Social Support and Resilience to Stress Across the Life Span: A Neurobiologic Framework

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This review discusses selected neurobiologic and genetic factors—including noradrenergic and hypothalamic-pituitary-adrenal axis markers, oxytocin pathways, and serotonin transporter and brain-derived neurotrophic factor gene polymorphisms—in the context of resilience to stress, with an emphasis on social support. Social support's impact on medical and psychiatric health outcomes is reviewed, and putative mediators are discussed. The reviewed literature indicates that social support is exceptionally important to maintaining good physical and psychological health in the presence of genetic, developmental, and other environmental risks. Future studies should continue to explore the neurobiologic factors associated with social support's contribution to stress resilience.

Introduction

Neurobiology of resilience to stress is an area of emerging interest. Many psychosocial factors appear to be associated with stress resilience. To date, stress inoculation, exercise, active coping, dispositional optimism, and social support have been shown to predict favorable outcomes after exposure to traumatic stress [1]. In this article, we first review some of the neurobiologic factors associated with stress resilience and then focus on the relationships among resilience, certain types of social support, health outcomes, and potential neurobiologic mechanisms that may explain social support's positive effects across the life span.

Putative Mechanisms Underlying Stress Resilience

Psychological stress leads to alterations in several neurochemicals that modulate neural circuits thought to be related to resilience, including circuits involved in the regulation of reward, fear conditioning, and social behavior [2]. For the purposes of this review, we highlight noradrenergic and pituitary markers, although others undoubtedly are also implicated in the emerging neurobiology of resilience [2].

During threatening situations, the sympathetic nervous system (SNS) releases epinephrine and norepinephrine to facilitate self-protective behaviors. Unconstrained SNS hyperresponsiveness may increase the risk for chronic anxiety and hypervigilance—responses that have been found in individuals diagnosed with post-traumatic stress disorder (PTSD) [3]. However, psychologically resilient individuals seem to maintain SNS activation within an optimal window that is high enough to respond to danger but not so high as to produce incapacity, anxiety, and fear [2,4,5]. Two neurochemicals that help to maintain SNS activity within an optimal window or range are neuropeptide Y (NPY) and galanin, which are released with norepinephrine when the SNS is strongly activated [1]. NPY inhibits the continued release of norepinephrine to prevent the SNS from "overshooting." In animals, NPY has been shown to have anxiolytic effects [6]. In depressed patients with low NPY levels, antidepressants have been shown to increase NPY [7]. High NPY levels during extreme training conditions are associated with better performance in highly resilient special operations soldiers (Special Forces) [5,8]. In contrast, combat-related PTSD has been associated with low resting and stress-induced NPY levels [9]. Galanin modulates anxiety-related behaviors by reducing the firing rate of the locus coeruleus. Stress is associated with increased norepinephrine release in the amygdala, and intra-amygdala injection of galanin blocks the anxiogenic effects of stress in rats [10,11]. In light of these findings, NPY and galanin emerge as pos-

sible stress resilience factors that serve as brakes on the overactivated noradrenergic system [2].

In addition to the SNS, the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the stress response. Stress exposure leads to the release of corticotropin-releasing hormone (CRH), which then stimulates adrenocorticotropic hormone (ACTH) release from the pituitary gland. ACTH in turn affects levels of cortisol and dehydroepiandrosterone (DHEA). Cortisol has highly complex effects on the organism, including increased arousal, selective attention, mobilization of energy stores, and memory consolidation. Cortisol is also known to inhibit growth, contain the immune response, and regulate brain regions important to the stress response [12]. However, cortisol's advantageous effects are short-lived. Chronically elevated cerebrospinal fluid CRH has been linked to major depression and PTSD in humans, and extreme elevations of cortisol in animals can have toxic effects on the body and brain, including neural degeneration in the hippocampus, a structure involved in learning and memory [13]. Damage to the hippocampus may weaken its ability to reduce HPA activation, resulting in even greater glucocorticoid levels, and a vicious cycle may ensue. DHEA is co-released with cortisol under conditions of extreme stress and may serve a protective function [14]. CRH-1 receptor activation has been associated with anxiety-like responses, whereas CRH-2 receptor stimulation has been associated with anxiolytic-like responses [15,16]. Regulation of these two CRH receptor types may well influence psychological and physiologic responses to stress. Administering corticotropin-releasing factor antagonists and/or DHEA under conditions of high stress may increase psychobiological resilience in some individuals [17]. Estrogen appears to have a beneficial short-term effect by blunting the HPA axis and noradrenergic responses to stress [18]; however, long-term elevations of estrogen caused by chronic stress may enhance HPA axis responses [2].

Brain circuits that regulate memory function, motivation, reward, responses to fear, and adaptive social behaviors play a central role in stress resilience, possibly by influencing pertinent personality traits. For example, optimal neural reward and motivation pathway functioning under challenging circumstances may be associated with an ability to maintain optimism when exposed to chronic stress and an unrewarding environment [2]. Optimal functioning of neural reward and motivation pathways may foster stress resilience by also facilitating social and altruistic behavior [19]. Reward circuits are regulated by a complex interplay of glutamate, *N*-methyl-D-aspartate receptors, dopamine, and dopamine receptors. Genetic and/or environmentally induced abnormalities in these functional interactions could facilitate vulnerability or resistance to anhedonia and hopelessness in the face of stress [2].

Resilience may be conceptualized as a capacity to be resistant to fear conditioning and/or a propensity to acquire fear extinction quickly and efficiently after exposure to a traumatic event. Various animal models have been studied to explore the neuroanatomic basis of fear conditioning. The medial prefrontal cortex and amygdala currently are considered the key brain structures in the formation and extinction of fear conditioning. The central nucleus of amygdala sends information to the brain stem and initiates fear responses (eg, freezing, elevated heart rate, and skin conductance) upon exposure to conditioned stimuli. LeDoux and Gorman [20] argued that active coping with the reminders of a traumatic event may prevent the conditioned fear response by engaging a different part of the amygdala, the basal nucleus, which sends information to the ventral striatum as opposed to the brain stem. It has been hypothesized that the optimal activation of the basal amygdala may enhance resilience by helping an organism actively cope with the reminders of a traumatic event instead of displaying disabling conditioned fear responses [20].

Genetic factors undoubtedly play a central role in stress vulnerability and resilience. For example, it is now well established that a polymorphism in the serotonin transporter (5-HTT) influences liability for major depression by increasing an individual's susceptibility to stressful life events [21]. Caspi et al. [21] showed that the long (l) allele of the *5-HTT* gene attenuates the effects of stressful life events by decreasing the risk for major depression and suicide attempts. This was the first genetic variant identified as an inherited "resilience factor." The same genetic polymorphism has been shown to decrease vulnerability to social stressors in women [22]. Kaufman et al. [23] reported that the brain-derived neurotrophic factor (*BDNF*) gene and *5-HTT* genes, in conjunction with low social support, cumulatively increased the depression risk in children. These preliminary findings are consistent with the stress-diathesis theory, which proposes that environmental stressors cause psychiatric symptoms only in the presence of genetic or developmental vulnerabilities. Individuals who carry certain alleles may be resilient to the effects of stress and its psychological sequelae. This inherited biologic resilience may be considered a first-line defense against the effects of stress and trauma. With the identification of additional "resilience genes" and the mechanisms via which they counter environmental stress, we may be able to conceptualize new biologic interventions to administer in the immediate aftermath of trauma to increase the victim's resilience.

Resilience to stress is unlikely to be explained by a single neurotransmitter, neuropeptide, hormone, or neural pathway. Investigators are now attempting to study multiple neurobiologic factors that can be used to create a profile that characterizes stress-resilient individuals.

Social Support and Resilience to Stress

Social support, defined as "support accessible to an individual through social ties to other individuals, groups,

and the larger community" [24], appears to be an exceptionally important stress resilience factor. Several lines of evidence indicate that positive social support reduces risk for PTSD and attenuates PTSD's impact on functional outcomes [4]. There has been growing interest within the scientific community in exploring social support's effects on medical and psychiatric morbidity and the neurobiologic mediators of these effects. We first review the emerging literature on the neurobiologic mediators of social bonding and support. We then present some of the literature focusing on the relationship between certain types of social support and health outcomes in various life stages with putative biopsychosocial mechanisms that may help to explain social support's beneficial impact across the life span.

Poor social support

Much preclinical literature has documented the deleterious effects of poor social support on health. For example, in a variety of animals, social isolation has been associated with increased heart rate and blood pressure, hypercortisolemia, and atherosclerosis; during separation and isolation, resting heart rate increases but returns to normal when cynomolgus monkeys are reunited with their social group [25]. Cortisol rises in squirrel monkeys [26] and wild baboons [27]. At postmortem examination, atherosclerosis has been found to be significantly greater in swine that have been isolated [28] and in female monkeys [25] living alone compared with those living in social groups. It also has been reported that chronic stress and lack of social support increase cardiac risk (eg, endothelial injury increases platelet accumulation), in part through prolonged sympathetic activation [29].

Potential mediators of social support

The literature suggests that neurobiologic factors play a role in forming social attachment and in mediating social support's beneficial effects on reversing stress-related behavioral and neuroendocrine changes. The neuropeptides oxytocin and vasopressin appear to regulate social attachment and promote positive social interactions in animals [30]. For example, type and duration of social attachments in voles have been shown to be associated with differential oxytocin and vasopressin receptor expression patterns in the ventral pallidum and medial amygdalae. Prairie voles, which are more social than montane voles, have more oxytocin receptors in the nucleus accumbens compared with montane voles, which typically avoid social contact, except during mating.

Oxytocin enhances maternal care and the learning of social cues in rats. Furthermore, it has anxiolytic effects that are associated with attenuated secretion of ACTH and corticosterone in lactating rodents. Maternal deprivation is associated with reduced cerebrospinal oxytocin levels and impairment in the ability to use social bonding to buffer against stressors in adult monkeys [31].

Preliminary evidence indicates that oxytocin is also implicated in regulating human social behavior. The Trier Social Stress Test is a laboratory stressor that involves simulating an aversive job interview and public speaking with negative feedback. Individuals who participated typically experienced robust increases in anxiety and salivary cortisol. However, those who were administered oxytocin reported lower anxiety and reduced cortisol responses during the test compared with those who received placebo. The same was true for people who were accompanied by a friend during the test. [32]. In this same study, individuals with the least amount of anxiety and lowest cortisol responses to stress were those who received the combination of oxytocin and social support. Taken together, these results suggest that oxytocin may inhibit the HPA axis reactivity to stress and promote social behavior. Results from a preliminary study suggest that at the neurocircuitry level, social support may modulate ventral anterior cingulated cortex and right dorsolateral prefrontal cortex activation in response to threat of shock [33•]. Future studies should continue to explore the neurobiologic basis of social bonding and the mediators of social support in humans [34•].

Maternal social support and childhood outcomes

Social support has been shown to have beneficial effects on pregnancy outcomes. Studies have examined the amount, type, and quality of social support received during pregnancy to determine its effect on several pregnancy outcomes, including labor complications, birth weight, Apgar scores, gestational age, and intelligence scores in offspring. For example, Elsenbruch et al. [35] prospectively studied 896 women who were classified as having low, medium, or high perceived social support. Measures were taken in the first trimester of pregnancy and after pregnancy completion. Results indicate that lack of social support can have adverse effects on pregnancy outcomes, including child body length, birth weight, and pregnancy complications, particularly if the woman smoked during pregnancy. Slykerman et al. [36] interviewed 550 European mothers of 3.5-year-old children who had enrolled in the Auckland Birthweight Collaborative Study when their children were born to determine whether an association exists among maternal stress, social support during pregnancy, and intelligence tests performed on their preschool children. Results indicated an association among maternal stress, lack of social support, and lower intelligence test scores, suggesting that social support may protect against the negative effects of maternal stress on intelligence. Herwig et al. [37] interviewed 100 mothers and their children who participated in a German mother–child rehabilitation program and found that maternal social support during pregnancy moderated behavioral problems in the offspring. Overall, these studies suggest that social support may influence pregnancy outcomes by acting as a protective measure against the deleterious effects of stress.

What are the mediators between maternal social support and childhood health outcomes? Yale Child Study Center researchers showed that mothers who maltreated their children had significantly fewer friends in their social support networks and reported less interaction with friends [38]. This study suggests that maternal social support may protect against psychiatric morbidity in the child by reducing the risk for maltreatment. Maternal social support may also enhance infant–mother attachment and thus buffer the association between family distress and negative childhood outcomes [39].

Early childhood: stress sensitization versus stress inoculation

It is well established in rodent and primate models that early variable and prolonged maternal separation is associated with heightened stress sensitivity or stress sensitization, as evidenced by enhanced release of ACTH [40] and cerebrospinal norepinephrine [41] and decreased inhibitory γ-aminobutyric acid-ergic tone and exaggerated behavioral reactivity in response to acute stress [42]. In rhesus monkeys, early social deprivation induces cognitive impairment, anxiety, and exaggerated neurobiologic stress reactivity in adulthood [43]. However, subsequent supportive maternal caregiving may reverse neurobiologic and behavioral alterations induced by early social deprivation [42,44]. These alterations, most notably HPA axis sensitization, also may be reversed by many psychotropic agents, such as selective serotonin reuptake inhibitors. In addition, cross-fostering experiments indicate that increased handling and maternal care may also reduce stress sensitivity associated with heritable factors in rats [45]. Taken together, these studies suggest that social support is an important resilience factor that may moderate the gene–environment interactions in the expression of stress response and the ensuing allostatic load.

Whereas early exposure to severe stress can cause sensitization of neurobiologic systems and behaviors, early mild to moderate stressors can actually have the opposite effect and result in stress inoculation. For example, when squirrel monkeys were exposed to brief, controlled, intermittent episodes of maternal separation during postnatal weeks 17 to 27, they exhibited lower basal plasma ACTH and cortisol, lower stress-induced cortisol levels, and diminished anxiety responses compared with nonstressed squirrel monkeys upon exposure to a novel environment [46]. These stress-inoculated monkeys were found to have superior prefrontal cortex function at 18 months of age compared with non–stress-inoculated monkeys [47].

Stress inoculation also likely occurs in humans, although relatively little formal published research has been conducted in this area. In a distressing laboratory test among adolescents, heart rate and blood pressure were reduced in individuals who had been exposed to mild stress in childhood [48]. In another study, hospitalized children who had had a previous positive experience of briefly separating from their parents while staying with their grandparents experienced less stress during their hospital stay [49]. However, no human studies to date have prospectively demonstrated a causal link between earlier stressful experiences and the development of stress resistance. Furthermore, the neurobiology underlying this probable link in humans is largely unknown.

Stress inoculation is a dynamic process that stands in contrast to stress sensitization, which involves chronic high stress exposure. The latter causes HPA axis overreactivity and is associated with impaired coping and psychiatric morbidity. However, stress inoculation confers stress resistance, possibly via brief, well-contained activations of the HPA axis and boosting of prefrontal cortex function, which may in turn optimize the neuroendocrine response to stress and enhance coping-oriented behavior. Subsequently, these changes likely reduce the allostatic load and help to prevent stress-related psychopathology. However, one can speculate that the same type and degree of stress may be inoculating for one individual and sensitizing for another. It may be speculated that the presence or absence of social support would predict in part whether a stressor will sensitize or inoculate an individual to future stressors. Further studies involving humans are needed to decipher the parameters of the complex relationship between stress inoculation and stress sensitization.

Social support and gene–environment interactions during development

As stated previously, genetic factors are thought to play an important role in predicting resilience to stress. Following the groundbreaking findings of Caspi et al. [21] that showed that a polymorphism in the promoter region of the serotonin transporter gene (*5-HTTLPR*) moderates an individual's susceptibility to life stressors, many studies have examined gene–environment interactions during child development. In a pioneering study, Kaufman et al. [50] reported that the combination of two short alleles of *5-HTTLPR* and maltreatment predict the highest depression scores. In a subsequent study, Kaufman et al. [23] demonstrated that positive social support can greatly reduce risk for depression in children with a history of maltreatment. Strikingly, this protective effect was most pronounced for maltreated children who were carriers of the previously mentioned genetic risk factors for depression. Taken together, these results clearly demonstrate that social support is an extremely important resilience factor that moderates risk for psychiatric morbidity caused by genetic and environmental factors in children.

Adulthood: health outcomes and behavioral mediators of social support

Many investigators have studied social support's impact on health outcomes during adulthood [51]. High levels of social support seem to reduce mortality and morbidity associated with many medical illnesses. For example,

Alameda County Studies showed that within a 9-year period, residents with strong social ties were significantly less likely to die from cardiovascular illness, stroke, and cancer [52]. Sapolsky [29] argued that the effect size of social support on all-cause mortality was similar to the effects of hypertension, nicotine dependence, and obesity. Mitchinson and colleagues [53•] recently showed that the degree of social connectedness positively correlates with postoperative pain in surgical patients. High levels of social support are associated with a reduced risk for comorbid depression in patients with multiple sclerosis [54], cancer [55], and rheumatoid arthritis [56]. Social support also moderates the functional impairment seen in depressed patients and predicts higher rates of remission of depressive symptoms [57,58]. Moreover, social support has been shown to be associated with a reduced risk for combat-related PTSD in Vietnam veterans [59]. Johnson et al. [60] argued that many Vietnam veterans found "homecoming" to be highly stressful due to lack of social support, which may have then increased their risk for PTSD. Similarly, poor social support seems to increase the risk for depression onset and relapse [61] and treatment resistance in dysthymia [62]. The association between social support and positive health outcomes is not unique to a particular sociodemographic or patient population. In fact, this relationship has been demonstrated in highly different populations, including—but not limited to—parents of seriously ill children, pregnant women, unemployed people, and college students [49].

Researchers have proposed several behavioral mediators via which social support may exert its protective effects. Rozanski et al. [63] speculated that social support's positive impact on physical health may be explained by the fact that individuals with good social support are less likely to engage in risky behaviors. Fontana et al. [64] argued that social support improves mental health by preventing negative cognitive appraisals. Resilient individuals are more likely to use active coping strategies in response to stressful life events [4]. Holahan et al. [65] reported that social support reduced the risk for depression in patients with heart disease by facilitating active coping styles. However, it may be argued that individuals who use active coping are more likely to attract social support than those who rely on passive avoidance coping.

Conclusions

Our review points out that resilience to stress is influenced by multiple genetic, neurobiologic, developmental, psychological, and social factors that interact in a complex fashion. Overwhelming evidence indicates that social support is immensely important in predicting health outcomes and resilience from infancy to old age. The optimal source of social support seems to depend on the developmental stage of the person receiving the support. For example, parental support seems to be more valuable in early adolescence [66] than in late adolescence. It has been shown that the perception of social support is associated with the degree of social interaction in older adults and with instrumental support in younger adults [67]. Moreover, the type of social support seems to be important in conferring resilience to stress. In a sample of adult childhood sexual abuse survivors, a combination of self-esteem support (the individual perceives that he or she is valued by others) and appraisal support (the individual perceives that he or she is capable of getting advice when coping with difficulties) was most useful in preventing PTSD development [68]. The neurobiology of human social bonding is highly complex and far from being understood. Similarly, the neurochemical mediators of social support's positive impact on mental and physical health outcomes are largely unknown. Preliminary studies suggest that oxytocin facilitates social bonding and may dampen HPA axis reactivity to psychological stressors in humans. Future studies likely will continue to explore the many complex interactions among genetic, neurobiologic, developmental, and psychosocial factors that impact resilience to stress.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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