequences of adrenal steroid action over the life span.

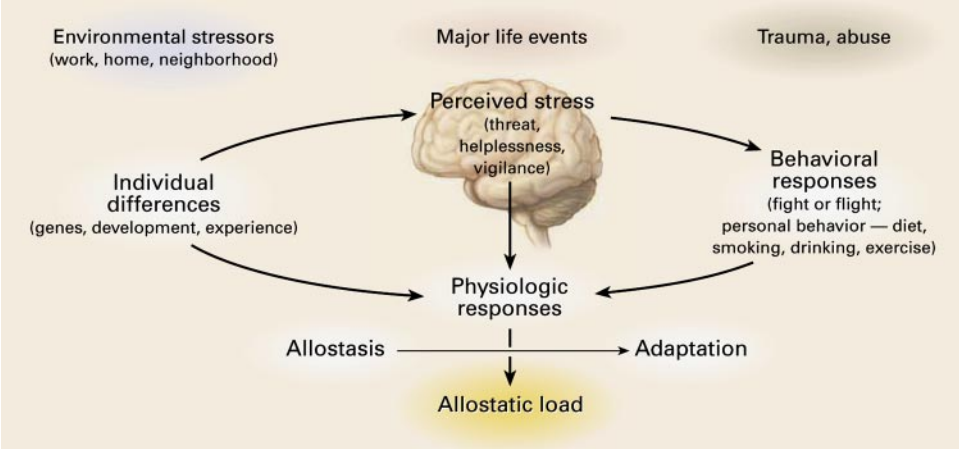

FIG. 1. Central role of the brain in allostasis and the behavioral and physiological response to stressors. [From McEwen (211), copyright 1998 Massachusetts Medical Society.]

A. Stress, Aging, and the Hippocampus

In neuroscience and neuroendocrinology, the studies of Landfield (171) and Sapolsky (311) were among the first to call attention to how aging and adrenal stress hormones impact the hippocampus. The hippocampus also plays a role in shutting off the HPA stress response, and damage or atrophy of the hippocampus impairs the shut off and leads to a more prolonged HPA response to psychological stressors (134, 141). This led to the "glucocorticoid cascade hypothesis" of stress and aging (311). Longitudinal studies on aging human subjects support this model. For example, the work of Lupien et al. (186) revealed that progressive increases in salivary cortisol during a yearly exam over a 5-yr period predicted reduced hippocampal volume and reduced performance on hippocampal-dependent memory tasks.

While the initial view of aging in the hippocampus favored the notion of a loss of neurons, subsequent studies on animal models of aging have favored a loss of synaptic connectivity or impairment of synaptic function,

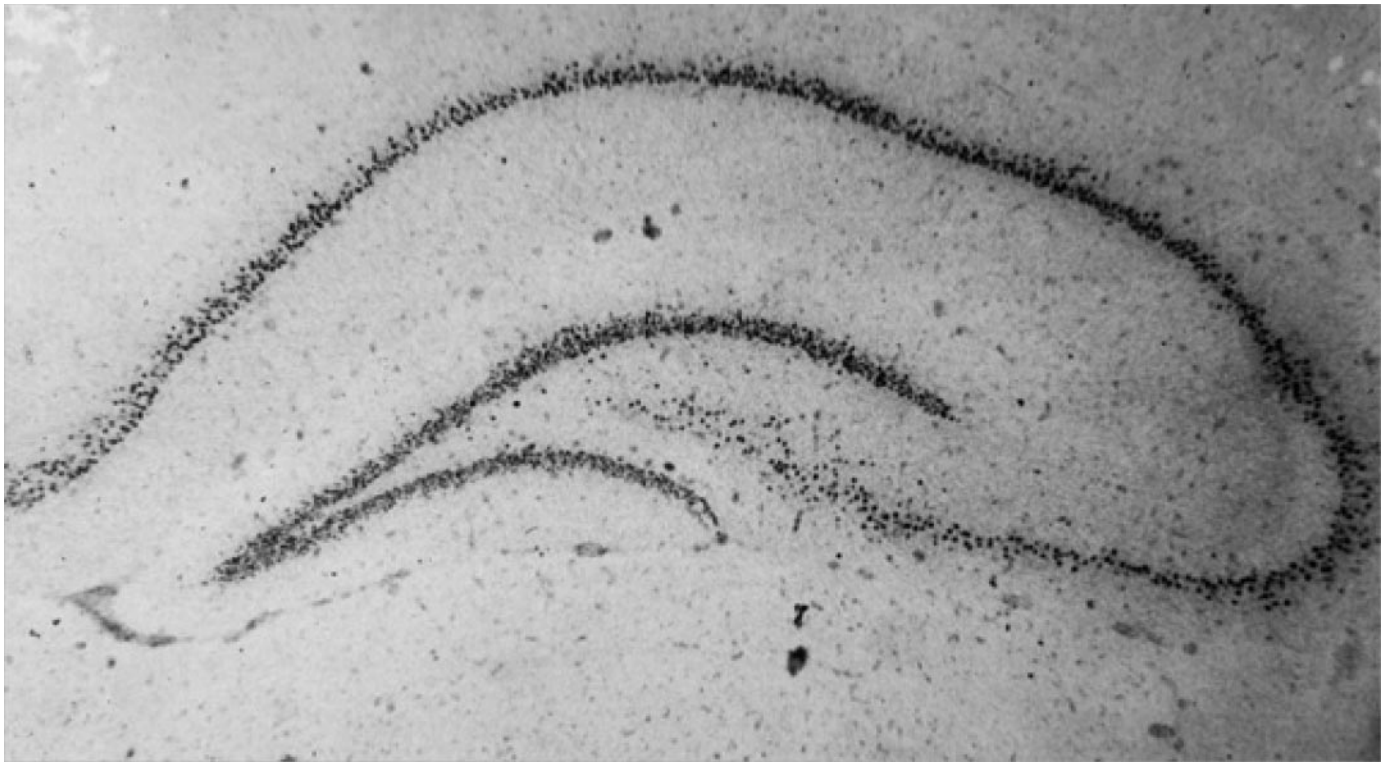

FIG. 2. Autoradiogram shows uptake and retention of [^{3}H]corticosterone by principal neurons of Ammon's horn and dentate gyrus of bilaterally adrenalectomized, adult rats. [Modified from Gerlach and McEwen (116).]

although with some indication that the aging human hippocampus may lose neurons (115, 287, 289, 377). As discussed later in this review, besides glucocorticoids, excitatory amino acids in the hippocampus play a prominent role in the aging process and the damage that can result from the severe stress of ischemia or seizures (310), as well as in the reversible stress-induced remodeling of neurons in the hippocampus. Before discussing these topics in section IV, there are other factors that contribute to hippocampal function and influence the aging process.

B. Role of 11-Hydroxysteroid Dehydrogenase Type 1 and Other Regulators of Glucocorticoid Availability

The glucocorticoid access to the brain and the metabolism of glucocorticoids in brain tissue both play important roles in determining the magnitude of glucocorticoid effects on the hippocampus (Fig. 3). Corticosteroid binding globulin (CBG) in blood determines the level of free corticosterone (or cortisol in human) that can gain access to the brain (325) and the multiple drug resistance P-glycoprotein (MDRpG) limits the access of synthetic glucocorticoids such as dexamethasone, as well as cortisol (not produced by the rat adrenal) to the rodent brain (147, 225). As a result of this protective barrier, low doses of dexamethasone, for example, can produce a hypocorticosteroid state by acting on the pituitary to shut off corticosterone production (146). Both corticosterone and 11-dehydrocorticosterone (11-DHC, the rat equivalent of cortisone in corticosterone secreting species) gain ready access to brain tissue, where 11-DHC (and cortisone in cortisol secreting species) can be reactivated by the enzyme 11-hydroxysteroid dehydrogenase type 1 (11-HSD1), which reactivates 11-dehydrocorticosterone to corticosterone and cortisone to cortisol. Mice with a genetic deletion of 11-HSD1 show a lesser age-related decline of cognitive function compared with wild-type mice (393). [It is noteworthy that mice with overexpression of 11-HSD1 in visceral fat develop visceral obesity and the metabolic syndrome (203).] The actions of 11-HSD1 in brain may have relevance for the age-related loss of cognitive function in humans described above, since even short-term treatment of people with metabolic syndrome and elevated cortisol levels with an inhibitor of 11-HSD1 has been reported to have beneficial effects on cognitive function (306) (Fig. 3).

C. Metabolic Hormones Affect the Hippocampus

Besides glucocorticoids and excitatory amino acids, a number of protein hormones have been shown to affect the hippocampus (Fig. 4). The hippocampus has receptors for insulin-like growth factor I (IGF-I) and insulin (91), and it responds to circulating insulin to translocate glucose transporters to cell membranes (269). Circulating IGF-I is a key mediator of the ability of physical activity to increase neurogenesis in the dentate gyrus of the hippocampal formation (1, 48). IGF-I is taken up into brain via a transport system different from that which transports insulin, although there is some overlap (280, 396). IGF-I is a member of the growth hormone family, and growth hormone is implicated in cognitive function and mood regulation (90, 248). Growth hormone is expressed in the hippocampus where it is upregulated by acute stress and also, in females, by estradiol (90). Interestingly, although growth hormone mRNA is expressed in hippocampus (89), growth hormone also enters the brain in

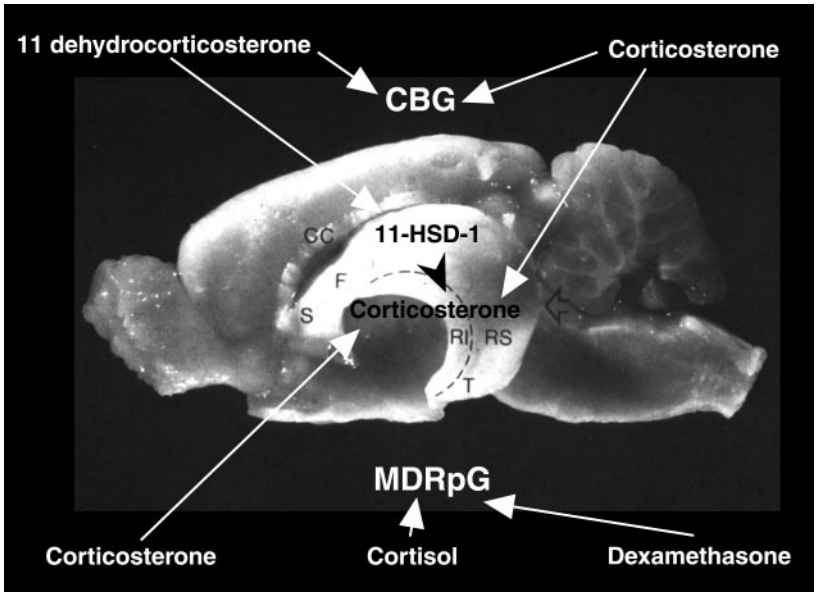

FIG. 3. Access of glucocorticoids to receptors in hippocampus and other brain regions is regulated by 3 factors: corticosteroid binding globulin (CBG), multiple drug resistance P-glycoprotein (MDRpG), and metabolism by 11-hydroxysteroid dehydrogenase type 1 (11 HSD-1). CBG in the blood binds natural glucocorticoids such as corticosterone, cortisol, and their 11-dehydro-metabolites, but not the synthetic glucocorticoid dexamethasone; only unbound steroid is able to enter the brain. However, MDRpG at the blood-brain barrier actively transports synthetic steroids (such as dexamethasone), and to some extent 17-hydroxylated natural steroids, such as cortisol, out of the brain so that they do not enter very readily and only at high doses. Thus MDRpG retards the entry of cortisol into the brain, especially in the rodent, but does not affect corticosterone, which enters readily. In brain tissue, the enzyme 11 HSD-1 converts 11-dehydro-metabolites of corticosterone and cortisol back to the parent steroid, thus "reactivating" these glucocorticoids. See text for details.

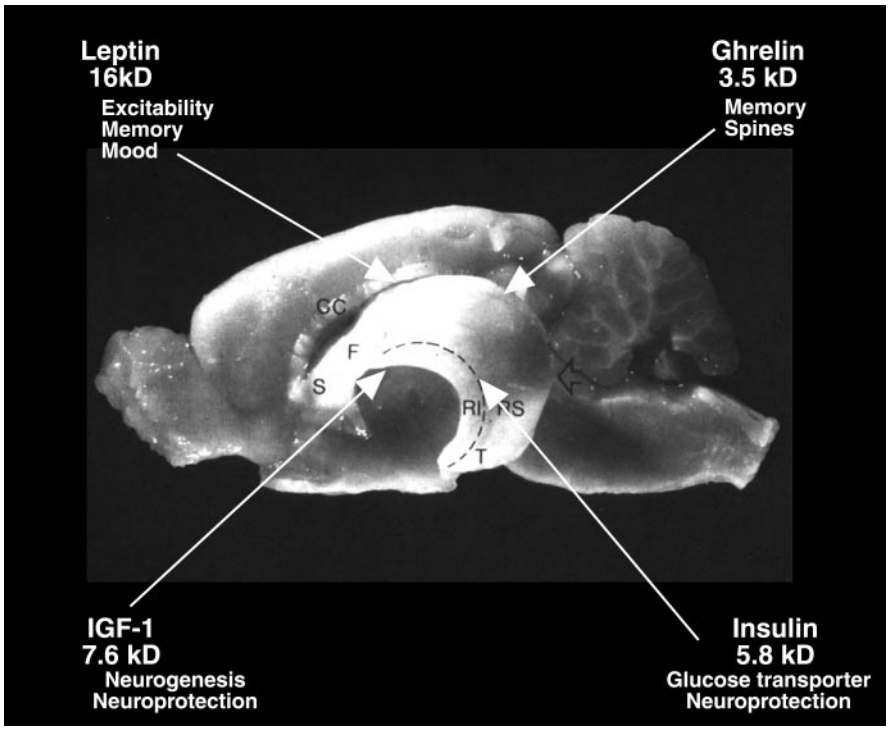

FIG. 4. Four peptide/protein hormones, insulin-like growth factor I (IGF-I), insulin, ghrelin, and leptin, are able to enter the brain and affect structural remodeling or other functions in the hippocampus. A transport process is involved, and specific receptors are expressed in hippocampus as well as in other brain regions. See text for details. Molecular sizes are indicated for each hormone along with their molecular size in kiloDaltons (kDa): ghrelin, 3.5 kDa; leptin, 16 kDa; insulin, 5.8 kDa; IGF-I, 7.6 kDa.

small amounts from the circulation, although not by a specific transport system (256).

Furthermore, circulating ghrelin, a proappetitive hormone, has been shown to increase synapse formation in hippocampal pyramidal neurons and to improve hippocampal-dependent memory (86). Ghrelin is transported into brain via a saturable system (20), and receptors for ghrelin are expressed in hippocampus, as well as in other regions of the brain (397).

Another metabolic hormone, leptin, has been found to exert antidepressant effects when infused directly into the hippocampus (184). Leptin is transported into the brain, and both glucose and insulin mediate the ability of fasting to increase leptin transport into the brain (151). Leptin receptors are found in hippocampus among other brain regions, and leptin has actions in hippocampus that reduce the probability of seizures and enhance aspects of cognitive function (131) (Fig. 4).

Thus far, there is little information that would indicate the cellular and molecular mechanisms by which these hormones produce their effects and whether they interact with some of the other factors that will be discussed below in connection with mechanisms of structural plasticity in the hippocampus. Nevertheless, it is clear that metabolic factors involving glucose regulation play a role in hippocampal volume change in the human hippocampus in mild cognitive impairment with aging (69). In rodents, fatty Zucker rats have poorer hippocampal-dependent memory than lean Zucker rats, as well as impaired translocation of an insulin-dependent glucose transporter to hippocampal membranes (381). Moreover, a diet rich in fat has been shown to impair hippocampal-dependent memory (380), and a combination of a high-fat diet and a 3-wk predator exposure causes retraction of dendrites in the CA3 hippocampus even though neither treatment alone had this effect (21). The topic of dendritic retraction and memory impairment by chronic stress will be revisited below in section IV.

D. Experiential Determinants of Brain and Body Aging

There are enormous individual differences in the response to stress, based on the experience of the individual early in life and in adult life, and some of the mediators described above may be involved. This section summarizes some of these early life experiences and the animal models that have been used to demonstrate them.

As for the role of experiences, positive or negative experiences in school, at work, or in romantic and family interpersonal relationships can bias an individual towards either a positive or negative response in a new situation. For example, someone who has been treated badly in a job by a domineering and abusive supervisor and/or has been fired will approach a new job situation quite differently than someone who has had positive experiences in employment.

Early life experiences perhaps carry an even greater weight in terms of how an individual reacts to new situ-

ations. Early life physical and sexual abuse carry with it a life-long burden of behavioral and pathophysiological problems (104, 132). Moreover, cold and uncaring families produce long-lasting emotional problems in children (291). Some of these effects are seen on brain structure and function and in the risk for later depression and posttraumatic stress disorder (152, 153, 360).

E. Animal Models of Early Life Experience

Animal models have been useful in providing insights into behavioral and physiological mechanisms (Table 1). Early life maternal care in rodents is a powerful determinant of life-long emotional reactivity and stress hormone reactivity, and increases in both are associated with earlier cognitive decline and a shorter life span (51, 107). Strong maternal behavior, involving licking and grooming of the offspring, produces a "neophilic" animal that is more exploratory of novel environments and less emotionally reactive and produces a lower and more contained glucocorticoid stress response in novel situations; poor maternal care leads to a "neophobic" phenotype with increased emotional and HPA reactivity and less exploration of a novel situation (223). Effects of early maternal care are transmitted across generations by the subsequent behavior of the female offspring as they become mothers, and methylation of DNA on key genes appears to play a role in this epigenetic transmission (107, 371).

The effects of maternal care explain at least part of the effects of "neonatal handling" that involved the short-term separation of pups from their mothers (178) (Table 1). The neonatal handling procedure overcomes the deleterious effects of prenatal stress to increase emotionality of offspring (366). Interestingly, more prolonged separation of pups from mothers increases emotionality and stress reactivity, in part by decreasing maternal care when pups are returned to their mothers (271), and an enriched environment during the peripubertal period ameliorates these deficits (108) (Table 1).

However, in rodents, abuse of the young, i.e., rough handling by the mother, is associated with an attachment to, rather than an avoidance of, the abusive mother, an effect that increases the chances that the infant can continue to obtain food and other support until weaning (346). One way to demonstrate the positive, rather than avoidance, effects of aversive stimuli in neonates is via shock-odor conditioning. In this paradigm, neonates become attracted to the odor, at least until they are almost 2 wk of age, when the presence of the mother during conditioning leads to an attraction to the odor paired with shock (see Table 1). As for mechanism, the presence of the mother is able to suppress the pup's corticosterone production, which otherwise would increase an aversive reaction. This has been demonstrated by overriding the maternal suppression of HPA activity rat pups by implanting corticosterone in the amygdala; this manipulation instates fear and fear conditioning and produces an aversive reaction (237).

Increased emotional reactivity and fear of novelty in young rats, whatever its cause, has consequences for longevity and for cognitive function. Male rats were screened at 43 days old for anxiety and divided into "high" and "low" anxiety groups and then subjected to 21 days of daily restraint stress when they were 72 days old; compared with the "low" anxiety" group given chronic stress and also compared with unstressed controls, the "high" anxiety rats showed impaired spatial memory in a subsequent test using the Y maze (27). In another study, the profiling of anxiety in even younger rats also has predictive power: male rats that were "neophobic" as pups continued this pattern into adult life and showed a significantly shorter life span by ~200 days compared with young rats that were "neophilic," that is, showed lower cortisol and emotional reactivity to novelty (51). However, the cause of death for the neophobic male rats was unclear. A subsequent study of female rats focused on tumors as the likely cause of death of neophobic females, which died 6 mo sooner than neophilic females. In contrast to the story for males, neophobic females had lower

TABLE 1. *Experiential influences on brain development in rodent models*

	Nature of Treatment	Sensitive Period or Range	Effect Later in Life
Prenatal stress (189, 366)	Noise, restraint	Last week of gestation	Neophobia, increased HPA reactivity
Postnatal handling (178)	Brief separation from mother	Postnatal days 1–14	Neophilia, decreased HPA reactivity
Maternal care (107, 223)	Licking and grooming of pups	Postnatal days 1–14	Neophilia, decreased HPA reactivity
Maternal separation (271)	Prolonged separation from mother	Postnatal days 1–14	Neophobia, increased HPA reactivity
Novelty exposure (351)	Exposure to novelty	Postnatal days 1–21	Enhanced spatial working memory, social competition, larger HPA response to unexpected stressor
Aversive conditioning (237, 238)	Odor-shock conditioning	Postnatal day 8*	Odor preference
		Postnatal day 12–15†	Odor preference
		Postnatal day 12–15‡	Odor avoidance
		Postnatal day 23*	Odor avoidance

* With or without mother present. † With mother present. ‡ Without mother. Please see text for description.

corticosterone levels than their neophilic counterparts, and they showed abnormal patterns of prolactin and estrogen secretion, pointing away from glucocorticoid dysregulation as the sole cause of pathophysiology (52). Yet, not all consequences of the neophilic state are necessarily beneficial. For example, in mice, neonatal handling, the procedure that induces the neophilic state, increases the damage associated with elevated corticosterone during ischemia, at least in part by increasing poststroke proinflammatory cytokine expression (74). The underlying mechanisms are as yet unexplored.

It is important to note that other conditions that affect the rearing process can also affect emotionality in offspring. For example, uncertainty in the food supply for rhesus monkey mothers leads to increased emotionality in offspring and possibly an earlier onset of obesity and diabetes (71). On a more positive side, the experience of novelty has beneficial effects for cognitive function and social interactions that go beyond the maternal influence (351) (Table 1). Exposure of pups to novelty away from the home environment in a carefully controlled paradigm that dissociates maternal individual differences from a direct stimulation effect on the offspring resulted in enhancement of spatial working memory, social competition, and corticosterone response to an unexpected stressor during adulthood compared with their home-staying siblings. These functional enhancements in novelty-exposed rats occurred despite evidence that maternal care was preferentially directed toward home-staying instead of novelty-exposed pups, indicating that a greater maternal care is neither necessary nor sufficient for these early stimulation-induced functional enhancements (351).

Early life experiences have effects on human physiology and behavior. Prenatal stress is believed to be a factor in causing preterm birth, as well as full-term birth with low birth weight (25, 364). Low birth weight is a risk factor for cardiovascular disease and high body mass (25, 274). Childhood experiences in emotionally cold families increase the likelihood of poor mental and physical health later in life (291), and abuse in childhood is a well-known risk factor for depression, posttraumatic stress disorder, idiopathic chronic pain disorders, substance abuse, antisocial behavior, as well as obesity, diabetes, and cardiovascular disease (14, 104, 132). Chaos in the home environment is a key determinant of poor self-regulatory behaviors, a sense of helplessness and psychological distress (102), as well as increased body mass and elevated blood pressure (101).

F. Genetic Factors

So far, this review has emphasized the important role of the environment and experiences of individuals in health outcomes, but clearly genetic differences also play an important role. This review will not attempt to summarize this growing area of investigation, but rather note some of the most prominent recent evidence showing that different alleles of commonly occurring genes determine how individuals will respond to stressful life experiences. For example, the short form of the serotonin transporter is associated with a number of conditions such as alcoholism (26, 133), and individuals who have this allele are more vulnerable to respond to stressful experiences by developing depressive illness (50). In childhood, individuals with an allele of the monoamine oxidase A gene are more vulnerable to abuse in childhood and more likely to themselves become abusers and to show antisocial behaviors compared with individuals with another commonly occurring allele (49). Yet another example is the consequence of having the Val66Met allele of the brain-derived neurotrophic factor (BDNF) gene on hippocampal volume, memory, and mood disorders (57, 130, 142, 265, 349). A mouse model of this genotype has revealed reduced dendritic branching in hippocampus, impaired contextual fear conditioning, and increased anxiety that is less sensitive to antidepressant treatment (56). Finally, alleles of the glucocorticoid receptor gene found in the normal population confers a higher sensitivity to glucocorticoids for both negative feedback and insulin reponsiveness (138) or glucocorticoid resistance (358), and there is evidence of increased likelihood of depression in several alleles and increased response to antidepressants in one of them. Therefore, the importance of continuing to identify candidate genes, as well as the subtlety of gene-environment interactions, should be clear from this brief overview.

III. PROTECTIVE AND DAMAGING EFFECTS OF STRESS MEDIATORS

A. Stress, Allostasis, and Allostatic Load

There are two key aspects of the stress response (211). On the one hand, the body responds to many experiences by releasing chemical mediators, for example, catecholamines that increase heart rate and blood pressure. These mediators promote adaptation to an acute stressor, as well as to simple acts like getting out of bed in the morning or climbing a flight of stairs. On the other hand, chronic elevation of these same mediators, e.g., chronically increased heart rate and blood pressure, can cause pathophysiological changes, for example, in the cardiovascular system that result, over time, in pathophysiological conditions like atherosclerosis, which can result in strokes and myocardial infarctions.

Because of the paradoxical actions of these mediators in both protection and damage, and also because the word *stress* has ambiguities and connotations that inter-

fere with its precise use, the term *allostasis* was introduced by Sterling and Eyer (342) to refer to the active process by which the body responds to daily events and maintains homeostasis (allostasis literally means "achieving stability through change"). Because chronically increased allostasis can lead to pathophysiology, we introduced the term *allostatic load or overload* (see distinction below) to refer to the wear and tear that results from either too much stress or from inefficient management of allostasis, such as not turning off the response when it is no longer needed (211, 216, 218). Other forms of allostatic load/overload are summarized in Figure 5 and involve not shutting off the response efficiently, not turning on an adequate response in the first place, or not habituating to the recurrence of the same stressor and thus dampening the allostatic response.

B. Protection and Damage: The Two Sides of the Response to Stressors

Thus protection and damage are the two contrasting sides of the physiology involved in defending the body against the challenges of daily life, whether or not we call them "stressors." Besides epinephrine and norepinephrine, there are many mediators that participate in allostasis, and they are linked together in a network of regulation that is nonlinear, meaning that each mediator has the ability to regulate the activity of the other mediators,

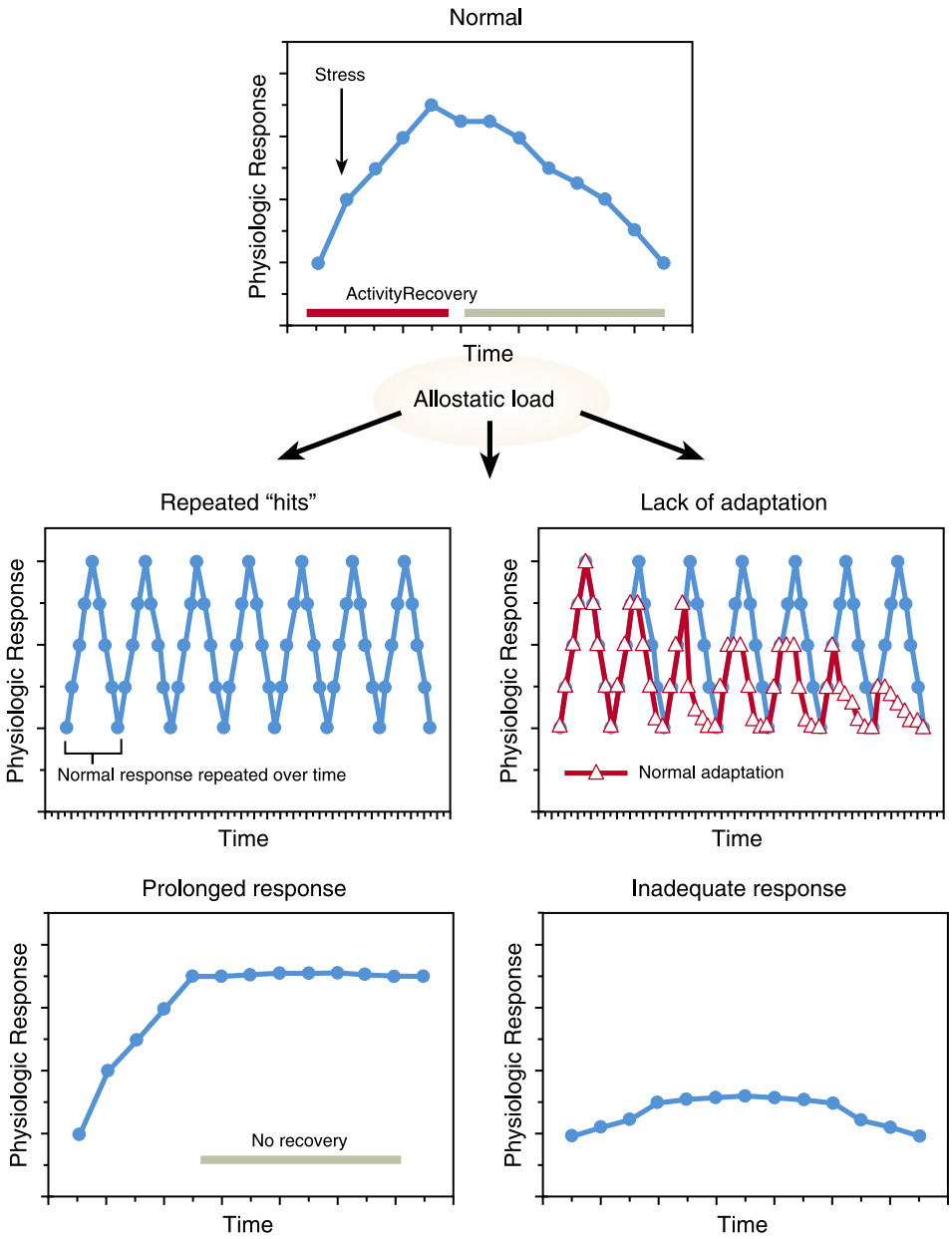

FIG. 5. Four types of allostatic load. *Top panel*: illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The remaining panels illustrate four conditions that lead to allostatic load: *top left*, repeated "hits" from multiple stressors; *top right*, lack of adaptation; *bottom left*, prolonged response due to delayed shut down; *bottom right*, inadequate response that leads to compensatory hyperactivity of other mediators (e.g., inadequate secretion of glucocorticoid, resulting in increased levels of cytokines that are normally counterregulated by glucocorticoids). [From McEwen (211), copyright 1998 Massachusetts Medical Society.]

sometimes in a biphasic manner. For example, glucocorticoids produced by the adrenal cortex in response to ACTH from the pituitary gland is the other major "stress hormone." Yet, pro- and anti-inflammatory cytokines are produced by many cells in the body, and they regulate each other and are, in turn, regulated by glucocorticoids and catecholamines; that is, whereas catecholamines can increase proinflammatory cytokine production (32), glucocorticoids are known to inhibit this production (313). And yet, there are exceptions, e.g., proinflammatory effects of glucocorticoids that depend on dose and cell or tissue type (88, 190). The parasympathetic nervous system also plays an important regulatory role in this nonlinear network of allostasis, since it generally opposes the sympathetic nervous system and, for example, slows the heart, and it also has anti-inflammatory effects (35, 355).

What this nonlinearity means is that when any one mediator is increased or decreased, there are compensatory changes in the other mediators that depend on time course and level of change of each of the mediators. Unfortunately, biomedical technology cannot yet measure all components of this system simultaneously and must rely on measurements of only a few of them in any one study. Yet the nonlinearity must be kept in mind in interpreting the results.

C. Stress in the Natural World

The operation of allostasis in the natural world provides some insight into how animals use this response to their own benefit or for the benefit of the species. As an example of allostasis, in springtime, a sudden snowstorm causes stress to birds and disrupts mating, and stress hormones are pivotal in directing the birds to suspend reproduction, to find a source of food, and to relocate to a better mating site or at least to delay reproduction until the weather improves (379). As an example of allostatic load, bears preparing to hibernate for the winter eat large quantities of food and put on body fat to act as an energy source during the winter (244). This accumulation of fat is used, then, to survive the winter and provide food for gestation of young; in contrast, the fat accumulation occurs in bears that are captive in zoos and eating too much, partially out of boredom, while not exercising (218). The accumulation of fat under these latter conditions can be called "allostatic overload" referring to a more extreme condition that is associated with pathophysiology. Yet, allostatic overload can also have a useful purpose for the preservation of the species, such as in migrating salmon or the marsupial mouse, that die of excessive stress after mating. The stress and allostatic load are caused for salmon, in part, by the migration up the rapidly flowing rivers but also because of physiological changes that represent accelerated aging and include suppression of the immune system (103, 120, 205). One beneficial result of eliminating the adult salmon is freeing up food and other resources for the next generation. In the case of the marsupial mouse, it is only the males that die after mating, and the hypothesized mechanism is a response to mating that reduces the binding protein CBG for glucocorticoids and renders them much more active throughout the body, including likely suppressive actions on the immune defense system (62).

D. Being "Stressed Out": Example of Sleep Deprivation and Its Consequences

The common experience of being "stressed out" has as its core the elevation of some of the key systems that lead to allostatic overload: cortisol, sympathetic activity, and proinflammatory cytokines, with a decline in parasympathetic activity. Nowhere is this better illustrated than for poor or inadequate sleep, which is a frequent result of being "stressed out." Sleep deprivation produces an allostatic overload that can have deleterious consequences.

Because the brain is the master regulator of the neuroendocrine, autonomic, and immune systems, as well as behavior (211) (Fig. 1), alterations in brain function by chronic stress can, therefore, have direct and indirect effects on the cumulative allostatic overload. Reduced sleep duration has been reported to be associated with increased body mass and obesity in the NHANES study (113). Sleep restriction to 4 h of sleep per night increases blood pressure, decreases parasympathetic tone, increases evening cortisol and insulin levels, and promotes increased appetite, possibly through the elevation of ghrelin, a proappetitive hormone, along with decreased levels of leptin (174, 334, 335). Moreover, proinflammatory cytokine levels are increased with sleep deprivation, along with decreased performance in tests of psychomotor vigilance, and this has been reported to result from a modest sleep restriction to 6 h/night (361).

Allostatic overload resulting from chronic stress in animal models causes atrophy of neurons in the hippocampus and prefrontal cortex, brain regions involved in memory, selective attention, and executive function, and causes hypertrophy of neurons in the amygdala, a brain region involved in fear and anxiety as well as aggression (213) (see sect. IV). Thus the ability to learn and remember and make decisions may be compromised by chronic stress and may be accompanied by increased levels of anxiety and aggression.

Sleep deprivation causes cognitive impairment. Sleep deprivation in rats using a treadmill for 96 h has been reported to decrease proliferation of cells in the dentate gyrus of the hippocampal formation by as much as 50% (126). A similar effect has also been reported by keeping

rats in a slowly rotating drum, but here again, there is a question of how much physical activity and physical stress may have contributed to the suppression of cell proliferation (296). Nevertheless, sleep restriction by novelty exposure, a more subtle method, prevented the increased survival of new dentate gyrus neurons promoted by spatial training in a Morris water maze (128).

Indeed, with respect to memory and cognitive performance, there are numerous reports of impairments following sleep deprivation in animal models. For example, sleep deprivation by the platform (or flower pot) method resulted in impaired retention of passive avoidance memory, a context-dependent fear memory task (326), as well as impaired performance of spatial memory in the Morris water maze (395) and a reduction in long-term potentiation in the CA1 region of the hippocampus (159).

Sleep deprivation by gentle stimulation or novelty in the aftermath of contextual fear conditioning has been reported to impair memory consolidation (123). Moreover, a 6-h period of total sleep deprivation by novelty exposure impaired acquisition of a spatial task in the Morris water maze (125). Furthermore, a 4-h period of sleep deprivation by gentle stimulation impaired the late-phase long-term potentiation (LTP) in the dentate gyrus 48 h later but had the opposite effect to enhance late-phase LTP in the prefrontal cortex (297). Sleep fragmentation, produced by movement on a treadmill every 2 min, resulted in a complete suppression of LTP in the CA1 region of the hippocampus as well as impairing the acquisition of spatial learning, although long-term depression (LTD) and paired pulse facilitation were unaffected (353).

There is evidence not only for cognitive impairment resulting from sleep restriction, but also for altered neural levels of cytokines, oxidative stress markers, and brain glycogen levels, that may contribute to the impairment of function. With respect to proinflammatory cytokines, IL-1β mRNA levels in brain are reported to increase following sleep deprivation by gentle handling and to be higher in daytime (during the normal sleep period in rodents) than in darkness (during the normal activity time for rodents) (350). Closely related to inflammatory processes through the actions of NADPH oxidase (58, 352) is oxidative stress involving the generation of free radicals. Sleep deprivation in mice for 72 h by the "flower pot" or platform method has been reported to increase oxidative stress in hippocampus as measured by increased lipid peroxidation and increased ratios of oxidized to reduced glutathione (326).

Another noteworthy effect of sleep deprivation is to regulate the level of glycogen, found predominantly in white matter, that is reported to decrease by as much as 40% in rats deprived of sleep for 24 h by novelty and gentle handling and reversed by recovery sleep (40, 164). It is noteworthy that glycogen in astrocytes is able to sustain axon function during glucose deprivation in CNS white matter (374).

Sleep deprivation has also been associated with increases in fighting behavior after deprivation of rapid-eye-movement (REM) sleep (81); there is also a report of increased aggression in the form of muricide, i.e., killing by rats of mice, after phencyclidine administration following sleep deprivation (241). These findings may be related to the finding of increased aggression among cage mates in rats subjected to 21 days of 6 h/day of chronic restraint stress during the resting period when some sleep deprivation may occur (385). Interestingly, however, there are also anxiety-reducing effects of certain types of sleep deprivation. For example, a 12-h sleep deprivation that is applied by using a slowly rotating drum that minimizes physical stress, but does produce locomotor activity, reversed the decreased open field behavior induced by a single social defeat (224), and another study has shown that total sleep deprivation reduces immobility in a Porsolt swim test, which is regarded as a sign of behavioral depression (182). These interesting findings are perhaps related to the reported acute antidepressant effects of sleep deprivation in humans (261).

IV. THE BRAIN AS A TARGET OF STRESS AND ALLOSTATIC LOAD

The brain is a target of stress and stress hormones, and the processes of allostasis and allostatic load are exemplified by how different brain regions respond to acute and chronic stressors. Because the hippocampus was the first higher brain center that was recognized as a target of stress hormones, it has figured prominently in our understanding of how stress impacts brain structure and behavior. The following discussion builds on the earlier discussion of the role of the hippocampus in HPA regulation and the aging process, and it considers both the positive and negative effects of stress on memory, as well as the gradual changes in hippocampal structure and function associated with prolonged or repeated stress. Effects of stress on the amygdala and prefrontal cortex will then be summarized.

A. The Hippocampus: Stress-Induced Excitability Enhancement Versus Suppression

The hippocampus expresses both type I (mineralocorticoid, MR) and type II (glucocorticoid, GR) receptors, and these receptors mediate a biphasic response to adrenal steroids in the CA1 region, although not in the dentate gyrus (143), which, nevertheless, shows a diminished excitability in the absence of adrenal steroids (200). Other brain regions, such as the paraven-

tricular nucleus, lacking in MR but having GR, show a monophasic response (143) (Fig. 6). Adrenal steroids exert biphasic effects on excitability of hippocampal neurons in terms of long-term potentiation and primed burst potentiation (85, 257, 259) and show parallel biphasic effects upon memory (279).

1. Role of genomic and nongenomic mechanisms

In considering possible mechanisms for the biphasic responses, the coexpression of MR and GR in the same neurons could give rise to heterodimer formation and a different genomic activation from that produced by either MR or GR homodimers (143). In addition, deletion of the type I (MR) receptor by genetic means has revealed that MR are required for nongenomic regulation of glutamatergic transmission by glucocorticoids (148), a phenomenon that involved glucocorticoid enhancement of extracellular levels of glutamate (359) that plays an important role in both modulatory and excitotoxic effects of glucocorticoids (see sect. IV*B4*). Although beyond the scope of this review, the subject of nongenomic actions of adrenal steroids has taken on increasing importance in view of the discovery of adrenal steroid receptors that are G protein coupled in the amphibian brain (252), as well as glucocorticoid receptor immunoreactivity in postsynaptic and other nonnuclear regions of neurons in the rodent brain (145, 179) and a large number of reported rapid, nongenomic actions of adrenal steroids (36, 197). Hence, it is perhaps not surprising that there are conditions involving neural transmission that favor either rapid positive or

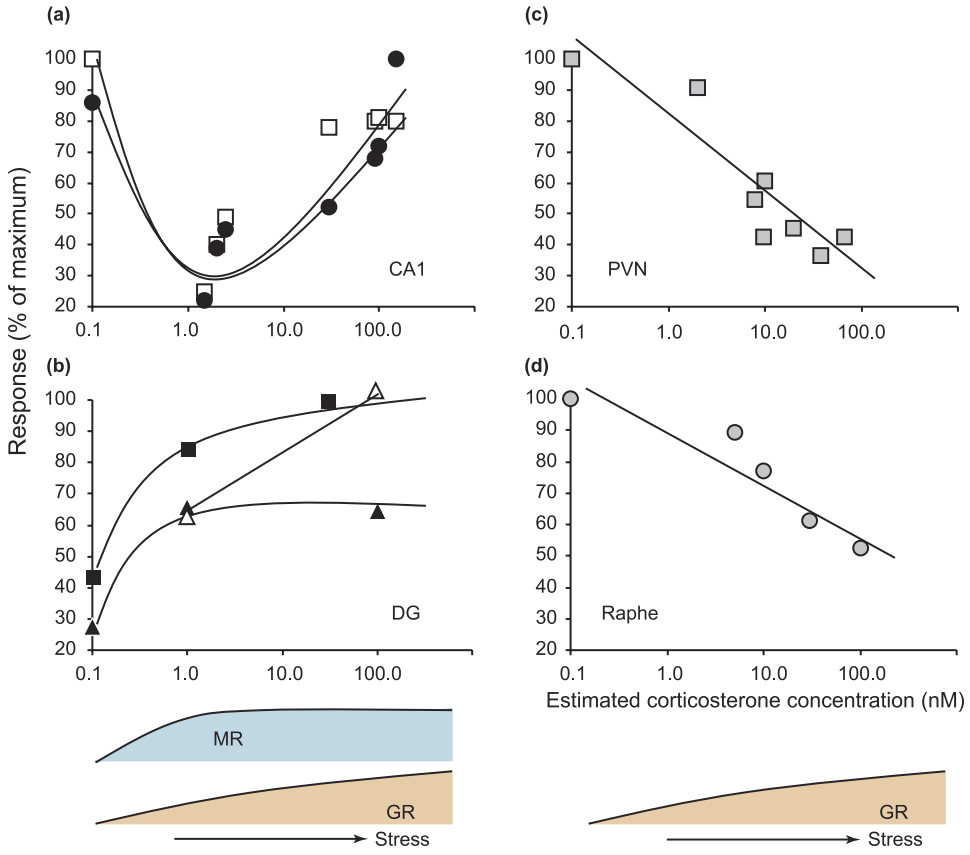

FIG. 6. Dose-response relationships of the cellular effects of corticosterone in the brain. Dose-response relationships are shown for the CA1 hippocampal area (*A*), the dentate gyrus (*B*), the PVN of the hypothalamus (*C*), and the dorsal raphe nucleus (*D*). Graphs show hormone responses expressed as a percentage of the maximal response in these brain regions. The concentration of corticosterone is an approximate estimate of the local concentration based on the solutions perfused on in vitro preparations or derived from the plasma concentration when fluctuations in hormone levels were accomplished in vivo. *A*: in the CA1 area, both the amplitude of depolarization-induced calcium currents (white squares) and the hyperpolarization caused by serotonin 1A receptor activation (black circles) display a U-shaped dose dependency. The descending limb is linked to the activation of mineralocorticoid receptors (MRs), whereas the ascending limb is associated with gradual glucocorticoid receptor (GR) activation in addition to already activated MRs, as occurs after stress. *B*: dentate gyrus granule neurons show a clear MR-dependent effect on the field potential (black squares) and the single-cell response (black triangles) caused by activation of glutamate AMPA receptors. Although these cells also abundantly express GRs, high doses of corticosterone do not cause additional changes in the signal, except when tested in chronically stressed rats (white triangles). *C*: neurons in the PVN (*C*) and the raphe nucleus (*D*) express GRs primarily. In these cells, a linear dose dependency is seen for the frequency of spontaneous γ-aminobutyric acid $(GABA)_A$-receptor-mediated synaptic events (gray squares) and the inhibition caused by serotonin 1A receptor activation (gray circles). [From Joels (143), with permission from Elsevier.]

negative actions of adrenal steroids on processes such as learning and memory.

Although much of the work on MR and GR has been done on rat and mouse brains, it is important to note that the rhesus monkey hippocampus has a predominance of MR and relatively less GR compared with rodent species (305). This finding may have important implications for the effects of adrenal steroids on learning and vulnerability to stress and excitotoxicity, as well as age-related changes discussed earlier.

2. The conditional nature of adrenal steroid actions on memory

Emotional arousal for a rodent by being placed in a novel environment is required for adrenal steroids to enhance object recognition memory, that involves the hippocampus; the effects of adrenal steroids on this memory show an inverted U-shaped dose response (250). Moreover, spatial memory in a Morris water maze, a stressful behavioral task, is facilitated by adrenal steroids in wild-type mice, but this facilitation is lacking in mice with a dimerization-deficient GR (249). In the study involving novelty-induced emotional arousal, the dose range of corticosterone is such that both GR and MR occupancy are involved (250). Yet, prior habituation to the novel environment, thus removing the emotional arouse of novelty, abolishes the facilitation (250). Moreover, corticosterone doses that facilitate memory at 24 h posttraining inhibit memory retention at 1 h posttraining (250). The inhibition of memory retrieval by acute corticosteroid administration is a phenomenon that has also been reported (82, 246, 247, 301), and biphasic effects of corticosteroids on working memory have been described (187).

In providing a framework for understanding these phenomena, Joels et al. (144) propose a very plausible unifying theory, which states that ". . . stress will only facilitate learning and memory processes: *1*) when stress is experienced in the context and around the time of the event that needs to be remembered, and *2*) when the hormones and transmitters released in response to stress exert their actions on the same circuits as those activated by the situation, that is, when convergence in time and space takes place" (see Fig. 7). According to their view, "the mechanism of action of stress hormones, particularly corticosteroids, can explain how stress within the context of a learning experience induces focused attention and improves memory of relevant information."

B. The Hippocampus: Structural Remodeling

Another way that stress hormones modulate function within the brain is by changing the structure of neurons. As already noted, the hippocampus is one of the most sensitive and malleable regions of the brain. Within the hippocampus, the input from the entorhinal cortex to the dentate gyrus is ramified by the connections between the dentate gyrus and the CA3 pyramidal neurons. One granule neuron innervates, on the average, 12 CA3 neurons, and each CA3 neuron innervates, on the average, 50 other CA3 neurons via axon collaterals, as well as 25 inhibitory cells via other axon collaterals. The net result is

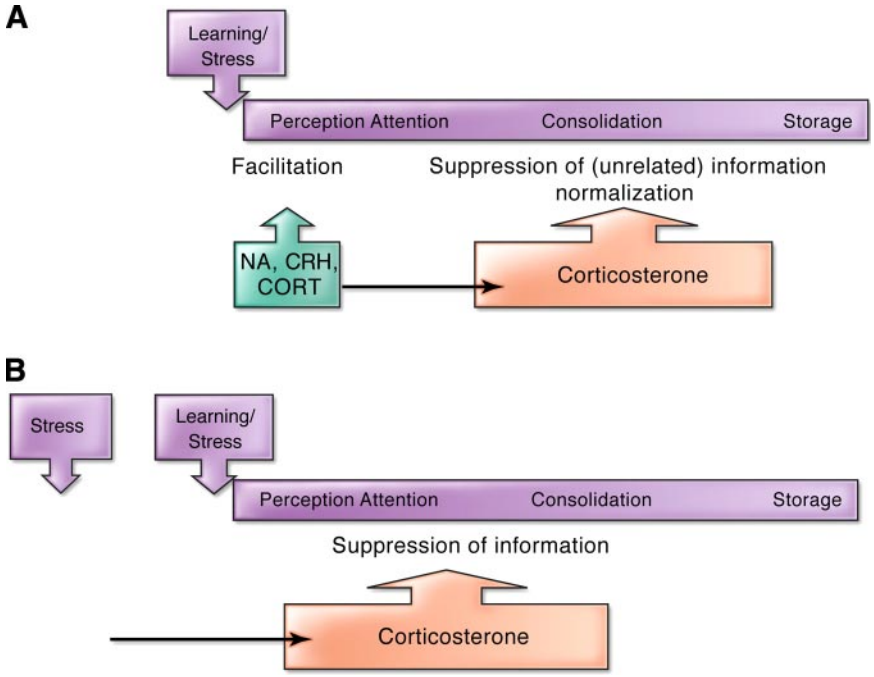

FIG. 7. Opposing effects of stress on learning depend on the timing of the events. *A*: stress within the context of a learning situation leads to the release of norepinephrine (NA), corticotropin releasing hormone (CRH), and cortisol (CORT), all of which are active in the brain at the time that the initial phases of learning take place. At this stage, the neurotransmitters and hormones facilitate the ongoing process. Corticosterone, however, also initiates a gene-mediated pathway, which will elevate the threshold for input unrelated to the initial event and restore neuronal activity (normalization), with a delay of more than an hour. *B*: if an organism has been exposed to a stressor some time before the learning process takes place, the gene-mediated suppression of activity will have developed by the time that acquisition occurs. Under these conditions corticosterone will impair learning processes. [From Joels et al. (144), with permission from Elsevier.]

a 600-fold amplification of excitation, as well as a 300-fold amplification of inhibition, that provides some degree of control of the system (212).

As to why this type of circuitry exists, the dentate gyrus-CA3 system is believed to play a role in the memory of sequences of events, although long-term storage of memory occurs in other brain regions (180). But, because the dentate gyrus (DG)-CA3 system is so delicately balanced in its function and vulnerability to damage, there is also adaptive structural plasticity, in that new neurons continue to be produced in the dentate gyrus throughout adult life, and CA3 pyramidal cells undergo a reversible remodeling of their dendrites in conditions such as hibernation and chronic stress, including a combination of food restriction and increased physical activity (170, 194, 212, 272, 273). The role of this plasticity may be to protect against permanent damage, or it may enhance vulnerability to damage, a topic that is discussed below. Whatever the physiological significance of these changes, the hippocampus undergoes a number of adaptive changes in response to acute and chronic stress.

1. Replacement of neurons in dentate gyrus

One type of change involves replacement of neurons. The subgranular layer of the dentate gyrus contains cells that have some properties of astrocytes (e.g., expression of glial fibrillary acidic protein) and that give rise to granule neurons (155, 320). After bromodeoxyuridine (BrdU) administration to label DNA of dividing cells, these newly born cells appear as clusters in the inner part of the granule cell layer, where a substantial number of them will go on to differentiate into granule neurons within as little as 7 days. In the adult rat, 9,000 new neurons are born per day and survive with a half-life of 28 days (46). There are many hormonal, neurochemical, and behavioral modulators of neurogenesis and cell survival in the dentate gyrus, including estradiol, IGF-I, antidepressants, voluntary exercise, and hippocampal-dependent learning (1, 76, 356). Neurochemical systems that regulate neurogenesis are summarized in Figure 8 and Table 2 and include excitatory amino acids, serotonin, norepinephrine, benzodiazepines, endogenous opioids, BDNF, and IGF-I, as well as glucocorticoids. With respect to stress, certain types of acute stress and many chronic stressors suppress neurogenesis or cell survival in the dentate gyrus, and the mediators of these inhibitory effects include excitatory amino acids acting via NMDA receptors and endogenous opioids (121). The topic of the regulation of neurogenesis is revisited in section VI.

2. Remodeling of dendrites and synapses

Another form of structural plasticity is the remodeling of dendrites in the hippocampus, amydala, and prefrontal cortex. In hippocampus, chronic restraint stress (CRS; daily for 21 days) causes retraction and simplification of dendrites in the CA3 region of the hippocampus (212, 332). Such dendritic reorganization is found in both dominant and subordinate rats undergoing adaptation to

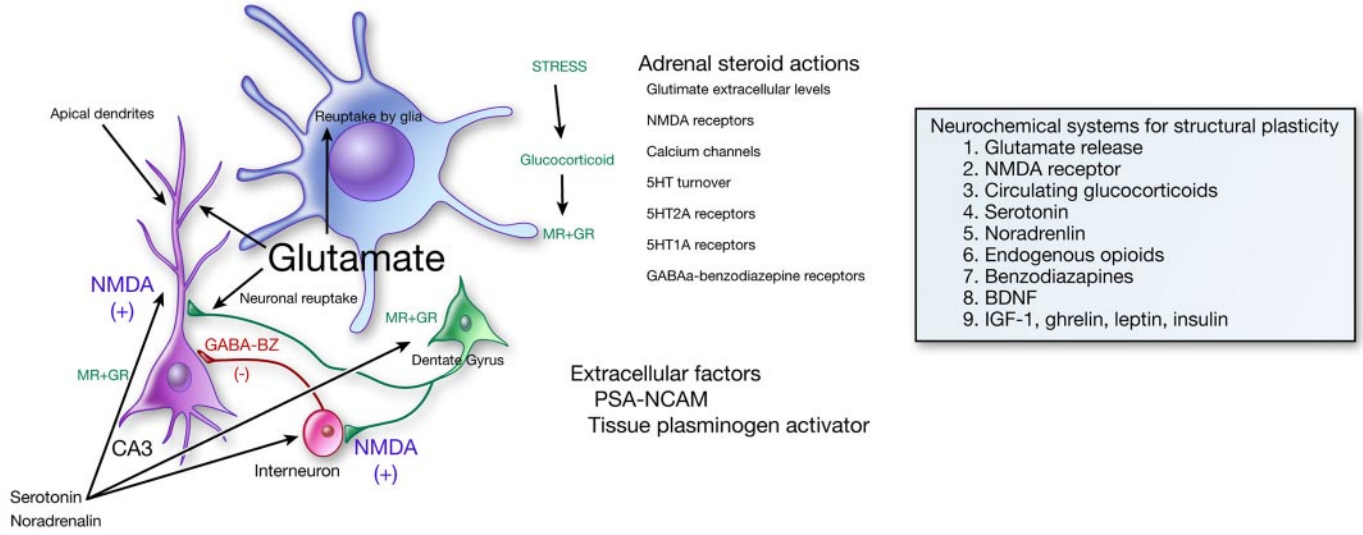

FIG. 8. Structural plasticity in hippocampus involving synaptogenesis (S), neurogenesis (N), and dendritic remodeling (D) involves multiple neurochemical systems, evidence for which is summarized below and in the text. Table 2 summarizes interactions of adrenal steroids with key neurochemical systems involved in structural remodeling. *1*) Glutamate release and reuptake: S, N, D, see text; *2*) NMDA receptor activation, blockade: S, N, D, see text; *3*) circulating glucocorticoids involving both mineralocorticoid (MR) and glucocorticoid (GR) receptors: S, N, D, see text; *4*) serotonin: N (136); *5*) norepinephrine: N (294); *6*) endogenous opioids: N (97); *7*) benzodiazepines: N, D (163, 192); *8*) brain-derived neurotrophic factor (BDNF): N, D, see text; *9*) IGF-I, insulin, ghrelin, and leptin: S, N, see text.

TABLE 2. *Adrenal steroid actions on neurochemical systems in hippocampus*

Extracellular glutamate
Adrenalectomy prevents stress-induced rise of extracellular glutamate (183)
Glucortcoids increase extracellular glutamate (232, 339)
Stress induces Glt-1, glutamate transporter (290)
NMDA receptors
Glucocorticoids upregulate NR2A&B (NMDA) receptor subunit mRNA (372)
Calcium currents
Glucocorticoids increase calcium conductances (157)
Glucocorticoids downregulate calcium extrusion pump (30)
Adrenal steroids biphasically regulate voltage-induced calcium currents (149)
5-HT system
Adrenal steroids are required for stress-induced serotonin turnover (18, 166, 328, 348)
Adrenal steroids biphasically regulate 5-HT1A receptors (54, 143, 228)
GABA benzodiazepine receptors
Differential regulation of $GABA_A$ receptor subunit mRNA levels by ADX and corticosterone (253, 254)
Opioids
Glucocorticoids reverse ADX decrease in dynorphin in dentate gyrus (354)
Glucocorticoids upregulate preproenkephalin mRNA in hippocampus (7)

psychosocial stress in the visible burrow system, and it is independent of adrenal size (219). It also occurs in psychosocial stress in intruder tree shrews in a resident-intruder paradigm, with a time course of 28 days (193), a procedure that, it should be noted, does not cause a loss of pyramidal neurons in the hippocampus (362). The mossy fiber input to the CA3 region at the stratum lucidum appears to drive the dendritic remodeling, since it is the apical dendrites above this input that retract (212).

Moreover, the thorny excrescences (giant spines) upon which the mossy fiber terminals form their synapses show stress-induced modifications (343). CRS caused retraction of thorny excrescence that was reversed after water maze training. In restrained rats that were water maze trained, postsynaptic density (PSD) volume and surface area increased significantly, and the proportion of perforated PSDs almost doubled after water maze training and restraint stress. Moreover, the numbers of endosome-like structures in thorny excrescences decreased after restraint stress and increased after water maze training (343). The number of active synaptic zones between thorny excrescences and mossy fiber terminals is rapidly modulated during hibernation and recovery from the hibernating state (194). The thorny excrescences are not the only spines affected by CRS. Dendritic spines also show remodeling, with increased spine density reported after chronic restraint stress on apical dendrites of CA3 neurons (347) (Fig. 8).

3. Puberty as a key stage of brain maturation and stress sensitivity

Puberty is a developmental period of great change in brain and body, and peripubertal male and female rats show a prolonged HPA response to acute stressors compared with adults (299, 300). While this prolonged response is not altered by the presence or absence of gonadal hormones (299, 300), 7 days of repeated restraint stress in male rats causes the HPA response to shut off more efficiently in the peripubertal rats and more slowly in the adult rats (298). Moreover, as noted earlier in this review, prepubertal rats that show higher anxiety respond to repeated stress as adults with a greater impairment of spatial memory in a Y maze and also show higher basal levels of corticosterone 1 mo after the end of chronic stress (27).

Although 3–4 wk of chronic stress in adult rats causes a reversible reduction in remodeling of dendrites and suppression of neurogenesis, prepubertal rats do show a delayed and prolonged effect of chronic stress on hippocampal development. A chronic variable stress regimen for 4 wk starting at postnatal day 28, prior to the onset of puberty, resulted in a stunting of growth of the CA1 pyramidal cell layer and in the dentate gyrus-granular cell layer, as well as the CA3 pyramidal cells, and yet there was no reduction of neuron number (140). The reduced volume was evident at 3 wk but not at 24 h after chronic stress and was accompanied by impairments in Morris water-maze performance and sustained downregulation in the basal hippocampal GR gene expression, and deficits in the shut-off of acute stress-induced corticosterone secretion (140).

Although the mechanism for the developmental effects of repeated stress are not known, data summarized at the beginning of this section suggest that the HPA axis is likely to play some role, as it does in stress effects on the adult hippocampus (see sect. v). Indeed, daily corticosterone treatment from 0–30 days resulted in a reduction of both volume and neuron number in both CA3 and dentate gyrus, whereas treatment of rats with daily corticosterone injections for 30–90 days starting in adult life produced no reductions of neuron number but did reduce volume of CA3 and dentate gyrus (333). Other differences between the effects of chronic corticosterone treatment and chronic stress will be discussed again below.

4. Mechanisms of structural remodeling

Exploration of the underlying mechanism for this remodeling of dendrites and synapses reveals that it is not adrenal size or presumed amount of physiological stress per se that determines dendritic remodeling, but a complex set of other factors that modulate neuronal structure (212) (Fig. 8 and Table 2). Indeed, in species of mammals that hibernate, dendritic remodeling is a reversible pro-

cess and occurs within hours of the onset of hibernation in European hamsters and ground squirrels, and it is also reversible within hours of wakening of the animals from torpor (17, 194, 272, 273). This implies that reorganization of the cytoskeleton is taking place rapidly and reversibly and that changes in dendrite length and branching are not "damage" but a form of structural plasticity.

Regarding the cellular and molecular mechanisms underlying structural remodeling, adrenal steroids are important mediators of remodeling of hippocampal neurons during repeated stress, and exogenous adrenal steroids can also cause remodeling in the absence of an external stressor (192, 332). The role of adrenal steroids involves many interactions with neurochemical systems in the hippocampus, including serotonin, endogenous opioids, calcium currents, GABA-benzodiazepine receptors, and excitatory amino acids (212), as summarized in Figure 8 and Table 2 (213). Central to all of these interactions is the role of excitatory amino acids, such as glutamate. Excitatory amino acids released by the mossy fiber pathway play a key role in the remodeling of the CA3 region of the hippocampus, and regulation of glutamate release by adrenal steroids may play an important role (212). The role of factors in regulating dendritic remodeling and synaptogenesis is summarized in Figure 8 and Table 2.

Among the consequences of restraint stress is the elevation of extracellular glutamate levels, leading to induction of glial glutamate transporters, as well as increased activation of the nuclear transcription factor phosphoCREB (384). Moreover, 21 days of CRS leads to depletion of clear vesicles from mossy fiber terminals and increased expression of presynaptic proteins involved in vesicle release (124, 196). Taken together with the fact that vesicles which remain in the mossy fiber terminal are near active synaptic zones and that there are more mitochondria in the terminals of stressed rats, this suggests that CRS increases the release of glutamate (196).

Extracellular molecules play a role in remodeling. Neural cell adhesion molecule (NCAM) and its polysialated-NCAM (PSA-NCAM), as well as L1 are expressed in the dentate gyrus and CA3 region and the expression of both NCAM, L1, and PSA-NCAM are regulated by 21 days of CRS (307). Tissue plasminogen activator (tPA) is an extracellular protease and signaling molecule that is released with neural activity and is required for chronic stress-induced loss of spines and NMDA receptor subunits on CA1 neurons (260).

Within the neuronal cytoskeleton, the remodeling of hippocampal neurons by CRS and hibernation alters the acetylation of microtubule subunits that is consistent with a more stable cytoskeleton (31) and alters microtubule-associated proteins, including the phosphorylation of a soluble form of tau, that is increased in hibernation and reversed when hibernation is terminated (17). Another cytoskeletal molecule is called M6a, a transmembrane glycoprotein belonging to the PLP family (11). Although the PLP family is the most abundant protein of central nervous system myelin, M6a is a neuronal protein, and its knock-down by siRNA results in decreased filopodial number and decreased synaptophysin expression, whereas overexpression of M6a has the opposite effect (11). Repeated stress in both rodents and tree shrews decreases M6a expression, an effect that is prevented by treatment with an antidepressant, tianeptine, that prevents stress-induced remodeling of dendrites in the CA3 region of the hippocampus (12). Chronic psychosocial stress in the tree shrew also downregulated a number of other gene transcripts associated with neurotrophic effects and cytoskeletal plasticity, including nerve growth factor (NGF) (13).

Neurotrophic factors also play a role in dendritic branching and length. For example, BDNF +/− mice show a less branched dendritic tree and do not show a further reduction of CA3 dendrite length with chronic stress, whereas wild-type mice show reduced dendritic branching after chronic stress (A.-M. Magarinos, B. McEwen, unpublished observations). At the same time, overexpression of BDNF prevents stress-induced reductions of dendritic branching in the CA3 hippocampus and results in antidepressant-like effects in a Porsolt forced-swim task (122). However, there is contradictory information thus far concerning whether CRS reduces BDNF mRNA levels in hippocampus, with some reporting a decrease (330) and other studies reporting no change (140, 169). This may reflect the balance of two opposing forces, namely, that stress triggers increased BDNF synthesis to replace depletion of BDNF caused by stress (202). BDNF and corticosteroids appear to oppose each other, with BDNF reversing reduced excitability in hippocampal neurons induced by stress levels of corticosterone (129).

Corticotrophin releasing factor (CRF) is a key mediator of many aspects related to stress (165). CRF in the paraventricular nucleus regulates ACTH release from the anterior pituitary gland, whereas CRF in the central amygdala is involved in control of behavioral and autonomic responses to stress, including the release to tPA that is an essential part of stress-induced anxiety and structural plasticity in the medial amygdala (204). CRF in the hippocampus is expressed in a subset of GABA neurons (Cajal-Retzius cells) in the developing hippocampus, and early life stress produces a delayed effect that reduces cognitive function and the number of CA3 neurons, as well as decreased branching of hippocampal pyramidal neurons (43, 44). Indeed, CRF inhibits dendritic branching in hippocampal cultures in vitro (55) (105).

5. *Functional consequences of structural remodeling in hippocampus*

CRS for 21 days causes impairments in memory in a radial arm maze and in a Y maze that can be prevented by

agents such as Dilantin and the antidepressant tianeptine, which prevent stress-induced remodeling of CA3 dendrites (65, 185, 391). In another study using a 1-mo chronic variable stress paradigm, stressed rats took longer to train in the initial Morris water maze trial the day after the last stress session, and they also were impaired in learning a new platform location in a probe trial (332). The effects of chronic stress on both morphology and learning disappeared within 1–2 wk after cessation of the daily stress regimen (68, 332), suggesting that it serves an adaptive function and does not constitute "damage." This notion, discussed above in relation to the dendritic remodeling during hibernation, is supported by the fact that dominant rats in a social hierarchy have somewhat larger reductions of CA3 dendritic length and branching compared with subordinate rats in the hierarchy, with both groups showing shorter dendrites than rats housed in groups in ordinary cages; adrenal size was larger in the subordinate rats (219).

Thus it is attractive to suppose that remodeling of dendrites in hippocampus is not only an adaptation to a behavioral situation but also possibly a protective strategy to reduce excitatory input and prevent permanent damage (212). Yet, there is evidence for enhancement of ibotenic acid-induced excitotoxic damage in the CA3 region in rats given 21 days of chronic restraint compared with unstressed rats (67). Interestingly, ibotenic acid damage to CA1 is not enhanced by chronic stress, and female rats do not show the stress-induced sensitization of damage in either CA3 or CA1 (67), nor do female rats show stress-induced remodeling of CA3 dendrites (112). Thus it is tempting to conclude that the remodeling of dendrites enhances excitotoxicity (64), but the only way to test that is to prevent remodeling and determine whether this makes damage less or worse. It is conceivable that damage would be much worse if dendritic remodeling were prevented, due to increased sensitivity to glucocorticoids (see below) along with undiminished excitatory input.

In spite of the focus on dendritic remodeling after repeated stress, it is apparent that chronic stress causes other changes in the brain besides dendritic remodeling in CA3, including effects on dentate gyrus neurogenesis (267), dentate gyrus dendritic remodeling (332), and dentate gyrus LTP (258). Moreover, 21 days of chronic restraint alters the ability of acute stress to affect hippocampal functions such as spatial memory, and here a change in sensitivity to glucocorticoids is involved (64). Using metyrapone to acutely reduce corticosterone levels in rats given 21 days of CRS resulted in prevention of the impairment of spatial memory seen in chronically stressed animals (392). And, yet, corticosterone levels in chronically stressed rats were only marginally higher during spatial maze training than in control rats during the maze training, indicating that there had been either a shift in sensitivity of the hippocampus to corticosterone or a qualitative change towards inhibition of the spatial task (392). Whatever the mechanism, these results also highlight the fact that stress-induced dendritic retraction, which was unlikely to have reversed itself in a matter of several hours during Y-maze training and metyrapone treatment, is not a sufficient condition for impairment of hippocampal dependent spatial memory (64). Rather, increased sensitivity to glucocorticoids is also a factor.

C. Variable Glucocorticoid Involvement in Structural Plasticity

There are a number of examples of altered responses to glucocorticoids in relation to structural plasticity. For neurogenesis in dentate gyrus, elevated glucocorticoid levels in an enriched environment or during physical activity are associated with increased neurogenesis and/or cell survival, even though there are other conditions in which glucocorticoids suppress neurogenesis (231). Chronicity of glucocorticoid elevation may play a role, with acute glucocorticoid elevation suppressing cell proliferation and prolonged glucocorticoid exposure ceasing to have this effect (231). Chronic restraint stress is known to reduce dentate gyrus proliferation, whereas acute restraint does not have any measurable effect (266). In contrast, the ability of physical activity to elevate neurogenesis depends on the social housing environment, that is, individual housing of rats that results in elevated corticosterone levels prevented running from acutely increasing neurogenesis. Yet, reducing corticosterone levels by adrenalectomy and supplementation with corticosterone in the drinking water reinstated the positive effect of exercise on neurogenesis (345).

This implies a shift in glucocorticoid sensitivity, and a possible factor may be excitatory neurotransmission. NMDA receptors play a role in regulation of neurogenesis, having both positive and negative effects in different experimental settings (242), and blocking NMDA receptors prevents acute glucocorticoid effects on neurogenesis (47), indicating that the role of excitatory amino acids is a primary one. In this connection, it is important to recall the different effects of stress on memory that depend on the state of arousal and the timing with the learning situation (144) (see Fig. 7). Moreover, the possible involvement of nongenomic effects of adrenal steroids must be considered (see above).

1. Effects of chronic glucocorticoid administration on morphology and memory

Chronic corticosterone treatment by injection or by passive administration in the drinking water are both able to cause dendrites to retract in CA3 hippocampus (192, 332, 389). Moreover, the effects of injected corticosterone are known to be blocked by Dilantin, an inhibitor of ion

channels that has antiepileptic effects, a result that is consistent with the evidence that glutamate is involved in remodeling (370). Yet, there is an important difference between the effects of repeated stress and chronic glucocorticoid exposure, in that chronic corticosterone treatment was reported to reduce the volume fraction occupied by mitochondria in the CA3 region (61) while, as noted earlier, 21 days of CRS increases mitochondrial profiles in mossy fiber terminals (196). This suggests that somewhat different mechanisms may be involved in effects of CRS and corticosterone in hippocampus, a possibility that is supported by the finding that, while both corticosterone treatment in the drinking water and 21 days of CRS both caused CA3 remodeling when given alone, the combination of CRS plus corticosterone treatment abolished the morphological change (195). These mechanistic differences remain to be determined.

In spite of the possible differences in mechanism, chronic corticosterone treatment and chronic restraint or immobilization stress both cause impairment of hippocampal-dependent memory tasks, although there are differences in magnitude of effect that appear to be dependent on dose of corticosterone, duration of treatment, age of rat being treated, and whether or not the cognitive task is a demanding one (15, 23, 24, 34, 60, 77, 99, 221). These studies indicate that only more prolonged treatment by higher glucocorticoid doses are able to impair performance on more demanding tasks involving hippocampal function and that they do so under conditions in which there is no neuronal loss but there are reductions in volume of hippocampal neuropil that may be due to loss of glia cells or reduction of dendritic length and branching. Given these results with rodents, it is not so surprising that a relatively modest regimen of cortisol treatment for 12 mo did not cause outright neuronal loss in the pigtail macaque hippocampus (177).

D. Prefrontal Cortex and Amygdala

Acute and repeated stress (21 days of CRS) also cause functional and structural changes in other brain regions such as the prefrontal cortex and amygdala. CRS and chronic immobilization caused dendritic shortening in medial prefrontal cortex (41, 70, 168, 282, 284, 332, 363, 373) but produced dendritic growth in neurons in amygdala (363), as well as in orbitofrontal cortex (181). These actions of stress are reminiscent of recent work on experimenter versus self-administered morphine and amphetamine, in which different, and sometimes opposite, effects were seen on dendritic spine density in orbitofrontal cortex, medial prefrontal cortex, and hippocampus CA1 (295). For example, amphetamine self-administration increased spine density on pyramidal neurons in the medial prefrontal cortex and decreases spine density on orbitofrontal cortex pyramidal neurons (75).

Along with many other brain regions, the amygdala and prefrontal cortex also contain adrenal steroid receptors (6, 8); however, the role of adrenal steroids, excitatory amino acids, and other mediators has not yet been studied in detail in these brain regions, in contrast to the hippocampus. Nevertheless, glucocorticoids do appear to play a role, since 3 wk of chronic corticosterone treatment was shown to produce retraction of dendrites in medial prefrontal cortex (373), although with subtle differences in the qualitative nature of the effect from what has been described after chronic restraint stress (283). Another study determined the effect of adrenalectomy or either chronic treatment for 4 wk with corticosterone or dexamethasone on volume and neuron number in the prefrontal cortex (53). Dexamethasone treatment at a dose that may have been high enough to enter the brain (although this was not directly measured) caused a loss of neurons in layer II of the infralimbic, prelimbic, and cingulate cortex, whereas corticosterone treatment reduced the volume but not the neuron number of these cortical regions (53). The dexamethasone treatment was particularly effective in impairing working memory and cognitive flexibility using working memory task in a Morris water maze (53). Effects of chronic stress were not investigated in this study. These data notwithstanding, the cautions expressed above concerning differences between chronic stress and chronic glucocorticoid treatment must be kept in mind for the prefrontal cortex, as well as the amygdala, that has not been studied yet in this regard.

Behavioral correlates of CRS-induced remodeling in the prefrontal cortex include impairment in attention set shifting, possibly reflecting structural remodeling in the medial prefrontal cortex (181). Attention set shifting is a task in which a rat first learns that either odor or the digging medium in a pair of bowls predicts where food reward is to be found, then new cues are introduced and the rat needs to learn which ones predict the location of food (33). There is also a report that chronic restraint stress impairs extinction of a fear conditioning task (230). This is an important lead since the prefrontal cortex is involved in extinction, a type of learning (309), but much more research is needed to explore the complex relationship between stress, fear conditioning, extinction, and possible morphological remodeling that may well accompany each of these experiences.

Regarding the amygdala, chronic stress for 21 days or longer not only impairs hippocampal-dependent cognitive function (212) but it also enhances amygdala-dependent unlearned fear and fear conditioning (68), which are consistent with the opposite effects of stress on hippocampal and amygdala structure. Chronic stress also increases aggression between animals living in the same cage, and this is likely to reflect another aspect of hyperactivity of the amygdala (385). Moreover, chronic corticosterone treatment in the drinking water produces an anxiogenic

effect in mice (16), an effect that could be due to the glucocorticoid enhancement of CRF activity in the amygdala (72, 198).

As for mechanism of remodeling, besides the possible role of glucocorticoids and excitatory amino acids, tPA is required for acute stress to activate not only indices of structural plasticity but also to enhance anxiety (227). These effects occur in the medial and central amygdala and not in basolateral amygdala, and the release of CRF acting via CRF-1 receptors appears to be responsible (204). Nothing is yet known about the role of tPA, if any, in the prefrontal cortex, although tPA does appear to play a role in stress-induced reductions of spine synapse number in the CA1 region of the mouse hippocampus (260), as noted earlier.

BDNF may also play a role in amygdala, since overexpression of BDNF, without any applied stressor, enhances anxiety in an elevated plus maze and increases spine density on basolateral amygdala neurons, and this occludes the effect of immobilization stress on both anxiety and spine density (122). As noted above for hippocampus, BDNF overexpressing mice also show reduced behavioral depression in the Porsolt forced-swim task and show protection against stress-induced shortening of dendrites in the CA3 region (122).

E. Interactions Between Amygdala, Prefrontal Cortex, and Hippocampus

The prefrontal cortex, amygdala, and hippocampus are interconnected and influence each other via direct and indirect neural activity (9, 118, 208, 209, 264). For example, inactivation of the amygdala blocks stress-induced impairment of hippocampal LTP and spatial memory (160), and stimulation of basolateral amygdala enhances dentate gyrus field potentials (139) while stimulation of medial prefrontal cortex decreases responsiveness of central amygdala output neurons (281). The processing of emotional memories with contextual information requires amygdala-hippocampal interactions (268, 293), whereas the prefrontal cortex, with its powerful influence on amygdala activity (281), plays an important role in fear extinction (229, 236). Because of these interactions, future studies need to address their possible role in the morphological and functional changes produced by single and repeated stress.

F. Sex Differences in Stress Effects

There are sex differences in the effects of stress on the hippocampus and amygdala, whereas nothing is yet known about the prefrontal cortex in this regard. Chronic foot shock stress for 3 wk caused a decrease in proliferation in dentate gyrus in singly housed male rats but caused an increase in proliferation in female rats, and both effects were prevented by group housing (375). CRS-induced retraction of dendrites in the CA3 region of hippocampus is found in males but not in females unless the females are ovariectomized (112; G. Wood and B. McEwen, unpublished observations). Chronic restraint stress for 21 days has been reported to either enhance or have no effect on performance of female rats in a spatial learning task, while having an inhibitory effect in males (37, 38, 66, 185, 220). Interestingly, as noted above, females did not show the chronic stress-induced enhancement of ibotenic acid-induced damage in the CA3 region, in contrast to chronically stressed male rats (67). In basolateral amygdala, chronic restraint stress increased dendritic length in males and in estradiol-treated females, but not in ovariectomized females (Wood and McEwen, unpublished observations). Furthermore, as another example of a sex difference, acute tail shock restraint stress produces opposite effects on classical eye blink conditioning, enhancing performance in males and reducing it in females (383), and both developmental and adult activation effects of gonadal hormones are involved (324). Further discussion of sex differences is beyond the scope of this article, and the reader is referred to reviews on why sex differences are important for the study of brain function (45, 161, 215).

V. TRANSLATION TO HUMAN BRAIN, BEHAVIOR, AND SOCIAL ORGANIZATION

Translation of the already vast amount of information on stress effects on the brain and body from animal models to the human organism, and vice versa, is an enormous challenge, yet there has already been considerable progress, some of which has already been noted throughout this review. This section addresses three topics with a distinct human flavor: *1*) evidence for stress and glucocorticoid effects on human brain structure and activity in mood and anxiety disorders, chronic pain states, and in relation to gastrointestinal activity and food intake control; *2*) new insights into brain-body interactions associated with "positive health" and low self-esteem; and *3*) current understanding as to how socioeconomic status affects brain and body health. Indeed, the translation is not one-way, and a significant part of the information on brain-body interactions and health implications has come from studies on human populations and individuals. The discussion in this section of the review will pave the way for the next section, namely, a discussion of brain-centered interventions for our own species that will reduce stress and the negative consequences of allostatic overload.

A. Brain Structure and Function

Much of the impetus for studying the effects of stress on the structure of the human brain has come from the animal studies summarized thus far. Although there is very little evidence regarding the effects of ordinary life stressors on brain structure, there are indications from functional imaging of individuals undergoing ordinary stressors, such as counting backwards, that there are lasting changes in neural activity that coincide with the elevation of cortisol levels (368). Moreover, the study of depressive illness and anxiety disorders has also provided some insights. Life events are known to precipitate depressive illness in individuals with certain genetic predispositions (50, 156, 158). Moreover, brain regions such as the hippocampus, amygdala, and prefrontal cortex show altered patterns of activity in PET and fMRI and also demonstrate changes in volume of these structures with recurrent depression, namely, decreased volume of hippocampus and prefrontal cortex and amygdala (92, 321, 323). Yet, amygdala volume has been reported to increase in the first episode of depression, whereas hippocampal volume is not decreased (111, 191).

Studies of autopsy tissue from individuals suffering from long-term major depression have provided some insights into what may be going on. They have revealed loss of glial cells and not neurons in hippocampus (344), which is consistent with, but not proof of, a retraction of dendrites in this brain region. The amygdala and prefrontal cortex of chronically depressed individuals also show evidence of glial cell loss (286, 322).

Although there is dysregulation of cortisol secretion in many people with depressive illness (394), it is not clear so far whether the elevation or dysregulation of cortisol plays a direct role in changes in brain structure and function. However, Cushing's disease provides some clues of what cortisol can do. In Cushing's disease, there are depressive symptoms that can be relieved by surgical correction of the hypercortisolemia (240, 338). Both major depression and Cushing's disease are associated with chronic elevation of cortisol that results in gradual loss of minerals from bone and abdominal obesity. In major depressive illness, as well as in Cushing's disease, the duration of the illness and not the age of the subjects predicts a progressive reduction in volume of the hippocampus, determined by structural MRI (323, 337).

Moreover, there are a variety of other anxiety-related disorders, such as posttraumatic stress disorder (PTSD) (39) (270) and borderline personality disorder (94), in which atrophy of the hippocampus has been reported, suggesting that this is a common process reflecting chronic imbalance in the activity of adaptive systems, such as the HPA axis, but also including endogenous neurotransmitters, such as glutamate.

More generally, it has been known for some time that stress hormones, such as cortisol, are involved in psychopathology, reflecting emotional arousal and psychic disorganization rather than the specific disorder per se (303). Thus the dysregulation of cortisol and other mediators that form the network of allostasis, as summarized earlier in this review, is likely to play a role in many psychiatric disorders as well as systemic disorders such as diabetes in which there are often psychiatric manifestations (288). Indeed, another important factor in hippocampal volume and function is glucose regulation, as noted above in section II. Poor glucose regulation is associated with smaller hippocampal volume and poorer memory function in individuals in their 60s and 70s who have "mild cognitive impairment" (MCI)(69), and both MCI and type 2, as well as type 1, diabetes are recognized as risk factors for dementia (80, 127, 255).

Not all the effects of elevated HPA activity are bad in terms of brain function, and in the case of PTSD, there is evidence that inadequate cortisol responses to traumatic events make an individual more vulnerable to developing PTSD (316–318). A recent animal stress study using the Lewis rat, which produces low levels of glucocorticoid in response to stress, provides supporting information, in that corticosterone administration before exposure to predator stress in the form of well-soiled cat litter reduced the poststress anxiety (63).

B. Stress, Fatigue, and Idiopathic Pain Disorders

There are a number of syndromes that have overlapping occurrence with PTSD and with each other. Chronic fatigue syndrome (CFS) and idiopathic chronic pain conditions, such as fibromyalgia and irritable bowel syndrome (IBS), appear to reflect an imbalance in mediators of allostasis, as depicted in Figure 5*D* (84, 110, 206). These conditions are also associated with symptoms of PTSD (110). Multiple mediators of allostasis and end points of allostatic load are reported to be altered, for example, in CFS, accompanied by low aldosterone, low urinary cortisol, and elevated waist-hip ratio, as well as increased bodily pain and poor physical functioning (119, 199). Lower than normal cortisol and aldosterone are associated with higher than normal levels of proinflammatory cytokines in CFS (110, 233). However, a specific and uniform dysfunction of the HPA axis is unlikely to be a key feature of CFS; rather, imbalances in other hormones such as dehydroepiandrosterone (DHEA) and abnormal serotonergic function are also implicated, along with the above-mentioned elevations in cytokines, pointing to a broader disruption of the network of allostasis (59). Yet, certain alleles of the glucocorticoid receptor have been associated with CFS (285).

There is also an overlap of these symptoms with those of "burnout," a condition associated with emotional

exhaustion, depersonalization, lack of satisfaction with personal accomplishment, and low self-esteem (114, 137, 277). Although lower than normal cortisol has been reported in burnout along with higher than normal sensitivity to dexamethasone suppression of the HPA axis, this is not always reported, and the underlying physiology is undoubtedly more complex, as it appears also to be for CFS and idiopathic chronic pain disorders (234, 235, 331). Increased risk for type 2 diabetes has been reported in chronic burnout in otherwise healthy individuals (226).

Psychological distress and strong emotions play an important role in promoting the symptoms of idiopathic pain disorders such as IBS, fibromyalgia, and temperomandibular joint disorder (87, 135, 292). In IBS, as also in other chronic pain conditions, there are alterations in activation of brain regions associated with central arousal, pain, and strong emotions, including brain stem, the insula, amygdala, hippocampus, and cingulate cortex among other brain regions (19, 172, 207, 243, 388). Reduction in dopaminergic activity in the nucleus accumbens may play a key role along with elevated NMDA receptor-mediated activity in brain regions, including the hippocampus (386, 387). Elevated CRF is associated with sensory and emotionally driven pain symptoms, although not with CFS (222). One of the unanswered questions is whether there is structural remodeling of brain areas involved in these processes, which, along with chemical imbalances in 5-HT-, CRF-, dopamine-, and NMDA-mediated neural activity, would help explain the apparent sensitization of the brain to pain stimuli. When considering pain and brain activation associated with pain, it is important to recognize the role of brain mechanisms in the placebo effect, in which perceptions of pain can be manipulated by expectations (28, 365). This further emphasizes the importance of cognitive processes in top-down regulation of the body.

C. Stress and Cognitive Control of Food Intake

Along with sleep deprivation (sect. III), stress often triggers eating of comfort foods (78). Besides the hypothalamus (98), the hippocampus has also been linked to disturbances of food intake and body weight regulation, primarily for its ability to limit unrestricted food intake. Lesions of the hippocampus lead to increased body mass due to increased food intake (79). Obese and recovered obese subjects differ from lean individuals in showing lesser activation of posterior hippocampus after consuming a satiating meal; the persistence of activity in never-obese lean individuals is consistent with other findings that the hippocampus actively contributes to control of food intake (79, 83). This conclusion is further supported by a study of electrical stimulation-induced vagus nerve activity leading to gastric distension as a satiety inducer, in which the right hippocampus showed increased activation that was associated with scores on an "emotional eating" measure (367). Besides hippocampus, gastric distension increased activity in right anterior cerebellum, orbitofrontal cortex, and striatum, regions previously shown to be involved in drug craving, suggesting a broader role of these brain structures in regulating the craving for rewarding stimuli (367).

D. New Insights Into Positive Health and Self-Esteem as Brain-Body Interactions

"Positive health" and self-esteem are two uniquely human-oriented concepts that, nevertheless, have been recently subject to illumination based on the concepts and findings discussed in this review. Having a positive outlook on life and good self-esteem appear to have long-lasting positive health consequences (275), and good social support has a positive influence to reduce the measures of allostatic overload (319). Positive affect, assessed by aggregating momentary experiences throughout a working or leisure day, was found to be associated with lower cortisol production and higher heart rate variability (showing higher parasympathetic activity, a sign of cardiac health), as well as a lower fibrinogen response to a mental stress test (341).

On the other hand, poor self-esteem has been shown to cause recurrent increases in cortisol levels during a repetition of a public speaking challenge in which those individuals with good self-esteem are able to habituate, i.e., attenuate their cortisol response after the first speech (162). Furthermore, poor self-esteem and low internal locus of control have been related to 12–13% smaller volume of the hippocampus, as well as higher cortisol levels during a mental arithmetic stressor (276, 278). As noted above in section II, the elevated cortisol may be both a cause and a result of the smaller hippocampus, which is consistent with the glucocorticoid cascade hypothesis of Sapolsky (311).

Related to both positive affect and self-esteem is the role of friends and social interactions in maintaining a healthy outlook on life. Loneliness, often found in people with low self-esteem, has been associated with larger cortisol responses to wakening in the morning and higher fibrinogen and natural killer cell responses to a mental stress test, as well as sleep problems (340). On the other hand, having three or more regular social contacts, as opposed to zero to two such contacts, is associated with lower allostatic load scores (319).

E. Socioeconomic Status and Health

Differences in income and education, collectively referred to as "socioeconomic status" (SES) have significant

effects on mortality and morbidity for a number of diseases, with low SES faring worse than middle SES and much worse than high SES individuals in industrialized western societies (4, 5). The SES differences are also evident, in a linear fashion from low to high SES, for predisease conditions such as obesity and metabolic syndrome (42) and fibrinogen (201, 378), as well as substance abuse and anxiety and mood disorders (210). Subjective SES, that is, where people rate themselves on a scale of income and education, is also an effective predictor of health status (329, 390). Possible mediators of the subjective SES-health link include negative affect over such issues as economic insecurity associated with low SES and sense of control related to socioeconomic position (329), as well as low self-esteem.

VI. MANAGEMENT OF CHRONIC STRESS AND ALLOSTATIC LOAD AND OVERLOAD

A. Brain-Centered Interventions

Because the brain is the central organ of the stress response, it is a primary target for interventions intended to reduce the burden of chronic stress, as defined by the concept of allostatic load and overload. In general, brain-centered interventions are very familiar in everyday life. They involve changing behavior and life-style, for example, by improving sleep quality and quantity, improving social support, and cultivating a positive outlook on life, along with maintaining a healthy diet, avoiding smoking, and engaging in regular, moderate physical activity.

These types of changes are usually more easily said than done. Yet, policies of government and the private sector can play a major role in promoting this, as they have done for smoking cessation and wearing of seat belts in automobiles, by creating incentives at home and in work situations and also by building community services and opportunities that encourage the development of beneficial individual life-styles.

The intention of this section of the review is not to exhaustively review this area; that is the subject of textbooks of health psychology and the target of policy discussions at all levels of government and in the private sector. Rather, this portion of the review will discuss physiologically relevant aspects of an area that is now called "social neuroscience" (http://www.social-neuroscience.com/) that is beginning to address the effects of the social environment on the brain and the physiology that it regulates. We shall make note of some of the recent work on effects and mechanisms of two types of interventions for stress and allostatic load, namely, exercise and social support, and the combination of the two, after first acknowledging the important role of pharmaceutical agents along with their limitations.

B. Pharmaceutical Agents

It is important to note that there are many useful pharmaceutical agents, such as sleep medications, anxiolytics, beta blockers, and antidepressants, that counteract some of the problems associated with being stressed out. Likewise, drugs that reduce oxidative stress or inflammation, block cholesterol synthesis or absorption, and treat insulin resistance or chronic pain can help deal with the metabolic and neurological consequences of being "stressed out." All of these medications are valuable to some degree, yet each one has its side effects and limitations, as illustrated by recent problems with the cyclooxygenase-2 inhibitors for chronic inflammatory pain (308).

Because of the nonlinearity of the systems of allostasis, the consequences of any drug treatment may be either to inhibit the beneficial effects of the systems in question or to perturb other systems that interact with it in a direction that promotes an unwanted side effect. An example is the use of anti-inflammatory agents to treat fever associated with an infection (245). Because the fever is a sign of the body's attempt to fight the infection, it is unwise to suppress the fever completely. On the other hand, septic shock represents the excessive, unregulated response of the defense system to an infection that can be lethal (35, 245). Thus some means of containing such responses are needed, and both glucocorticoids and activation of parasympathetic responses are helpful (35, 239). In addition to pharmaceuticals, there are two behavioral interventions, namely, physical activity and social support, where there has been some progress in understanding how they may benefit brain and body functions associated with allostasis and allostatic load.

C. Physical Activity

A sedentary life-style is a major risk factor for many of the diseases of modern life including obesity, diabetes, cardiovascular disease, depression, and dementia, and recent studies have shown that moderate physical activity can be beneficial for the brain and cardiovascular and metabolic systems (22, 29, 167, 263, 302). Voluntary physical activity has been shown to increase neurotrophin expression in cortex and hippocampal regions of the brain (73), as well as to increase neurogenesis in the dentate gyrus of young as well as aging animals (357). One mechanism for these effects involves the actions of circulating IGF-I, which is taken up by the brain and acts via receptors found in the hippocampus, as summarized early in this article. Moreover, increased neurogenesis in dentate gyrus has been linked to the actions of antidepressant drugs, providing a potential parallel with the antidepressant actions of physical activity (95, 251). Increased neurogenesis improves memory (382), and new neurons are

believed to participate in learning of hippocampal-dependent tasks (176). Although the role of neurogenesis in dentate gyrus is still controversial, new neurons appear to be more excitable and may contribute to greater cognitive flexibility (150, 382). Related to effects of exercise on neurogenesis is the effect of dietary restriction, which also increases neurogenesis and elevates the level of BDNF in hippocampus (173). BDNF is an important factor in current thinking about the actions of antidepressant treatments (369), including the consequences for hippocampal volume, memory, and mood disorders of having the Val66Met allele of the BDNF gene (130, 142, 265, 349).

D. Social Support

Another behavioral intervention that has begun to be investigated in terms of brain and body health is "social support." Social support "is composed of emotional and instrumental support. It is an advocative interpersonal process characterized by reciprocal exchange of information; it is context specific and it results in improved mental health" (106). Social support in the form of having regular social contacts with supportive friends or family or health professionals, who provide emotional support and provided useful information, has been shown to reduce the allostatic load score, which measures key physiological markers related to chronic stress and a potentially health-damaging life-style (319). Social support also ameliorates the type of chronic stress in caregivers that has been associated with reduced length of telomeres in white blood cells (100). So far nothing is known about how social support may benefit brain circuits that are affected by chronic stress and allostatic load, although it is clear that social support has beneficial effects on mood and overall mental health (3, 175, 315, 327).

Beyond the question of how emotional and instrumental support benefit the individual, a somewhat broader review of social support is how the policies of government and employers act to encourage creation of a compatible social environment for adopting health-promoting behaviors. The Acheson Report (2) from the United Kingdom in 1998 recognized that no public policy of virtually any kind should be enacted without considering the implications for health of all citizens. Thus basic education, housing, taxation, setting of a minimum wage, and addressing occupational health and safety and environmental pollution regulations are all likely to affect health via a myriad of mechanisms. At the same time, providing higher quality food and making it affordable and accessible in poor, as well as affluent neighborhoods, is necessary for people to eat better, providing they also learn what types of food to eat (93). Likewise, making neighborhoods safer and more congenial and supportive (154, 304) can improve opportunities for positive social interactions and increased recreational physical activity. However, governmental policies are not the only way to reduce allostatic load. For example, businesses that encourage healthy life-style practices among their employees are likely to gain reduced health insurance costs and possibly a more loyal workforce (10, 262, 376).

Finally, there are programs in existence that combine some of the key elements just described, namely, physical activity and social support, along with one other ingredient that is hard to quantify, namely, finding meaning and purpose in life. One such program is the Experience Corps that takes elderly volunteers and trains them as teachers' assistants for younger children in the neighborhood schools (109). Not only does this program improve the education of the children, it also benefits the elderly volunteers and improves their physical and mental health and slows age-related decline of function (314). It will be important to see how this program may more directly benefit the function of the brain circuits that are responsive to chronic stress and allostatic load. This program has now been adopted as a key part of a successful political campaign for the governorship of the state of Maryland (Abbruzzese, R. O'Malley and Brown Release Detailed Plan to Support Maryland's Aging Population. Press Release, Jan. 24, 2006), illustrating that politicians and policy makers do sometimes make use of what physiology and neuroscience are learning.

VII. CONCLUSIONS

The intent of this review has been not only to summarize salient facts pertaining to the central role of the brain in the effects of stress on brain-body interactions over the life course, and the protective and damaging paradox of these interactions, but also to provide a conceptual framework for future studies that will infuse physiology and neuroscience into the better mechanistic understanding of complex stress-related social problems and their solution by every means available: biological, behavioral, sociological, and political.

As the interpreter of and responder to what is stressful, the adult brain is a malleable organ and adapts structurally and functionally to experiences including those which are stressful and potentially deleterious. These changes do not necessarily constitute "damage" but may, nevertheless, be long lasting, and it is their spontaneous reversal or reversal by behavioral and pharmaceutical means that may be the key to treatment of anxiety, mood, and other stress-related behavioral disorders.

Events early in life affect how the brain responds to stressors throughout adult life and influences the aging process as well as susceptibility to the diseases of modern life, such as cardiovascular disease, diabetes, and depression. This connection occurs in part because the nervous

system regulates and responds to systemic processes via the neuroendocrine, autonomic, and immune systems. Social factors, along with physical activity, have a powerful impact on brain development, structure, and function throughout the life course and thereby affect the health of the body as well. Therefore, manipulations of the social environment via policies of government and the private sector, along with promoting increased physical activity, health life-style, and social support at an individual level, can help encourage individual behavior change, that, in turn, is an effective way of counteracting the deleterious effects of chronic stress as an adjunct and, in some cases, alternative to pharmaceutical therapy.

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