Toward an Integrated Neurobiology of Panic Disorder

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Panic disorder is a common psychiatric illness that causes considerable short- and long-term morbidity. Although drug treatment and cognitive behavior therapy are beneficial, the etiology of panic disorder and the mechanisms of effective treatment remain unclear. Developments in the preclinical neuroanatomy and neurophysiology of neuronal structures relevant to fear and anxiety promise to provide fresh insights into the neurobiology of panic. In this article, we propose a functional neuroanatomic model of fear and anxiety and review brain imaging studies of panic disorder with this model in mind. In addition, we discuss the implications of integrating functional neuroanatomy and the clinical neurochemistry of panic disorder. An integrated neurobiology of panic disorder will provide a broader conceptual framework with which to tackle the complex questions about the pathophysiology and treatment of this condition. *(J Clin Psychiatry 1997;58[suppl 2]:4–11)*

Panic disorder is a common and often chronic psychiatric illness that initially causes unprovoked, intense episodes of fear. Symptoms typically associated with panic attacks include symptoms of autonomic overactivity (such as sweating, palpitations, flushing, and dizziness) and psychological symptoms (such as depersonalization, fear of dying, and fear of losing control). Hyperventilation and paresthesias are other common symptoms of panic attacks. Agoraphobia is a disabling and common complication of repeated panic episodes.

Panic disorder is a substantial public health problem in terms of overutilization of health care services, lost productivity, and decreased quality of life.[1] Recent developments in our understanding of the functional neuroanatomy of fear and anxiety[2–4] coupled with our current neurochemical knowledge of panic disorder promise to expand our concepts of the phenomenology, clinical course, pathophysiology, and response to treatment of this disabling condition.

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FUNCTIONAL NEUROANATOMY OF FEAR AND ANXIETY

A thorough understanding of the principal neuronal structures mediating mammalian fear and anxiety behaviors and their interrelationships is necessary for generating new hypotheses on the nature of clinical anxiety syndromes such as panic disorder. Key neuronal mechanisms thought to underlie fear and anxiety can be linked to their putative anatomic substrates. Mechanisms especially relevant in this context include fear conditioning, which involves the acquisition of learned responses to specific fear stimuli. A similar type of learning, contextual conditioning, refers to conditioning to a place or situation, in which multiple stimuli may become associated with fearful behavior. Contextual conditioning may be pertinent to our understanding of complex human anxiety disorders, such as panic disorder, while fear conditioning may be the neurophysiologic basis of specific phobias.

Amygdala

The amygdala, a structure in the temporal lobe, is ideally situated anatomically to coordinate mammalian fear behaviors and responses. It sends efferent projections to a wide range of target structures (cortical and subcortical) implicated in fear and anxiety.[5] The principal efferent projections are to the (1) primary and association sensory cortices; (2) prefrontal cortices; (3) hippocampus and olfactory cortex; (4) ventral striatum, including the nucleus accumbens, which is implicated in reward conditioning; (5) bed nucleus of the stria terminalis, a major corticotropin-releasing factor pathway linked to contextual condi-

tioning; (6) hypothalamus; and (7) thalamus. Extensive projections (almost entirely from the central nucleus of the amygdala) also lead to brainstem structures such as the dorsal motor nucleus of the vagus (important for cardiovascular regulatory control), the parabrachial nucleus (involved in respiratory regulation), the locus ceruleus, and the dopaminergic nuclei A8, A9, and A10 located in the ventral tegmental area (relevant to reward conditioning). From an anatomic perspective, the amygdala appears to be a central structure for coordinating the cognitive, affective, neuroendocrine, cardiovascular, respiratory, and musculoskeletal components of fear and anxiety responses (reference 3 and Charney DS, unpublished data, 1996).

The amygdala receives afferent projections from many fear-relevant brain systems, making it a key area for fear stimulus processing and interpretation. Many of these afferents are reciprocal connections from the structures mentioned above. The afferent projections to the amygdala include those from the (1) sensory and association cortices (excitatory amino acid neurotransmission); (2) thalamus; (3) hypothalamus; (4) monoaminergic nuclei (locus ceruleus, dopaminergic nuclei, and dorsal raphe nuclei); and (5) parabrachial nucleus, which projects back to the central nucleus. Interoceptive afferents project from visceral structures. The amygdala has sensory information channeled to it from exteroceptive and interoceptive mechanisms, while higher-order sensory data are relayed to it from the sensory cortices. These inputs may enable the amygdala to assess and interpret the significance of a given threat.

Many studies have provided data directly linking the amygdala to fear and anxiety behaviors. Electrical stimulation of the amygdala elicits fear-like behaviors in animals[6] and associated physiologic changes, such as increases in respiration, blood pressure, heart rate, fear-related facial movements, certain reflex behaviors (such as the startle reflex[5]), and levels of plasma corticosterone.[7] Clinical studies of patients with temporal lobe epilepsy have shown that electrical stimulation of the amygdala triggers complex fear states that appear to have a flashback-like quality.[8] These human data suggest that the amygdala plays an important role in retrieving affectively charged memories stored in cortical structures. This process appears to be an integral part of the threat-appraisal function of the amygdala. Studies evaluating the effect of amygdaloid lesions in different animal species have generally found that such lesions substantially reduce fear behaviors.[6] In addition, lesions impair the ability to attach affective significance to sensory stimuli; in monkeys, this has resulted in abnormal social behavior.

Ablation of the amygdala (particularly the central nucleus) also interferes with the acquisition of conditioned fear, as measured by the fear-potentiated startle reflex and other paradigms.[5] Studies using direct recording methods of amygdala neurons during different behavioral states have confirmed that the amygdala helps determine the emotional responses to sensory stimuli.[9] Thus, a substantial body of evidence indicates that the amygdala has a significant role in mediating fear and anxiety behaviors.

Locus Ceruleus

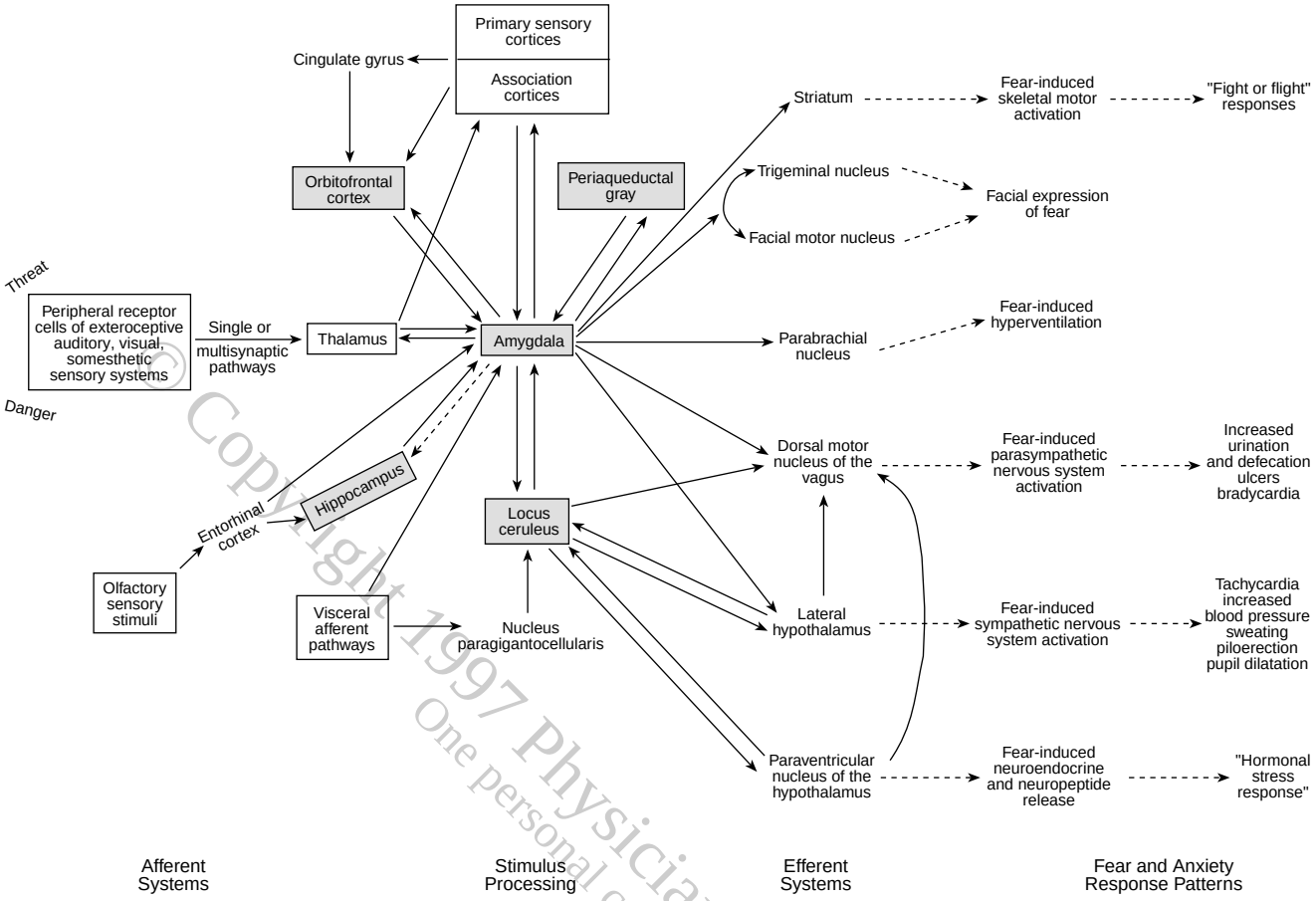
The locus ceruleus is the principal norepinephrine-containing nucleus in the mammalian brain. Neuropeptide Y and galanin are colocalized with norepinephrine in locus ceruleus neurons and may act as neuromodulators of norepinephrine function.[10] The locus ceruleus receives afferent information from the sensory systems that monitor the internal and external environments.[11] Interoceptive information is channeled through several brainstem nuclei, including the nucleus paragigantocellularis (PGi)[12,13] and the nucleus prepositus hypoglossi and thence to the locus ceruleus. Exteroceptive information may be relayed via cortical afferents from the insular, orbital, and infralimbic cortices (glutamatergic projections). Thus, the locus ceruleus-norepinephrine system may have a significant role in processing fear-related stimuli. Alternatively, the locus ceruleus-norepinephrine system may affect fear-related processing by sending efferents to multiple brain target areas implicated in anxiety and fear behaviors, such as the amygdala, hippocampus, hypothalamus, cortex, and spinal cord.[14] Thus, the norepinephrine system has the necessary anatomic connections to assist in implementing fear responses to threatening stimuli.

Multiple lines of evidence link norepinephrine system functioning with fear and anxiety behaviors. Electrical stimulation of the locus ceruleus produces fear behaviors in monkeys,[15] while exposure of freely moving cats to dangerous or threatening situations results in increased locus ceruleus firing.[16] Bilateral lesions of the locus ceruleus in monkeys are associated with decreased fear behaviors.[15] Preclinical work suggests that the norepinephrine system is stress-responsive, is involved in behavioral sensitization to stress, and mediates fear conditioning.[17] These mechanisms may be relevant to the pathogenesis of panic disorder. In addition, the central and peripheral norepinephrine systems function in a parallel fashion,[18] which has significance for clinical panic disorder, where internal and external cues are known to trigger panic episodes.

Other Structures Involved in Fear and Anxiety

A number of other neural structures may have a role in fear and anxiety behaviors. The thalamus functions as a sensory relay station, channeling environmental stimuli to the sensory cortices and the amygdala. The hippocampus may function in contextual conditioning in animals via a neural circuit that includes the entorhinal cortex and the amygdala.[19] A neuronal network between the hippocampus, cortical structures, and amygdala may be involved in cognitive attributions about fear stimuli and may enhance memory function to facilitate adaptive responses.

Figure 1. Model of the Functional Neuroanatomy of Fear and Anxiety*



*From Charney and Deutsch,[4] with permission.

As mentioned earlier, the hypothalamus mediates sympathetic activation (lateral hypothalamus) and stress-induced neuroendocrine and neuropeptide release (the paraventricular nucleus and supraoptic nucleus release corticotropin-releasing factor, vasopressin, and oxytocin). The midbrain periaqueductal gray (PAG) area appears to be closely linked to initiation of fear-induced behavioral responses. Imminent threat (e.g., a predator attack), relayed through inputs from the amygdala, elicits active defensive behaviors (lateral PAG), while a lesser threat (e.g., predator nearby) triggers freezing behavior via the ventrolateral PAG.[20] Lesions in this region reduce certain fear behaviors, such as freezing and conditioned freezing. Dorsal PAG electrical stimulation in animals and humans produces a panic-like state and has recently been proposed as a laboratory model of clinical panic.[21]

The orbitofrontal cortex has rich reciprocal interactions with subcortical limbic structures. These interactions may be required to select and plan behavioral responses to threat, as well as to monitor the effectiveness of these responses. Lesions in the orbitofrontal cortex may produce resistance to extinction of conditioned fear responses and maladaptive persevering behaviors in response to threat.[22] Some data also implicate the anterior cingulate gyrus in fear and anxiety behaviors.[23]

NEURONAL MODEL OF FEAR AND ANXIETY

A model summarizing the functional relationships between the diverse neuronal structures implicated in fear and anxiety is shown in Figure 1. This model includes structures and pathways involved in the transmission of sensory data to signal processing areas in the cortices, entorhinal cortex, limbic areas (amygdala, hippocampus), and brainstem structures (PGi, locus ceruleus). Once a threat or fear stimulus is assessed through a process of integrating past and present experiences, the processing areas (orbitofrontal cortex, amygdala) formulate and select a fear or anxiety response. Key structures that implement the response include the locus ceruleus (norepinephrine activation triggers autonomic and neuroendocrine responses via the hypothalamus and parallel peripheral autonomic responses via the PGi), the hypothalamus (auto-

Table 1. Brain Imaging Findings in Panic Disorder*

Imaging Technique	Finding	Pathologic Significance
Computed tomography	Right parahippocampal infarct associated with panic disorder.[26] Left frontoparietal tumor linked to panic disorder.[27]	Structural lesions may be a predisposing or perpetuating factor in some cases of panic disorder. Head computed tomography or MRI are indicated for atypical presentations.
MRI	Some evidence of structural lesions, but no specific pattern.[28] Right medial temporal lobe dysmorphias in lactate-sensitive panic disorder greater than those in controls.[29]	Structural changes could result from chronic panic disorder.
PET-rCBF	Right parahippocampal gyrus rCBF increased at rest in lactate-sensitive panic disorder versus controls.[30]	Trait overactivity in limbic structures could predispose to spontaneous panic attacks.
PET-FDG	Right greater than left hippocampal, decreased left inferior parietal and anterior cingulate glucose metabolism during an auditory discrimination task in panic disorder versus controls.[31]	Abnormal information processing of sensory stimuli may lead to abnormal cognition in panic disorder.
SPECT-rCBF	Bilateral frontocortical reductions in rCBF following yohimbine-induced panic in panic disorder versus controls.[32]	During panic attacks, altered frontal lobe functioning may impair normal executive abilities. Norepinephrine system hyperactivity may mediate this dysfunction in clinical panic disorder.
SPECT-rCBF	Resting blood flow defects in left and right hippocampi. Increased rCBF in right inferior frontal cortex and left occipital cortex in lactate-sensitive, drug-naive panic disorder versus controls.[33]	Memory dysfunction is a possible early manifestation of panic disorder. Norepinephrine and serotonin system dysregulation may predispose to agoraphobia.
SPECT-neuroreceptor	Left lateral temporal lobe decrease in iomazenil tracer activity in panic disorder versus dysthymia.[34]	Benzodiazepine/GABA subsensitivity may contribute to abnormal stimulus processing in panic disorder. Benzodiazepine agonists used in treatment may compensate for these processing errors.
MRS	Abnormal brain lactate increases provoked by hyperventilation in panic disorder.[35]	Trait respiratory pH/CO_2 chemoreceptor hypersensitivity in panic disorder. Chronic or intermittent hyperventilation in panic disorder may elevate central nervous system lactate levels, which in turn trigger further spontaneous panic attacks.

*Abbreviations: MRI = magnetic resonance imaging; PET = positron emission tomography; rCBF = regional cerebral blood flow; FDG = fluorodeoxyglucose; SPECT = single photon emission computed tomography; MRS = magnetic resonance spectroscopy; GABA = gamma-aminobutyric acid.

nomic and neuroendocrine components of the fear response), dorsal motor nucleus of the vagus (parasympathetic nervous system activation), parabrachial nucleus (fear-induced hyperventilation), trigeminal nucleus and facial motor nucleus (facial expression of fear), and striatum and PAG (fear-induced skeletal or motor activation, i.e., "fight or flight" response).

In our model, the amygdala is at the center of fear and anxiety responses because of its extensive afferent and efferent connections to many of the other fear-relevant neuronal structures discussed and because of the impressive functional data linking it to neural processes pertinent to fear and anxiety behaviors, such as fear conditioning, sensitization, and extinction.[5,9]

NEUROIMAGING IN PANIC DISORDER

A growing imaging data base suggests that patients with panic disorder have structural and functional brain abnormalities. In general, there is some evidence of hippocampal and right parahippocampal lesions in patients with panic disorder. Frontal cortical abnormalities also have been reported in panic disorder, but it is unclear whether these are part of a common mechanism present in both pathologic and normal anxiety states, which may involve other structures, such as the anterior cingulate gyrus.[24,25] Panic disorder imaging findings (Table 1[26–35]) implicate some of the candidate structures discussed earlier. Neuroimaging techniques also provide a unique opportunity to integrate the functional neuroanatomy, neurochemistry, and phenomenology of panic disorder.

NEUROCHEMISTRY OF PANIC DISORDER

Clinical research on the neurochemistry of panic disorder tends to focus on a candidate neurotransmitter system. Investigators then probe the system with available pharmacologic tools to detect differences between patients and control subjects in behavioral, physiologic, and neuroendocrine responsiveness. Data collected in this fashion have strengthened the case for some specific abnormality in the system in question.

Norepinephrine

A considerable body of evidence implicates the norepinephrine system in the pathophysiology and treatment of

panic disorder. Abnormalities of the presynaptic α_2-adrenoceptor in panic disorder have been identified in studies conducted with the α_2-antagonist yohimbine and the α_2-agonist clonidine. Patients with panic disorder are abnormally sensitive to the effects of yohimbine challenge, experiencing a high rate of panic attacks accompanied by increases in plasma levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG).[36] Yohimbine sensitivity is relatively specific to panic disorder, with posttraumatic stress disorder being a notable exception. Interestingly, patients with panic disorder also have abnormal responses to clonidine challenge. They exhibit greater hypotension, decreased plasma MHPG, and less sedation than control subjects in response to clonidine, suggesting α_2-receptor hypersensitivity in panic disorder.[37]

An intrinsic α_2-adrenoceptor abnormality or a dysregulation in other afferent neuronal systems controlling α_2-adrenoceptor functioning may account for these data. There is also evidence of subsensitivity of central postsynaptic α_2-adrenoceptors in panic disorder, based on the observation of blunted growth hormone responses to clonidine.[38] However, this abnormality is shared by patients with depression, generalized anxiety disorder, and social phobia. Some researchers, finding that patients with panic disorder are sensitive to isoproterenol challenge, have proposed a hypothesis of increased peripheral β-adrenoceptor sensitivity in panic disorder.[39] The ability of other challenge probes, such as caffeine and carbon dioxide, to trigger panic anxiety in patients with panic disorder may be partly a function of their ability to influence norepinephrine system functioning. The norepinephrine system also is implicated in the response of patients with panic disorder to treatment with tricyclic antidepressants and monoamine oxidase inhibitors, agents that directly modulate norepinephrine functioning.

Serotonin

There is an evolving preclinical literature on the role of serotonin in the pathogenesis of anxiety.[40] A number of clinical studies, comprehensively reviewed elsewhere,[41,42] have attempted to assess the role of serotonin abnormalities in panic disorder. The serotonin-releasing agent fenfluramine is anxiogenic in patients with panic disorder but tends to increase generalized or anticipatory anxiety rather than true panic. Examination of postsynaptic serotonin receptor function in panic disorder with the mixed serotonin agonist-antagonist *m*-chlorophenylpiperazine has produced equivocal results. Thus, the postsynaptic serotonin receptor supersensitivity hypothesis of panic disorder requires further evaluation.

Several serotonin receptor subtypes have been implicated in panic disorder. For example, data generated from challenge work with ipsapirone implicate the serotonin-1A receptor in panic disorder. Furthermore, the selective serotonin-3 antagonist ondansetron may be an effective pharmacotherapy for panic disorder.

Although the precise role of the serotonin system in the pathophysiology of panic disorder requires further evaluation, the role of serotonin in treating panic disorder is more established, with growing evidence of the clinical efficacy of serotonin selective reuptake inhibitors (SSRIs). Recent work suggests that part of the mechanism of clinical improvement of panic disorder with SSRIs is due to serotonin-norepinephrine interactions.[43]

Lactate and Carbon Dioxide

An impressive data base exists on the panicogenic effects of lactate and carbon dioxide in panic disorder.[44,45] However, despite this extensive experience, the neurobiological mechanisms underlying these effects remain obscure. Lactate-induced panic is well replicated, specific to panic disorder, and attenuated by antipanic pharmacotherapies. Acute changes in plasma carbon dioxide also can precipitate panic in patients with panic disorder. For example, voluntary hyperventilation causes hypocapnia and induces panic symptoms. Interestingly, hyperventilation produces a disproportionate increase in brain lactate in patients with panic disorder, possibly by hypocapnia-induced decreases in cerebral blood flow.[35] Acute hypercapnia, produced by rebreathing a 5% carbon dioxide mixture, also is panicogenic.

That both hypocapnia and hypercapnia trigger panic in patients with panic disorder is not easily explained. Carbon dioxide fluctuations and lactate may elicit panic by activating a suffocation false-alarm response in patients who have a preexisting hypersensitivity of their suffocation-alarm mechanism.[44]

Benzodiazepine and Gamma-Aminobutyric Acid

Benzodiazepine receptor agonists produce neuronal inhibition via benzodiazepine receptor modulation of the gamma-aminobutyric acid ($GABA_A$) receptor mechanism, which leads to a variety of pharmacologic effects, including anxiolysis, muscle relaxation, and sedation. Benzodiazepine antagonists occupy the benzodiazepine receptor site without producing pharmacologic effects, while inverse agonists, such as certain beta-carbolines, are anxiogenic and proconvulsant.[46] High-potency benzodiazepine receptor agonists, such as alprazolam and clonazepam, have marked antipanic effects and are considered standard pharmacotherapies for panic disorder.

Following up on treatment response data, several research groups have looked more closely for abnormalities in the benzodiazepine receptor in patients with panic disorder. Some data suggest subsensitivity of benzodiazepine receptors in this population.[47] The benzodiazepine antagonist flumazenil was reported to be panicogenic in patients with panic disorder but not in healthy control subjects.[48] Thus, patients with panic disorder may have an intrinsic

benzodiazepine receptor abnormality or a deficiency of an endogenous anxiolytic agent.

With respect to GABA itself, inhibition of GABA synthesis in the dorsomedial hypothalamus of rats sensitized them to lactate-induced anxiety in one laboratory model of panic disorder.[49] As yet, no specific defect in GABA functioning has been identified in patients with panic disorder.[50]

Peptides

The role of cholecystokinin (CCK) and other neuropeptides in panic disorder has generated much interest. The anxiogenic effects of CCK are thought to be mediated via the CCK_B receptor. Drug-free patients with panic disorder are more sensitive to the anxiogenic properties of the CCK_B agonists CCK-4 and pentagastrin than healthy control subjects, consistent with postsynaptic CCK_B receptor supersensitivity in panic disorder.[51,52] The CCK_B antagonist compounds, such as L-365,260, decrease the anxiogenic effects of CCK-4.[53] However, whether CCK_B antagonists have clinical efficacy in panic disorder is uncertain.[54]

Other neuropeptides involved in hypothalamic-pituitary-adrenal axis regulation may be abnormal in patients with panic disorder.[42] For example, some investigators have observed blunted adrenocorticotrophic hormone responses to corticotropin-releasing factor challenge in patients with panic disorder. However, levels of corticotropin-releasing factor in the cerebrospinal fluid of patients with panic disorder were similar to those of control subjects in one study,[55] suggesting that tonic hypersecretion of corticotropin-releasing factor is not part of the pathophysiology of panic disorder, in contrast to posttraumatic stress disorder and depression. Current development by pharmaceutical companies of corticotropin-releasing factor antagonist compounds may greatly advance research in this area.

The finding of blunted growth hormone responses to growth hormone-releasing factor in patients with panic disorder is consistent with hypothalamic-pituitary-adrenal axis abnormalities. Another neuropeptide of interest in panic disorder is neuropeptide Y. Recent data indicate that plasma neuropeptide Y levels are abnormally elevated in panic disorder, perhaps reflecting a compensatory response to norepinephrine system overactivity.[56] Neuropeptide Y-1 receptor agonists are a promising target for anxiolytic drug development.[57] Further evaluation of neuropeptides and their interactions with the classic neurotransmitter systems in panic disorder is warranted.

INTEGRATED NEUROBIOLOGY OF PANIC DISORDER

The model presented in Figure 1 allows for the development of pathology in different, interacting neuronal systems, in contrast to earlier conceptions of the pathophysiology of panic disorder that focused excessively on one neuronal structure or neurotransmitter system. While initially useful, these unitary models are limited in their explanatory and predictive power as the pathophysiology literature has become more complex and seemingly contradictory.

Integrating functional neuroanatomy and clinical neurobiology provides a broader understanding of the clinical features and course of panic disorder. Spontaneous panic attacks can be viewed as resulting from specific abnormalities in the efferent systems of our model. For instance, overactivity in the locus ceruleus-norepinephrine system or parabrachial nucleus (possible locus of a putative suffocation-alarm mechanism) may be the neural basis of spontaneous and nocturnal panic attacks. Pathology in the signal-processing part of the neuronal model may account for other features of panic disorder. For example, the neural mechanisms of fear and contextual conditioning, coordinated via the amygdala and other associated structures, provide a model for the development of agoraphobic behaviors. Disruption of neural mechanisms that subserve extinction may increase our understanding of treatment refractoriness and chronicity in panic disorder.

The neural mechanism of behavioral sensitization provides a framework for understanding the contribution of trauma and life events to the onset of clinical panic disorder. Sensitization processes may account for illness chronicity and recurrence in certain cases of panic disorder. Neurotransmitters implicated in the neural mechanisms discussed above include serotonin, norepinephrine, dopamine, *N*-methyl-D-aspartate, glutamate, benzodiazepine/GABA, corticotropin-releasing factor, and possibly other neuropeptides, such as CCK and neuropeptide Y. Pathology in the afferent loops of the neuronal model may account for other clinical features of panic disorder, such as hypochondriasis and sensation sensitivity.

An integrated neurobiology of panic disorder promises to increase our understanding of the mechanisms of effective treatment. Psychotherapies, particularly cognitive and behavior therapies, may work by interrupting fear and contextual conditioning mechanisms. They also may facilitate extinction of phobic pathology through the acquisition of conditioned inhibitors (cues that compete with and modulate conditioned fear). Acquisition of conditioned inhibitors may involve a neuronal loop between the bed nucleus of the stria terminalis, amygdala, and hippocampus. Psychotherapy may also work at the molecular level to alter stress-related gene expression and protein synthesis or to influence mechanisms, such as long-term potentiation, implicated in learning and memory acquisition in fear-related neuronal structures.

A more complete model for the mechanisms of successful pharmacotherapy in panic disorder may result from an improved understanding of the functional neuroanatomy of fear and anxiety. In the future, drug develop-

ment may center on candidate peptides or neurotransmitters beyond the classic systems already implicated in panic disorder. Efforts may focus on developing highly selective drugs that target anatomic structures, such as the amygdala, strongly implicated in fear and anxiety.

CONCLUSION

A functional neuroanatomic appraisal of panic disorder may provide a fruitful point of departure for generating and testing new research hypotheses on the nature of this condition. Some of the key structures discussed in our neuronal model have already been implicated in the pathophysiology of panic disorder in studies conducted with powerful imaging techniques. The ability of such techniques to map out electrical and chemical events with increasing anatomic precision allows us to scrutinize the evanescent psychopathology of panic disorder and its neurobiological basis more clearly than ever before.

Drug names: alprazolam (Xanax), clonazepam (Klonopin), clonidine (Catapres), fenfluramine (Pondimin), flumazenil (Mazicon), isoproterenol (Isuprel and others), yohimbine (Yocon and others).

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Discussion

Neurobiology of Panic Disorder

Dr. Rosenbaum: Much of our understanding of the neurobiology of panic disorder is related to the study of normal fear reactions. However, some observations suggest that panic is not just fear, since fearful persons typically do not experience the same symptoms, such as the sensation of choking or smothering, as patients with panic disorder.

Dr. Charney: Approximately 30% of healthy persons have extreme responses to fear, danger, and trauma; these persons may experience many of the same symptoms as those with panic disorder. I'm not sure there is a homogeneous response to fear.

Data from positron emission studies of depression indicate that the function of some of the same brain structures changes in depressed patients and nondepressed persons asked to imagine themselves as being depressed or sad. However, these changes are in opposite directions. For example, in normal sadness, blood flow increases to the prefrontal cortex. In depressed patients, blood flow to this area slightly decreases. Thus, normal anxiety or depression may not be a good model for pathologic conditions.

Dr. Ballenger: Which neurochemical do you believe is most involved in the pathophysiology of panic disorder?

Dr. Charney: I am not a fan of serotonin. I think panic disorder results from an interaction of the basic systems that modulate behavior, such as the norepinephrine system.

Dr. Rosenbaum: Researchers are now beginning to talk about "neural nets."

Dr. Charney: I think that is a somewhat better explanation. One advantage of developing neural nets, or circuits, is that you can ask, "Which neurochemicals and neuropeptides are in the circuit to give you a hypothesis for panic disorder?" This is important because we do not have an animal model for panic disorder, although we do have such models for stress.

Dr. Barlow: What about Grey's elaboration of the fight-flight system versus the behavioral inhibition system and how these relate to the septal-hippocampal circuits? Would you consider this a reasonable basis for a possible animal model of panic disorder?

Dr. Charney: A useful animal model of panic disorder requires that the animals have spontaneous panic attacks. I don't know how we would measure that or determine when it is happening.

Dr. Barlow: Grey has traced different circuits in rats and found that the locus ceruleus plays a central role in the stress response, or what we might call anxiety. The locus ceruleus circuit is highly responsive to unconditioned stimulation, and thus, stress responses are learned very quickly. Animals, and perhaps humans, may have biologically lower thresholds to this type of response. Thus, there would not be a spontaneous panic, in the sense that there is no antecedent.

Dr. Charney: That is why there are good animal models of fear conditioning, which is part of panic disorder. However, the spontaneous aspect is difficult to mimic.

Trauma and Panic Disorder

Dr. Marshall: Dr. Rosenbaum, what relationship have you found between trauma and panic disorder?

Dr. Rosenbaum: From our reviews of structured diagnostic patient interviews in our studies of patients with panic disorder, we found that a considerable number of patients offer a history of some traumatic event. Yet this finding presents us with a "chicken and egg" dilemma. For example, if you have an arousal diathesis, are you more likely to experience events as traumatically? Are you more likely to experience actual trauma? Are you more likely to remember it? Are you more likely to be affected by it? If so, years later it may be more likely to come up in a diagnostic interview.

When the trauma occurs is also relevant. If it happens before age 5, it may alter the developing neurobiology dramatically.

Dr. Charney: The issue of early trauma in patients with panic disorder is underappreciated. One study showed that children who were physically or sexually traumatized before age 5 have tremendous psychiatric difficulties as adults. The single most common disorder in these sexually abused children is agoraphobia. The memory of a traumatic event could change the threshold response to events in the environment. This is consistent with data that patients with panic disorder look at environmental events in quite a different way.

Dr. Rosenbaum: We have speculated that decreasing acute arousal after trauma by, for example, administering a drug such as a β-blocker might decrease the level of arousal in an inhibited child and ultimately decrease the risk of developing an anxiety disorder as an adult.

Dr. Pollack: Is it possible that benzodiazepines, if used at particular times, might prevent learning of phobic behaviors?

Dr. Charney: Benzodiazepines may prevent patients from remembering or associating a particular situation with fear.

Dr. Davidson: The relationship between posttraumatic stress disorder and panic disorder is interesting. We might assume that persons with posttraumatic stress disorder are genetically predisposed to developing panic disorder–type states after exposure to trauma. Yet, at least two studies have shown that persons with posttraumatic stress disorder do not have an increased rate of panic disorder in their families. These results indicate a phenotypic similarity between the illnesses but genetic differences.

Dr. Pollack: Should we direct treatment for patients with panic disorder at helping them overcome the identified trauma?

Dr. Rosenbaum: Some data suggest that revisiting trauma is bad for the patients and suppressing or forgetting the event is the best way to adapt to it.

Dr. Shear: Revisiting the trauma in the course of therapies without giving the patient coping skills can be counterproductive.

Dr. Ballenger: It's a very emotional experience, somewhat along the lines of Dr. Shear's emotion-focused treatment. Yet, in most cases, you are not attacking the trauma at age 4 and correcting the experience. That could be dangerous.

Dr. Charney: Clinicians should not focus on early trauma to the exclusion of later established treatments.

Dr. Davidson: First, we need to be mindful that patients with panic disorder may have had a history of early trauma, but it may not mean anything with regard to the current management of panic disorder. Second, the trauma could require some direct attention. Third, treatment-resistant patients may not respond to therapy because of unrecognized posttraumatic stress disorder.

Etiology of Panic Disorder

Dr. Rosenbaum: Panic disorder results from a biological-environmental interaction. Genes do not make behavior; they have to interact with something to shape the outcome.

Dr. Rapaport: The etiology of panic disorder is considerably more complex than our discussion indicates. For example, we have not discussed the role of cytokines in modulating responses in patients with panic disorder. Panic disorder is a syndrome involving a variety of pathophysiologic mechanisms. What we need to look for are common pathways.