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Neurobiology and Mechanisms of Antidepressant Treatment Response in Anxiety

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ABSTRACT *~ The functional anatomy of anxiety focuses on a central fear response system with the amygdala serving as a pivotal hub. Critical in understanding the different forms of human anxiety is the relationship of the amygdala with the prefrontal executive systems that mediate cognitive and other functions. Examining the time-sequenced activation of neural centers allows the exploration of preconscious (implicit) and conscious processing of information and sheds light on the nature of emotions and cognitions. Mechanisms of treatment response in anxiety can be modeled based on brain function. Psychotherapy focusing on cognitive behavioral techniques uses a top-down approach. Pharmacological treatments with antidepressants are currently known to influence brainstem monoaminergic systems at the molecular level with physiological consequences, the "stress" axis to enhance negative feedback, neurogenesis in the hippocampus, and neurosteroids involved in enhancing γ-aminobutyric acid transmission. An important question is: Which of these effects provides a differential benefit in anxiety versus depression?*
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Introduction

Terms such as *fear* and *anxiety* are often used interchangeably. Fear, however, refers largely to a reaction to a physical threat, while anxiety may be described as a reaction to a threat to the symbolic or psychological self. Fear also implies imminent threat while anxiety connotes apprehension or dread based on predicting threat.

There are several dimensions to the experience of anxiety, including emotional (angst), cognitive (uncontrollable worry, poor concentration), somatic (muscle tension, autonomic symptoms, somatic preoccupation), and behavioral (irritability, restlessness). Anxiety may be sudden and paroxysmal as in panic attacks,

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experienced more continuously as in generalized anxiety disorder, the result of intrusive abhorrent ideas as in obsessions or memories (eg, posttraumatic stress disorder [PTSD]), or associated with and therefore triggered by specific situations that lead to avoidance or phobias.[1]

An understanding of the neurobiological mechanisms underlying human anxiety is critical for provision of optimal care for individuals struggling with pathologic anxiety and for the discovery of new treatments. Knowledge gained from the neurosciences provides insight into the neural circuits that underlie the experience of anxiety. The primordial value of fear in evolutionary survival would suggest their mediation by more primitive phylogenic and ontogenic structures. Preclinical and brain imaging studies indicate the existence of a central fear/anxiety neurocircuit with structures in the so-called limbic brain, such as the extended amygdala, which are critical nodes.[2,3] But how do activities in these neural circuits result in the different (including subjective) manifestations of anxiety, and how do treatments such as antidepressants bring about benefit?

FUNCTIONAL ANATOMY OF ANXIETY

Several lines of evidence can be conceptually synthesized to develop models of the functional anatomy of anxiety. These models can be matched with clinical presentations to develop hypotheses that can be tested and validated.

Considerable evidence indicates that the amygdala is a critical hub in the phytogenetically older limbic and paralimbic brain circuits that represent a central fear/anxiety system. An almond-shaped structure in the medial temporal lobe, the amygdala consists of several cell groups critical for the processing of emotional experiences. The efferent projections of the amygdala through the central nucleus project to hypothalamic and brainstem target areas, which mediate the specific signs and symptoms of anxiety.[4] Under neutral conditions, highly processed sensory information from various areas of the cortex reach the amygdala through the lateral and basolateral nuclei. However, under threatening conditions, input occurs directly from the early components of the sensory pathways (ie, thalamus), bypassing the more processed, time-consuming cortical input.[5] A faster fear and anxiety response favors survival.

The ventral fear/anxiety system is closely and reciprocally connected to the executive systems mapped to the dorsal phylogenetically newer prefrontal cortex. Under nonthreatening conditions, there is a flexible and reciprocal interplay in the activity of the ventral and dorsal systems with adaptive modulation of emotional, appetitive, and physiological

responses.[6] Willful choice of behavioral output emerges, and behaviors can be modified in the service of longer-term goals.[7] Threat requires a quicker and specific pattern of responses to enhance survival. More time-consuming cortical influences are taken offline, and behavioral responses are now driven primarily by neurocircuits centered in the amygdala. These amygdala-centered responses are emotional and noncognitive (ie, automatic, predetermined, and species-typical).

Pathological states such as anxiety disorders may have a similar profile with emotional responses and emotional memories achieving primacy. Anxiety disorders can thus be viewed as exaggerated or inappropriate emotional responses that are less amenable to executive control.[8] Cognitive processes are captive to and interlocked with emotional responses via positive feedback. Choice in the process and content of cognitions is restricted to catastrophic concerns, experienced as worry. Shifts in cognitive set or flexible modification of preexisting threat schemas require strenuous effort.[9] There is a consequent failure to accommodate novel or contrasting information into anxious cognitive schemas.[10-15] Successful intervention aims to normalize the reciprocal influences between these dorsal and ventral systems.[6,16]

Sequential Activation

The time sequence for activation of centers in the neural circuits can be mapped and may provide valuable insight into the nature of the anxiety response. Functional brain-imaging studies in the rhesus monkey estimated the sequence and timing of a behavioral response to a neutral stimulus.[17,18] Information is processed in individual centers prior to its relay to the next appropriate center. Each relay station takes approximately 20–30 ms to filter the information it receives, process it, and direct it onward. In the rhesus monkey, a visual stimulus that triggers the choice of a hand movement takes 180–260 ms based on the complexity of the stimulus. In humans, activation of a similar neural circuit is estimated to be 300–350 ms, presumably because of the increased complexity of information processing. Conscious awareness of the stimulus is projected to occur approximately halfway through this sequence.[19]

Preconscious or implicit processing in humans has been examined using the paradigm of presenting an image of affectively valenced faces (eg, fearful, happy, or neutral) so briefly (ie, 33–40 ms) that it is not consciously perceived. The correlated neural activity associated with such stimuli can be examined using functional magnetic resonance imaging (fMRI) techniques. Studies have reported heightened amygdala reactivity to facial expressions of negative (especially fearful) affect. The

amygdala is thus involved in nonconsciously labeling incoming stimuli with respect to their potential emotional or survival significance and activating other brain regions to initiate more extended processing or responses.[20] This is consistent with evidence of a direct pathway from sensory systems to the amygdala that allows rapid, precognitive orienting and response to stimuli that match primitive or previously associated threat templates. Conscious, cognitive, and willful monitoring of these responses requires greater processing and extended time.[21]

So how does the human brain decide to trigger the anxiety response in specific circumstances? The choice of which motivational (ie, fear or pleasure) system is activated and thus the nature of the emotional response would be based on innate threats or on previous emotional memories that had resulted in fear conditioning. Patterns of stimuli that match those of a previous traumatic experience will trigger the conditioned fear response. The cognitive response will be congruent with the flavor of the emotional response. The content of the threat-derived cognitive response will be to expect catastrophe, which can present as worry. Based on several variables, including the intensity of the anxiety response, the worry may be consciously overdriven by cognitive choice.

Cognitive responses are the result of temporally later and more complex processing and therefore have the characteristics evident in executive functions. Thus, cognition is more reasoned and, being conscious, is under willful control. Cognition, however, is more time sequenced and serial, making it more goal directed. Language allows the capacity for nuanced differentiation in content, making it more specific.

Emotional responses such as anxiety are derived from the early, initially nonconscious processing of information, resulting in the subsequent emergence of subjective and conscious feelings. The characteristics of emotions and feelings are therefore a consequence of such early processing of information. Emotions are thus global and based on an early choice of the motivational system that is activated. Thus, feelings are globally flavored (eg, as threatening or pleasurable). However, potentially multiple motivational systems can be concurrently activated, allowing the experience of complex mixed emotions. Emotions are experiential and associative, because memories are tagged based on their emotional flavor.

The anxiety response can be triggered by external sensory input and internal somatic input (bottom-up), or cognitively (top-down). Bottom-up anxiety responses are triggered automatically, and their early components are nonconscious. Such emotional responses are not under willful control, and the conscious brain cannot turn back time to control an event that has already occurred implicitly. A degree of cognitive

control of the anxiety response is possible because of the interrelationship of the prefrontal executive centers and the subcortical circuits involving the amygdala. Cognitive mechanisms can set the threshold for the responsivity of the amygdala and can thus influence the likelihood and intensity of the anxiety response and modify their behavioral expression. A cognitive set consistent with the emotional fear response can positively feed forward and spiral the anxiety into more intensive states. Negative feedback from a cognitive position (that the reality of a situation is not threatening) can mitigate the emotional fear/anxiety response. This is consistent with the cognitive model of depression developed by Beck and others.

The mechanisms of top-down influences are under exploration.[22,23] Anxiety responses triggered through top-down mechanisms are more amenable to cognitive techniques of control. A rational approach to assessing the degree of threat can be taken.

FORMS OF ANXIETY

Fear and anxiety responses can present in different but overlapping forms. Three such responses can be distinguished. The first is analogous to acute fear and occurs in response to an unconditioned threat (eg, a predatory animal or a life-threatening situation for humans). The emotional memory of that experience can be triggered by cues associated with that experience. Such a cued response is termed "fear conditioning." Fear conditioning is dependent on coincidence detection at the neuronal level, and the *N*-methyl-D-aspartate receptor is uniquely qualified to provide such recognitions and to enhance the subsequent synaptic messaging.

Anxiety may be experienced when an individual is exposed to the environment (or context) in which the fear conditioning occurred. Such contextually triggered responses may be closer to the concept of anxiety because the context is associated with or predicts the threat. The hippocampus has a role in contextual anxiety because it is critical for processing declarative and spatial memory. Contextual conditioning also involves glutamatergic activity, and evidence supports specific modulation by glutamate transporters in the CA1 region.[24] Circuits involving the hippocampus and components of the extended amygdala (ie, the bed nucleus of the stria terminalis) appear to be critical for contextually driven anxiety. Contextual association may or may not be conscious.

The key neurotransmitters in the fear/anxiety response are the fast-acting ones such as γ-aminobutyric acid (GABA) and the excitatory amino acid, glutamate. Their activity is modulated by monoaminergic neurotransmitters, such as serotonin, which gauge the significance of

the information and moderate responses. Thus, serotonin strongly influences the anxiety response. The activity of the serotonin system is modulated by a variety of factors, including the efficiency of the serotonin transporter. The serotonin transporter gene is a single gene located on the 17th human chromosome, and a promoter region is genetically polymorphic, resulting in short and long allele versions. The short allele is estimated to be present in roughly two thirds of the United States' population. A recent fMRI study reported that individuals with the short allele had enhanced amygdala activity when exposed to faces expressing negative affects compared with individuals with the long allele.[25] This could be one of several genetic factors that predict an enhanced anxiety response. Life experiences may sensitize the ongoing activity of this system, ultimately crossing a threshold of intensity into pathology.

An fMRI study in patients with major depression reported increased response of the amygdala to masked fearful faces compared with normal controls.[26] The paradigm presented a face expressing fear briefly (40 ms), such that the individual was unaware of the stimulus. The fearful face was subsequently masked with a neutral face projected for 160 ms, which resulted in conscious awareness. Such an approach examines the preconscious responses without the confounding of conscious cognitive processing. Treatment with a selective serotonin reuptake inhibitor (SSRI) reduced the exaggerated amygdala responses; this is consistent with the suggestion that treatment with a potent serotonin reuptake inhibitor diminishes the intensity of emotional responses and allows greater choice in cognitive responses.

Potential Mechanisms of Antidepressant Efficacy

Antidepressant medications, particularly those that have prominent inhibitory effects on the serotonin transporter, are efficacious in each of the major anxiety disorders.[27] What mediates the therapeutic efficacy of antidepressants in anxiety and depressive disorders? There are multiple known effects of antidepressants that may individually or in concert result in broad therapeutic effects. An intriguing question then is: Which of those effects mediates the benefit specifically in anxiety disorders?

Transporter and Receptor Effects

Preclinical studies of antidepressants initially focused on their acute effects. These included the inhibition of the reuptake of serotonin and norepinephrine, as well as effects on specific pre- and postsynaptic receptors. Chronic treatment with antidepressants results in adaptive changes in the activity of serotonin and norepinephrine such that

ultimately their efficacy is enhanced.[28] Serotonin and norepinephrine circuits are examples of value systems that continuously and flexibly assess information about the internal milieu as well as the external environment.[29] Relevant information is selected, prioritized, and processed because of the diffuse influence of serotonin and norepinephrine on large proportions of synapses relevant to emotions, cognition, and behavior.

Chronic antidepressant treatments down-regulate β-adrenergic receptors and enhance serotonergic functional output.[30,31] Such receptor changes and functional alterations initiated by antidepressants modify the tonal activity and setpoint of these value systems. Antidepressants thus broadly influence the serotonin and norepinephrine systems to modify early stages of information processing, much of which occurs prior to conscious awareness, and are therefore outside willful choice. How do such effects ultimately have downstream corrective effects on the pathophysiology of anxiety and depressive disorders? What are the specific molecular cascades that mediate the subsequent complex behavioral effects of antidepressant medications?

Recent studies have suggested a molecular mechanism for the therapeutic benefits of antidepressants such as serotonin reuptake inhibitors. The immediate effect of inhibition of the serotonin transporter initiates an intracellular cascade ultimately influencing synaptic plasticity. The cascade involves molecular signaling through regulation of dopamine and cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein of molecular weight 32,000 (DARPP-32).[32] DARPP-32 increases phosphorylation of the metabotropic glutamate α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor in critical anatomical sites including the cortex, hippocampus, and striatum. Preclinical behavioral tests and other lines of evidence suggest these molecular effects are pivotal steps in mediating the therapeutic effects of SSRIs.

The Role of the Stress Response

Antidepressants moderate the response to stress. Arousal, an aversive response leading to avoidance, and perception of uncontrollability are key components defining the stress response.[33] Increased input from the amygdala to the hippocampus appears to be an important mediator in determining whether the arousal is considered stressful and its consequent negative effects (eg, alterations in neuronal morphology and effects on memory).

Corticotropin-releasing factor (CRF) is the major regulator of the stress response. CRF-containing neurons are present not only in the

hypothalamus, but in the cerebral cortex, limbic, and brainstem areas as well. Thus, CRF is well positioned to mediate the endocrine, autonomic, behavioral, emotional, and other responses to stress.[34] Centrally administered CRF induces signs and symptoms of anxiety and depression in animals. An increasing body of data supports the role of CRF and the activity of the hypothalamic pituitary adrenal (HPA) axis abnormality in clinical depression and PTSD.[35] One could postulate that in several anxiety disorders, there is an exaggerated activity of the HPA axis, while in major depression and PTSD, there is a dysregulated feedback of the HPA axis with downstream consequences.

In major depression, studies have reported hypercortisolemia, elevated levels of CRF concentrations in the cerebrospinal fluid, and decreased glucocorticoid receptor number in lymphocytes. There is also nonsuppression of cortisol in the dexamethasone suppression test. In addition, CRF infusion results in a blunted response of adrenocorticotropic hormone (ACTH), yet a normal cortisol response. This suggests a resting elevation of central CRF activity in major depression.[36]

The HPA axis is influenced by monoaminergic activity such as serotonin and norepinephrine. The hormonal output of the HPA axis activation is the release of cortisol in humans. Stress-induced activation of the HPA axis results in the long-term elevation of glucocorticoid levels (cortisol) in depression. Cortisol provides negative feedback to terminate activation of the HPA axis through enhanced function and increased glucocorticoid receptor (GR) expression in the hippocampus. There are two types of glucocorticoid receptors: higher affinity type 1 (GR-1), and lower affinity type 2 (GR-2).[37] GR-1 receptors are important in the physiological activity of the HPA axis, such as circadian fluctuation, while GR-2 receptors are more relevant in pathologic states of activation, such as in hemodynamic shock and during major psychological stress. Sustained increases in glucocorticoid levels, such as those seen in states of chronic stress, can decrease the survival of neurons by decreasing neurotrophic factors like brain-derived neurotrophic factor (BDNF). The reduced volume of the hippocampus in depressed patients could be the result of such glucocorticoid-induced atrophy of specific cells or some correlated activity.[38]

Synthesizing the preclinical and clinical findings, it would seem that there is considerable overlap between the endocrine correlates of major depression and the long-term consequences of stress early in life. Early life experiences can result in a setpoint for the neuroendocrine response to stress. Such imprinting of environmental experiences during critical periods early in life can result in substantial differences in individual responses to stress later in life. Early-life stress seems to persistently

increase CRF neuronal activity, leading to down-regulation of the pituitary corticotrophs, which results in a blunted ACTH responsiveness.

Treatment with antidepressants can reduce CRF activity. In animal studies, the endocrine effects of early-life stress can be reversed with the use of antidepressants. The pharmacological buffering of these responses by antidepressants can potentially relieve the individual from such programmed responses and may allow a greater repertoire of behavioral choices as a response to stress.

Antidepressant therapy may directly or indirectly up-regulate GR activity, normalizing HPA axis activity, particularly its offset with the termination of stress.[39] Preclinical studies on the effects of antidepressants on GR expression suggest that tricyclic antidepressants, which have predominantly greater noradrenergic effects than serotonergic antidepressants, seem to have prominent effects on GR-2 expression. This could well be because of the role of the GR-2 in pathological activation of the HPA axis. Serotonergic antidepressants may have a more potent effect on GR-1 expression. These differential effects of serotonergic versus noradrenergic antidepressants on GR-1 and GR-2 may underlie the pharmacological suggestion of superior efficacy of serotonergic antidepressants in anxiety disorders and the superior efficacy of medications affecting both serotonin and norepinephrine in major depression, particularly in the melancholic subtype and in those requiring hospitalization.[27,40]

Neurogenesis

Antidepressants enhance neurogenesis in the hippocampus. Chronic antidepressant treatments (both serotonergic and noradrenergic) result in a sustained activation of the intracellular cAMP signal transduction pathway. One consequence is the increased expression of the transcription factor, cAMP response element-binding protein, which regulates specific genes[41] such as the gene for BDNF. A nerve-growth factor, BDNF increases the survival and growth of specific neurons such as the CA3 pyramidal cells in the hippocampus. Chronic antidepressant treatment increases BDNF gene expression in the hippocampus.

What is the clinical consequence of enhanced neurogenesis? Enhancing hippocampal activity potentially allows a larger repertoire of information processing in the critical circuits involving the hippocampus and the working memory function of the dorsolateral prefrontal cortex. Enhanced working memory would allow the individual to process larger blocks of information and not be overwhelmed by negative emotional responses. The individual is less likely to be overwhelmed by excessive emotional responses, particularly emotions such as fear and anxiety. This

effect dovetails well with the report of patients responding to antidepressants. These patients describe a greater control of their responses such that they have the option of a cognitive response and are not simply prisoners of their more automatic and global emotional response.

Neurosteroids

Neurosteroids such as 3α-hydroxy-5α-pregnane-20-one (ALLO) are derivatives of cholesterol that bind with high affinity to the $GABA_A$ receptor and enhance GABA effects in the brain. Pharmacological agents such as benzodiazepines have a similar effect, and are potent anxiolytic agents without direct antidepressant properties. Pharmacological models of anxiety include inverse agonist activity through the benzodiazepine receptor.[42] ALLO, but not other neurosteroids, is reduced in the cerebrospinal fluid of individuals with unipolar depression, and 8–10 weeks of SSRI treatment normalizes ALLO levels in the cerebrospinal fluid.[43] The effects of SSRI treatment specifically on anxiety is not reported. Additionally, it is not known whether nonserotonergic antidepressants would have a similar effect.

CONCLUSION

With advances in the neurosciences, an evolving understanding of the brain mechanisms of anxiety is emerging. Much of the conceptual syntheses are currently speculative but provide a beginning perspective on the functional anatomy and pathophysiology underlying anxiety disorders. Understanding the mechanisms of treatment response, both pharmacological and psychotherapeutic, can enhance the delivery of appropriate treatments to individual patients and aid in the discovery of more specific and improved treatments. ✤

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