The Neuroanatomy of 5-HT Dysregulation and Panic Disorder

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The advent of highly effective antipanic medications with specific serotonin reuptake inhibition as a mechanism of action has prompted the need for new pathophysiological models of panic disorder. The authors attempt an integration of the emerging basic science literature regarding the neuroanatomy and physiology of the mammalian central serotonin nervous system, its influence on neural substrates that underlie fear and defense responses, and the clinical literature pertaining to serotonin-related abnormalities in panic disorder. A neuroanatomical model for the potential sites of action of the specific serotonin reuptake inhibitors in panic disorder is proposed.

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The massive evolutionary expansion of the neocortex to its present human form may be the single largest factor predisposing our species to a variety of affective and behavioral disorders.[1] Progressive increases in myelination and the number of projection sites of the ascending serotonergic tracts in the raphe cortical tract, presumably occurring throughout hominid evolution, have resulted in huge increases in the speed and complexity of thought processing in humans when compared with primates and lower animals. Unfortunately, this evolutionary advantage may be, we would speculate, at the cost of an increasingly sensitive serotonin (5-HT) system that is more prone to dysregulation in a variety of regions—particularly in its interaction with other neurotransmitter systems and with neuronal substrates that control thought, complex behaviors, and affect.

Consequently, serotonergic dysregulation may be a central theme in many anxiety disorders, including panic disorder. A plausible explanation for the efficacy of serotonin-specific reuptake inhibitors (SSRIs) in treating panic disorder requires the exploration of new pathophysiological models. The exploration of 5-HT mechanisms does not imply that other neurotransmitter systems play any less of a role in the pathogenesis of panic disorder. In fact, the possibility exists that 5-HT

[†]In memory of Gregory Grove and his fine scholarship.

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function is generally intact in panic disorder and that SSRIs work by compensating for malfunction in other neurotransmitter systems.

GENERAL NEUROANATOMY OF THE ROSTRAL 5-HT SYSTEMS

Both limbic and cortical structures (especially the prefrontal cortex) appear to be primary areas innervated by rostral 5-HT projections. Caudal 5-HT projections, although probably of major significance for autonomic control, are not a focus of this article. Postmortem radiolabeling experiments in humans indicate that outside the raphe nuclei, the highest concentrations of 5-HT in the forebrain can be found in the hippocampus, the cingulate gyrus, the amygdaloid complex, the prefrontal cortex, cortical areas associated with sensation, the substantia nigra, the basal ganglia, the hypothalamus, and the substantia innomata.[1-3]

Histochemical studies suggest that two rostrally projecting serotonergic nuclei supply cortical and subcortical regions: the dorsal raphe nucleus (DRN) and the median raphe nucleus (MRN). These two nuclei project to distinct loci and regions, subserving either independent or parallel physiological functions.[3] The MRN projects largely to the hypothalamus and limbic system structures; the DRN projects primarily to forebrain structures, the basal ganglia, and other hypothalamic nuclei.[2] Considering their respective projection sites, it is plausible that the MRN may play a more significant role in mediating or modulating fear and anxiety and their attendant autonomic disturbances (as in anticipatory anxiety and panic attacks), whereas the distribution of the DRN's axonal fibers may, to a greater extent, influence cognition and motoric behavior (such as catastrophic cognitions and phobic avoidance).

TABLE 1. Differences between the dorsal raphe nucleus and the median raphe nucleus

Dorsal Raphe Nucleus	Median Raphe Nucleus
Projections	
Caudate nucleus	Amygdala nuclei[a]
Lentiform nucleus	Hippocampus
Substantia nigra (pars compacta)	Lateral habenula[a]
Thalamic nuclei	Entorhinal cortex
Ventral medial hypothalamus	Lateral hypothalamus
All cerebral cortical lobes	Temporal lobe cortex
Periaqueductal grey	Mammilary bodies
Locus ceruleus[a]	Ventral tegmental area
Characteristics	
Less myelination	More myelination
Smaller axons	Larger axons
Small, irregular varicosities	Large, regular varicosities
More diffuse connections	More precise connections
May be damaged/destroyed by neurotoxins 5-DHT, MDA, etc.	Not prone to damage by DRN neurotoxins
More homotypic collaterals	Less homotypic collaterals
70% of neurons possess 5-HT	35% of neurons have 5-HT

Note: This table originally appeared in Törk and Hornung[3] and is reprinted by permission. 5-HT = serotonin; 5-DHT = 5,7-dihydroxytryptamine; MDA = 3,4-methylenedioxyamphetamine; DRN = dorsal raphe nucleus.

[a]Overlap exists among these projections, but in each case the major source of 5-HT is cited.

Morphological Considerations

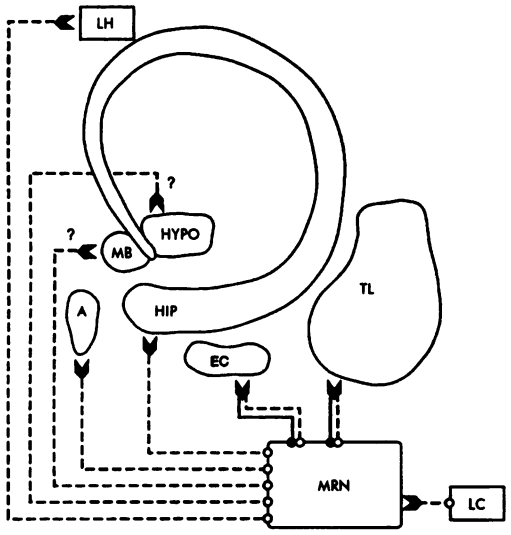
Axonal projections from the MRN and DRN operate through a system of diffuse vesicles that discharge at both nondistinct and highly selective loci upon depolarization.[1,4] Overlap of MRN and DRN axons, particularly in ascending tracts such as the medial forebrain bundle and the dorsal raphe cortical tract, as well as the presence of local serotonergic fibers in the reticular formation, may obscure the independent action of these nuclei. Some generalizations about the DRN and the MRN may, nevertheless, be made, as summarized in Table 1.[3]

Efferent Pathways

Axons from the MRN (Figure 1) project primarily to the hippocampus, the entorhinal cortex, the lateral hypothalamus, the lateral habenula, the amygdala nuclei, the mammillary bodies, the parietal cortex, and some areas of the temporal lobe. Compared with the projections of the DRN, these axons contain more myelin, consist of relatively larger diameter fibers, have a higher proportion of direct synaptic contacts, and communicate via fewer (but larger) synaptic vesicles.[5] The relationship between the limbic system and the MRN is reflected in the fact that the MRN is the site of the greatest number of rostral serotonergic cell bodies, and the limbic centers contain the highest concentrations of serotonin in the brain (outside the raphe nuclei), stemming from extensive MRN axonal projections.[3]

Conversely, axonal projections from the DRN tend to be relatively smaller and more diffuse in nature and to have much less myelination, smaller varicosities, and fewer direct synapses than those of the MRN. These fibers are less hardy than those of the MRN and may be damaged by agents such as 5,7-dihydroxytryptamine (5,7-DHT), parachloroamphetamine, and 3,4-methylenedioxyamphetamine (MDA) that will not harm the larger axonal projections of the MRN.[6] DRN axons (Figure 2) innervate areas of the prefrontal cortex, the basal

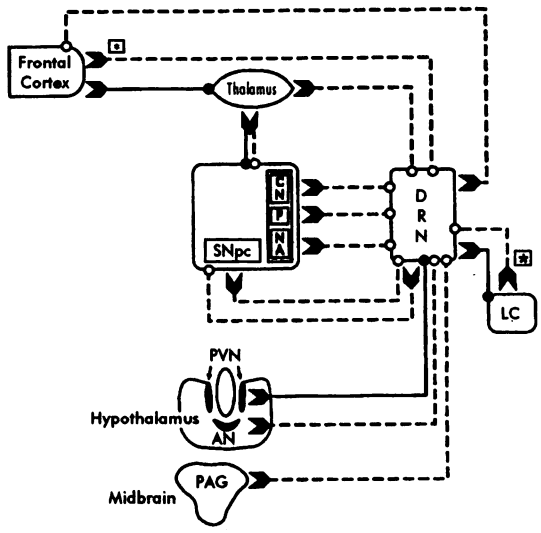
FIGURE 1. Projections of the median raphe nucleus.



MRN = Median raphe nucleus
LC = Locus ceruleus
TL = Temporal lobe
EC = Entorhinal cortex
HIP = Hippocampus
A = Amygdala
MB = Mammiliary bodies
HYPO = Hypothalamus
LH = Lateral habenula
? = Preliminary data only

Stimulatory
Inhibitory

FIGURE 2. Projections of the dorsal raphe nucleus.



DRN = Dorsal raphe nucleus
LC = Locus ceruleus
AN = Arcuate nucleus (of hypothalamus)
PVN = Paraventricular nucleus (of hypothalamus)
SNpc = Substantia nigra pars compacta
CN = Caudate nucleus
P = Putamen
NA = Nucleus accumbens
FC = Frontal cortex
PAG = Periaqueductal grey

Stimulatory
Inhibitory

[*] Inhibitory signal may be downgraded by increased density of 5-HT_2 receptors

ganglia (caudate and lenticular nuclei), the thalamus, the paraventricular nucleus and arcuate nucleus (AN) of the hypothalamus, the periaqueductal grey (PAG), the locus ceruleus (LC), and the substantia nigra (SN).

Afferent Pathways

Afferent neuronal projections to the DRN and MRN are important factors in the regulation of the rostral serotonergic system. The DRN receives afferents from many loci (Figure 2), including the lateral habenula, the lateral hypothalamic area, the PAG, the LC, and the SN. Electrical stimulation of the lateral habenula and SN result in primary inhibitory responses in the DRN, depressing the spontaneous firing of these neurons.[7] Habenular stimulation results in an indirect inhibitory pathway to 5-HT DRN neurons via GABAergic interneurons located within the DRN, and the dopaminergic neurons of the substantia nigra pars compacta (SNpc) send direct inhibitory projections to the serotonergic neurons of the DRN. As mentioned above, DRN neurons project back to the SNpc, suppressing SNpc neuronal activity with 5-HT.

The DRN also receives two major excitatory inputs. Projections from both the LC and the lateral hypothalamus stimulate DRN serotonergic neurons.[7] Serotonergic projections from the DRN inhibit the firing of LC neurons, and noradrenergic innervation from the LC excites DRN neurons.[7] This feedback relationship mutually regulates the actions of these critically important nuclei, intimately relating both the noradrenergic and serotonergic neurotransmitter systems.

The MRN receives afferent projections (Figure 1) from the lateral habenula, the lateral hypothalamus, the LC, and the PAG, as well as from other sources.[3,8] Those from the lateral hypothalamus, the lateral habenula, and the LC appear to be inhibitory.

SEROTONIN FUNCTION IN PANIC DISORDER

Evidence for Serotonin Dysfunction

As in a variety of psychiatric disorders, the serotonergic neurotransmitter system has previously been implicated both directly and indirectly in panic disorder.[9] Direct evidence for serotonergic dysregulation or dysfunction in panic disorder patients stems from an increasing number of studies comparing panic disorder patients either with normal control subjects or other subgroups of patients without these disorders. Some of

these studies have yielded results indicating significant differences in:

1. Peripheral biological markers of serotonergic function, such as reduced 5-HT platelet transporter sites.[10–13]
2. Anxiogenic responses to particular direct and indirect 5-HT agonists, such as fenfluramine, mCPP, and clomipramine,[14–17] suggesting hypersensitive postsynaptic 5-HT receptors.
3. Exaggerated neuroendocrine responses to direct or indirect 5-HT agonists.[14,15,18]
4. Treatment efficacy of the SSRIs, which directly alter the function of the serotonergic system through specific serotonin reuptake blockade at neuronal uptake transporter sites.[19–21]
5. Patients with panic disorder, in contrast to other psychiatric disorders, show initial SSRI hypersensitivity, manifest as a jitteriness syndrome, consistent with upregulation of certain postsynaptic elements of the 5-HT system (reviewed by Coplan et al.[9]).

The view of supersensitive postsynaptic 5-HT receptors has not routinely been supported. Studies using the serotonergic precursors tryptophan[22] or 5-hydroxytryptophan[23] have not demonstrated differences between panic patients and healthy control subjects. Neuroendocrine studies in healthy volunteers indicate that the prolactin response to tryptophan is blocked by the 5-HT_{1A} antagonist pindolol and the nonspecific 5-HT antagonist metergoline. However, ritanserin, a 5-HT_{2A}/5-HT_{2C} antagonist, did not block the prolactin response to tryptophan (see Deakin[24] for review). 5-HT precursor challenges may produce preferential binding to 5-HT_{1A} receptors, which may not be associated with the anxiogenic effects observed in panic disorder subjects with the other 5-HT agonists.

In addition, studies using the intravenous form of mCPP, regarded primarily as a 5-HT_{2C} agonist, did not initially reveal between-group biochemical or behavioral differences.[25] Subsequent studies by the Yale group, in a lower mCPP dose range, yielded statistically increased panic effects in patients compared with control subjects, but blunted prolactin responses in female panic patients.[26] Finally, Judd et al.[27] were not able to demonstrate distinguishable neuroendocrine effects for the serotonin-specific stereoisomer dextrofenfluramine, casting doubt on the specificity of previous findings that racemic *dl*-fenfluramine possesses significant dopaminergic effects.

Neuroimaging Studies in Panic Disorder

Current neuroimaging studies provide further clues to integrating the neuroanatomy of the DRN and MRN with the pathophysiology of 5-HT dysregulation in panic. These studies have yielded significant findings—often unilateral in nature—in the temporal lobe, prefrontal, and limbic regions. In one study,[28] 40% of panic disorder patients (vs. 10% of normal control subjects) were found to have abnormal MRIs, the majority of these abnormalities occurring in the temporal lobe. Moreover, abnormal signal activity and asymmetric atrophy were found mostly in the right temporal lobe. In patients who were vulnerable to lactate-induced panic, Reiman et al.[29] found asymmetrical parahippocampal activity (right greater than left) and increased activity subjacent to the superior colliculi (perhaps the PAG) during panic attacks. The retraction of certain findings (temporal poles being confused with masticatory muscles) by Drevets et al.[30] should not detract from the many other positive findings of that study, which were carefully checked (Drevets et al., personal communication, 1996). Nordahl et al.[31] also found parahippocampal asymmetry in panic disorder patients, and de Cristofaro et al.,[32] during baseline SPECT studies of panic disorder patients, discovered hippocampal hypoperfusion bilaterally and an abnormal asymmetry, right greater than left, in the inferior frontal cortical region. Continuing the theme of abnormal prefrontal neuronal activity, Kuikka et al.[33] reported, in a SPECT study, increased right-to-left asymmetry of uptake of the radiolabeled benzodiazepine antagonist [^{123}I]iomazenil of the inferior and middle prefrontal cortex in patients with panic disorder compared with control subjects. These studies provide preliminary evidence concerning the neuroanatomical substrates involved in the panic process.

NEUROANATOMICAL SUBSTRATES IN PANIC DISORDER

We now proceed, using the above preclinical and clinical neuroanatomical and 5-HT-related information, to outline the putative neuroanatomical "circuitry" in panic disorder, creating two basic subdivisions: the "efferent" division, which is that neural substrate component that elaborates the clinical symptoms of panic disorder, and the "afferent" division, which is that neuroanatomical mechanism whereby endogenous or extraneous stimuli may activate the efferent limb.

The Efferent Limb

Limited clinical findings during stereotaxic brain surgery on humans (secondary to electrical stimulation) is suggestive of central neuroanatomical substrates involved in panic disorder. More specifically, the dorsal periaqueductal grey, the medial hypothalamus, and the

amygdala have been implicated as structures that appear to be involved in the mediation of panic or anxiety (reviewed by Graeff[34]).

During the electrical stimulation of the dorsal PAG in humans, Nashold et al.[35] have documented "strong reactions in most patients. Feelings of fear and death were often expressed. Autonomic activation such as contralateral piloerection and sweating, increase in the pulse and respiratory rate, blushing over the entire face and neck . . . were noted" (p. 194). Indeed, these symptoms are quite reminiscent of the criteria for ideal panic disorder probes postulated by Gorman et al.,[36] suggesting that stimulation of the dorsal PAG may be a key event in triggering panic. Deakin and Graeff[37] posit that this may be a site of activation during acute unconditioned aversive stimuli—such as pain, asphyxia, and innate fear-inducing stimuli—producing panic, fight, flight, or freezing behaviors in animals and humans. Additionally, this state may be homologous to the "suffocation alarm" model proposed by Klein,[38] in which panic disorder patients with poor PAG regulatory control respond with panic attacks and escape responses during the administration of respiratory panicogens.

DRN Inhibition of the Periaqueductal Grey: Deakin and Graeff[37] suggest that 5-HT inhibition of the dorsal PAG via the DRN may be crucial in preventing panic responses. In rat studies, electrical stimulation of the DRN and microinjections of both 5-HT and 5-HT reuptake blockers into the dorsal PAG all attenuated PAG-induced "panic," supporting the hypothesis of DRN restraint of the PAG.[39,40] Noradrenergic innervation of the PAG is mediated by the locus ceruleus via the dorsal tegmental bundle, and Gray[41] interestingly notes that LC innervation of the PAG is inhibitory. As a final note, the PAG also has GABAergic receptors that may be responsive to the inhibitory effects of high-potency benzodiazepines.

The Central Nucleus of the Amygdala and Fear Response: Both emotional and visceral fear responses that resemble panic, as well as *déjà vu*-type responses, which are in fact more consistent with temporal lobe epilepsy, have been observed in humans during electrical stimulation of the amygdala.[42] In other studies, electrical stimulation of the human amygdalofugal pathway—which projects from the central nucleus of the amygdala to the periaqueductal grey, the solitary nucleus, the parabrachial nucleus, the nucleus ambiguus (dorsal motor nucleus of the vagus [DMNV]), and the paraventricular nucleus of the hypothalamus (PVN)—promotes strong fear responses (see Graeff[34] for review). Primate studies have replicated electrical stimulation findings of emotional and visceral fear responses in humans, and ablation of the amygdala in monkeys causes a loss of fear responses to formerly threatening stimuli.[8] Consequently, Deakin and Graeff[37] suggest that the amygdala may play an important role in attaching emotional significance to stimuli, especially in aversive classical conditioning.[43–45] DRN hyperactivity and/or MRN hypoactivity may lead to overactivity of the central nucleus of the amygdala (and the closely related bed nucleus of the stria terminalis). The central nucleus of the amygdala has been posited to play a role in fear and anticipatory anxiety (as in generalized anxiety disorder) rather than in frank panic.[34] However, the ventral amygdalofugal pathway projects to the PAG, both directly and indirectly (via the PVN), implicating 5-HT–induced amygdaloid hyperactivity in the mediation of anticipatory anxiety as well as induction of a priming process of the PAG, lowering its threshold for the occurrence of panic.

Locus Ceruleus Function and Panic: Electrical stimulation and lesioning studies in primates[42] suggest possible involvement of the locus ceruleus in panic disorder. The effects of unilateral electrical stimulation of LC electrodes on chair-restrained monkeys included consistently induced or increased startling, hand wringing, struggling, pupillary dilation, piloerection, alerting, blood pressure, pulse rate, and respiration rate. Conversely, bilateral electrothermic lesions of the LC produced an absence of emotional responses to threats, decreased anxiety as measured by scratching and self-mouthing behaviors, and dramatic increases in eating and drinking. Some of the many efferent tracts of the LC include projections to the DRN, the PAG, and excitatory input to both the PVN and the basolateral and central nuclei of the amygdala.[41] However, inconsistent peripheral markers of noradrenergic activity at baseline, no increases in serum 3-methoxy-4-hydroxyphenylglycol (MHPG) during respiratory panicogen or spontaneously induced panic attacks, and the ineffectiveness of imipramine in blocking yohimbine-induced anxiety in panic disorder patients (reviewed by Klein[38]) do not support a central role of the LC in mediating the efferent limb of panic. Nevertheless, it appears that the efferent tracks of the LC may play an important role in mediating anticipatory anxiety and priming panic through amygdaloid and, ultimately, PAG stimulation.

Anxiety Versus Panic Efferents: In contrast to substrates causing panic, Deakin and Graeff[37] liken anxiety to a state that results from acute conditioned aversive stimuli—consisting of fear and anticipatory anxiety, but not of overt panic. Furthermore, the authors cite evidence that the amygdaloid-hippocampal system may play a

key role in assessing the magnitude of a particular threat and that the rostral serotonergic system may function by preventing panic responses so that organisms can learn to respond to aversive stimuli in more adaptive ways than through sheer panic. Increased DRN activity to the amygdalohippocampal areas is associated with an increase in anxiety. Conversely, stimulation of the DRN putatively increases restraint of the PAG, warding off potential panic.[39] Hence, the authors suggest that anxiety may prevent panic rather than lead to panic responses that are behaviorally maladaptive.

Conclusions Regarding the Efferent Limb: Considering the discrepancies in responses to panicogens and the wide variety of probes (and situations) that may cause panic and anxiety, several points are suggested by these findings:

1. Although the efferent limb of panic is potentially mediated by the PAG, several afferent limbs stemming from a variety of pharmacological or experiential stimuli may produce panic via a variety of paths.
2. Some afferent pathways that are anxiogenic but not panicogenic in normal subjects may be panicogenic in some panic disorder patients.
3. Anxiety may have a less panicolytic effect in panic disorder patients than in normal control subjects.

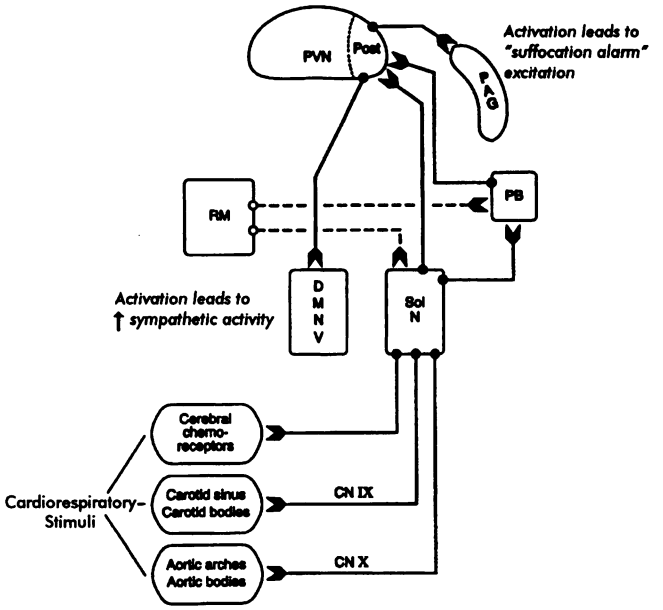
These and other theories of pathogenesis are discussed below in an exploration of possible afferent limbs in panic.

Afferent Limbs of Panic (Overstimulation Models)

There appear to be at least three afferent routes through which, when overstimulated, panic may be mediated in panic disorder patients:

A Viscerosensory Pathway (Figure 3): This is a caudal pathway from peripheral and/or central chemoreceptors to the PAG, which may be activated by a variety of stimuli, including respiratory panicogens (doxapram,[46] carbon dioxide[36,47]), acid-base abnormalities (sodium-DL-lactate, sodium-D-lactate, sodium bicarbonate, hyperventilation[48,49]), or perhaps baroreceptor stimulation (isoproterenol[50]). This path probably relies on excitatory amino acid systems.[51] The key structures involved are the caudal portion of the solitary nucleus, where gut peptides such as cholecystokinin may act,[52] and the parabrachial nucleus. The primary evidence for this path is the existence of the respiratory panicogens.[36] In this model, transient changes in pH or sympathetically induced increases in aortic and carotid pressure may stimulate peripheral or central chemoreceptors or

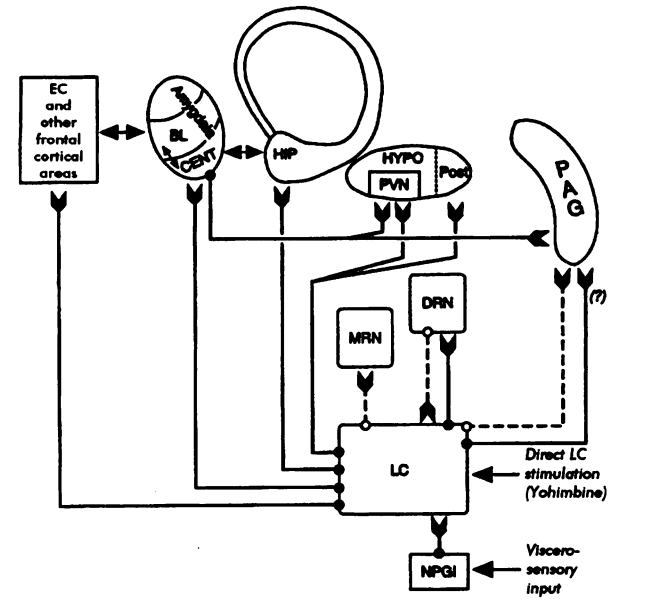
FIGURE 3. A putative viscerosensory pathway in panic disorder.



peripheral baroreceptors. Peripherally mediated afferent impulses are propagated via cranial nerves IX and X to the caudal solitary nucleus. Ventral medullary (central) chemoreceptors also conduct visceral information to the solitary nucleus. The caudal portion of the solitary nucleus both transmits viscerosensory information to the parabrachial nucleus and participates in cardiovascular, respiratory, visceral, and autonomic reflexes via projections to the spinal cord and other medullary neurons (such as the intermediolateral nucleus and the nucleus ambiguus).[53] The parabrachial nucleus is a center for coordinating autonomic, endocrine, and additional visceral functions, relaying viscerosensory information to the amygdala. The ventral amygdalofugal pathway (VAP) projects back to the parabrachial and solitary nuclei, to the paraventricular nucleus of the hypothalamus, the nucleus ambiguus, the DMNV, and, most importantly, directly to the PAG.

Both the solitary nucleus and the parabrachial nucleus also send viscerosensory information directly to the posterior hypothalamus for coordination of visceral and neuroendocrine responses, and the hypothalamus responds by relaying efferent information back to the solitary and parabrachial nuclei, as well as to the DMNV and the PAG.

FIGURE 4. A noradrenergic pathway in panic disorder.



A final and perhaps most pertinent pathway entails direct projections from the chemoreceptors and baroreceptors directly to the PAG (see Handley[54] for review).

Serotonin-containing neurons located primarily in the MRN exert predominantly inhibitory effects on brainstem nuclei that control cardiovascular and ventilatory function. Moreover, MRN innervation of the hippocampal-amygdaloid complex, the primary limbic recipient of viscerosensory afferents, exerts inhibitory effects via 5-HT_{1A} receptors.[55,56]

A Noradrenergic Pathway (Figure 4): Stimulation of the locus ceruleus results in excitation of a variety of structures, including the basolateral and central nuclei of the amygdala, the paraventricular nucleus of the hypothalamus, the hippocampus, the entorhinal cortex, a variety of other cortical regions, and the PAG. All of these projections may play a role in indirectly stimulating the PAG. Additionally, the LC inhibits the MRN. Thus, LC hyperactivity may play a role in exacerbating anxiogenic responses; this is so because the MRN, through inhibitory 5-HT_{1A} receptors, attenuates activities of limbic structures (such as dorsal hippocampus and amygdala[55,56]) and brainstem nuclei that regulate cardiorespiratory function.[1,57] Yohimbine or other stimuli that increase the firing of the LC may induce panic through one or more of these pathways.

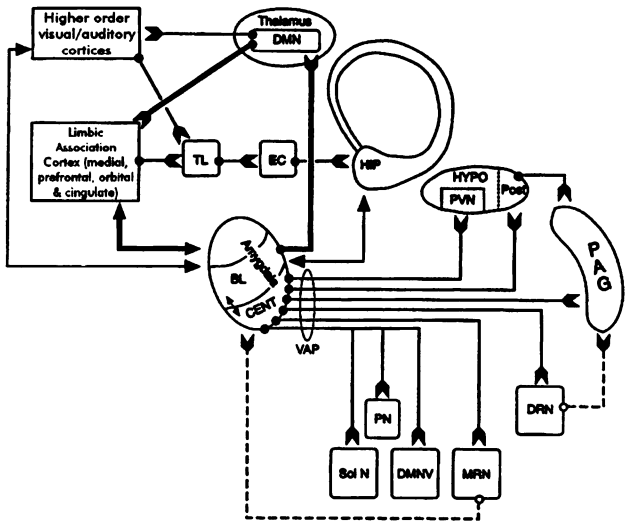
Another alternative, posed by Gorman et al.,[36] is that the LC may also be stimulated by the medullary nucleus paragigantocellularis, which receives stimulatory glutamatergic afferents from the solitary nuclei,[51] postulated to participate in the viscerosensory pathway. Through acute stimulation of the DRN by the LC, catastrophic cognitions and phobic responses may be generated following right prefrontal cortical activation. Coplan et al.[58] have recently reported that fluoxetine reduces basal noradrenergic activity as well as reducing noradrenergic volatility as measured by plasma MHPG levels. The effects of serotonin reuptake inhibition on the noradrenergic system were associated with generalized improvement in panic symptomatology. This view has not been supported by studies of Goddard et al.,[59] where SSRIs in panic disorder patients failed to attenuate yohimbine-induced MHPG increases. Thus, it remains to be determined whether SSRIs mediate antipanic effects, in part, through the noradrenergic system.

A Visuospatial/Auditory Pathway (Figure 5): This may comprise a predominant pathway in situational panic. Visual stimuli are received in the primary visual cortex (calcarine fissure) and sent to higher order visual centers. Object vision (of crowds, for instance) is conducted to the inferior temporal lobe, and spatial vision (such as vision of moving traffic or bridges) is conducted to the posterior parietal cortex. Higher order auditory and visual cortical centers project to cortical association areas and then communicate reciprocally with the basolateral nucleus of the amygdala.

The basolateral nucleus also projects to the dorsomedial nucleus of the thalamus, which ramifies back to frontal cortical areas via the anterior limb of the internal capsule. Thus, dysregulation or overstimulation of this amygdaloid-thalamic-cortical-amygdaloid circuit could theoretically produce a positive feedback loop similar to the striatal-thalamic-cortical-striatal loops postulated in OCD.[60] This formulation may explain the anecdotal anxiolytic efficacy of capsulotomy, which would theoretically block this "reentrant" circuit. Higher order cortical regions also communicate with the hippocampus via interconnected cortical association areas that feed into the dentate gyrus of the hippocampus through the entorhinal cortex of the parahippocampal gyrus—a locus found to be abnormal in radiological studies of panic disorder patients sensitive to sodium lactate.[29] Intra-amygdaloid connections between the basolateral and

FIGURE 5. Cortical pathways in panic disorder for visuospatial, auditory, and cognitive panicogenic stimuli.

DMN = Dorsomedial nucleus



TL = Temporal lobe
EC = Entorhinal cortex
BL = Basolateral nucleus
CENT = Central nucleus
HIP = Hippocampus
PVN = Paraventricular nucleus
HYPO = Hypothalamus
PAG = Periaqueductal grey
DRN = Dorsal raphe nucleus
MRN = Median raphe nucleus
DMNV = Dorsal motor nucleus of the vagus
Sol N = Solitary nucleus
PN = Parabrachial nucleus

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central nucleus of the amygdala could activate the ventral amygdalofugal pathway in this model, stimulating the PAG. In this model, SSRI-induced increases in MRN neuronal activity may interrupt the hyperactive circuitry by inhibition of the cortex and amygdalohippocampus. Modulation of DRN neuron firing patterns and/or postsynaptic receptor modification may reduce overactivity of the cortical and thalamic components of the circuit.

SUMMARY AND INTEGRATION

A wide variety of stimuli may trigger panic attacks in panic disorder patients, and thus we will attempt to justify a hypothetical model that involves multiple pathways, converging into a final common path that induces stimulation of the primitive alarm present in the ventral amygdalofugal pathways and dorsal periaqueductal grey.

The afferent limb of panic may be tempered at multiple sites by SSRIs that facilitate neurotransmission by functional or dysfunctional 5-HT-releasing neurons arising from the median raphe nucleus. The hyperactive dorsal raphe, in turn, exerts restraint of the periaqueductal grey. However, this restraint is tenuous, as manifested by the occurrence of panic attacks, suggesting periods of relative dorsal raphe hypoactivity. We would hypothesize that dorsal raphe hyperactivity elaborates anticipatory anxiety via amygdalohippocampal projections and catastrophic cognitions, dysphoric affect, and phobic avoidance through prefrontal projections. Clinical observation suggests that anticipatory anxiety is only sometimes effective in warding off panic and that panic attacks, especially in the initial stages of the condition, are frequently spontaneous. We would therefore hypothesize that DRN activity fluctuates between hyper- and hypoactivity, where hypoactivity is the "unguarded" state (for example, behavioral relaxation leading to panic). Therefore, by enhancing serotonin neurotransmission, SSRIs provide stable periaqueductal inhibition through the DRN, thereby blocking panic, and temper hyperactivity of the ventral amygdalofugal pathway through the MRN, thus reducing anticipatory anxiety and fear. We would further hypothesize that once subcortical stabilization has been achieved, spontaneous diminution of dorsal raphe firing parallels reduction of phobic avoidance and catastrophic cognitions.

Handley[54] has lucidly described the inherent paradox of anxiety and serotonin function, which is viewed as a stress-responsive system. The preclinical literature has generally suggested that increases of 5-HT are associated with anxiety and decreases are associated with impulsivity/aggressivity. The latter pertains generally to the clinical 5-HT literature. Since the advent of the SSRIs, agents which, by general consensus, increase 5-HT neurotransmission, the traditional view has been contradicted. How can low 5-HT therefore be compatible with panic disorder? [61] Handley[54] posits that many aggressive or impulsive patients are also anxious and suffer panic attacks. However, this approach does not address the majority of panic patients, who are either inhibited or not impulsive.

As described above, we have attempted to reconcile these discrepancies by indicating that the 5-HT system in panic suffers from cybernetic dyscontrol, that is, a bidirectional failure of neurotransmitter homeostasis.[9] Thus, the DRN may be hyperactive during periods of anticipatory anxiety and phobic avoidance, and, consistent with the preclinical literature, inhibit ongoing behavior and restrain PAG activity and panic. Many patients continue in that state for years. However, in

this precarious predicament any relative hypoactivity, perhaps secondary to a failure to mount the appropriate response to stress or due to other environmental factors, will result in loss of DRN-mediated PAG restraint, and panic will result. This view, however, is not supported by tryptophan depletion studies by Goddard et al.,[62] where reduction of 5-HT neurotransmission was not associated with panic. Provocative stimuli were not applied in those experiments and would be of interest. The authors of the current paper propose a model that, although speculative, does not rely on rheostat (5-HT excessively high or low) conceptualization. A model of 5-HT dysfunction that stems from homeostatic failure may provide a future framework for reconciling discrepant data of the complex function of 5-HT systems in anxiety and panic.

Finally, given the many neuroimaging findings of abnormal asymmetry, it is possible that unilateral disease, either of structures regulated by the 5-HT system or of the 5-HT system itself, could have a major effect on the regulatory capacity of the serotonergic system. Particularly, the midline 5-HT system may be poorly designed to regulate unilateral diseased structures and contralateral normal structures simultaneously.

CONCLUSION

Much research is still needed to definitively identify the actual neuroanatomical substrates mediating panic disorder. Nevertheless, plausible models of pathogenesis involving serotonergic dysregulation, such as those presented here, may be generated from past and current research. The DRN's restraint of the periaqueductal grey and the MRN's regulatory role for the amygdala-hippocampus and brainstem may play an important role in panic and anxiety. Recent scanning studies suggest that cortical interactions to and from raphe nuclei must be more closely scrutinized. Data suggesting a role for receptor abnormalities in panic disorder pathogenesis are contradictory, and further studies with more specific or potent probes may clarify this area. The pathophysiology of 5-HT in relationship to abnormalities of asymmetry also warrants consideration.

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