Effects of Early Adverse Experiences on Brain Structure and Function: Clinical Implications

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Child abuse is associated with markedly elevated rates of major depression and other psychiatric disorders in adulthood. This article reviews preclinical studies examining the effects of early stress, factors that modify the impact of these experiences, and neurobiological changes associated with major depression. Preclinical studies demonstrate that early stress can alter the development of the hypothalamic-pituitary-adrenal axis, hypothalamic and extrahypothalamic corticotropin releasing hormone, monoaminergic, and γ-aminobutyric acid/benzodiazepine systems. Stress has also been shown to promote structural and functional alterations in brain regions similar to those seen in adults with depression. Emerging data suggest, however, that the long-term effects of early stress can be moderated by genetic factors and the quality of the subsequent caregiving environment. These effects also can be prevented or reversed with various pharmacologic interventions. Preclinical studies of early stress can provide valuable insights in understanding the pathophysiology and treatment of major depression. They also can provide an important tool to use to investigate interactions between genes and environments in determining an individual's sensitivity to stress. More research is needed to understand how inherent factors interact with experiences of abuse and other psychosocial factors to confer vulnerability to develop depression. Biol Psychiatry 2000;48:(8) 778–790 © *2000 Society of Biological Psychiatry* a+ 15

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Introduction

Child abuse is a pervasive social problem that is frequently associated with long-term significant psychiatric sequelae. Each year there are more than one million substantiated reports of child maltreatment (U.S. Department of Health and Human Services, National Center on Child Abuse and Neglect 1997), and numerous studies indicate that countless other cases never come to the attention of authorities (e.g. Wolfner and Gelles 1993). In clinic (Brown and Anderson 1991; Windle and Houston 1995), community (Bifulco et al 1991), and representative epidemiologic samples (Holmes and Robins 1987), experiences of early child maltreatment have been associated with elevated rates of major depression (MDD), anxiety, and other psychiatric disorders.

Preclinical studies suggest that stress early in life can promote long-term changes in multiple neurotransmitter systems and brain structures implicated in the etiology of MDD (Arborelius et al 1999; Heim et al 1997). It is hypothesized that neurobiological changes associated with adverse early experiences can confer a vulnerability for the development of MDD and other psychiatric disorders. It is also suggested that preclinical studies of early stress can provide a valuable model for understanding the pathophysiology of MDD, even when it occurs independent of early childhood trauma (Charney and Deutch 1996).

This article is organized into five sections. The first section reviews functional connections among key structures and neurotransmitter systems involved in the initiation and control of the stress response. The second section reviews preclinical studies examining the long-term effects of early stress on hypothalamic-pituitary-adrenal (HPA) axis function and central corticotropin releasing hormone (CRH), monoaminergic (norepinergic, dopaminergic, serotonergic), and γ-aminobutyric acid/benzodiazepine (GABA/BZ) systems. Structural and functional brain changes associated with early or severe stress are also reviewed. The next section reviews factors that modify the impact of early stress, and pharmacologic interventions that can prevent or reverse the neurobiological alterations are delineated. Lastly similarities in the neurobiological correlates of stress and depression in adults are highlighted, and the clinical implications of the research are discussed.

Key Structures and Neurotransmitter Systems Involved in the Stress Response: Overview

The brain appears to respond to stress in a complex and orchestrated manner, with both general and stimuli-spe-

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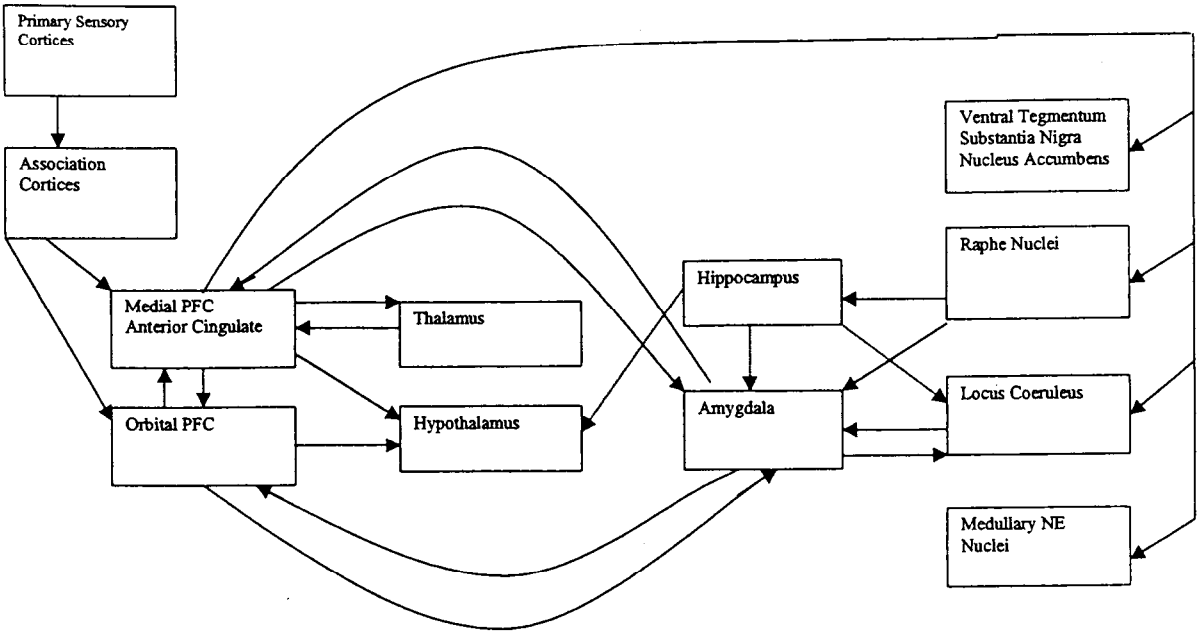

Figure 1. Key cortical and subcortical structures involved in the stress response. The medial prefrontal cortex (PFC), anterior cingulate, and orbital PFC relay information from primary sensory and association cortices to subcortical structures involved in the stress response. The medial and orbital PFCs are reciprocally interconnected. The medial and orbital PFCs provide direct inputs to the hypothalamus and are reciprocally connected with the amygdala. Not shown in the diagram are indirect connections from these prefrontal structures to the hypothalamus and amygdala via inputs to the periaqueductal gray and parabrachial nucleus. The medial PFC is also reciprocally connected with the mediodorsal thalamic nucleus and has extensive connections with the ventral tegmental area, substantia nigra, nucleus accumbens, raphe, locus coeruleus, and brainstem autonomic nuclei. These connections facilitate initiation and regulation of the endocrine response to stress that is mediated by the hypothalamic–pituitary–adrenal (HPA) axis, and the autonomic response to stress that is promoted by the locus coeruleus. Connections among brainstem nuclei, the hippocampus, amygdala, and HPA axis are detailed in Figure 2. Solid line, stimulatory inputs; dotted line, inhibitory inputs; NE, norepinephrine.

cific components to the stress response (Lopez et al 1999). Knowledge about the structural and functional components of the stress system is still evolving. The review of the stress response included in this section is not exhaustive. It focuses on key components of the stress system and emphasizes the structures and neurotransmitter systems most extensively studied in preclinical studies examining the long-term effects of early stress. The reader is referred to Chrousos (1998) and Lopez et al (1999) for a more detailed discussion of the central and peripheral components of the stress system.

Figure 1 depicts the functional connections among the different cortical and subcortical brain regions involved in the stress response. There is growing appreciation of the role of cortical inputs, with medial prefrontal cortex (PFC), anterior cingulate, and orbital PFC currently understood to play an important role in relaying information from primary sensory and association cortices to subcortical structures involved in the stress response (Lopez et al 1999). Medial and orbital PFC are reciprocally interconnected, and each has indirect connections with the hypothalamus and amygdala via inputs to the periaqueductal gray and parabrachial nucleus (An et al 1998; Bernard and Bandler 1998; Krout et al 1998). The medial and orbital prefrontal cortices also provide direct inputs to the hypothalamus and are reciprocally connected with the amygdala (Ongur et al 1998). These prefrontal regions appear to be critical in restraining the acute stress response and facilitating negative feedback inhibition of the system (Herman and Cullinan 1997). The medial prefrontal cortex (mPFC) also is reciprocally connected with the mediodorsal thalamic nucleus (Groenewegen 1988) and has extensive connections with the ventral tegmental area, substantia nigra, nucleus accumbens, raphe, locus coeruleus, and brainstem autonomic nuclei (Drevets et al 1998).

Figure 2 depicts in more detail the relationships among subcortical structures involved in the stress response and the neurotransmitter systems involved in the transmission of information between the different brain regions. Corticotropin releasing hormone is the neurohormone that initiates the endocrine response to stress. It is secreted from the paraventricular nucleus (PVN) of the hypothalamus. Among the numerous inputs to the PVN, noradrenergic inputs are primary in promoting the synthesis and release of CRH into the median eminence and hypophysial portal system (Plotsky et al 1989). The main noradrenergic

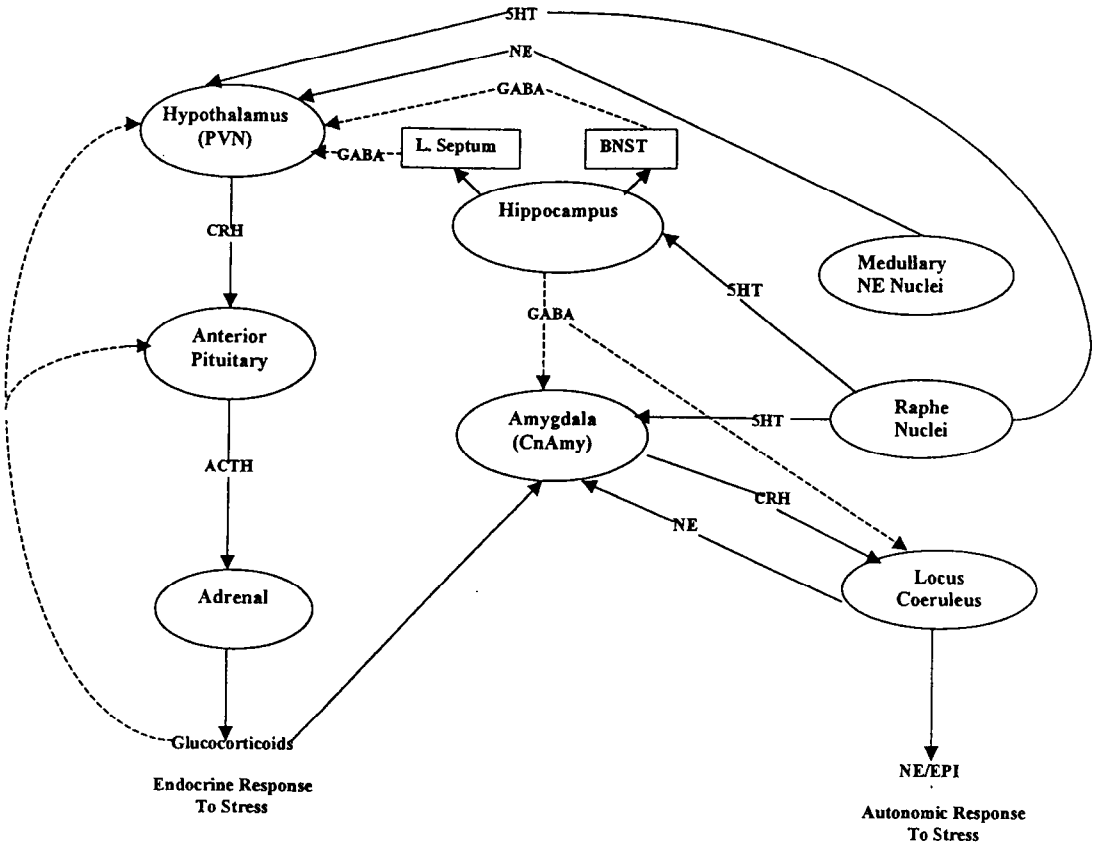

Figure 2. Key subcortical structures and neurotransmitter systems involved in the stress response. The release of corticotropin-releasing hormone (CRH), a neurohormone, from the paraventricular nucleus (PVN) of the hypothalamus initiates the endocrine response to stress. Then CRH promotes the release of adrenocorticotropin (ACTH) from the pituitary, which initiates the release of glucocorticoids from the adrenals. Glucocorticoids provide negative feedback at the pituitary and PVN, among other sites. The release of CRH from the PVN is modified by multiple neurotransmitters, but norepinephrine (NE) inputs from medullary nuclei provide the primary stimulus for CRH synthesis and release. In addition, CRH acts as a neurotransmitter to initiate the autonomic response to stress. The autonomic component of the stress response is initiated by CRH inputs from the central nucleus of the amygdala (CnAmy) to the locus coeruleus. Glucocorticoids provide positive stimulation to the CnAmy, which promotes the synthesis and release of CRH. The hippocampus serves to inhibit the stress response via multiple direct and indirect γ-aminobutyric acid–ergic (GABAergic) inputs to the PVN, amygdala, and locus coeruleus. The stress response is further modified by serotonin (5-HT) inputs from the raphe nuclei to the PVN, hippocampus, and amygdala. GABAergic interneurons located at each of the structures likely further modify stress reactivity, as do connections from multiple other brain regions including the prefrontal cortex, thalamus, association cortex, and mesocortical and mesolimbic structures. Solid lines, stimulatory inputs; dotted lines, inhibitory inputs; L. Septum, lateral septum; BNST, bed nucleus stria terminalis; EPI, epinephrine.

inputs into the PVN appear to be derived from medullary sources, the nucleus of the solitary tract (NTS) and the ventrolateral medullary oblongata (Pacak et al 1995). Corticotropin releasing hormone then binds to receptors at the anterior pituitary gland and, through a cascade of intracellular events, increases pro-opiomelanocortin (POMC) gene expression and the release of POMC-derived peptides such as adrenocorticotropin and β-endorphin. Adrenocorticotropin (ACTH) then promotes the synthesis and release of glucocorticoids (cortisol in primates, corticosterone in rats) from the adrenal cortex (Arborelius et al 1999). Glucocorticoids regulate energy substrate availability and utilization and provide negative feedback to the stress system at the pituitary, hypothalamus, and other central sites involved in the stress response.

In addition, CRH appears to act centrally as a neurotransmitter to initiate the autonomic and behavioral changes observed in response to stress (Valentino et al 1998), as central nervous system administration of CRH has been found to produce physiologic and behavioral changes similar to those reported in animals subjected to stress (Owens and Nemeroff 1991). Centrally administered CRH antagonists also have been found to reduce stress induced increases in plasma catecholamines, tyrosine hydroxylase mRNA in the locus coeruleus (LC), and CRH mRNA and type 1 CRH receptor mRNA in the PVN (Jezova et al 1999).

The LC appears to be the critical site in initiating the catecholamine response to stress because local application of exogenous CRH in the LC has been found to increase norepinephrine (NE) release in the PVN, hippocampus, and prefrontal cortex (Page and Abercrombie 1999; Valentino et al 1998). The LC receives endogenous CRH inputs from the central nucleus of the amgydala (CnAmy). The amygdala is activated during stress by ascending catecholamine neurons originating in the brainstem and by cortical association neurons involved in processing stressful stimuli via direct and indirect medial and orbital prefrontal cortical connections (Lopez et al 1999). Corticotropin releasing hormone neurons of the CnAmy respond positively to glucocorticoids and activate the LC/NE component of the stress system (Lopez et al 1999).

The hippocampus, in contrast, serves to inhibit the stress response via multiple direct and indirect links with several of the brain structures activated during stress (Lopez et al 1999). For example, CRH synthesis in the CnAmy is inhibited by GABA inputs from the hippocampus (Owens and Nemeroff 1991). The hippocampus also inhibits the LC via direct connections and inhibits the PVN via indirect inputs through the lateral septum and bed nucleus of the stria terminalis.

The stress response is further modified by serotonin inputs from the dorsal and median raphe to the basolateral and central nucleus of the amygdala, serotonin inputs from the dorsal raphe to the PVN, and serotonin inputs form the median raphe to the hippocampus (Lopez et al 1999). These latter serotonin (5-HT) neurons terminate on inhibitory GABA neurons.

Both the PVN CRH and LC/NE systems also innervate the mesocortical and mesolimbic components of the dopaminergic (DA) system (Chrousos 1998). The mesocortical system includes DA neurons of the ventral tegmentum that send projections to the medial prefrontal cortex, and the mesolimbic system consists of DA neurons from the same region that innervate the nucleus accumbens. The mesocortical system is involved in anticipatory and cognitive functions and exerts a suppressive effect on the stress system, and the mesolimbic system is involved in processing motivation and reward aspects of experience.

Neurobiological Effects of Early Stress: Preclinical Studies

Building on the seminal work of Levine and colleagues (Coe et al 1978; Levine et al 1993; Wiener et al 1987), numerous investigators have demonstrated long-term neurobiological changes in animals subjected to multiple prenatal and postnatal stress paradigms (Graham et al 1999; Takahashi and Kalin 1991). Similar neurobiological alterations have been reported across experimental conditions, with multiple systems implicated in the pathophysiology of depression affected by these investigational manipulations.

Extensive research has been conducted examining the neurobiological effects of early maternal separation, with these experiences associated with increased CRH and NE drive in adulthood (Francis et al 1999a; Ladd et al 1996; Liu et al 2000). Rat pups separated from their mothers 6 hours per day during the first 3 weeks of life have been found to have increased basal and stress induced ACTH concentrations and decreased CRH binding in the anterior pituitary (Ladd et al 1996). Maternal deprivation has also been associated with increased CRH mRNA expression in the hypothalamic paraventricular nucleus (PVN) and increased CRH concentration in the median eminence (Plotsky and Meaney 1993). It also has been associated with increased CRH mRNA expression in the CnAmy, increased CRH content in the parabrachial nucleus (a region that adjoins the LC, increased CRH binding in the LC, and increased NE concentration in the PVN (Menzaghi et al 1993). Nonhuman primates subjected to maternal separation early in life have also been found to have elevated cerebral spinal fluid NE in response to an acute stressor (Kraemer et al 1989). For reviews, see Francis et al (1999) and Ladd et al (2000).

The increase in CRH and NE drive in maternally deprived rats also is associated with a decrease in tone of the inhibitory GABA/BZ system (Caldji et al 2000; Francis et al 1999b). Specifically, adult rats subjected to repeat separations from their mothers during the first 3 weeks of life have been found in adulthood to have reduced $GABA_A$ receptor binding in the CnAmy, basolateral nuclei of the amygdala (BnAmy), and the frontal cortex. They also have been found to have reduced central benzodiazapine binding in the CnAmy, BnAmy, LC, and NTS. These effects were associated with decreased expression of mRNA for the γ_2 subunit that encodes for the benzodiazapine site of the $GABA_A$ receptor. In addition, adult rats separated from their mothers during the first 3 weeks of life also had increased mRNA expression for the α_2 and α_3 subunits and decreased expression of the α_1 subunit mRNA (Caldji et al 2000). This profile is associated with decreased GABA binding (Wilson 1996). It is likely that the dampened GABAergic tone in rats exposed to maternal separation animals contributes to the enhanced CRH expression in the amygdala and the increased stress-induced activation of the noradrenergic systems (Francis et al 1999b).

In a set of related experiments (Braun et al 2000; Poeggel et al 1999), Braun and colleagues examined the impact of early maternal separation and social isolation on the development of efferents to frontal areas believed to be analogous to the mPFC in humans and other primates.

Specifically, Octodon Degus rodents were separated from their mothers three times a day for 1 hour from postnatal day 1 to postnatal day 21. After weaning, the deprived animals were reared in isolation in single cages until postnatal day 45. They were then sacrificed, and monoamine fiber innervation to the frontal areas was examined using immunocytochemical detection of tyrosine hydroxylase (TH) and 5-HT.

When compared with rodents reared under undisturbed conditions, maternally deprived and socially isolated rats had significantly reduced TH-positive fiber innervation in the precentral medial, anterior cingulate, and prelimbic cortex subdivisions of the mPFC and increased 5-HT-positive fiber densities in the infralimbic cortex (nomenclature according to Groenewegen 1988). The number of TH-positive somata in the ventral tegmental area and in the substantia nigra did not differ between the groups, suggesting that the reduced fiber densities were likely due to suppressed axonal sprouting and aborization. Maternally deprived and socially isolated animals, in addition to having altered DA/5-HT balance in the mPFC, were also found to have a significant decrease of nicotinamide adenine dinucleotide phosphate (NADPH)-diphorase-reactive neurons in the anterior cingulate cortex and the core region of the nucleus accumbens, as well as a trend for reduced NADPH-diphorase-reactive neurons in the infralimbic, precentral medial, and prelimbic prefrontal areas (Poeggel et al 1999). Because some NADPH-containing neurons have been found to be GABAergic, the reduced NADPH-diphorase neurons may represent a loss of inhibitory interneurons in this cortical region, which plays a critical role in integrating affective and cognitive information processing.

Rhesus monkeys reared under isolated nursery conditions from 8 weeks of age also have been found to exhibit enhanced anxiety, increased self-directed behaviors, decreased social interaction, and impaired cognitive performance when tested at 18 to 24 months of age (Sanchez et al 1998). These animals also have shown reductions in medial and caudal midbody corpus callosum volume, probably reflecting a reduction in the number of cross-hemispheric fibers (Sanchez et al 1998). The nursery-reared animals also exhibited increased CRH1 receptor binding sites in the dentate gyrus of the hippocampus and the orbital prefrontal cortex, with increased CRH2 receptor binding in amygdala subregions (Sanchez et al 1999). These findings do not contradict the hypothesis concerning the role of central CRH oversecretion in the pathophysiology of depression because peptide oversecretion does not always result in receptor down regulation and has been found to cause upregulation in certain brain regions (Imaki et al 1996; Mansi et al 1996).

In an attempt to more closely parallel the experience of neglectful parenting and exposure to stressful environments in young human infants, Coplan et al (1996) subjected macaque infant–mother dyads to variable foraging demands. Primates in the low foraging demand condition had easy access to food; primates in the high foraging demand condition had to work hard to find food, but foraging demands and food supply were predictable; and primates in the variable foraging demand condition experienced changing and unpredictable access to food. In adulthood, consistent with the maternal deprivation rodent studies discussed above, monkeys reared in the variable foraging condition had higher cerebral spinal fluid CRH concentration than did monkeys reared under the two other more predictable and less stressful experimental conditions (Coplan et al 1996). The variable foraging condition was also associated with over activity of the NE system, with these animals as adults showing enhanced behavioral response to yohimbine, an α_2 adrenergic antagonist (Rosenblum et al 1994).

In contrast, to the negative effects of early stress, rats provided positive stimulation via 15 minutes of handling per day during the first 3 weeks of life have been found to have reduced stress reactivity in adulthood compared with nonhandled or maternally separated rats (Plotsky and Meaney 1993). Specifically, in adulthood, rats handled in the first 3 weeks of life showed decreased fearfulness in novel environments. The neurobiological alterations associated with early handling are essentially the opposite of those reported in maternally separated rats. Handled rats showed reduced ACTH and corticosterone response to exogenous stressors, with quicker return of corticosterone to baseline levels. They showed enhanced negative feedback of circulating glucocorticoids and increased glucocorticoid receptor mRNA expression and glucocorticoid receptor number in the hippocampus and the frontal cortex, sites involved in the inhibitory control of CRH synthesis in PVN neurons. Accordingly, handled rats had reduced CRH mRNA levels in the PVN and reduced basal CRH concentration in the median eminence. Handled rats also had reduced CRH mRNA concentrations in the CnAmy and lower CRH content in the LC (Francis et al 1999b; Ladd et al 2000). They also had attenuated CRH induced activation of the LC and smaller resulting increases in extracellular NE levels in the PVN after acute restraint stress (Liu et al 2000). Handled rats had increased $GABA_A$ receptor levels in noradrenergic cell body regions of the LC and NTS, as well as increased central benzodiazepine receptor levels in the CnAmy, LC, and NTS (Francis et al 1999b). In addition, handled rats had attenuated age-related cell loss in the hippocampus and improved performance on hippocampal mediated cognitive tasks (Meaney et al 1991, 1993). For reviews, see Ladd et al (2000) and Francis et al (1999b).

The maternal deprivation and postnatal handling studies clearly highlight the importance of early experience on the development of the brain and multiple neurotransmitter systems. The stress effects on hippocampus development are likely mediated by a minimum of three forms of structural plasticity: neuronal atrophy, neurotoxicity, and neurogenesis. Neuronal atrophy in the CA3 region of the hippocampus can be caused by 3 weeks of exposure to stress or stress levels of glucocorticoids (Sapolsky 1996; Woolley et al 1990). At this level, glucocorticoids produce a reversible decrease in number of apical dendritic branch points and length of apical dendrites of sufficient magnitude to impair hippocampal dependent cognitive processes (Watanabe et al 1992). More sustained stress or glucocorticoid exposure can lead to neurotoxicity—actual permanent loss of hippocampal neurons. Rats exposed to high concentrations of glucocorticoids for approximately 12 hours per day for 3 months experience a 20% loss of neurons specific to the CA3 region of the hippocampus (Sapolsky et al 1985). Evidence of stress-induced neurotoxicity of cells in this region has been reported in nonhuman primates as well (Sapolsky 1996; Uno et al 1994). Reductions in hippocampal volume may also be affected by decreases in neurogenesis (Gould and Cameron 1996). The granule cells in the dentate gyrus of the hippocampus continue to proliferate into adulthood, and neurogenesis in this region is markedly reduced by stress. See articles in this volume by Sapolsky, Gould, and McEwen for further discussion of these topics.

Factors Moderating the Impact of Early Stress

The studies reviewed in the prior section demonstrate that early life experiences can have profound effects on brain structure and function; however, there is emerging data to suggest that the subsequent caregiving environment can moderate the adverse effects of early stress. In conducting the handling experiments, Meaney and colleagues noted that there were marked differences in the maternal behavior of the mothers of handled and nonhandled pups, with the former group spending significantly more time licking and grooming their offspring than the latter group (B. C. Woodside, M. J. Meaney, J. Jans, unpublished observations).

To determine if the differences in maternal behavior were related to differences in stress reactivity of handled and nonhandled rats, Meaney and colleagues examined multiple indices of stress reactivity in adult rats reared by mothers with similar naturally occurring differences in maternal behaviors (Caldji et al 1998; Francis et al, unpublished data; Liu et al 1997) 1999). They found that the adult offspring of high licking and grooming mothers reared without any experimental manipulations showed greater exploration in novel environments and had reduced plasma ACTH and corticosterone response to acute stress. The animals also showed increased hippocampal glucocorticoid receptor mRNA expression, enhanced glucocorticoid negative feedback sensitivity, and decreased hypothalamic CRH mRNA levels. They also had decreased CRH mRNA expression in the CnAmy, increased central benzodiazepine receptor number in the CnAmy and LC, decreased CRH receptor density in the LC, and decreased stress induced NE secretion from the PVN. These results parallel the findings observed in handled rats and suggest that maternal licking and grooming behaviors may "program" the development of the neural systems that mediate reactivity to stress (Caldji et al 1998). These studies raised questions as to whether the neurobiological changes associated with handling were due to the early experimental manipulation or to subsequent differences in maternal behavior.

To determine if the neurobiological changes associated with early handling could be altered by subsequent caregiving experiences, rat pups exposed to early handling or maternal separation experiences were cross-fostered with dams whose pups were assigned the same or opposite condition (Gonzalez et al 1999). In the initial set of experiments, handled pups were either cross-fostered to other dams assigned to the handled condition or to dams assigned to the maternal separation condition. Similar cross-fostering was performed on pups exposed to the maternal separation condition. When tested as adults, the handled pups cross-fostered to dams assigned to the maternal separation condition reacted to novel stressors like rats subjected to maternal separation during the neonatal period. Conversely, maternally separated pups reared by dams assigned to the handling condition were more similar to handled animals.

In a second set of experiments (Gonzalez et al 1999), dams assigned the handling and maternal separation conditions were provided with an age-matched foster litter during the period when their own pups were away. This simple manipulation seemed to normalize maternal behavior by the dams whose pups were separated for 180 minutes, and the adult offspring that had been assigned to the maternal separation condition appeared similar to handled animals rather than similar to maternally separated animals. These findings are consistent with the results of studies examining the effects of prenatal stress. In these studies "adoption" with "optimal parenting" also has been found to reverse the HPA axis alterations typically observed in these experiments (Barbazanges et al 1996; Maccari et al 1995). These results are consistent with emerging data delineating the seminal role of different components of mother–infant interaction (e.g., tactile

stimulation) in regulating physiologic systems involved in the stress response (Caldji et al 1998; Kuhn and Schanberg 1998).

The cross-fostering experiments clearly demonstrate that the effects of early experiences can be moderated by subsequent rearing experiences. Because the influence of genetic factors or strain effects has been well established in preclinical studies of stress reactivity (Dhabhar et al 1997), the cross-fostering studies raise questions as to whether manipulations in parenting can overcome genetic and breed differences in stress reactivity. To address this question, Meaney and colleagues subjected BALB/cByJ and C57BL/6ByJ mice to early handling experiences and randomly assigned them to BALB/cByJ or C57BL/6ByJ mothers for subsequent rearing (Anisman et al 1998; Zaharia et al 1996). The BALB/cByJ mice are inherently high reactors and have elevated corticosterone and brain catecholamine responses to acute stressors. In addition, mice of this strain exhibit impaired performance on a Morris water-maze that is exacerbated by foot-shock application. Early handling of BALB/cByJ mice reduced the learning impairments seen when mice were tested in the Morris water-maze as adults and prevented stress-induced elevations of corticosterone and disturbances with task performance. Likewise, cross-fostering BALB/cByJ mice with C57BL/6ByJ dams prevented corticosterone hyperactivity and performance deficits; however, cross-fostering and handling did not alter stress-induced changes in NE concentration in the hypothalamus, LC, hippocampus, or prefrontal cortex. Early handling and cross-fostering of the more resilient C57BL/6ByJ mice had no impact on maze performance, corticosterone stress reactivity, or brain NE. A similar set of findings was reported by investigators studying two different high- and low-reactive rat species (Steimer et al 1998). Effects of handling and cross-fostering were only observed in the high-reactive rats, and these experimental manipulations only affected stress induced corticosterone levels, not central NE measures.

These studies highlight the need for a better understanding of the interactions between genes and environmental interactions in determining an individual's stress reactivity and vulnerability to depression. They suggest that species with more intrinsic reactivity are more responsive to the effects of environmental manipulations than are less intrinsically reactive species and that environmental manipulations have greater impact on some neurobiological systems (e.g., HPA axis) than on others (e.g., central NE). The clinical and research implications of these findings are far reaching. They imply that there are multiple pathways to the development of depression and that phenotypes with similar neurobiology may have distinct etiologies. The Human Genome Project and evolving methodologies such as gene chips that permit the simultaneous analysis of thousands of genes will help to identify the relevant genes that promote hyperstress reactivity and will facilitate the identification of homogenous subgroups of patients with depression for future neurobiological and genetic studies (Watson and Akil 1999).

Neurobiological Effects of Early Stress: Pharmacologic Prevention and Treatment

The long-term, stress-related changes in brain structure can be altered by multiple pharmacologic interventions. Emerging data suggest that in addition to glucocorticoids, serotonin and excitatory amino acids (EAA) are involved in the mechanisms that promote neuronal atrophy, neurotoxicity, and neurogenesis (Gould 1999; McEwen et al 1997; Sapolsky 1996). Consistent with these findings, several classes of medications have been found to prevent dendritic atrophy caused by stress, including serotonin reuptake enhancers (e.g., tianeptine), benzodiazepine agonists (e.g., adinazolam), the antiseizure drug phenytoin (which reduces EAA release), and adrenal steroid inhibitors (Magarinos et al 1999; McEwen et al 1997; Sapolsky 1996). Tianeptine, in addition to preventing reduction in number of apical dendritic branch points and length of apical dendrites, also reverses already established hippocampal atrophy (Magarinos et al 1999). Surprisingly, given the clinical effectiveness of selective serotonin reuptake inhibitors (SSRI) in treating depression, fluoxetine and fluvoxamine do not block dendritic atrophy caused by repeated restraint stress (Magarinos et al 1999). Paroxetine, an SSRI with less serotonergic-specific properties can reverse the HPA axis alterations observed in adult rodents subject to repeat maternal separation during the neonatal period (Plotsky, unpublished data). In addition, in adult primates subject to maternal deprivation in infancy, electroconvulsive therapy and chronic tricyclic antidepressant (e.g., imipramine) treatments have also been found to reverse HPA axis overactivation following acute and chronic stress (Lopez et al 1999; Suomi 1991).

Similarities in the Neurobiological Correlates of Stress and Depression: Clinical Implications

As outlined in Table 1, many of the biological alterations associated with early stress have been reported in adults with depression and other stress-related disorders. For example, adults with depression have been reported to have multiple alterations of the HPA axis, including increased basal cortisol secretion (Schildkraut et al 1989), reduced negative feedback as evidenced by dexamethasone nonsuppression (American Psychiatric Association

Table 1. Neurobiological Effects of Early Stress: Clinical Implications

Preclinical findings	Clinical findings	The implications
1. Early stress is associated with increased central CRH and NE drive in adulthood.	Adults with depression have increased CSF CRH and NE secretion. Many effective antidepressants downregulate central NE receptors.	The CRH antagonist drugs may represent a new class of antidepressant and anxiolytic medications.
2. Early stress promotes decreased tone in the inhibitory central GABA/BZ system.	Adults with depression have reduced cortical GABA.	Medications that selectively modulate in specific brain regions the biosynthesis of ALLO, a neurosteroid that potently facilitates GABA transmission, may be another novel class of antidepressant and anxiolytic medication.
3. Early stress is associated with altered development of monoaminergic fibers in the mPFC.	Studies of adults with depression have reported structural and functional alterations in the mPFC and in connected brain regions (e.g., amygdala).	Better understanding of the mechanisms involved in the development of mPFC fibers may also identify noval targets for pharmacologic treatments for MDD.
4. Early stress is associated with hippocampal atrophy.	Clinical investigations utilizing MRI indicate that adults with depression have reduced hippocampal volume. Degree of atrophy correlates with total duration of illness, raising questions as to whether these changes represent primary disturbances associated with depression onset or secondary brain changes related to recurrence.	Longitudinal studies of depressed patients with repeat neurobiological assessments at different stages of illness are needed (e.g. first episode vs. third or greater). Early and aggressive therapeutic intervention may be important in preventing neurobiological alterations associated with MDD.
5. Effects of early stress can be moderated by subsequent caregiving experiences.	Clinical studies also indicate that positive attachment relations can ameliorate the deleterious effects of early abuse.	This highlights the importance of clinical interventions aimed at securing permanent and secure placements for maltreated children to optimize the likelihood of good long-term outcomes.
6. Effects of early stress can be moderated by genetic factors.	Twin studies suggest that individuals at high genetic risk for affective disorders are more likely to develop depression following stressful life events than are individuals at low genetic risk.	The human genome project and evolving technologies will help to identify the relevant genes that infer risk.

CRH, corticotropin-releasing hormone; NE, norepinephrine; CSF, cerebrospinal fluid; GABA/BZ, γ-aminobutyric acid/benzodiazepine; ALLO, allopregnanolone; mPFC, medial prefrontal cortex; MDD, major depression; MRI, magnetic resonance imaging.

1987; Carroll 1982); and blunted ACTH secretion in response to administration of endogenous CRH (Gold et al 1986; Holsboer et al 1987; Plotsky et al 1998). They also have been found to have increased central CRH drive, as evidenced by reports of elevated concentrations of cerebral spinal fluid CRH (Nemeroff et al 1992), and reduced CRH receptor binding site number in the frontal cortex of suicide victims (Nemeroff et al 1988). Depressed adults also have been found to have higher cerebral spinal fluid NE concentration (Wong et al 2000) and decreased cortical GABA measured in vivo using proton magnetic resonance spectroscopy (Sanacora et al 1999). Altered DA/5-HT balance also has been reported in adults with depression (Reddy et al 1992), with fluoxetine treatment associated with increases in cerebral spinal fluid DA/5-HT metabolite concentration ratios (De Bellis et al 1993; for a discussion of the similarities in the neurobiological correlates of stress and clinical findings in studies of patients with posttraumatic stress disorder, see Arborelius et al 1999; Charney et al 1998).

Studies of adults with depression have also reported structural and functional alterations in the mPFC. Specifically, adults with depression have been found to have reduced gray matter volume in the subgenual PFC (Drevets et al 1997), as well as decreased blood flow and glucose metabolism in this region (Drevets et al 1992). In addition, preliminary histopathologic data from the subgenual PFC suggest that depressed patients have a decrease in glia number in this region without a corresponding loss of neurons (Drevets et al 1998). Reduced glucose metabolism in the ventromedial PFC (Buchsbaum et al 1997) and decreased blood flow in the dorsal anterior cingulate also has been reported in depressed patients (Mayberg et al 1997). These two regions are contained in

the mPFC and overlap with the subgenual PFC. Altered glutamatergic transmission also has been reported in the anterior cingulate of depressed patients (Auer et al 2000).

Structural changes in the hippocampus have also been reported in several (Bremner et al 2000; Mervaala et al 2000; Shah et al 1998; Sheline et al 1996), but not all (Axelson et al 1993; Hauser et al 1989; Vakili et al 2000), studies of adults with depression. In two of the positive studies, degree of hippocampal atrophy was found to correlate with total duration of illness (Bremner et al 2000; Sheline et al 1996). This raises questions as to whether these changes represent primary disturbances associated with the onset of disorder or secondary brain changes related to recurrence and extended glucocorticoid exposure. Hippocampal volume reductions also have been reported in adults with posttraumatic stress disorder (Bremner et al 1995, 1997; Gurvits et al 1996; Stein et al 1997). Adults with depression also have been found to have a reduced volume of core amygdala nuclei (Sheline et al 1998), with abnormalities in resting blood flow and glucose metabolism reported in this area as well (Drevets et al 1999).

The section on factors that modify the impact of early stress discussed the importance of subsequent positive rearing experiences in ameliorating the deleterious effects of postnatal stress. As in the preclinical studies, the availability of a supportive parent or alternate guardian has been demonstrated to be one of the most important factors that distinguishes abused children with good developmental outcomes from those with more deleterious outcomes (Kaufman and Henrich 2000; Pynoos et al 1995). The importance of positive attachment relationships in modifying the adverse effects of early abuse has been demonstrated in studies examining the development of depressive disorders in maltreated children (Kaufman 1991), the intergenerational transmission of abuse (Egeland et al 1988; Kaufman and Zigler 1989), the persistence of antisocial behavior from adolescence to adulthood in maltreated youth involved with protective services (Widom 1991), and the severity of posttraumatic stress reactions in response to a wide array of stressors (Pynoos et al 1995). Facilitating the formation of permanent and secure positive relations is essential in promoting adaptive outcomes for children with a history of early child abuse and is an important focus for intervention with this clinical population (Kaufman and Henrich 2000; Larrieu and Zeanah 1998). Unfortunately, the development of positive and secure attachments is compromised for many maltreated children by failures in the child protection system (for further discussion, see Kaufman and Zigler 1996).

The section on factors that modify the impact of early stress also discussed the importance of genetic factors in modifying the impact of postnatal stress. Family and twin studies of adults with depression have highlighted the importance of genetic factors in understanding individual differences in stress reactivity and vulnerability to develop MDD. For example, in a recent, large, population-based twin study, individuals at high genetic risk for affective disorders were found to be more vulnerable to develop depression following stressful life events than were individuals at low genetic risk (Kendler et al 1995). Genetic and environmental effects are not easily separated, however, as both parent and child genetic factors influence the quality of the parent–child relationship and subsequent environmental experiences (Kendler 1996). More research is needed to understand the manner in which inherent factors interact with experiences of abuse and other psychosocial stressors to confer a vulnerability to develop depression (Kaufman et al 1998). Because child abuse is associated with an increased risk for a range of disorders (e.g., posttraumatic stress disorder, alcohol abuse, antisocial personality), a better understanding of the relevant genetic and environmental risk factors will help to explain differences in the clinical outcome of adults with a history of early child abuse.

Many of the medications found to prevent or reverse the behavioral and neurobiological effects of early stress discussed in the section on pharmacological interventions are effective agents in the treatment of adult depression. The finding of central CRH overdrive in preclinical studies of early stress and clinical studies of depressed adults suggest that CRH antagonists may represent a novel and effective antidepressant and anxiolytic medication for the treatment and prevention of stress-related mood and anxiety disorders (Arborelius et al 1999; Holsboer 1999). CRH_1 antagonist drugs are currently being developed, and randomized controlled trials in clinical populations will be forthcoming. Drugs that selectively modulate the biosynthesis of allopregnalone, a neurosteroid that potently facilitates central GABA transmission, may represent another novel class of antidepressant and anxiolytic medication (Guidotti and Costa 1998). No such medications currently exist.

There are currently few preclinical studies examining possible gender and developmental differences in the long-term impact of early stress on prepubertal, postpubertal, and mature rats, and available data are often conflicting. Preclinical studies highlight the importance of gender factors in understanding individual differences in stress reactivity (Bagdy 1998; Patchev and Almeida 1998). Data examining developmental changes in the acute effects of stress in rodents and nonhuman primates of different ages also suggests that this is an important focus of future research because the neurobiological changes associated with the acute-stress response change with age (Pihoker et al 1993; Suomi 1991; Vazquez 1998). In

addition, because many of the medications that are efficacious in adults with depression are no better than placebo in the treatment of children and adolescents with depression (Keller et al 1998), the utilization of a developmental framework in future preclinical and clinical studies will help to enhance our understanding of maturational changes in the long-term effects of early stress and help to explain developmental differences in the neurobiological correlates and treatment response of depressed patients of various ages.

Conclusion

The problem of child maltreatment is enormous in terms of both its costs to the individual and to society. Despite decades of preclinical research documenting the effects of early stress on the HPA axis and more recent research demonstrating the impact of stress on brain development, there has been surprisingly little research on the neurobiological sequelae of child abuse. Given the pervasiveness of this social problem, there is an urgent need for more research in this area.

The preclinical studies reviewed in this manuscript have important implications for understanding the pathophysiology and treatment of MDD. The studies provide a valuable heuristic for generating hypotheses regarding neurotransmitter systems, cortical structures, and neuronal circuits involved in the etiology of depression and suggest novel pharmacologic interventions that warrant future experimental investigation. They also highlight the importance of increasing our understanding of the genetic and environmental factors that confer vulnerability for the development of depression and other stress-related disorders.

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