The psychobiology of resilience and vulnerability to anxiety disorders: implications for prevention and treatment

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Much of the research on the neurobiology of human anxiety disorders has focused on psychopathological abnormalities in patients with anxiety disorders. While this line of research is obviously important, more investigation is needed to elucidate the psychobiology of resilience to extreme stress. Study of the psychobiology of resilience has the potential to identify neurochemical, neuropeptide, and hormonal mediators of vulnerability and resilience to severe stress. In addition, the relevance of neural mechanisms of reward and motivation, fear responsiveness, and social behavior to character traits associated with risk and resistance to anxiety disorders may be clarified. These areas of investigation should lead to improved methods of diagnosis, novel approaches to prevention, and new targets for antianxiety drug discovery.

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The anxiety disorders, including panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and posttraumatic stress disorder (PTSD), are among the disabling medical disorders. They frequently begin early in life, are characterized by repeated episodes and chronicity, and can have serious medical and psychological consequences leading to functional disability in many patients.

These disorders are currently diagnosed using standardized diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*] and *International Classification of Diseases* [*ICD-10*]), which are almost exclusively based upon phenomenology, and not genetics, etiology, or pathophysiology.[1] This has hampered progress in some spheres, since these disorders, as currently diagnosed, are often comorbid with each other, and advances in preclinical and clinical neuroscience suggest that there may be overlapping circuit and neurochemical modulation of behaviors that characterize one or more of these disorders.[2]

Clinical neurobiological research pertaining to these anxiety disorders has been dominated by investigations directed toward identifying dysfunctional neural circuits and neurochemical systems, vulnerability genes, and psychopharmacology. While this makes obvious sense, there has been far too little clinical research on neurobiological factors that may convey protection from anxiety disorders and promote psychobiological resilience in the face of stress that commonly increases psychopathology. This type of research may facilitate the discovery of preventative approaches to anxiety disorders. Further, by reducing reliance on the standardized diagnostic classification systems noted above, while increasing our knowledge of the neural circuits that mediate behavioral and psychological responses to threat, fear conditioning, reward behavior, and social attachment—circuits relevant to essentially all of the anxiety disorders—the opportunity exists to estab-

Selected abbreviations and acronyms

AS	*anxiety sensitivity*
BI	*behavioral inhibition*
CeA	*central nucleus of the amygdala*
CRH	*corticotropin-releasing hormone*
CS	*conditioned stimuli*
DHEA	*dehydroepiandrosterone*
GAD	*generalized anxiety disorder*
LC	*locus ceruleus*
LTP	*long-term potentiation*
NAc	*nucleus accumbens*
NE	*norepinephrine*
NPY	*neuropeptide Y*
PD	*panic disorder*
PFC	*prefrontal cortex*
PTSD	*posttraumatic stress disorder*
SAD	*social anxiety disorder*
US	*unconditioned stimuli*
VTA	*ventral tegmental area*

lish a "new neurobiology" of anxiety disorders that may result in a radically different classification system that is based upon etiology and pathophysiology.

In this context, this review will consider anxiety disorders from the perspective of the psychobiological mechanisms of both resilience and vulnerability to extreme stress. Implications for an improved diagnostic system, discovery of genes related to resilience and vulnerability, and the discovery of novel therapeutics related to prevention and treatment will be highlighted.

Psychological characteristics of resilience

The majority of research on resilience in the face of adversity focuses on early childhood and adolescence. Investigations of the effects of war, family violence, poverty, and natural disasters on children have revealed a consistent pattern of individual characteristics associated with successful adaptation. These include good intellectual functioning, effective self-regulation of emotions and attachment behaviors, positive self concept, optimism, altruism, a capacity to convert traumatic helplessness into learned helpfulness, and an active coping style in confronting a stressor.[3-5]

In contrast to the research in children, studies of resilience in adults has focused on studies of men in combat. However, this work is applicable to other professions, such as firefighters and police, in which danger is ever present and effective action under stress is imperative. Characteristics associated with high performance under stress include altruism, compassion, and an ability to function effectively despite high levels of fear. These include an ability to bond with a group with a common mission, a high value placed in altruism, and the capacity to tolerate high levels of fear and still perform effectively. Most courageous individuals are not fearless, but are willing and able to approach a fear-inducing situation despite the presence of subjective fear and psychophysiological disturbance.[6-8]

Some individuals are capable of extraordinary resilience in the context of one type of situation (those involving physical danger such as combat), but not another (those involving emotional abuse and neglect). It is likely that different psychological attributes are required for successful adaptation depending upon the circumstances.

Selected psychological characteristics related to the risk of anxiety disorders

Several psychological factors have been associated with increased risk for anxiety disorders. Among the most intensively researched has been the concept of *anxiety sensitivity* (AS). AS has been defined as the individual response to physiological alterations associated with anxiety and fear. Patients with anxiety disorders have exaggerated psychological reactions that are reflective of misinterpretation of bodily cues such that the patient misperceives these sensations inappropriately as being harmful and dangerous, leading in a circular fashion to increased anxiety and fear. AS is associated with a selective cognitive bias toward threat.[9] AS predicts the frequency and intensity of panic attacks. There is evidence that parental concern about anxiety increases AS in their children. AS appears to be a trait abnormality and increases the risk for anxiety disorders. Increased AS can be reduced by cognitive behavioral therapy.[10]

Kagan, Rapee, and others have investigated whether specific temperamental factors affect the development of anxiety disorders in children and adolescents.[11-17] It has become clear that some children have an inherited neurobiological predisposition to increased physiological reactivity and anxious symptoms in the context of unfamiliar environments and, consequently, are more vulnerable to one or more of the anxiety disorders.[14] Kagan estimates that roughly 20% of healthy children are born with such a temperamental bias termed behavioral inhibition (BI). Environmental influences intersect with temperament and

by adolescence approximately one-third of BI children ultimately exhibit indications of serious social anxiety.[18] In a recent study by Biederman and colleagues, BI was associated with SAD in children whose parents had PD.[19] These data suggest that parental PD and childhood could be used to identify children at high risk for SAD. Rapee believes that inhibited temperament in preschool years is a relatively strong predictor of anxiety disorders in middle childhood, a reasonable predictor of adolescent anxiety disorders, and a weak to moderate predictor of adult anxiety disorders.[11]

Kagan has also suggested that BI children may be especially susceptible to anxiety or PTSD after threatening events.[14] Studies of children who developed anxiety following a traumatic event suggest that a prior avoidant personality was a major risk factor.[19] However, it is noteworthy that the majority of BI children do not develop anxiety disorders in later adult life, indicating the importance of other intervening biological and genetic factors.

The presence of BI and evidence of insecure attachment to caregivers both contribute to the variance in the expression of anxious symptoms in preschoolers.[20] This may be related to the findings that parental overprotection, excessive criticism, and lack of warmth are risk factors for the appearance of anxiety disorders in childhood. Environmental risk factors for the development of anxiety disorders (as well as depression) include poverty, exposure to violence, social isolation, and repeated losses of interpersonal significance.

The neurobiological phenotype and genotype associated with temperamental risk factors for anxiety disorders, such as AS and BI, remain to be precisely defined. However, a recent imaging study by Schwartz and colleagues revealed the presence of amygdala hyperactivity in adult subjects with a history of BI as children.[21]

Given the clinical importance of the interaction between genetic and environmental risk factors, research is needed to identify the mediating neurobiological factors. The neurochemical responses to stressful life events may account, in part, for the ability of severe stress to increase the risk of anxiety disorders in vulnerable individuals.

Neurochemical response patterns to extreme stress: resilience and vulnerability to anxiety disorders

A number of neurotransmitters, neuropeptides, and hormones have been linked to the acute psychobiological response to stress and the longer-term psychiatric outcome. We will review the role of those neurotransmitters, neuropeptides, and hormones that have been shown to be significantly altered by psychological stress, have important functional interactions, and mediate the neural mechanisms and neural circuits relevant to the regulation of reward, fear conditioning, and social behavior. An attempt will be made to identify a putative neurochemical profile that characterizes psychobiological resilience and has predictive value as to whether or not stress will increase the risk of anxiety disorders.

Cortisol and DHEA

Psychological stress has been demonstrated to increase the synthesis and release of cortisol. Cortisol has many different functions including mobilization of energy stores, increased arousal, vigilance, focused attention, and memory formation, inhibition of the growth and reproductive system, and containment of the immune response. The behavioral effects of cortisol are due, in part, to regulatory effects on the hippocampus, amygdala, and prefrontal cortex (PFC).[22,23] Glucocorticoids enhance amygdala activity, possibly as a consequence of increased corticotropin-releasing hormone (CRH) function in the central nucleus of the amygdala (CeA).[24-26] Cortisol also increases the effects of CRH on conditioned fear,[27] and facilitates the encoding of emotion-related memory.[28] Many of the effects of cortisol, particularly those outside the hypothalamo-pituitary-adrenal (HPA) axis, are mediated via an interaction with the glucocorticoid receptor (GR). A role for the GR in anxiety modulation is suggested by studies indicating that GR knockout mice have a phenotype characterized by reduced anxiety responses to stress.[29]

Another adrenal steroid that is intimately involved in the stress response is dehydroepiandrosterone (DHEA). DHEA is secreted with cortisol in response to fluctuating adrenocorticotropic hormone (ACTH) levels.[30] There is evidence that DHEA possesses antiglucocorticoid and antiglutamatergic properties in the brain.[31-33] Since peripherally produced DHEA is thought to be a major source of brain DHEA, it is likely that within the brain regionally specific metabolism of DHEA may ultimately control the nature of DHEA's effects on cognition and behavior.[34]

There are emerging data that DHEA may be involved in the reason why some people are resilient in the face of psychological stress. In patients with PTSD (Rasmussen AM, unpublished data), decreased DHEA reactivity to

adrenal activation is associated with increased severity of PTSD. In a recent study of elite special operations soldiers, negative correlations between DHEA/cortisol ratios and dissociation during prolonged and extreme training stress, and between DHEA or DHEA-sulfate (DHEA-S) levels in the recovery period and better overall performance were observed.[35] In addition, there are several studies reporting negative associations between plasma DHEA levels and depressive symptoms and the antidepressant effects of DHEA.[36-39] Future studies need to focus possible mechanisms underlying the effects of DHEA[40,41] and most importantly possible roles for DHEA in other anxiety disorders aside from PTSD.

Corticotropin-releasing hormone

CRH is another important mediator of the stress response,[42] as reflected by the stress-induced release of CRH from the hypothalamus into the hypthalamo-pituitary portal circulation resulting in activation of HPA axis and the increased release of cortisol and DHEA. The extrahypothalamic effects of CRH are also important. The following brain regions have neurons that contain CRH: the PFC, the cingulate cortex, the CeA, the bed nucleus of the stria terminalis (BNST), the nucleus accumbens (NAc), the periaqueductal gray (PAG), and brain stem nuclei, such as the major norepinephrine (NE)–containing nucleus, the locus ceruleus (LC) and the serotonin nuclei in the dorsal and median raphe.[43]

Amygdala CRH neuronal hyperactivity may mediate fear-related behaviors, while excessive cortical CRH may reduce reward expectation. Early life stress results in chronic elevation of brain CRH activity and the individual response to heightened CRH function may depend upon the social environment, past trauma history, and behavioral dominance.[44] The CRH-1 receptor has been linked to the anxiogenic actions of CRH. CRH-1 receptor knockout mice have reduced anxiogenic responses to stress and CRH-1 receptor antagonist drugs have anxiolytic effects in laboratory animals.[45] In contrast, preliminary data suggest that stimulation of the CRH-2 receptor results in reduced anxiety-related behaviors.[46]

Research into the role of CRH in the pathophysiology of anxiety disorders has been limited by the lack of CRH receptor ligands useful for brain imaging in human subjects. Increased cerebrospinal fluid (CSF) levels of CRH have been linked to PTSD by several studies.[47,48] Psychobiological resilience may be related to an ability to restrain the initial CRH response to acute stress. Too few investigations have been conducted in other anxiety disorder patient groups to form definitive conclusions regarding the pathophysiological role of CRH.

LC-NE system

Activation of the LC results in increased release of NE in LC projection regions, such as the amygdala, PFC, and the hippocampus. The LC is activated by a variety of endogenous (hypoglycemia, decreased blood volume, decreased blood pressure, altered thermoregulation, and distention of colon and bladder) and exogenous (environmental stress, threat) stressors. Such activation is likely important to survival from a life-threatening situation and serves as a general alarm function.[49]

The ability of acute stress to activate both the HPA and LC-NE systems facilitates the encoding and relay of aversively charged emotional memories beginning in the amygdala. The amygdala and the LC inhibit the PFC, and stimulate hypothalamic CRH release. These feedback loops among the PFC, amygdala, hypothalamus, and brain stem noradrenergic neurons contain the elements for a sustained and powerful stress response.[22]

Psychological resilience and reduced anxiety responses to stress are probably associated with LC-NE system activation, which stays within a window of adaptive elevation required to respond to danger, but not so high as to produce incapacity, anxiety, and fear. If unchecked, persistent hyperresponsiveness of the LC-NE system will contribute to chronic anxiety, fear, intrusive memories, and increased risk of hypertension and cardiovascular disease. In some patients with PD and PTSD, there is evidence of heightened LC-NE activity.[50-53] More research is needed to determine the role of the LC-NE system in GAD and SAD.

There is preliminary evidence that β-receptor antagonist treatment shortly after traumatic stress exposure may have beneficial and perhaps preventative effects.[54,55] α_1 receptor blockade with prazosin has been shown to reduce nightmares and associated sleep disturbances in PTSD.[56]

Neuropeptide Y

Neuropeptide Y (NPY) is among the most abundant neuropeptides in mammalian brain with high concentrations in the LC[57]; paraventricular nucleus of the hypothalamus[58]; septohippocampal neurons[59]; nucleus of soli-

tary tract; and ventrolateral medulla.[60] Moderate levels are found in the amygdala, hippocampus, cerebral cortex, basal ganglia, and the thalamus.[61]

NPY has been shown to have anxiolytic activity and to impair the consolidation of memories. These effects are mediated at least, in part, by NPY-1 receptors in the amygdala.[62-66] The anxiolytic effects of NPY may also involve effects on LC function, since NPY reduces the firing of LC neurons via the NPY-2 receptor.[67] Another brain region possibly underlying the anxiolytic action of NPY is the hippocampus. Rats with hippocampal NPY overexpression have reduced sensitivity to the behavioral consequences of stress and impaired spatial learning.[68]

The functional interactions between NPY and CRH may be related to vulnerability to anxiety disorders.[69,70] Preclinical studies have shown that NPY counteracts the anxiogenic effects of CRH and a CRH antagonist blocks the anxiogenic effects of an NPY-Y1 antagonist.[71] Thus, it has been hypothesized that the balance between NPY and CRH neurotransmission is important to the expression of stress-induced anxiety and fear.[72] In general, brain regions that express CRH and CRH receptors also contain NPY and NPY receptors and the functional effects are often opposite especially in the LC[72-74] amygdala,[75,76] and the PAG.[77,78]

An upregulated NPY system may therefore contribute to psychological resilience. Supportive of this notion are the findings of studies in special operations soldiers under extreme training stress that indicate high NPY levels are associated with better performance.[79] Patients with PTSD have been shown to have reduced plasma NPY levels and a blunted yohimbine-induced NPY increase.[80] Additionally, low levels of NPY have been found in depressed patients, and a variety of antidepressant drugs increase NPY levels.[81] Studies of NPY function in patients with a spectrum of anxiety disorders is now indicated.

Galanin

Galanin is another neuropeptide shown to have anxiolytic properties.[82] Investigations in rats have demonstrated that galanin administered centrally modulates anxiety-related behaviors[83,84] and galanin receptor knockout mice exhibit an anxious phenotype.[85]

Galanin is closely associated with ascending monoamine pathways. Approximately 80% of noradrenergic cells in the LC coexpress galanin. Galanin-containing neurons originate in the LC, which innervates forebrain and midbrain structures including the hippocampus, hypothalamus, amygdala, and PFC.[86,87] Functional interactions with the NE system is evidenced by the observation that galanin reduces the firing rate of the LC, possibly by stimulating the galanin-1 receptor (Gal-R1), which acts as an autoreceptor.[88,89]

These results support the idea that the noradrenergic response to stress is associated with the release of galanin in CeA and PFC, which may then buffer the anxiogenic effects of NE. Thus, the net behavioral response due to stress-induced NE hyperactivity may depend upon the balance between NE and NPY and galanin neurotransmission. This hypothesis is consistent with evidence that release of neuropeptides preferentially occurs under conditions of high neurotransmitter activity.[90,91] In this context, it is important to assess galanin function in subjects exposed to traumatic stress, and patients with PTSD and other anxiety disorders. Galanin and NPY receptor agonists may represent novel targets for antianxiety drug development.

Serotonin

There is emerging evidence that serotonin neuronal function may be related to vulnerability to anxiety disorders, particularly in the context of adverse life events. The key question is what aspects of serotonin function are most involved. Preclinical studies of transgenic mice have provided important clues to the answers to this question. The behavioral phenotype of serotonin (5-hydroxytrytamine) 5-HT_{1A} knockout mice includes increases in anxiety-like behaviors.[92,93] These behaviors are mediated by postsynaptic 5-HT_{1A} receptors in the hippocampus, amygdala, and cortex.[94] A finding of potential clinical relevance is that embryonic and early postnatal shutdown of 5-HT_{1A} receptor expression produces an anxiety phenotype that cannot be rescued with restoration of 5-HT_{1A} receptors. In contrast, when 5-HT_{1A} receptor expression is reduced in adulthood and then reinstated, the anxiety phenotype is no longer present.[94]

These results indicate that altered function of 5-HT_{1A} receptors early in life may produce long-term abnormalities in the regulation of anxiety behaviors. A possible mechanism related to this observation is early life stress increases CRH and cortisol levels, which in turn downregulate 5-HT_{1A} receptors resulting in lower threshold for anxiogenic stressful life events. Alternatively, 5-HT_{1A} receptors may be decreased on a genetic basis. Consistent

with at least a partial genetic diathesis is the finding that the density of 5-HT_{1A} receptor is reduced in depressed patients when depressed as well as in remission.[95] Examination of 5-HT_{1A} receptor density in patients with anxiety disorders while ill and in remission is now indicated. Drugs with full agonist effects at the postsynaptic 5-HT_{1A} receptor may be effective anxiolytic medications in children, adolescents, and adults with anxiety disorders. There is also evidence that the serotonin transporter (5-HTT) plays a role in the vulnerability to anxiety disorders. Transgenic mice with a *5-HTT* knockout exhibit an excessive anxiety phenotype.[96] These mice also do not show the expected behavioral changes following treatment with selective serotonin transporter inhibitor antidepressant drugs.[97] A very exciting recent report found that human subjects with a specific polymorphism of the *5-HTT* gene (allele) are particularly vulnerable to depression following the experience of adverse life events.[98] Similar gene-environment investigations are needed in patients with anxiety disorders.

Benzodiazepine

Exposure to inescapable stressors produce decreases in benzodiazepine receptor binding in the cortex, with some studies showing a decrease in the hippocampus.[99]
Neuroimaging studies reveal reduced cortical and subcortical benzodiazepine receptor binding in patients with PTSD and PD.[101-103] The findings could be related to a downregulation of benzodiazepine receptor binding following exposure to the stress. Further assessment of benzodiazepine receptors in other anxiety disorders, such as GAD and SAD, is needed.
A preexisting low level of benzodiazepine receptor density or an excessive downregulation of benzodiazepine receptors following stress may be a genetic risk factor for the development of stress-related anxiety disorders. Drugs with selective action at the α_2 and α_3 subunits of the benzodiazepine-GABA receptor may be effective and safe anxiolytics for stress-induced anxiety.

Testosterone

Psychological stress is associated with decreases in testosterone levels.[104] Physically and psychologically stressful training exercises produce a reduction in testosterone levels in elite special forces.[79] Decreased testosterone from exposure to stress may be caused by decreased leutinizing hormone–releasing hormone (LHRH) synthesis at the hypothalamus or leutinizing hormone (LH) secretion in the pituitary. Alternatively, another possible mechanism involves a recently identified hypothalamic-testicular pathway that is independent of the pituitary, but travels through the spinal cord. This pathway appears to mediate the effect of CRH to decrease testosterone levels. Hence, hypothalamic increases in CRH produced by psychological stress may be associated with decreased testosterone by stimulating the neural pathway that interferes with Leydig cell function independently of the pituitary.[105]
The role of testosterone in the pathophysiology of anxiety disorders in men has scarcely been researched. There is a recent report of reduced CSF testosterone levels in PTSD patients, which were negatively correlated with CSF CRH concentrations. There was no correlation between plasma and CSF testosterone levels.[106] Testosterone administration may be helpful for male patients with low preexisting testosterone secondary to chronic severe psychological stress.

Estrogen

There is abundant preclinical and clinical literature demonstrating consistent gender differences in stress responsiveness.[107] Preclinical studies have revealed that female rats consistently show greater increases in corticosterone and ACTH in response to acute and chronic stressors. These differences have generally been attributed to activational effects of gonadal steroids on elements of the HPA axis in females.[108]
Studies in human populations suggest that female subjects respond with greater HPA activation to stressors involving interpersonal concerns (social rejection) and male subjects to achievement-oriented stressors.[107] The role of estrogen in these differential responses remains to be studied. Estrogen has been shown to blunt HPA axis responses to psychological stress in postmenopausal women[109,110] and to blunt the ACTH response to CRH in postmenopausal women with high levels of body fat. In addition, 8 weeks of estrogen supplementation to perimenopausal women blunted the systolic and diastolic blood pressure, cortisol, ACTH, plasma epinephrine and NE, and total body NE responses to stress.[111]
Women commonly suffer more from anxiety disorders than men. Women also appear to be more sensitive to the effects of traumatic stress. One survey found that 31% of women and 19% of men develop PTSD when exposed to

major trauma.[112] However, the role of estrogen in the development of PTSD and other anxiety disorders has not been extensively investigated. On the basis of the data reviewed above, short-term increases in estrogen following stress exposure might be beneficial because of its ability to blunt the HPA axis and noradrenergic response to stress. However, long-term stress-related elevation in estrogen might be detrimental because of the estrogen-induced decreases in the 5-HT_{1A} receptor number and function.

Neurochemical response patterns related to resilience and vulnerability to extreme stress

The above section identifies several possible mediators of the psychobiological response to extreme stress and how each may contribute, alone or through functional interactions, to resilience or vulnerability to anxiety disorders. The finding that many of these measures have important functional interactions is supportive of the concept of developing a more integrative measure. One prediction is that individuals in the highest quartile for measures of HPA axis, CRH, LC-NE, and estrogen activity and the lowest quartile for DHEA, NPY, galanin, testosterone, and 5-HT_{1A} receptor and benzodiazepine receptor function will have an increased risk for anxiety disorders. In contrast, a resilient profile will be characterized by individuals with the highest measures of DHEA, NPY, galanin, testosterone, and 5-HT_{1A} receptor and benzodiazepine receptor function and the lowest levels of HPA, CRH, and LC-NE activity. The mediators of the stress response identified in this review are not meant to be an exhaustive or definitive list. For example, glutamate and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), and neuropeptides, such as substance P and cholecystokinin, could have been included. Longitudinal community-based surveys of the effects of extreme stress on the development of anxiety disorders should be considered to determine whether markers such as those above or others can be utilized to develop a measure of stress-related neurochemical response patterns that will be of predictive value.

Psychological characteristics of resilience and neural mechanisms of reward, fear conditioning, and social behavior

In recent years, significant advances have been made in understanding how the brain regulates reward and motivation (hedonia, optimism, learned helpfulness), learns, remembers, and responds to fear (effective behaviors despite fear), and develops adaptive social behaviors (altruism, bonding, teamwork). The neural mechanisms that mediate these functions are relevant to how an individual responds to extreme stress and may account, at least in part, for the character traits reviewed above that relate to resilience and vulnerability to anxiety disorders.

Regulation of reward

The proper functioning reward pathways and hedonic tone in the context of chronic stress and an unrewarding environment may be critical to maintaining optimism, hopefulness, and a positive self concept following exposure to extreme stress. Reward systems in resilient individuals may be either hypersensitive to reward or resistant to change despite chronic exposure to neglect and abuse.

Mesolimbic dopamine pathways have been shown in reward, motivation, and hedonic tone. The firing pattern of ventral tegmental area (VTA) neurons are sensitive readouts of reward expectations in nonhuman primates. Dopamine neurons increase when rewards occur without being predicted or better than predicted. The neurons show no change when rewards occur as predicted and decreased activity when rewards are omitted or less than predicted.[113] Functional interactions among glutamate, NMDA receptors, dopamine, and dopamine receptors are critical to the proper functioning of reward circuits. The medial prefrontal cortex (mPFC) receives glutamatergic input from the amygdala and sends glutamatergic projections to the NAc and the VTA. Electrical stimulation of the mPFC is thought to be rewarding because it causes glutamate release in the VTA and dopamine release in the NAc. In contrast, the drug of abuse, phencyclidine, is rewarding due to its antagonism of NMDA-type glutamate receptors in the NAc and mPFC.[114]

Genetic factors may contribute to sensitivity to the behavior effects of dopamine-enhancing drugs. There may be an endophenotype related to resistance to anhedonia and hopelessness in the face of stress.[115] Increasing dopamine function in the NAc, orbitofrontal cortex, and the VTA and NMDA receptor blockade in the NAc and mPFC may enhance sensitivity to reward. Therefore, psychostimulants, dopamine reuptake inhibitors, monoamine oxidase B (MAO-B) inhibitors (selegiline), dopamine receptor agonists (pramipexole), and NMDA receptor antagonists

(memantine) may be useful for treating anhedonia and hopelessness resulting from traumatic stress exposure. There have been almost no studies of the functioning of reward-related neurochemistry and neural circuitry in anxiety disorders. Such investigations should be conducted and may contribute to our understanding of stress-induced anhedonia and its relationship to the development of anxiety disorders.

Neural mechanisms of anxiety and fear

Fear conditioning

In many patients with anxiety disorders, especially those with PTSD and PD, fear conditioning causes vivid recall of memories of traumatic events, autonomic hyperarousal, and even flashbacks elicited by sensory and cognitive stimuli associated with prior traumas. Consequently, patients may begin to avoid these stimuli in their everyday life or a numbing of general emotional responsiveness may ensue. Resilience to the effects of severe stress may be characterized by the capacity to avoid overgeneralizing specific conditioned stimuli to a larger context (as seen in GAD), reversible storage of emotional memories, and facilitated extinction.

Fear conditioning is conceptualized as a form of associative learning in which subjects come to express fear responses to neutral conditioned stimuli (CS), which are paired with aversive unconditioned stimuli (US). As a consequence of this pairing, the CS acquire the ability to elicit a spectrum of behavioral, autonomic, and endocrine responses that normally would only occur in the context of danger. Fear conditioning can be adaptive and enable efficient behavior in dangerous situations. The individual who can accurately predict threat can engage in the appropriate behaviors in the face of danger. However, in patients with anxiety disorders, specific environmental features (CS) may be linked to the traumatic event (US), such that reexposure to a similar environment produces a recurrence of symptoms of anxiety and fear. Patients with anxiety disorders often generalize these cues and experience a continuous perception of threat to the point that they become conditioned to context. A chronic state of anxiety ensues.

The neural circuitry that mediates fear-conditioning phenomena has been well worked out. Cue-specific CS are transmitted to the thalamus by external and visceral pathways. Afferents then reach the lateral amygdala via two parallel circuits. A rapid subcortical path directly from the dorsal (sensory) thalamus and a slower regulatory cortical pathway encompassing primary somatosensory cortices, the insula, and anterior cingulate/PFC. Contextual CS are projected to the lateral amygdala from the hippocampus and perhaps the BNST. The long loop pathway indicates that sensory information relayed to the amygdala undergoes substantial higher level processing, thereby enabling assignment of significance, based upon prior experience, to complex stimuli.

A variety of behavioral and electrophysiological data has led LeDoux and colleagues to propose a model to explain how neural responses to the CS and US in the lateral amygdala could influence long-term potentiation (LPT)–like changes that store memories during fear conditioning. This model proposes that calcium entry through NMDA receptors and voltage-gated calcium channels (VGCCs) initiates the molecular processes to consolidate synaptic changes into long-term memory.[116] Short-term memory requires calcium entry only through NMDA receptors and not VGCCs.

This hypothesis leads to several predictions that may have relevance to psychological responses to stress and vulnerability to anxiety disorders. It suggests that blocking NMDA receptors in the amygdala during learning should impair short- and long-term fear memory. This has been demonstrated in rodents.[117-119] Valid human models of fear conditioning and the availability of the NMDA receptor antagonist, memantine, should permit this hypothesis to be tested clinically. If memantine impairs the acquisition of fear in humans, it may have utility in the prevention and treatment of anxiety disorders such as PTSD. Blockade of VGCCs appear to block long-term but not short-term memory.[120] Therefore, clinically available calcium channel blockers such as verapamil and nimodipine may be helpful in diminishing the intensity and impact of recently acquired fear memory and be relevant to the treatment of anxiety disorders.

Consolidation

The discussion above has focused primarily upon the neural mechanisms related to the coincident learning of the US-CS association in the lateral amygdala. However, there is significant evidence that a broader neural circuitry underlies fear memory. Studies using inhibitory avoidance learning procedures have been used to sup-

port the view that the amygdala is not the sole site for fear learning, but, in addition, can modulate the strength of memory storage in other brain structures.[121]

A variety of neurotransmitters and neuropeptides influence consolidation of memory for inhibitory avoidance training. Infusions of drugs affecting GABA, opioid, glucocorticoid, and muscarinic acetycholine receptors into the basolateral amygdala (BLA) have dose- and time-dependent effects on memory consolidation.[121] NE infused directly into the BLA after inhibitory avoidance training enhances memory consolidation indicating that the degree of activation of the noradrenergic system within the amygdala by an aversive experience may predict the extent of the long-term memory for the experience.[122]

Activation of CRH receptors in the BLA by CRH released from the CeA facilitates stress effects on memory consolidation. As reviewed above, there are important functional interactions between CRH and NE systems, including a role in memory consolidation. Memory enhancement produced by CRH infusions in the hippocampus are blocked by propranolol and the noradrenergic toxin DSP-4, suggesting CRH through a presynaptic mechanism stimulates NE release in the hippocampus.[123]

These data support the concept that CRH interacts with the noradrenergic system via an interaction with glucocorticoids to consolidate traumatic memories. Individuals with excessive stress-induced release of CRH, cortisol, and NE are likely to be prone to the development of indelible traumatic memories and associated reexperiencing symptoms. Administration of CRH antagonists, glucocorticoid receptor antagonists, and β-adrenergic receptor antagonists may prevent these effects in subjects vulnerable to anxiety disorders such as PTSD, PD, and SAD.

Reconsolidation

A process in which old, reactivated memories undergo another round of consolidation has been termed reconsolidation.[124-126] Repeated reactivation of these memories may serve to strengthen the memories and facilitate long-term consolidation.[127,128] Each time a traumatic memory is retrieved, it is integrated into an ongoing perceptual and emotional experience and becomes part of a new memory. Moreover, recent preclinical studies indicate that both consolidated memories for auditory fear conditioning, which are stored in the amygdala,[129] hippocampal-dependent contextual fear memory,[124] and hippocampal-dependent memory associated with inhibitory avoidance[125] are sensitive to disruption upon reactivation by administration with a protein synthesis inhibitor directly into the amygdala and hippocampus, respectively. The reconsolidation process results in a reactivated memory trace, which returns to a state of lability and must undergo consolidation once more if it is to remain in long-term storage. This process has enormous clinical implications ranging from a greater understanding of traumatic remembrance to neural mechanisms affected by psychotherapy.

The reconsolidation process involves NMDA receptors, β-adrenergic receptors, and requires cyclic AMP response element binding protein (CREB) induction.[130] NMDA receptor antagonists and β-receptor antagonists impair reconsolidation.[127,131] The effect of the β-receptor antagonist, propranolol, is greater after memory reactivation than when administered immediately after initial training. These results suggest that reactivation of memory initiates a cascade of intracellular events that involve both NMDA receptor and β-receptor activation in a fashion similar to postacquisition consolidation.

This remarkable lability of a memory trace, which permits a reorganization of an existing memory in a retrieval environment, provides a theoretical basis for both psychotherapeutic and pharmatherapeutic intervention for anxiety disorders exacerbated by traumatic stress exposure. Administration of β-receptor and NMDA receptor antagonists shortly after the initial trauma exposure as well as after reactivation of memory associated with the event may reduce the strength of the original traumatic memory. The effects of efficacious psychotherapies on memory reconsolidation should be investigated.

Extinction

Extinction is a process defined by a reduction in the conditioned fear responses. It forms the basis for exposure-based psychotherapies for the treatment of a variety of anxiety disorders, particularly those characterized by phobic behaviors. Individuals who show an ability to quickly attenuate learned fear through a powerful and efficient extinction processes may be less vulnerable to the development of anxiety disorders. They may also be less susceptible to the effects of intermittent exposure to fear stimuli, which can reinstate fear-conditioned learning.

Considerable advancement has been made in our understanding of the neural circuitry mediating extinction. It has been established that the mPFC plays an important

role in extinction. For example, destruction of the mPFC blocks recall of fear extinction,[132,133] indicating that the mPFC might store long-term extinction memory. An inadequate level of activation of the mPFC after extinction might lead to persistent fear responses.[134] Individuals with the capacity to function well following states of high fear may be characterized by potent mPFC inhibition of amygdala responsiveness. In contrast, patients with anxiety disorders, such as PTSD, may exhibit depressed ventral mPFC activity, which correlated with increased autonomic arousal after exposure to traumatic reminders.[135] We recently showed that PTSD patients had increased left amygdala activation during fear acquisition and decreased mPFC/anterior cingulate activity during extinction (Bremner JD et al, unpublished data). Similar abnormalities may exist in other anxiety disorder patients, most notably PD, and deserve further study. It has been proposed that potentiating NMDA receptors using the glycine agonist, D-cycloserine, may facilitate the extinction process when given in combination with behavioral therapy in patients with anxiety disorders.[136]

The neural basis of social behavior

As reviewed previously, characteristics associated with resilience include those related to altruism, optimism, social interaction, and the capacity to attract and use support provided by others.[3-5] Therefore, understanding the neural basis of altruism and other forms of adaptive social behavior may be relevant to a better conceptualization of the psychobiology of resilience.

Preclinical studies have used several rodent model systems to increase our knowledge of how the brain processes social information and regulates social behavior.[137] Perhaps the most informative model pertinent to the clinical situation is the oxytocin knockout mouse and the study of the neurobiology of social behaviors in prairie and montane voles. Oxytocin and vasopressin appear to play crucial roles in the social behavior of prairie voles. These peptides increase the amount of time a vole spends socially engaged and involved in the formation of the pair bond. The differences in social behavior are explained by the regional expression of these peptides in brain. Prairie voles, which are more socially active and monogamous, have high levels of oxytocin receptors in the NAc and BLA relative to montane voles.[138] Similarly, prairie voles have high densities of the vasopressin-la receptor in the ventral pallidum and medial amygdala compared with montane voles. Infusion of vasopressin has different effects in the two voles; prairie voles increase social interaction and montane voles increase nonsocial behaviors such as autogrooming.[139] The neural mechanisms responsible for the effects of oxytocin and vasopressin on social behavior are thought to involve the some of the same circuitry (NAc and ventral pallidum) as that involved in reward-related behavior. This suggests that activation of these brain regions during social interactions may facilitate the reinforcement of social behavior.

Highly resilient individuals have exceptional abilities to form supportive social attachments even in the context of largely unrewarding environments. In contrast, patients prone to anxiety disorders, especially those with SAD, may be characterized by impairments in neural circuitry mediating responses to reward and social interaction. Clinical research studies utilizing neural imaging techniques are now capable of assessing this circuitry in patients with anxiety disorders.

Future research directions

Examination of the neural circuits of reward, fear conditioning, extinction, and social behavior reveal that several brain structures are involved in more than one circuit.[2] This is most striking for the amygdala, NAc, and the mPFC. The amygdala has been most prominently identified as a critical structure in fear-conditioning studies; however, it also has a major role in reward mechanisms. The NAc is implicated in both reward and social behaviors and the mPFC is a component of all three circuits.

These observations raise many intriguing questions pertinent to our understanding of anxiety disorders. For example, does a particular level of amygdala function in fear conditioning relate in a predictable way to its function in the reward system? Does the finding of increased amygdala responsiveness to fear stimuli in anxiety disorders suggest that amygdala dysfunction will also be apparent in the study of reward in these disorders? The redundancy in the circuits mediating reward and social behavior, especially involving the NAc, suggest a functional interaction between these two circuits. When both systems are functioning well, positive social behaviors are reinforced. However, an inability to experience reward due to an impaired circuit may result in unrewarding social experiences, deficient social competence, and social withdrawal. This may be related to the neurobiological basis of SAD.

Most neuroimaging studies in patients with anxiety dis-

orders have investigated the functional status of fear, reward, and social behavior circuits in isolation and not in relation to each other.

This analysis suggests that assessment of the functional relationship among these circuits, including the associated neurochemical modulation, may be important in providing a more comprehensive and precise understanding of the contribution of these circuits to resilience and vulnerability to anxiety disorders. Such studies might identify crucial distinctions in the neural circuitry and neurochemistry specific to the different anxiety disorders. Ultimately, such work will be relevant to the discovery of more specific therapeutic approaches to these conditions.

The opportunity now exists to identify the genetic factors that contribute to the vulnerability to stress-related anxiety disorders. The recent identification of functional polymorphisms for the GR,[140] the α_{2C} adrenergic receptor subtype,[141] and for NPY synthesis[142] indicates the kind of opportunities that now exist to investigate the genetic basis of the adaptive and maladaptive neurochemical response pattern to stress.

Investigation of the genetic basis of the neural mechanisms of reward, fear conditioning, and social behavior is now commencing. There have been several recent advances in understanding the genetic contribution and molecular machinery related to amygdala-dependent learned fear. A gene encoding gastrin-releasing peptide (Grp) has been identified in the lateral amygdala. Mice with Grp receptor (GRPR) knockout have enhanced and prolonged fear memory for auditory and contextual cues, indicating that the Grp signaling pathway may serve as an inhibitory feedback constraint on learned fear.[143] The work further supports the role of GABA in fear and anxiety states[144] and suggests the genetic basis of vulnerability to anxiety may relate to GRP, GRPR, and GABA. A recent investigation in twins supports a genetic contribution to fear conditioning.[145] Genetic mechanisms affecting social affiliative behavior that may involve the vasopressin-la receptor, which can be evaluated in clinical populations.[146] Healthy subjects with the 5-HTT polymorphism that has been associated with reduced 5-HT expression and function and increased risk of depression following adverse life events[98] exhibit increased amygdala neuronal activity in response to fear-inducing stimuli.[147] These preclinical and clinical data suggest that multidisciplinary studies that use neurochemical, neuroimaging, and genetic approaches have the potential to clarify the complex relationships among genotype, psychobiological responses to stress, and vulnerability to anxiety disorders. ❑

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La psicobiología de la resiliencia y de la vulnerabilidad en los trastornos de ansiedad: consecuencias para la prevención y el tratamiento

Gran parte de la investigación de la neurobiología de los trastornos de ansiedad en humanos se ha centrado en las anomalías psicopatológicas de los pacientes con trastornos de ansiedad. Sin desconocer que esta línea de investigación es obviamente importante, se requiere de más estudios para clarificar la psicobiología de la resiliencia en el estrés extremo. El estudio de la psicobiología de la resiliencia tiene la capacidad potencial de identificar mediadores neuroquímicos, neuropéptidos y hormonales de vulnerabilidad y resiliencia en el estrés severo. Además se puede aclarar la importancia de los mecanismos neurales de recompensa y motivación, la sensibilidad al miedo y el comportamiento social para rasgos de carácter asociados con riesgo y resistencia en los trastornos de ansiedad. Estas áreas de investigación deberían conducir a mejores métodos diagnósticos, nuevos enfoques en la prevención y nuevos objetivos para el descubrimiento de fármacos ansiolíticos.

Psychobiologie de la résilience et vulnérabilité aux troubles anxieux : implications pour la prévention et le traitement

Une grande partie de la recherche sur la neurobiologie des troubles anxieux humains s'est axée sur les anomalies psychopathologiques des patients atteints de troubles anxieux. Bien que cette ligne de recherche soit à l'évidence importante, il faut plus d'investigations pour élucider la psychobiologie de la résilience au stress extrême. Potentiellement, l'étude de la psychobiologie de la résilience peut identifier les médiateurs neurochimiques, neuropeptidiques et hormonaux de la vulnérabilité et de la résilience au stress sévère. De plus, il est possible de clarifier la pertinence des mécanismes nerveux de récompense et de motivation, de réactivité à la peur et de comportement social vis-à-vis des traits de caractère associés au risque et à la résistance aux troubles anxieux. Ces aires d'investigation devraient conduire à l'amélioration des méthodes de diagnostic, à de nouvelles approches pour la prévention et à de nouveaux objectifs pour la découverte de médicaments dirigés contre l'anxiété.

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