The Myth of Panic Spontaneity: Consideration of Behavioral and Neurochemical Sensitization

Andrea L.O. Hebb[*,1,5] Gregory J. Anger[1], Paul D. Mendella[2], Fuschia M. Sirois[3], Robert W. Gilbert[4] and Robert M. Zacharko[5]

[1]*Dalhousie University, Department of Pharmacology, Halifax, Nova Scotia, Canada*

[2]*The Ottawa Hospital, Champlain District First Episode Psychosis Program, Ottawa, Ontario, Canada*

[3]*University of Windsor, Department of Psychology, Windsor, Ontario, Canada*

[4]*Dalhousie University, School of Health Sciences, Halifax, Nova Scotia, Canada*

[5]*Carleton University, Institute of Neuroscience, Ottawa, Ontario, Canada*

Abstract: Panic disorder is characterized by a progression of panic symptom severity with repeated attacks. Repeated panic episodes evoke heightened anticipatory anxiety, phobic avoidance and are typically associated with comorbid symptoms of depression. Due to the heterogeneity of the disorder, reliable neurochemical correlates attending panic have not been identified. However, variable neuropeptide interfacing with major and minor transmitter systems may modulate individual vulnerability to panic and account for variable panic profiles. The extensive colocalization of cholecystokinin (CCK) with other neurotransmitters, including dopamine (DA), enkephalin (ENK) and GABA, in specific central sites may influence various aspects of anxiety and panic. The behavioral correlates attending panic likely follow from variable neurochemical release and conditioning/sensitization. Clinicians maintain that recurrent panic attacks are spontaneous (unexpected, uncued) and fail to acknowledge the wealth of information implicating a prominent role for stressful life events in panic. Conditioning and sensitization of both behavior (e.g., fear-motivated) and neurochemical events (e.g., DA and CCK) in response to uncontrollable stressors parallel the diverse heterogeneity of panic amongst clinical samples. Cholecystokinin-4, pentagastrin, lactate acid, and CO_2 induce panic attacks that are dependent on subjective history, expectancy measures and panic profiles. Panic disorder is associated with chronic illness and familial sick-role modeling exacerbates the course of the illness. The current review outlines the evidence in support of a conditioning/sensitization model for panic, a model that may explain the variable efficacies of pharmacological interventions.

INTRODUCTION

Panic disorder is characterized by the repeated occurrence of panic attacks. During a panic attack, fear, shortness of breath, dizziness, heart palpitations, chest pain, sweating, faintness, paresthesia, nausea and cognitive symptoms including depersonalization and fear of losing control are typically reported [1]. Panic disorder is invariably associated with anticipatory anxiety [2, 3] and is characterized by phobic avoidance [1]. Indeed, agoraphobic behavior routinely accompanies panic disorder and is more prevalent among females [4, 5]. In any event, panic disorder with or without agoraphobia ordinarily persists for protracted periods and is accompanied by social and occupational impairments [6, 7], health risks [8-10] and comorbid psychiatric disturbances including changes in cognitive function [11], major depression [12, 13], schizophrenia [14] and substance abuse [15, 16].

Current neurochemical descriptors of panic are suggestive rather than persuasive and animal models of panic are provisional [17, 18]. Inferences concerning central correlates of panic have been derived from behavioral and neuro-chemical alterations attending systemic cholecysto-kinin (CCK) administration in paradigms that simulate anxiety [19, 20]. The panic properties of systemic CCK [21-23] prompt suggestion that brain stem and spinal respiratory and cardiopulmonary CCK sites contribute to panic [24-26]. Panic attacks have been posited to occur in the absence of demonstrable precipitants (e.g., DSM-IV), despite evidence that stressful life events precede panic [2, 3, 27-33]. This observation is appealing, although the distribution, severity and controllability of stressful life events have received poor clinical documentation. In any event, the proposal that panic or the symptoms of panic are influenced by a stressor-CCK interface is intriguing. In fact, evidence implicating CCK and panic is convincing and a dopamine (DA)/CCK link to the disorder has been derived from neurochemical and behavioral evidence with nonhuman experimentation. Embedded in this matrix are issues pertaining to validity and generalizability of nonhuman experimentation and operational definitions of psychological dysfunction.

Dopamine-CCK colocalization has been detected in mesocorticolimbic DA neurons [34]. Identification of same vesicle DA/CCK [35] is consistent with speculation that DA and CCK co-release contributes to psychological disturbance [34]. At the very least, the variable influence of CCK on central DA should provide species-specific behavioral

*Address correspondence to this author at the Department of Pharmacology, 15th Floor Sir Charles Tupper Building, Dalhousie University, 5850 College Street, Halifax, Nova Scotia, B3H 1X5, Canada; Tel: 902-494-2600; Fax: 902-494-6294; E-mail: alohebb@dal.ca

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correlates of anxiety. Stressful life events may precede panic in vulnerable individuals. Accordingly, the responsivity of DA and CCK to aversive life events may influence the severity of panic symptoms. Mild stressors promote mesocorticolimbic DA [36] and CCK release [37-39] in rats, while variations of stressor intensity favor mesocorticolimbic diazepam-binding inhibitor [40], corticotropin-releasing factor [41] or β-carboline release (e.g., β-CCE and β-CCM) [42] in sites responsive to stressor associated alterations of DA and CCK. Taken together, diverse anxiogenic agents are released by stressors and the proposal that panic occurs in response to innocuous events is neither parsimonious nor appealing [43]. The present review suggests that conditioning and sensitization of anxiety may promote gradients of psychological dysfunction that eventuate in panic. Such an analysis suggests that life events are appraised soon after panic and rumination defines situational variables and provides a framework concerning the risk value of environmental events.

Animal models of conditioning and sensitization focus on long-term neurochemical alterations attending psychostimulant administration and the influence of transmitter variations on locomotor activity and stereotypy [44, 45]. Although locomotor activity and stereotypy are not indices of anxiety, the neural mechanisms underlying behavioral sensitization affected by stressors and psychostimulants are relevant to panic induction. In this respect, emergence and aggravation of panic symptoms may be occasioned by the conditioned pairing of anxiogenic agents, including CCK, and stressful life experience(s). The nature and severity of the stressor dictates site-specific central CCK release [46, 47] and the sensitivity of the brain sites examined [38]. Such variables may define vulnerability to panicogenic environmental events. Exacerbation of panic symptoms might be occasioned by recurrent stressors, panic experience and/or cues associated with such stimuli. In this regard, panic profiles may parallel nonhuman instances of sensitization while comorbid psychological disorders, including depression may outline the variable contributions of experiential and organismic factors [48], including gender susceptibility [49-56] as well as environmental context and conditioning [57-62] to the expression of pathological states. Parametric analyses reveal variability in the induction, persistence and magnitude of effects relative to the behavior examined and the brain sites involved. In view of the observation that stressors and acute and chronic psychostimulant administration influence DA [63, 64] and CCK turnover [38, 39, 65-67] and both DA [31, 68] and CCK [69, 70] alterations appear in panic patients, it is suggested that neurotransmitter sensitization may contribute to panic symptoms.

A sensitization/conditioning account of panic is appealing because (a) protracted anxiety has been associated with central DA variations in nonhuman [71] and human subjects [72-75], (b) CCK/DA colocalization is prevalent in mesocorticolimbic sites associated with arousal, reward, learning/conditioning [76], (c) anxiety among nonhuman subjects is readily induced by CCK administration in animal models of anxiety including the elevated plus maze [77] and (d) stressor-associated environmental cues influence behavioral [78-80] and neurochemical change [81, 82] reminiscent of the anticipatory anxiety associated with panic disorder. This review attempts to determine whether there is sufficient evidence to suggest that panic symptoms occur spontaneously or follow from conditioning of central DA/CCK activity induced by anxiety provoking conditions. A synthesis of such information is not meant to characterize the human disorder but rather to evaluate a limited subset of symptoms, including but not limited to, anticipatory anxiety.

Central Dopamine Turnover: Prelude to Anxiety and Emergence of Panic Disorder

Investigations of the pathophysiology of panic have focused on the serotonergic (5-HT), noradrenergic (NE), and the GABA-benzodiazepine systems [83-90] among other neurotransmitters. Nevertheless, several lines of evidence suggest that DA may be involved in anxiety [68, 91] and panic [31, 68]. For anxiety, although there is a paucity of information for the role of DA in mediating clinical anxiety, mild stressors, that provoke mesocorticolimbic DA turnover, have demonstrable anxiogenic effects in the elevated plus maze [92-94] and fear potentiated startle [80] in rats. Such paradigm-associated anxiety, which is responsive to acute benzodiazepine administration, increased DA concentrations in the frontal and pyriform cortices, nucleus accumbens, septum, medial hypothalamus and amygdala [81, 95-98]. In the latter instance for panic, plasma and cerebrospinal homovanillic acid (HVA) concentrations, a DA metabolite, fail to discriminate panic and control subjects [29, 99, 100]. The lack of a neurochemical panic index is not without precedent since NE alterations, for example, have likewise failed to discriminate panic from non-panic subjects [101, 102]. Some laboratories have identified DA perturbations among panic patients with increased anxiety as measured on the Spielberger State Anxiety scale, augmented panic frequency in the 12 months preceding clinical interview and reduced symptom free periods relative to other panic patients [30, 31, 68]. Unfortunately, evidence for central DA and laboratory induced panic remains obscure. Laboratories that have assessed peripheral DA metabolites among normal subjects during laboratory exercises have failed to produce anxiety comparable to panic [103]. Indeed, there is no *a priori* reason to suspect that innocuous laboratory challenges will induce panic in patients with the disorder [104]. Still, contrived laboratory situations provoke panic in some panic patients [57] suggesting that some individuals are more vulnerable than others to the impact of specific environmental encounters. It would be of considerable advantage to secure measures of central DA prior to, during and following panic induction in a laboratory situation.

Populations in which panic have been well documented include Parkinsonian patients and persons with schizophrenia. Despite the neurodegenerative nature of Parkinson's disease and the veiling of central neurochemistry by therapeutic interventions, panic in Parkinson's disease and schizophrenia provides subtle evidence for the involvement of DA in the phenomenology of panic-like states. It is interesting that divergent alterations in DA associated with Parkinson's disease and schizophrenia are associated with the elicitation of panic-like symptoms. While mesocorticolimbic contribution to behavioral sensitization following stressor encounter [105, 106] has received extensive

documentation, nigrostriatal DA/CCK alterations may also alter sensitivity to stressors.

Nigrostriatal Dopamine and Cholecystokinin: Anxiety and Panic-Like Behavior in Parkinson's Disease

Parkinson's disease is characterized by insidious nigrostriatal DA and CCK depletion [107-112]. In addition to tremor, inertia, rigidity, bradykinesia, akinesia, flexed posture and gait disturbance, Parkinsonian patients experience mild depression and irritability as well as memory and attentional perturbations [111, 113-117]. L-dopa ordinarily ameliorates Parkinsonian associated motoric impediments but is ineffective in alleviating affective and cognitive symptoms of the disorder [111]. Advanced Parkinsonian stages reduce the efficacy of l-dopa in alleviating motor disturbance and not surprisingly symptom free intervals [118]. Parkinsonian patients experiencing daily on/off episodes report increased instances of anxiety and depression during l-dopa off stages [111, 119-121], prompting increased l-dopa therapy [122]. Alleviation of mood disturbance and anxiety at this juncture may be attributable to the l-dopa dose employed [123] or perhaps patient appraisal of restored motor function [73]. It should be considered that approximately 40% of l-dopa treated Parkinsonian patients [124-126] exhibit a DA mesocortico-limbic-associated psychosis [127, 128]. Protracted l-dopa treatment, therapeutic dose increases and episodic instances of pharmacological insensitivity to peripheral DA loading have been linked to the emergence of panic-like symptoms (2.6 ± 1.4 panic attacks per day) among Parkinsonian patients [73, 122]. Nevertheless, panic frequency comparison between Parkinsonian and panic patients is obscured in the latter instance by investigations that fail to provide definitive panic statistics. Despite such difficulties, Parkinsonian panic (a) represents a relatively severe version of the disorder, (b) is distributed equally among male (45%) and female subjects (55%) [122] and (c) only emerges during latter stages of the disease (e.g., 60-70 years of age). In contrast, panic patients are most likely to experience a panic episode when they are middle-aged, rarely following age 65, and the disorder is more prevalent among females [4]. Nigrostriatal degeneration may contribute to the paresthesia, burning sensations and discomfort emanating from the feet, chest or face immediately prior to panic [122]. Although a Parkinsonian focus on specific symptoms preceding panic has not been verified, such vigilance would parallel the documented physiological monitoring characteristic of panic subjects [129]. In this respect, distraction of Parkinsonian patients from antecedent neuromuscular perturbations attenuates panic [122].

It is unlikely that estrogen availability can account for panic among Parkinsonian patients. While panic frequency and severity could be reduced in female relative to male Parkinsonian patients owing to menopause onset, such predictions have not been verified. In fact, estrogen replacement has been associated with the alleviation [130] and the exacerbation [131] of panic symptoms in panic patients. Panic episodes characterized by pre-panic palpitation, chest discomfort, tightness of jaw, teeth grinding and muscle ache were attenuated by estrogen. In contrast, panic episodes lacking such a prominent motor profile are exacerbated by estrogen. In Parkinsonian patients, l-dopa fluctuations and panic are often coupled to mood alterations such as depression. Increased estrogen levels in female rats have been associated with an increase in the rewarding value of brain stimulation from the medial forebrain bundle [132]. Taken together, the demonstration that (a) estrogen alleviates l-dopa nigrostriatal perturbations, (b) l-dopa fluctuations are associated with cognitive alterations including depression and psychosis (e.g., mesocorticolimbic DA alterations) and (c) the demonstration that l-dopa motoric fluctuations and depression are associated with the development of panic among Parkinsonian patients preclude an estrogen-based argument. In effect, an estrogen hypothesis defining emergence, maintenance and exacerbation of panic in Parkinson's disease cannot readily account for the available data. In addition, the nature of the somatic experience per se does not appear to be relevant to the induction of panic. Rather, it seems that the intensity of the cognitive experience, regardless of the symptom cluster anticipated, may be sufficient to elicit panic. Such an interpretation suggests that panic emerges following rumination over perceptually defined salient cues in diverse pathological states (Fig. **1**). In effect, panic among cardiac patients [133], depressed subjects [13, 28, 134-142] or individuals with myasthenia gravis [9] is not surprising. Clearly, conspicuous neurochemical variations attending Parkinson's disease contribute to the emergence of somatic complaints and favor vigilance during treatment resistant intervals. In effect, fluctuations in Parkinsonian symptoms, coupled with pervasive, anticipatory stressors, may promote panic among treatment resistant Parkinsonian patients.

At first glance, it is not clear that panic among Parkinsonian patients contributes to the elucidation of the neural mechanisms associated with panic-like states and/or the putative influence of sensitization. These data merely suggest that panic-like symptoms in Parkinsonian patients follow from some neurochemical cascade elicited by DA denervation. Indeed, the appearance of panic-like symptoms in Parkinsonian patients coincides with the time course of mesolimbic DA denervation (e.g., VTA and prefrontal cortex) [143-145]. In addition to alterations in mesolimbic DA activity, post-mortem analyses of Parkinsonian brain tissue have also provided evidence for altered nigrostriatal CCK activity [107-110, 146]. Such changes in nigrostriatal CCK concentrations parallel indices of l-dopa treatment resistance (e.g., l-dopa resistant patients and animal model of Parkinson's disease [147-151] and symptom severity [107-110]). As such, it is conceivable that nigrostriatal DA/CCK and mesolimbic DA alterations contribute to the eventual expression of panic among Parkinsonian patients owing to the gradual denervation of mesocorticolimbic sites from the substantia nigra. In effect, panic associated with nigral denervation and prompted by l-dopa induced psychosis, suggests that a neurochemical depletion threshold may be attained during the latter stages of Parkinson's disease. Available evidence to date has certainly not established a causal role for mesocorticolimbic CCK and panic among Parkinsonian patients. At best, plasma CCK levels and post-mortem CCK-binding provide provisional indices of augmented CCK turnover in specific subject populations experiencing varying levels of anticipatory anxiety [152, 153]. Nevertheless, anticipatory anxiety among Parkinsonian

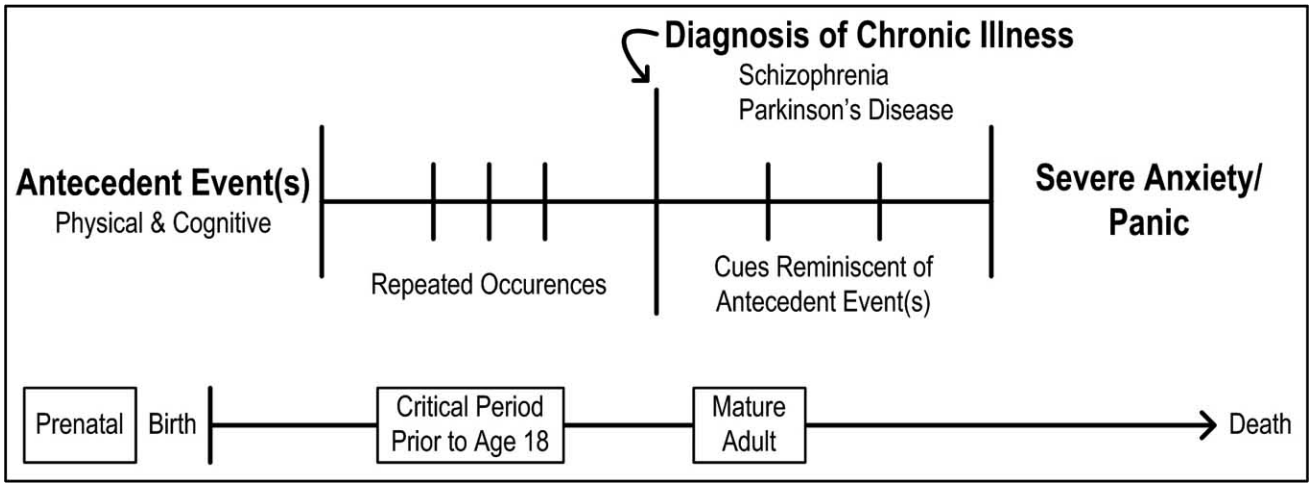

Fig. (1). Schematic diagram outlining the progression of events that leads to panic disorder. Initial antecedent events or mild stressful events elicit some physical or cognitive changes following the repeated occurrence of symptoms (subtle physical or cognitive) that culminate in severe anxiety states with disease progression. Interestingly, CCK alterations have been documented in schizophrenia and Parkinson's disease. Events may occur as early as before birth, with a critical period identified as prior to the age 18, and span across the lifetime.

patients may occur in response to the stressor-like experiences occasioned by the off stages of l-dopa therapy (c.f. stressor induced CCK alterations in nonhuman subjects, [38, 39, 67]). Indeed, variations of mesocorticolimbic CCK availability between DA-denervated Parkinsonian patients experiencing panic and age, sex and disease matched subjects would be intuitively appealing. While such provisional arguments must be held in abeyance, panic-like symptoms among Parkinsonian patients coincide with (a) changes in nigrostriatal CCK availability during the late stages of the disease and (b) the emergence of presumably enhanced stressor periods among Parkinsonian patients (c.f. DA/CCK interface following stressor imposition in nonhuman subjects, [38, 39, 154, 155]). However, the appearance of panic among Parkinsonian patients experiencing gradual exacerbation of cognitive dysfunction (e.g., impairments in memory and attention and the development of psychoses, [111]) and motoric debilitation (e.g., during l-dopa off periods and dyskinesias) lends support to a sensitization/conditioning hypothesis in the acquisition and expression of panic.

Dopamine and Cholecystokinin in the Mesocorticolimbic System: Anxiety and Panic-Like Behavior in Schizophrenia

Paranoid forms of schizophrenia have been associated with elevated anxiety as revealed by the Brief Psychiatric and Hamilton Anxiety Rating Scales [156-162]. These psychiatric patients routinely report experiencing a high incidence of daily life stressors (e.g., loss of social support, divorce, death of a loved one, impending job and/or residential changes and admission to a psychiatric facility) that exacerbate schizophrenic episodes [161, 163-172]. Moreover, repeated exposure to such life stressors increase anticipatory anxiety as revealed by exaggerated startle responsivity among individuals with schizophrenia [173, 174]. While atypical, severely stressful life events, including active military duty, for example, may precipitate psychotic episodes in vulnerable individuals [163], repeated experience with milder, stressful life events (e.g., loss of social support) over a few months has also led to schizophrenic symptom exacerbation, including psychosis [166]. In effect, elicitation and/or exacerbation of the symptoms of schizophrenia might be occasioned by a broad spectrum of life stressors, varying in severity and chronicity. Interestingly, panic and agoraphobia (e.g., 2.4 ± 1.4 attacks per week) have been reported among individuals with a history of paranoid schizophrenia (e.g., >4 years) by several different laboratories [72, 175-178]. The panic symptoms experienced by individuals with schizophrenia appear to represent a moderately severe panic course reminiscent of that experienced by Parkinsonian patients [179]. Characteristically, individuals with schizophrenia who experience panic-like symptoms tend to be socially introverted, consistent with pervasive paranoia and/or embarrassment associated with psychotic episodes [175, 178]. The frequency of panic-like symptoms among individuals with schizophrenia coincides with the psychotic episodes that are associated with anxious cognition, including rumination over agoraphobic fears and increased somatic perturbations [175, 178, 180, 181]. Indeed, preoccupation with and attention to somatic and cognitive perturbations punctuated with varying degrees of psychosis may contribute to panic symptoms in individuals with schizophrenia. While somatic monitoring in schizophrenia would parallel the physiological vigilance characteristic of panic [129], cognitive monitoring may be specific to schizophrenia. Individuals with schizophrenia are undoubtedly cognizant of the progression of schizophrenic symptomatology (see [182] for discussion of suicide prevalence among individuals with schizophrenia). However, severe schizophrenic illness may preclude cognitive intervention strategies with demonstrated efficacy on panic symptomatology in Parkinson's patients [122] and panic patients [183]. Nevertheless, panic symptom attenuation in schizophrenia coincides with decreased psychotic episodes (e.g., alprazolam, 2.5 - 5mg/day, [177, 178]) or reduced agoraphobic associated behavior (e.g., imipramine, 50mg/day, [175]). At this juncture, it is not readily apparent whether the neural mechanisms underlying schizophrenia are likewise conducive to the expression of panic. For example, psychosis has been demonstrated in panic patients. The appearance of psychosis among panic patients is related to the duration of panic (>10 years), severity (>3 panic

attacks/day) of panic symptomatology and the presence of agoraphobia [184-186]. Moreover, the relative risk for schizophrenia among panic patients appears to be conspicuously increased relative to the general population [185]. Taken together, central neurochemical alterations accompanying psychopathology and/or the gradual emergence of conditioned behavior (e.g., agoraphobia) may influence the course of panic-like symptoms.

Hypersensitivity of mesocorticolimbic DA activity, as measured by DA binding [187, 188], DA mRNA [189], positron emission tomography (PET) [190] and ^{123}I-IBZM SPECT [191, 192] among individuals with schizophrenia, appears to coincide closely with the expression of positive schizophrenic symptoms such as delusions and hallucinations [193, 194]. Notably, positive symptoms of schizophrenia are associated with social and agoraphobic fear [161]. It should be underscored that negative symptoms of schizophrenia such as poverty of speech, flattened affect and psychomotor retardation are not associated with hypersensitivity of mesocorticolimbic DA activity (see [195] for review) or panic. It should be considered that mesocorticolimbic hypersensitivity might follow from the chronic neuroleptic regimens employed to attenuate delusions and hallucinations [196]. Typically, delusions, hallucinations and phobic avoidance assessed by the Minnesota Multiphasic Personality Inventory (MMPI), Clinical General Impression (CGI) and the Brief Psychiatric Rating Scale (BPRS) [157, 159, 195, 196] are exacerbated over the course of the illness. The gradual exacerbation of schizophrenic symptoms has prompted suggestion that conditioning and/or sensitization of mesocorticolimbic DA (see [181, 197-199] for review of mesocorticolimbic DA and cognition; c.f. amphetamine psychosis, [200-203]) underlie(s) expression of at least some of the behaviors associated with schizophrenia [91, 187, 204, 205]. In addition to alterations of central DA activity, there are some data that outline a putative contribution of central CCK to the etiology and maintenance of schizophrenia [206-209]. Postmortem determinations have revealed increased CCK concentrations in the striatum and mesencephalon [210, 211] and reduced CCK availability in the amygdala and hippocampus [212-214] as well as concomitant reductions of CCK mRNA in the temporal and frontal cortices in neuroleptic treated individuals with paranoid schizophrenia relative to controls matched for age (65.8 ± 6.8 years), morbidity (e.g., heart disease and cancer) and postmortem delay (16.6±4.2 hours) [215]. Available studies to date have clearly not established a relationship between central CCK and panic in individuals with schizophrenia and investigations documenting central CCK variations among individuals with paranoid schizophrenia typically fail to document any symptoms reminiscent of panic. It is interesting, however, that postmortem CCK determinations in brain tissue have verified patterns of CCK activity within specific brain sites associated with positive and negative symptoms of schizophrenia. On the one hand, positive symptoms of schizophrenia, precipitated by increased DA activity [195, 196, 216, 217], are associated with a greater reduction in frontal cortex CCK mRNA compared to the temporal cortex. On the other hand, negative symptoms of schizophrenia are associated with reduced CCK mRNA in the temporal cortex, amygdala and hippocampus [215]. Panic attacks fluctuate with psychosis severity and it would be of interest to determine mesocortical CCK activity (e.g., PET scan) among individuals with schizophrenia during a panic episode. Curiously, neuroleptic strategies for schizophrenia (e.g., haloperidol) increase striatal and mesolimbic CCK concentrations [218, 219] and increase CCK binding (e.g., decreasing CCK tissue levels) in several cortical areas in nonhuman subjects that persist for several weeks [219-221]. Panic-like symptoms and exacerbation of schizophrenia following neuroleptic withdrawal [175, 222, 223] has been associated with increased CCK activity and concomitant release of the anxiogenic substances, corticotropin-releasing factor [224] and diazepam-binding inhibitor [225, 226].

While the panic properties of CCK-4 have been empirically documented among panic patients and healthy volunteers [21, 227], demonstration of the panic inducing properties of CCK-4 in individuals with schizophrenia is unavailable (c.f. CCK-8S administration in schizophrenia, [208, 228-234]). Recall that in individuals with schizophrenia, social and agoraphobic fear have been reported to precede panic attacks [175]. Interestingly, in rats, social isolation has been associated with an upregulation of CCK_2 receptors in the frontal cortex [235]. It is conceivable that some personality variables associated with schizophrenia (e.g., social introversion or social alienation) provide indices of panic susceptibility following CCK-4 challenge. For example, the intensity of somatic, affective and cognitive responsivity to CCK-4 (e.g., Panic Symptom Scale) in panic patients has been related to anxiety sensitivity (e.g., Anxiety Sensitivity Index) and self-alienation scores derived from the MMPI Social Inversion Subscales [22]. It would be of interest to determine the effects of CCK_2 antagonists, which attenuate the panicogenic effects of CCK-4 in panic patients [236], on agoraphobic fear and panic symptoms in individuals with schizophrenia (c.f. neuroleptic properties of CCK_2 antagonists in nonhuman preparations, [237]). If CCK_2 antagonists were efficacious in the treatment of panic symptoms among individuals with schizophrenia (e.g., psychosis, agoraphobia and/or social avoidance), it is conceivable that alterations in mesocorticolimbic CCK_2 receptor activity sustain expression of both schizophrenic and panic symptoms. Moreover, it should be considered that current therapeutic interventions (e.g., haloperidol), which promote increases in CCK activity in the frontal cortex of nonhuman subjects, might contribute to panic-like responses among individuals with schizophrenia. Taken together, alienation, introversion, panic and psychotic exacerbation may be associated with variants of enhanced CCK sensitivity and/or over activity of central DA and contribute to the expression of panic symptoms in individuals with schizophrenia.

Panic-like symptoms among individuals with schizophrenia are reminiscent of those reported by Parkinsonian patients and may be occasioned by (a) the prevalence or perceived prevalence of stressful life events, (b) alterations of central DA/CCK availability associated with chronic illness and/or (c) the chronicity of therapeutic interventions. Interestingly, Parkinsonian panic coincides with reduced l-dopa efficacy and l-dopa induced psychosis. Furthermore, autoradiographic data suggest comparable mesocorticolimbic DA receptor variations (e.g., frontal cortex and nucleus

accumbens) in paranoid schizophrenia and Parkinsonian patients experiencing l-dopa psychosis [145, 238-243]. The saliency of mesocorticolimbic DA/CCK alterations to the promotion of panic in individuals with schizophrenia and Parkinson's disease is obvious. Taken together, the repeated encounters with stressful life events may facilitate panic in Parkinsonian patients, individuals with schizophrenia and panic patients (see Fig. (**1**)). The clinical vantage (DSM-IV) typically asserts that stressful life events do not participate in the precipitation or maintenance of panic. However, panic often emerges in clinical populations with demonstrated vulnerability to stressful life events (e.g., depression, schizophrenia, Parkinson's disease). In order to determine whether stressful life events contribute to the provocation of panic symptomatology in individuals with schizophrenia, Parkinson's disease and panic disorder, the cumulative and proactive influence of stressors must be determined (e.g., sensitization).

Anxiogenic Indices Associated with Stressor Exposure: Nonhuman and Human Experimentation

Anxiety among nonhuman subjects has been defined as the behavioral response to unpredictable, novel or threatening stimuli, including uncontrollable footshock, in anxiety paradigms [78, 80, 94, 244]. Yet, it remains to be determined whether footshock is a suitable stressor in assessing anxiolytic efficacy. Examination of repeated anxiety provoking situations to the provocation of panic necessitates comparison of animal models that parallel the human condition. To date, adequate animal models of panic are lacking. It should be considered that fear conditioning (e.g., startle and freezing) in nonhuman subjects may provide a behavioral analogue of the anticipatory anxiety associated with panic disorder. It has been demonstrated, for example, that rats exposed to apparatus cues previously associated with footshock exhibited increased DA turnover in the prefrontal cortex [82] and amygdala [81] which was attenuated by low dose diazepam administration (1-5mg/kg). Conditioned fear paradigms employ rather mild stressors relative to paradigms assessing the behavioral repercussions of footshock. In any event, conditioned fear (e.g., freezing) has been reliably associated with elevated plasma ACTH, corticosterone and prolactin concentrations for at least 14 days post-stressor in rats [245]. In humans, conditioned fear or fear-enhanced startle has been linked to psychological disorders in which sustained and exaggerated reactivity to environmental stressors appears fundamental. For example, enhanced startle response has been routinely associated with posttraumatic stress disorder [246], schizophrenia [247] and panic [248, 249]. Interestingly, clinical investigations have demonstrated an enhanced startle reflex (e.g., eye-blink and heart rate) in response to a startle probe (e.g., binaural burst of 110 dB white noise, 50 msec duration) previously associated with graphic photographic slides (e.g., wounds or mutilated bodies) in normal subjects [250]. In panic patients, exaggerated fear-potentiated startle response has been detected in response to the threat of electric shock [57]. Anticipation of electric shock (e.g., 1.5 mA, 50 msec conducted through the median nerve of the wrist) administered during the final 10 seconds of a 45 second threat but not a 50 second no-threat condition, signaled by differential light cues, increased startle in panic patients relative to healthy controls. This startle response was largest in younger panic patients (e.g., <40 years) who also reported an increased frequency of panic attacks within the week prior to testing relative to older panic patients and age matched control subjects [251]. Taken together, the absence of a detailed retrospective clinical characterization of putative stressors and inadequate documentation of salient cue associated variables prevent an accounting of the ensuing panic histories of disparate panic subjects. Ultimately, startle latencies provide a potential measure of the developmental history of anticipatory anxiety and panic emergence. Indeed, Grillon *et al.* [251] reported that anticipated cue associated challenges in a simulated startle paradigm among young and older panic subjects elicit variable patterns of experimental compliance which influenced participation and anxiety induction.

Surprisingly, the contribution of mild stressors to anxiety induction in clinical applications has been neglected. It is intriguing that amygdaloid [252] and mesencephalic [253] input to the parabrachial nucleus sustains cardiovascular arousal and the VTA participates in the detection of salient and non-salient cues in rats [254]. Interestingly, panic patients with frequent panic episodes (e.g., >5.6 ± 2.3 attacks/week) exhibit heightened cardiovascular arousal, increased sympathetic/autonomic alterations and increased anxiety in response to innocuous stimuli relative to panic patients with less frequent panic attacks (1.5 ± 0.5 attacks/week) and normal subjects [255, 256]. Perhaps, sustained rumination and hypervigilance concerning encounters with situational challenges heighten anxiety. The contribution of such variables to the induction of panic certainly merits consideration. Yet, alterations of central anxiogenic activity accompanying panic and the identification of the parameters of putative stressors or the perceived saliency of environmental stimuli to the evocation of panic attacks have not been established. The demonstration that anticipation of stressful encounters influences CCK activity in humans [152, 153, 257] is certainly consistent with such an interpretation. Repeated low psychostimulant doses in rats were associated with alterations in CCK concentrations and CCK mRNA expression, which could be detected for several weeks following the last injection [65, 66]. Likewise, exposure to life stressors prior to age 19 has been documented to precipitate anxiety, depression and/or panic in some individuals [258, 259]. Indeed, familial illness and sick role behavior may also be salient to illness onset and the course of the psychological disturbance [260, 261]. Moreover, childhood behavioral problems (e.g., social withdrawal, anxiety/depression and aggression/delinquency) and the degree of emotional involvement demonstrated by parents to offspring with schizophrenia have been associated with poor prognosis, including psychotic relapse and comorbid affective disturbances [262, 263]. It should be noted parenthetically that nonhuman primates raised under stressful conditions (e.g., variable foraging demands) reveal aberrant behavior patterns (e.g., hyperactivity, clinging and behavioral inhibition) [264] and protracted increases in cerebrospinal corticotropin-releasing factor (CRF) availability [265] in adulthood compared to age- and sex-matched control subjects. To date, evidence for the enduring influence of site-specific central CCK alterations among

human or nonhuman primates exposed to early life stressors are unavailable. In effect, aberrant parental practices, sick-role modeling and excessive rumination may precipitate central CCK alterations that contribute to symptom exacerbation and panic emergence. Moreover, some investigators have suggested that decreased lymphocyte and cerebrospinal CCK-8 concentrations in panic patients may reflect enhanced CCK receptor sensitivity, reduced CCK receptor availability or perhaps compensatory reduction of CCK-8 concentrations secondary to increased CCK-4 activity [69, 70]. It should be considered that neurotransmitters colocalized with CCK, including DA, participate in the production or exacerbation of some of the symptoms associated with panic disorder. Dopamine alterations may be peculiar to panic patients with considerable anxiety and a relatively severe panic course [31, 68]. Moreover, DA alterations have been linked to the development of social phobia, a severe form of agoraphobia [100, 266]. Taken together, the nature of the panic experience and the frequency of stressful encounters may precipitate CCK release and determine the saliency of environmental conditions to panic induction.

Cholecystokinin, Anxiety and Panic Attacks

Molecular forms of CCK are cleaved from prepro-CCK and include CCK-8 sulfated (S), pentagastrin (CCK-5) and CCK-4 which are degraded by aminopeptidase (see [76] for review). Cholecystokinin-8S is the predominant central form of CCK and found in high concentrations in the cerebral cortex, nucleus accumbens, basal ganglia, thalamus, hypothalamus, periaqueductal grey, olfactory tubercle, olfactory bulb, VTA, some brain stem nuclei and the spinal cord [206, 267-272]. Cholecystokinin is colocalized with DA in the mesencephalon [273], CRF in the paraventricular nucleus of the hypothalamus [274], oxytocin in the supraoptic and paraventricular nucleus of the hypothalamus [275], substance P in the central gray projecting to the spinal cord [276], GABA in the amygdala, frontal cortex and hippocampus [277, 278] and enkephalin in the hippocampus ([279]; (see [280, 281] for review of antagonistic role of CCK and enkephalin in stress, anxiety, cognition and pain). As such, it is not surprising that CCK has been implicated in nocioception [282], learning and memory [283] as well as ingestive [284, 285], sexual and reproductive behavior [286] and panic [76, 287].

Central and gastrointestinal CCK receptors have been identified. The CCK_1 receptor distribution predominates in the gastrointestinal tract, area postrema, nucleus tractus solitarius, posterior nucleus accumbens, amygdala, septum, hypothalamus, dorsal raphe, cerebral cortex, ventral tegmental area, substantia nigra and hippocampus in rats and mice [288-290]. Sedative [230], ingestive [291], kindling [292], exploration [293], locomotion [294, 295] and cognitive [296] properties of the CCK_1 receptor have been amply demonstrated. Central CCK_2 receptors are distributed in the brainstem solitary complex, nigrostriatal, mesolimbic and mesocortical sites among nonhuman and human subjects and appear to play an anxiogenic (or pro-panic) role [297, 298]. Mice lacking CCK_2 receptors are less anxious, as measured by increased exploratory behavior in the elevated plus maze paradigm, than their wild type littermates [299, 300]. Although, peripheral and central CCK-8S administration in nonhuman subjects has been associated with anxiety in the elevated plus maze [301, 302] and light-dark paradigms [244], CCK-8S induces nausea and gastrointestinal malaise in human subjects [303, 304]. Either "illness behavior" and anxiety are not adequately differentiated in nonhuman subjects following CCK-8S administration or fundamental differences exist between the influence CCK agonists have on peripheral CCK receptors (i.e., those of the alimentary canal) in nonhuman and human subjects. In contrast, the selective CCK_2 agonist, CCK-4, induces anxiety in nonhuman subjects [20, 305] and promotes panic in panic patients and normal subjects [21, 23]. The differential propensity of CCK-8S and CCK-4 to provoke anxiety and/or panic in human subjects as well as rats and mice may be attributable to species variations [306], differential brain region sensitivity (e.g., amygdala, prefrontal cortex and nucleus accumbens, [307, 308]), drug route [309, 310] and/or paradigm specificity [308]. Clearly, discrepancies between clinical and nonhuman studies necessitate examination of methodological variables including drug schedule and experiential factors that influence sensitivity to CCK challenge and anxiety (panic) induction. The ensuing discussion will examine the contributions of CCK-8S, CCK-4 and pentagastrin to the provocation of anxiety in nonhuman and clinical subjects, the evidence supporting the contention that stressful life contribute to CCK-induced panic and the nature of panic symptoms in response to CCK administration. The diverse clinical profiles of panic suggest developmental stages of psychological dysfunction. Sensitization of central DA/CCK activity and cognitive processes (e.g., rumination and anticipatory anxiety) may underlie variability in effective pharmacological management of panic (Fig. **2**).

Cholecystokinin Induced Anxiety: Nonhuman Models

Chronic diazepam and alprazolam withdrawal have been associated with increased anxiety in human [311, 312] and nonhuman subjects [313]. Interestingly, chronic benzodiazepine treatment in rats decreases neural responsivity to microiontophoretic CCK-8S application in the frontal cortex and hippocampus [287, 314]. In contrast, termination of chronic diazepam treatment increases hippocampal and cortical CCK-8 binding in the rat [315]. In mice, the CCK_2 receptor antagonist, Cl-988, dose dependently (0.001-1.0 mg/kg^{-1}) antagonized the anxiogenic effects associated with diazepam withdrawal [313]. In rats, flumazenil (4 mg/kg i.p.) significantly antagonized the anxiogenic effects of the CCK_2 agonist, CCK-8S and the anxiolytic-like effects of the CCK_2 antagonist, L-365, 260 [310]. Moreover, rats rated anxious with respect to performance in the elevated plus maze exhibited a reduced benzodiazepine receptor density and increased CCK-8S binding in the frontal cortex relative to non-anxious counter-parts [315]. These data suggest that benzodiazepines suppress CCK-8S activity in the prefrontal cortex of anxious mice [20]. Moreover, the dose and nature of the CCK fragment employed suggests site-specific sensitivity to anxiogenic drug administration. It is conceivable that CCK fragments exert differential influence on central areas associated with anxiety emergence. Indeed, the central amygdaloid nucleus is conspicuously more

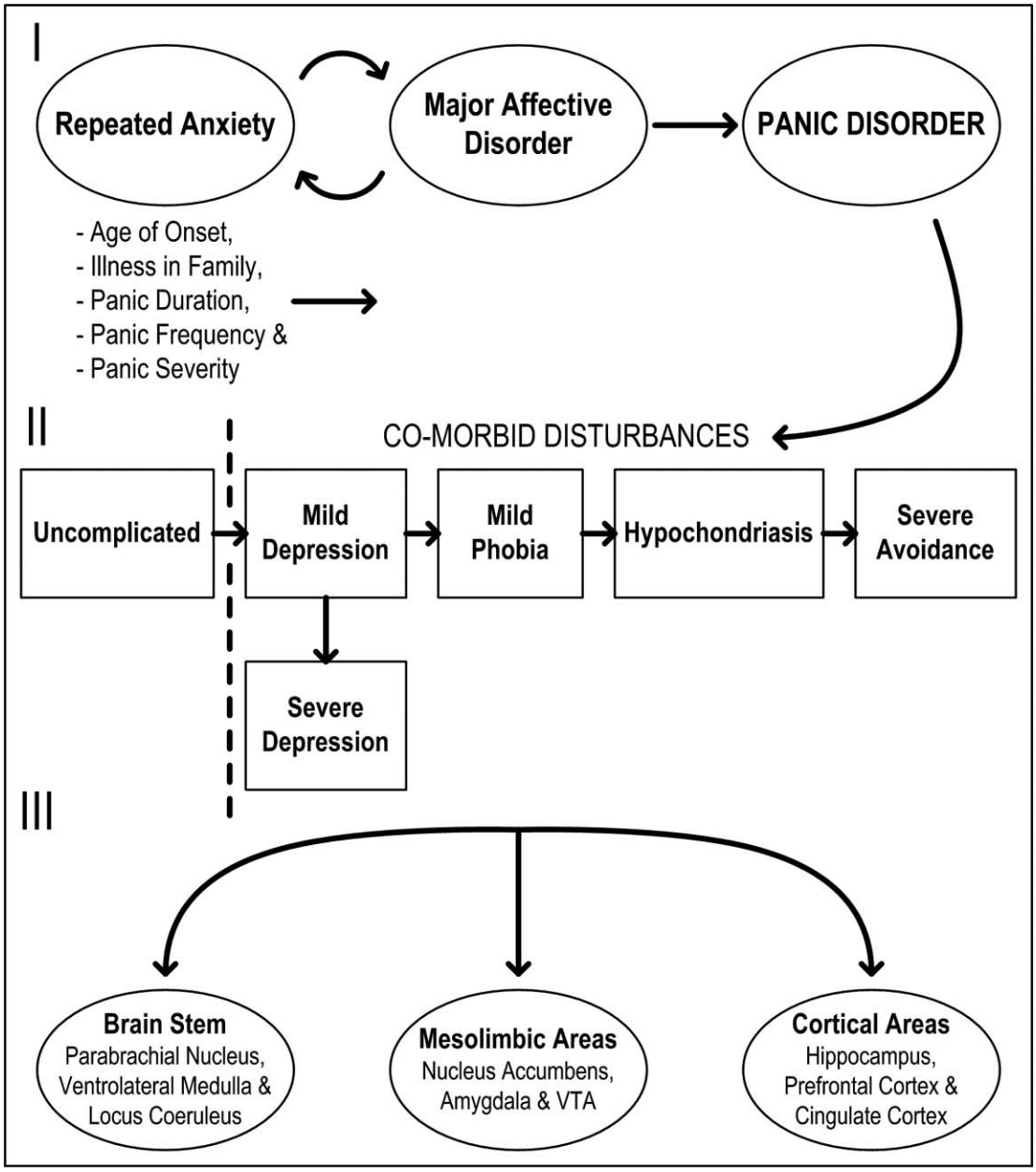

Fig. (2). Schematic illustration of the involvement of repeated anxiety episodes in panic (I), the developmental stages, or course, of panic and the precipitating variables that affect its course (II) as well as some of the central sites hypothesized to be involved in panic disorder (III). I. Repeated anxiety may precipitate major affective disorder while episodes of depression may lead to further increases in anxiety. Reciprocal influences on individual states of anxiety and depression may be influenced by subjective factors including chronic illness in the family, subject history or other stressors. Panic evolves following some time and the temporal parameters associated with the appearance of panic symptoms among various clinical populations have not been clearly determined. **II.** Panic symptoms, once present, may consist primarily of autonomic symptoms including cardiovascular perturbations or cognitive symptoms including depersonalization and fear of losing control without accompanying phobic or depressive symptoms. More commonly panic disorder is complicated with depression of varying severity, mild phobia, hypochondriasis, and/or severe avoidance behavior. The varying types of panic classifications may represent different developmental stages of panic. Moreover, age of onset, illness in the family, panic duration, panic frequency and panic severity may influence the progression of panic from uncomplicated panic episodes to panic with comorbid symptoms of depression and phobia. Moreover, such factors may also influence pharmacological management of panic. **III.** The developmental stages of panic appear to be characterized by prominent symptoms that may involve brain stem structures, mesolimbic areas or cortical areas. Uncomplicated panic, for example, may be primarily associated with cardiovascular and respiratory perturbations (e.g., brainstem) although anxiety (e.g., amygdala) and rumination (e.g., nucleus accumbens, VTA, prefrontal cortex) are also present. Co-morbidity with depression or phobia would typically involve mesencephalic (e.g., VTA), mesolimbic (e.g., nucleus accumbens, amygdala) and cortical areas (e.g., prefrontal cortex and cingulate gyrus). Repeated panic attacks likely alter the neurochemical substrates of the psychological disorder according to the sequence/frequency of panic intrusion or perhaps inter-panic interval. It is intriguing that the effectiveness of imipramine and alprazolam in alleviating panic symptoms varies with the severity of comorbid depressive symptoms or agoraphobia.

sensitive to CCK-4 than the prefrontal cortex or the nucleus accumbens in the startle paradigm [308]. Moreover, in exploration paradigms (e.g., light-dark task and elevated plus maze), low doses of ceruletide (CCK-8S agonist, 100 ng/kg^{-1}) and pentagastrin (CCK-5 agonist, 500 ng/kg^{-1}) are only anxiogenic among mice previously exposed to the stress of overcrowding. Significantly elevated doses of ceruletide and pentagastrin are required to induce comparable levels of anxiety among rats and mice housed in non-crowded conditions [77, 316]. Furthermore, investigations in non-human primates indicate that intravenously administered CCK-4 dose dependently (0.5- 4 mg/kg^{-1}) increased fear and defensive behaviors according to the baseline anxiety scores of animals and their social hierarchical position [317]. Apparently, antecedent environmental experiences interact with the nature of subsequent pharmacological challenges in provoking anxiety.

The demonstration that (a) anxious mice exhibit reduced benzodiazepine receptor density and increased CCK-8S binding in the frontal cortex relative to non-anxious mice [315], (b) strain-specific sensitivity in fear-motivated behavior appears among rats [318], (c) strain-specific behavioral and neurochemical variations appear among mice exposed to the elevated plus maze [319] and (d) differential behavioral and neurochemical sensitivity emerges among divergent inbred and outbred mouse strains challenged with anxiogenic agents (e.g., footshock, [320]) certainly provides evidence for the influence of genetic variables to the expression of anxiety. It is intuitively consistent to suspect that genetic variables and antecedent environmental stressors likewise contribute to the attenuation, exacerbation or maintenance of clinical anxiety. Alterations in CCK_2 receptor sensitivity in panic patients may also accompany increased anxiety following CCK administration. In view of differential post-mortem CCK receptor binding between panic prone Parkinsonian patients and individuals with schizophrenia, panic subjects would likely demonstrate variable central CCK receptor sensitivity to exogenously administered CCK fragments. Current empirical evidence supports altered basal CSF CCK concentrations in panic patients relative to control subjects [69, 70]. The inadequacy of such a comparison is apparent and functional indices of CCK turnover and/or CCK receptor sensitivity in discrete central sites among CCK challenged panic subjects are required.

Potential parallels between nonhuman experimentation employing CCK-8S and clinical data is compromised owing to the ineffectiveness of this CCK fragment in provoking anxiety in humans. Accordingly, comparison of nonhuman CCK-induced anxiety with chronic anxiety syndromes, including panic, in human subjects is limited to studies concerned with CCK-4 availability and CCK_2 receptor activation (e.g., [23, 321, 322]). However, the functional significance of central CCK_1 receptor sensitivity and density in areas involved in central respiratory and cardiovascular activity (e.g., the nucleus tractus solitarius and parabrachial nucleus) [253, 323, 324], motivation (e.g., nucleus accumbens) [325], attention (e.g., VTA) [254], and cognition (e.g., prefrontal cortex) [181] to anxiety among nonhuman subjects requires consideration. It will be recalled that panic patients engage in considerable somatic monitoring [129]. The neurocircuitry of brainstem sites involved in the modulation of respiratory and cardiovascular function as well as possible neurochemical correlates attending increased vigilance and a possible relation to panic have been discussed previously [326]. It is conceivable that hypochondriasis in panic may stem from alterations in CCK_1 receptor sensitivity following protracted vigilance.

Consideration of parallels between behavioral profiles drawn from animal models of anxiety and clinical panic symptoms should focus on behaviors that reflect comparable aspects of anxiety. For example, it appears that conditioned fear (e.g., anticipatory anxiety) and exploratory tendencies in novel environments (e.g., the response of an organism to a potentially threatening stimulus) provide indices of diverse aspects of anxiety [327]. Repeated exposure of rats to the elevated plus maze as an analogue of anticipatory anxiety has been criticized owing to the resistance of such behavioral tests to the anxiolytic influence of benzodiazepines [328, 329]. While questions relating to the validity of the elevated plus maze in evaluating anticipatory anxiety may be relevant, arguments pertaining to the efficacy of benzodiazepine intervention strategies may be misleading. For example, the nature of the anxiety experienced in the plus maze with repeated apparatus exposure undoubtedly varies with successive exposures to the stressor-like influence of the paradigm. In rodents the pattern of CCK release from specific mesocorticolimbic sites varies according to the nature and severity of the stressor [38, 39, 154, 155, 218]. In effect, repeated exposure of animals to the mild, anxiogenic influence of the elevated plus maze may augment CCK release and effect protracted alterations of CCK receptor sensitivity. In effect, the nature of the CCK associated experience has been altered and pharmacological responsivity might likewise be expected to vary. Taken together, reduced propensity of diazepam in alleviating anxiety associated with repeated maze exposure suggests that the neurochemical correlates of the stressor have been altered (e.g., conditioning/sensitization) [45, 330]. It is suspected that identification of some of the conditions (e.g., genetic and environmental) contributing to inter-individual sensitivity to CCK challenge paradigms, including efficacious anxiolytic applications, in nonhumans may parallel variable therapeutic efficacy of anti-panic drugs in clinical trials (Fig. **2**).

Cholecystokinin Challenge, Panic Induction and Clinical Investigations

The selective CCK_2 agonists, CCK-4 and pentagastrin, induce panic in healthy volunteers and panic patients [21, 25, 321]. Acute, oral L365, 260 administration (50 mg, 90 minutes prior to CCK-4 challenge) attenuates CCK-4 (50 μg) [331] but not lactate [322] induced panic in panic patients. The specificity of L365, 260 in attenuating CCK but not lactate-induced panic may suggest that there are different types of panic. Curiously, an acute, oral dose of the CCK_2 antagonist CI-988 (50 or 100 mg) 2 hours prior to CCK-4 challenge failed to attenuate CCK-4 (20 μg) induced panic in both normal subjects [332] and panic patients [333]. At this juncture it is not clear whether the efficacy of L365, 260, relative to CI-988, in attenuating CCK-4 panic is attributable to experimental protocol, pharmacological properties or panic profile. Nevertheless, it is likely that CCK-induced

panic symptoms including tachycardia, nausea and dyspnea stem from a CCK influence on selective brain stem nuclei. Cognitive variations attending CCK-induced panic, including anticipatory anxiety, are most likely attributable to mesolimbic and cortical sites secondary to brainstem activation (see [334, 335] for an accounting of such a conclusion with respect to cerebral blood flow and fMRI activity profiles in response to CCK-4 administration, respectively [321, 331]). While clinical responsivity to CCK-4 is well documented, there is considerable behavioral variability in the responsivity of panic patients and healthy volunteers to CCK challenge. For example, the panic inducing properties of relatively large CCK-4 doses (e.g., 25 or 50 μg) or pentagastrin (0.1-0.6 μg/kg) have been reliably demonstrated in several laboratories [21, 23, 25, 321, 336, 337]. However, elevated anxiogenic drug administration (a) confounds potential central variations describing inter-individual responsivity of clinical patients to CCK challenge and (b) prevents detection of the relative vulnerability of healthy control subjects to panicogenic agents. Indeed, the efficacy of CCK-4 in provoking panic-like symptoms appears to be dose dependent. For example, among panic patients the panic distribution was 17% (10 μg), 64% (15 μg), 75% (20 μg), 75% (25 μg) and 91-100% (50 μg) following the respective CCK challenge doses [336]. In an accompanying investigation, proportional panic frequencies of 11% (9 μg), 17% (25 μg) and 47% (50 μg) were detected following CCK challenge doses administered in control subjects [338]. These data suggest varied CCK response thresholds among panic patients that are lower than those of control subjects, which exhibit graded responsivity to CCK challenge. The lower threshold for response found in panic patients relative to controls, with respect to CCK-4 dosage, has been confirmed [339, 340]. Selection of the respective challenge doses of CCK obscures investigation of sensitization and/or conditioning by discounting subject variability and clinical history. Such an approach is unfortunate and counterproductive. In effect, the obvious differential sensitivities of clinical populations to CCK challenge require documentation of threshold CCK doses (e.g., initial challenge). Ensuing responsivity of panic patients to CCK should, at the very least, consider rechallenge with sub-threshold doses of CCK-4. The interval pertaining to CCK re-exposure for clinical investigations is not readily available although data derived from nonhuman experimentation suggests that protracted intervals may be required (see [244] for discussion of temporal influences on CCK sensitization). Individuals with panic display variable clinical histories, including age of onset, familial history, frequency and severity of panic as well as comorbid symptoms of depression and/or agoraphobia (Fig. **2**). The most appealing of such clinical accounts include instances where panic frequency and the appearance of agoraphobia are temporally exaggerated, suggesting an incremental basis to panic induction (e.g., [137]). Intuitively, it is appealing to consider that sub-threshold doses of CCK-4 in panic patients produce behavioral effects that mirror clinical panic exacerbation. To date, consideration of such factors and the potential contribution of these variables to long-term responsivity to CCK-4 challenge have not been adequately assessed (c.f. [45]). The anxiogenic efficacy of CCK in animals and nonhuman primates was clearly dependent upon antecedent environmental experiences, including the differential stressor influence of the paradigm considered [316, 317]. Such a comparison to panic patients appears to be a logical one. To be sure, it must be demonstrated that individual stressor and panic histories interact with CCK challenge to influence panic thresholds. Taken together, panic patients and control subjects demonstrate differential sensitivities to the panicogenic properties of CCK-4. Moreover, demonstration of enhanced CCK sensitivity following CCK-4 re-challenge underscores the need to (a) delineate an inter-drug interval conducive to behaviorally enhanced responsivity, (b) establish behavioral sensitivity to previously non-panicogenic doses of CCK-4 and (c) describe patient histories pertaining to effective challenge and rechallenge doses of CCK and the temporal parameters supporting sensitization.

The hypothesis that individuals exhibit differential sensitivities to the panicogenic properties of CCK-4, or to other panicogenic agents, is intriguing. At the very least, these data permit subject characterization according to organismic variables (e.g., baseline anxiety levels) and experiential factors (e.g., age of onset and severity of panic disorder). In effect, age of onset may provide one index of panic severity. For example, panic patients with a history of early life stressors, including childhood separation disorder or a family history of panic disorder with agoraphobia, exhibit an earlier age of onset of panic disorder relative to individuals who fail to report such events [341]. In this respect, severity of panic disorder may be operationally defined according to illness duration. Such an analysis would necessitate assessment of the cognitive repercussions associated with such an illness and individual perception of the saliency of such a stressor. In addition to illness duration, the severity of panic may be qualitatively assessed by panic frequency. Parkinsonian patients and individuals with schizophrenia with panic secondary to chronic illness have a relatively severe panic profile (e.g., 2.4 ± 1.4 panic attacks/week) [122, 175]. The appearance of panic attacks among late-stage Parkinsonian patients is interesting. In the clinical population, panic attacks rarely occur following age 65. Interestingly, a lower ^{3}H-CCK-8 hippocampal binding density [257] as well as decreased CCK mRNA in the hypothalamus and cerebral cortex [342] and increased CCK concentrations in the cerebral cortex [343] have been detected among rats 18-29 months of age relative to younger animals (i.e., 2-10 months). It would be of interest to determine if comparable alterations in CCK activity are evident in the amygdala and nucleus accumbens, for example, in animal models of Parkinson's disease. An analysis of mesolimbic sites may provide a CCK associated index of panic susceptibility that addresses the apparent delay of panic onset among Parkinsonian patients. Surely, subjective characteristics including identification of events precipitating panic (e.g., Parkinson's disease, schizophrenia and childhood anxiety separation) would evoke differential sensitivities to the panicogenic properties of CCK-4 among diverse clinical samples.

To date, clinical reports of CCK-4 induced panic, fail to identify subject characteristics or experiential variables that may influence responsiveness to CCK in normal subjects and panic patients. It should be noted parenthetically that panic attacks induced by CCK-4 occur within seconds (e.g., 20 ± 3

seconds) following systemic administration and appear to be similar to naturally occurring panic attacks (e.g., mean duration 20.7 ± 7.6 seconds) [21]. It appears that the assumption of panic spontaneity has been gleaned from the rapid induction of panic following a large, bolus injection of CCK-4 (50 μg). Moreover, the onset of "spontaneous" or induced (e.g., CO_2) panic symptoms over a longer period of time (e.g., time to peak intensity >10 minutes) is inconsistent with a panic description afforded by DSM-IV criteria [344, 345]. Such clinical definitions are counterintuitive particularly when it is considered that patients exhibiting panic attacks with latencies exceeding 10 minutes achieve peak intensity ratings comparable to those of panic patients with rapid symptom onset (see [345-347]). Curiously, immediate panic onset was characterized by increased phobic frequencies and elevated anticipatory anxiety while patients with more protracted latencies prior to panic onset exhibited more generalized anxiety symptoms [345]. Persistent fear of anticipated panic episodes has been recently proferred as a diagnostic criterion for panic disorder [344, 348]. While panic spontaneity is predicated on reduced latencies, it has been well documented that panic patients may experience a paucity of symptoms (e.g., 1-2 symptoms) prior to the emergence of symptom clusters (e.g., >4 symptoms). For example, life-threatening interpretation of vestibular symptoms including fear of fainting, chest pains, breathing difficulty or choking sensations have led to catastrophic interpretations [2]. Not only does the occurrence of limited symptoms prior to the development of panic and the "fear of fear" criterion argue against spontaneity but also is suggestive of a developmental panic course. Recent operational definitions of panic, including limited and situational panic attacks, contradict previous versions of panic spontaneity and inadvertently support the argument that panic attacks evolve from gradual symptom exacerbation. If there were indeed a developmental course of panic, influencing the temporal appearance and severity of symptomatology, panic patients would not only exhibit differential sensitivities to the panicogenic properties of CCK-4 but also exhibit enhanced responsivity to panic-associated cues. Indeed, in some instances the panicogenic properties of placebo have been demonstrated in panic patients [349]. Intuitively, panic attacks occurring in response to placebo procedures are suggestive of expectancy and likely reflect augmented basal anxiety levels. At this juncture, available clinical data do not readily identify laboratory setting and procedural details pertaining to blood pressure assessment and/or intravenous protocols as correlates of enhanced behavioral responsivity in clinical samples. Such an interpretation is hardly surprising, despite the accumulation of clinical evidence which argues for the lack of such an effect (c.f. [21, 350, 351]). To be sure, if environmental cues favor panic emergence; illness duration, severity of panic attacks, agoraphobia and associated rumination would likewise be expected to influence behavioral responsivity. Indeed, while a 20 μg oral dose of yohimbine induces panic in panic patients with more than 2.5 panic attacks/week, this identical dose of yohimbine is without effect among panic patients with a panic frequency of less than 2.5 panic attacks/week [352, 353]. Likewise, elevated basal indices of anxiety, increased panic frequency in the week prior to testing and panic associated somatic reporting were reliably associated with yohimbine induced panic attacks relative to panic patients which failed to report such indices [352, 354]. Similarly, intravenous lactate elicited panic in 75% of panic patients reporting a panic frequency exceeding 1 panic attack/week while no panic attacks emerged with such challenge among panic patients reporting frequencies of less than 1 panic attack/month [355]. It should also be considered that experimental setting and patient expectations including anticipatory reactivity and stressor controllability may influence the course of panicogenic challenge paradigms [356-358]. For example, panic patients provided with the expectancy of anxiety in CO_2 challenge investigations have a demonstrable increase in reported distress and elevated panic incidence relative to patients who have been instructed that control over CO_2 inhalation can be achieved [358]. Moreover, experimental protocols that minimize expectancy of panic averted the panicogenic properties of yohimbine (20 μg orally) [352, 354]. It should be underscored that anxiety-rating scales appear to provide inadequate assessment of anticipatory anxiety and are likely influenced by patient compliance and demand characteristics. In contrast, physiological measures (e.g., blood pressure, heart rate and cortisol responses) while providing more objective measures of anxiety [251, 357, 359, 360] are not invariably sensitive to expectancy. To be sure, it is rather curious that panic patients fail to report anticipatory anxiety in challenge studies or to provide physiological measures of expectancy yet consistently report a hyper-vigilant state consisting of somatic monitoring or environmental vigilance which may serve as predictors of panic. It should also be considered that clinical investigation, in some instances, permits patient-assisted low dose benzodiazepine maintenance. In addition, failure to substantiate plasma drug concentrations prior to challenge (e.g., [336]) may complicate experimental interpretation and mask pre-test anxiety measures. In view of the observation that lactate-, yohimbine- and CO_2-induced panic are influenced by rumination pertaining to panicogenic control and panic expectancy, it is likely that such factors also influence behavioral responsivity to CCK-4 administration. Further to this point, characterization of control subjects responsive to CCK-4 administration may provide salient information regarding panic vulnerability. For example, it has been demonstrated that 6 of 62 normal subjects subsequently reported a panic attack during the 12 month follow-up period following initial CO_2 challenge [361]. Unfortunately, the temporal distribution of life events preceding the panic attack as well as detailed subjective and familial history were inadequately detailed. Although the proactive influence of CCK-4 on subsequent panic attacks are not available, a parsimonious accounting of this peptide would favor the prediction that CCK-4 experience contributes to the development of panic. Clinical strategies would accordingly employ therapeutic interventions prior to the "second" panic episode that may interrupt, or at best delay, conditioning and/or sensitization of CCK dependent symptoms [330].

Pharmacological and Cognitive Management of Panic Disorder: Implications for Putative Differential Sensitivities Among Panic Patient Samples

Pharmacological management of panic disorder often includes chronic administration of imipramine (150-300 mg/day) with the benzodiazepine alprazolam (2-8 mg) as needed, although amitriptyline (150 mg/day) and clomipr-amine (150-225 mg/day), the irreversible monoamine

oxidase inhibitor phenelzine (45-90 mg/day), the reversible monoamine oxidase inhibitors moclobemide (300-600 mg/day) and brofaromine (150 mg/day) and certain selective 5-HT reuptake inhibitors are also used [183, 362-372]. Chronic imipramine administration in nonhuman subjects is associated with reduced cerebrospinal and plasma NE concentrations [373-375] and 5-HT [376, 377]. In rats, chronic administration of imipramine decreases the electrophysiological activity of the locus coeruleus [378]. Interestingly, imipramine has demonstrable effects on panic frequency with limited effects on phobic and agoraphobic behavior [379]. In contrast to imipramine, the efficacy of alprazolam in ameliorating panic cannot be attributed to enhanced GABA/benzodiazepine receptor influence [380]. Indeed, diazepam and alprazolam augment benzodiazepine receptor density in the frontal cortex, hypothalamus and hippocampus ([381]; c.f. benzodiazepine receptor binding in panic patients, [382]) and influence central NE [85, 373] and 5-HT activity [383] to a comparable degree in nonhuman and human subjects. Yet diazepam is therapeutically sterile in the treatment of panic [384] while alprazolam reduces panic frequency, anticipatory anxiety and phobic symptoms [385]. Taken together, these data would suggest that cascading neurochemical alterations associated with benzodiazepine-GABA receptor variations contribute to the therapeutic efficacy of chronic alprazolam treatment. In any event, these data suggest that pharmacological management of panic should be directed toward specific symptoms characterizing the psychological disorder. Nevertheless, the efficacy of pharmacological interventions among panic patients is often confounded by attrition, patient compliance, relapse following progressive drug taper [386-388] and drug side effects [384, 389-395]. Alprazolam for example, is associated with a lower attrition (5%), than imipramine (20%) or placebo (54%). The reduced attrition associated with alprazolam is most likely due to its reduced therapeutic latency (e.g., within one week) relative to imipramine (e.g., 4-8 weeks) or placebo on panic frequency, anxiety episodes, anticipatory anxiety and phobic symptoms [390, 395-397]. In the rat, acute (5 or 10 mg/kg) and chronic (10 mg/kg, 21 days) imipramine administration fails to attenuate fear potentiated startle [398]. In contrast, acute administration of alprazolam (1.0, 2.0, 3.0 mg/kg) 30 minutes prior to test, dose dependently attenuated startle [399]. The relative efficacies of alprazolam and imipramine in antagonizing fear potentiated startle in rats suggests that alprazolam may be more effective in influencing central sites underlying expression of startle and conditioned behavior, including the central nucleus of the amygdala (c.f. [400-404]) (Fig. **2**). Notably, central and basolateral nuclei amygdaloid neurochemical perturbations associated with benzodiazepine-GABA receptor variations including alterations in GABA and glutamate [252, 405-407] most likely potentiate the anxiolytic and anti-panic properties of alprazolam. The patient characteristics provided by Andersch *et al.* [390] as well as Klein [394] and Taylor *et al.* [395], for example, suggest that alprazolam is more effective than imipramine in alleviating anticipatory anxiety preceding panic (e.g., anticipatory intervals associated with panic expectancy, Sheehan Patient-Rated Anxiety Scale). In retrospect, it is curious that clinical reports outlining the panicogenic effects of CCK fail to acknowledge a role for anticipatory anxiety in panic. Such putative differences in anticipatory indices among panic and control subjects participating in CCK challenge paradigms, as well as paradigms that manipulate anticipatory anxiety, pose serious obstacles to detractors of an expectancy hypothesis. In effect, the demonstrable heterogeneity of treatment efficacy associated with chronic imipramine and alprazolam may well follow from the influence of such agents on variable developmental stages of panic disorder.

It is presumed that panic is a heterogeneous disorder comprised of patients who experience uncomplicated panic or, conversely, a complicated panic disorder syndrome consisting of panic with comorbid symptoms of mild or major depression and/or panic with varying degrees of phobic avoidance. While it has been well documented that recurrent anxiety episodes provoke depressive episodes, repeated anxiety episodes together with the affective disturbance of depression may evoke panic (see [137] for review). In any event, the temporal parameters and the contribution of intra- and inter-individual environmental precipitants have not been clearly established (Fig. **2**). Conceptually, the heterogeneity of panic types may coincide with differential stages of panic development. Regardless of psychiatric compartmentalization of panic, panic disorder is invariably progressive with evidence of symptom exacerbation. The adoption of limited panic and situationally provoked panic classifications and arbitrary acceptance of *ad hoc* patient categories provides tacit acceptance of a developmental course in panic. To be sure, it would be reasonable to suggest that premorbid patient characteristics, the duration of the illness, age of onset as well as the frequency and severity of panic episodes influence the expression or exacerbation of depression and phobic avoidance among individuals with panic disorder. Similar comparisons have been provided for depression and schizophrenia and there is no *a priori* reason to suspect a differential developmental course for panic disorder. In fact, uncomplicated panic and panic with comorbid depression and/or extensive phobic avoidance, on the other hand, may operationally define panic severity. Moreover, while responsivity to CCK challenge may vary with panic history, age of onset, illness duration and panic frequency, the efficacy of panic interventions would also be expected to vary with such variables (Fig. **2**).

Pretreatment measures of panic have revealed diminished panic frequency, anxiety (Hamilton Anxiety Rating scale), depression, phobia, paranoia and help seeking behaviors. Moreover, placebo may be sufficient to attenuate panic symptoms for at least the duration of an eight-week clinical trial [408, 409]. In general, it appears that subjects who respond to placebo have a less severe course of panic and high expectations for pharmacological improvement. Alprazolam and imipramine are equally effective in attenuating panic symptoms associated with uncomplicated panic disorder [370, 409]. It should be noted parenthetically that clinical accounts of panic reveal a depression comorbidity rate of 60-75% [410, 411]. Chronic imipramine intervention (150 mg/day, 4-8 weeks) is relatively effective in ameliorating panic symptoms in panic patients early in the course of the disorder where mild depressive symptoms are also detectable [412, 413]. Conditions favoring imipramine treatment include a relatively short duration of illness (e.g.,

1-2 years), younger age of onset (<40 years), comorbid mild depression and panic with no or limited agoraphobia characterized by respiratory distress [138, 414-416]. In contrast, alprazolam is less effective in alleviating panic symptoms among panic patients with comorbid mild depression [417] unless the disorder is accompanied by increased phobic avoidance and increased anticipatory anxiety. In such instances, alprazolam and imipramine are equally effective in alleviating panic symptoms [370]. Amitriptyline (150 mg/day) and phenelzine (60 mg/day) are also equally effective in alleviating panic symptoms associated with mild depression [418]. Patients with panic disorder with comorbid major depression are typically more anxious, fearful of criticism, unassertive and markedly impaired in various social areas compared to non-depressed panic patients [138, 419]. Moreover, panic patients with comorbid major depression are more likely to report earlier age of panic onset (<20 years), previous psychiatric hospitalizations, suicidal tendencies and increased suicide attempts than non-depressed panic patients [6, 420]. Typically, the perceived severity (e.g., disability scales) and frequency of panic among such patients is likewise increased [418, 421, 422] and phenelzine (75 mg/day) is more effective than imipramine and amitriptyline in ameliorating panic symptoms associated with major depression [418, 423, 424]. Conditions favoring alprazolam treatment include age over 40, lower baseline levels of anxiety (Hamilton Anxiety Rating Scale) and mild phobic symptoms (Phobia Rating Scale) [409]. Although the presence of phobic anxiety and avoidance is associated with a longer duration of illness [425] and an increased severity of panic disorder as measured by disability subscales [426], panic patients over the age of 40 tend to have a later age of panic onset (e.g., later clinical admission) [409] and evidence suggests that subjects with a later panic onset have a less severe and more treatment responsive illness [341]. Illness severity measures (e.g., disability scale and agoraphobic avoidance) are more pronounced in panic patients who experience a greater frequency of panic attacks (>2 attacks/week) compared to patients who experienced panic attacks at a lesser frequency (<2 attacks/week) and higher doses of alprazolam (5.2 ± 1.5 mg *vs* 3.0 ± 1.6 mg) are required to establish panic free periods [255, 427, 428]. At higher doses (150-250 mg/day, 4-8 weeks) imipramine is also effective in attenuating the severity of panic symptoms including measures of fear in nondepressed panic patients with agoraphobia although subjects continued to experience panic attacks [429]. Hypochondriasis may also be a form of sickness behavior that responds favorably to alprazolam. For example, alprazolam (5.8 mg/day 6 weeks) reduced hypochondriasis (e.g. Illness Behavior Questionnaire, [430]) including preoccupation with bodily sensations and fear of physical illness yet had no effect on panic frequency [431]. Extensive phobic avoidance, hypochondriasis and relatively high levels of anticipatory anxiety have been associated with non-responsiveness of panic symptoms to conventional drug therapies [432, 433]. Data suggests, however, that the reversible monoamine oxidase inhibitor, brofaromine, may be effective in ameliorating panic attack frequency associated with severe agoraphobia [434]. Typically cognitive and behavioral interventions, in addition to drug therapies, are utilized to reduce panic symptoms in otherwise treatment resistant patients although cognitive interventions may be employed prior to pharmacological therapy early in diagnosis [372, 412, 421, 435-437]. Moreover, the introduction of cognitive, behavioral or performance-based strategies in the treatment of panic disorder sustains improvement of panic symptoms during drug treatment and following drug taper [438-440]. Despite the demonstrated efficacy of most anti-panic medication in the attenuation of panic symptoms early in the disorder, panic progression typically necessitates adoption of protracted cognitive strategies. Such interventions may reduce the saliency of association cues since pharmacotherapy alone does not yield adequate long-term management of panic disorder. In fact, the effectiveness of performance-based treatment in alleviating phobic symptoms relies on subjective perceptions pertaining to performance adequacy or coping ability in specific tasks [441]. Taken together, baseline symptoms, panic frequency, depression severity, phobic avoidance and anticipatory anxiety are useful predictors of pharmacological efficacy on outcome scales.

It has been well documented that early diagnosis of panic facilitates the success of pharmacological and cognitive intervention strategies [137, 384, 385, 432]. Indeed, data derived from various laboratories suggest that the duration of panic disorder [425], the severity and frequency of panic attacks and agoraphobic avoidance [442] prior to treatment is negatively correlated with the efficacy of ensuing therapy. In many instances, illness chronicity appears to complicate treatment owing to the induction of agoraphobia and impairments of social interaction [425, 434]. Illness severity as measured by patient reports of more severe panic and agoraphobic symptoms, increased psychiatric hospitalizations and longer duration of panic were predictive of poor pharmacological and cognitive management compared to less severe courses of panic disorder [442]. Moreover, illness severity may also reflect an earlier age of onset and panic may be precipitated by childhood events. For example, investigators have alluded to a relationship between a history of childhood anxiety, including separation anxiety, school phobia and familial illness and the development of panic in childhood or early adulthood [260, 394, 421, 434, 443-445]. Nonhuman primates raised under stressful conditions (e.g., variable foraging demands) exhibit aberrant behavior (e.g., hyperactivity, clinging and behavioral inhibition among others) [264]. Studies of nonhuman primates also indicate that infant temperament and qualities of the maternal-infant relationship influence the intensity of separation anxiety. For example, peer-raised animals show exaggerated and persistent attachment behaviors (e.g., exhibit more despair on separation) and display alterations in central NE, DA and 5-HT concentrations relative to maternally fostered animals which may impede the infants later ability to cope with life-stressors [446]. Clinically, increased anxiety in childhood typically follows illness of a primary caregiver, with the imminent perception of possible death [447] and appears to be salient to the eventual induction of panic, [260, 447, 448]. Notably, illness and separation can exacerbate the frequency and severity of panic attacks [421, 447]. Not surprisingly, familial illness and sick role behavior can also influence the efficacy of anti-panic medications. For example, children who developed panic disorder following a bout of school

phobia respond well to the selective 5-HT reuptake inhibitor, citalopram (20 mg/day). Interestingly, however, panic free periods were temporally shorter among children whose mothers also suffered from panic disorder with agoraphobia [449]. Presentation of panic symptomatology following a history of childhood anxiety is typically more severe relative to panic symptoms in patients without a history of childhood anxiety [141, 421, 434, 450]. For example, at the time of initial panic assessment, patients with childhood anxiety are characterized by greater agoraphobic avoidance as measured by agoraphobic avoidance scales (e.g., Fear Questionnaire), a longer duration of panic (e.g., childhood onset), more frequent panic attacks and more severe anxiety as indicated by clinical global severity scales (e.g., frequency of panic attacks/week, intensity of anticipatory anxiety, degree of avoidance and degree of social role impairment) [451]. Patients with a childhood history of anxiety disorders also have a significantly higher rate of comorbidity including social phobia, generalized anxiety disorder, obsessive-compulsive disorder, major depression and a family history of anxiety disorders [445]. Moreover, panic disorder following a history of childhood anxiety is typically resistant to pharmacological treatment [434] and requires lengthy cognitive and psychological counseling [421, 447]. Taken together, clinical accounts of panic and the heterogeneity of individual treatment responses to alprazolam and imipramine, among others, reveal diversity in prominent symptoms associated with panic disorder. The presence of depression and agoraphobia reflect illness severity and influence the responsivity of panic symptoms to treatment. Moreover, untreated or inadequately treated panic symptoms worsen with time and the progression from uncomplicated to complicated instances of panic are predicated on panic frequency, severity of symptoms, age of onset, coping strategies and familial setting.

The clinical manifestation of panic among panic patients, individuals with Parkinson's disease and schizophrenia among others suggests that stressful life events or the perception of uncontrollable or unpredictable aversive events may influence the emergence and exacerbation of anxiety. Repeated panic experiences influence cognitive activity and may enhance vigilance and somatic monitoring. In nonhuman subjects, the intensity, duration, controllability, predictability and chronicity of an aversive encounter as well as experiential factors [452, 453] influence the effectiveness of stressors in modifying ensuing behavioral and neurotransmitter activity. Moreover, presentation of the cues associated with the initial stressor experience can influence the expression of pathology. Similarly, among individuals with diverse panic histories, fear motivated behavior including anticipation of subsequent panic attacks and the development of avoidance behavior are modulated by prior stressor experience (e.g., previous panic attacks) and the cues associated with prior panic episodes (e.g., assignment of a weighting scheme to specific environmental events, [454]). The contribution of mild, stressful life events and DA to the emergence and maintenance of panic symptoms requires clarification. It would be difficult to characterize Parkinson's disease, schizophrenia or major affective disorder with comorbid panic symptoms as mild disturbances from either physiological or cognitive vantages. Yet, sensitization of DA mechanisms and putative involvement with panic disorder is predicated on the assumption that pathology may be augmented owing to progressive encounters with mild, unpredictable and/or uncontrollable life events. It is conceivable that cognitive variations immediately preceding onset of Parkinson's disease or schizophrenia, for example, provide rather subtle cues pertaining to alterations in the emotional and/or physical lability of the individual. Nevertheless, repeated or relatively protracted indices of such cues may be sufficient to sensitize central neurochemical substrates. In addition, mild stressors or environmental cues that elicit comparable cognitive variations may sustain the neurochemical correlates of initial experiences. In effect, such a scenario may eventually define the profile of symptoms and determine vulnerability (e.g., latency to the emergence of psychological dysfunction) to anxiety disorders, including panic. The emergence of panic necessitates the coupling of conditioned/sensitized DA activity, the behavioral manifestation of such neurochemical activity and central CCK. Interestingly, data collected in this laboratory suggest that mild stressors reliably induce anxiety among nonhuman subjects and more importantly that these anxiogenic indices are exaggerated following central CCK administration at protracted intervals. In effect, long-term responsivity to stressful life events, CCK activation or cross-sensitization between CCK and stressors is dependent on the mild nature and the contextual cues associated with anxiogenic challenge. Notably, initial imposition of a severe stressor or re-exposure of animals to an equally severe stressor or a high dose of CCK does not induce a dissociable increase in behavioral responsivity. The duration of panic disorder prior to the emergence of symptom exacerbation would provide (a) an operational index of the time course of neurochemical sensitization and (b) provide evidence for, but not necessarily identification of, the influence of patient-specific stimuli contributing to illness progression. In accordance with such an argument, imipramine and alprazolam would be expected to exert an influence when administered relatively early in the course of the disorder (e.g., soon after sensitization) and likely prior to clinical diagnosis of panic. Moreover, the pharmacological efficacy of imipramine and alprazolam on panic symptoms in CCK-challenge studies would interact with the dose(s) of CCK employed and panic profile. For example, clinical investigations examining the anti-panic influence of imipramine on CCK-4 induced panic among panic patients revealed that a variable dose of imipramine (150-300 mg/day) and a fluctuating duration of imipramine treatment (3-26 months) was necessary to attain an eight week panic free period following a bolus injection of CCK-4 (50 μg) which subsequently attenuated panic attacks to a rechallenge dose of CCK-4 (20 μg). Notably, 18% of panic patients who had previously panicked with CCK-4 (50 μg) reported a panic attack upon rechallenge (20 μg CCK-4) [331]. Unfortunately, with respect to CCK-induced panic, panic was predicated on large CCK challenge doses and, from a pharmacological vantage, investigators failed to isolate specific patient characteristics and panic profiles that enhance pharmacological responsiveness or at the very least dictate the dose of imipramine required to attenuate panic naturally. At best, imipramine and alprazolam may prevent exacerbation of panic. Indeed, withdrawal of such therapeutic interventions ordinarily results in the re-

emergence and in some cases exacerbation of panic symptoms. To date, the role of CCK in the reemergence of panic symptoms following alprazolam withdrawal remains enigmatic (see [428, 455-457]). However, it should be emphasized that the symptoms diagnostic of Parkinson's disease, schizophrenia or other disorders associated with the emergence of panic worsen over time. In parallel, panic symptoms also are temporally exaggerated. In effect, once sensitization has occurred, the profile and/or progression of panic symptoms are relatively dependent upon host factors. Notably, the conditioning of both somatic and cognitive panic symptoms over time and the demonstrated long-term resistance of panic symptomatology to therapeutic interventions support an argument for sensitization [204, 458].

CONCLUSION

There is no evidence that panic attacks are spontaneous. However, available evidence points to a common etiology across disorders associated with panic. Clinically, the gradual exacerbation of anxiety-like behavior and the appearance of panic are reminiscent of the behavioral and neurochemical alterations in nonhuman subjects repeatedly exposed to anxiogenic stimuli. In fact, it is likely that panic disorder represents a constellation of sensitized behavioral responses (e.g., limited symptom attacks to a full blown panic attack with phobic avoidance) and the inter-subject variability may follow from the differential influence of organismic and experiential variables. Such claims are not surprising as sensitization/conditioning models have been offered as explanations for Parkinson's disease (e.g., l-dopa fluctuations), schizophrenia and depression. Moreover, it appears that variations of CCK availability in specific central sites are associated with variable panic profiles. To date, a conditioning/sensitization hypothesis of panic disorder has not been adequately assessed. To be sure, the nature of the challenge stimuli, including dose and drug schedule, as well as possible cross-sensitization of specific anxiogenic challenges with stressful life events and the long-term repercussions associated with challenge-induced panic in both normal and panic patients must be considered. Moreover, adequate measures of anticipatory anxiety are clearly needed. CCK availability is linked to colocalization of other neurotransmitters in distinct central sites which suggests that CCK may modulate (a) different aspects of anxiety, including anticipatory reactions to anxiogenic stimuli, (b) variations in cognitive arousal and vigilance and (c) sensitization and conditioning of behavior (e.g., phobic associations) and central neurochemical activity (e.g., DA and GABA). Likewise, multiple anxiogenic agents and putative neurotransmitters or neuromodulators in the mesencephalon, the limbic system as well as the prefrontal cortex and brain stem sites would appear to participate in the promotion of anxiety. In fact, it may be the failure of clinical investigations to appreciate the complex interaction of CCK with other neurotransmitter systems, the sensitization of such systems and the contributions of subjective factors to the nature and temporal progression of anxiogenic release that prevents adequate treatment of panic disorder. Conversely, it should be considered that elimination of panic might only occur with prophylactic treatment. In any event, identification of specific subject populations at risk for later development of panic disorder, necessitates empirical demonstration of differential thresholds for panic evocation (e.g., challenge studies) and detailed clinical histories which would demonstrate the circumstances under which panic can be reliably induced (e.g., environmental and cognitive). Taken together, a comprehensive analysis of panic and panic-like states requires attention to the specific details outlined in this review regarding dose of challenge, inter-challenge intervals, precise subject characteristics and panic history. Undoubtedly, exacerbation and maintenance of panic in chronic conditions, including Parkinson's disease and schizophrenia, and the divergent panic profiles among panic patients involves sensitization and conditioning of neurochemicals (e.g., DA/CCK) and increased rumination that ultimately influence the effectiveness of therapeutic regimens.

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