



Review article

Panic, suffocation false alarms, separation anxiety and endogenous opioids

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Abstract

This review paper presents an amplification of the suffocation false alarm theory (SFA) of spontaneous panic [Klein DF (1993). False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. *Arch Gen Psychiatry*; 50:306-17.]. SFA postulates the existence of an evolved physiologic suffocation alarm system that monitors information about potential suffocation. Panic attacks maladaptively occur when the alarm is erroneously triggered. That panic is distinct from Cannon's emergency fear response and Selye's General Alarm Syndrome is shown by the prominence of intense air hunger during these attacks. Further, panic sufferers have chronic sighing abnormalities outside of the acute attack. Another basic physiologic distinction between fear and panic is the counter-intuitive lack of hypothalamic–pituitary–adrenal (HPA) activation in panic. Understanding panic as provoked by indicators of potential suffocation, such as fluctuations in $p\text{CO}_2$ and brain lactate, as well as environmental circumstances fits the observed respiratory abnormalities. However, that sudden loss, bereavement and childhood separation anxiety are also antecedents of "spontaneous" panic requires an integrative explanation. Because of the opioid system's central regulatory role in both disordered breathing and separation distress, we detail the role of opioidergic dysfunction in decreasing the suffocation alarm threshold. We present results from our laboratory where the naloxone-lactate challenge in normals produces supportive evidence for the endorphinergic defect hypothesis in the form of a distress episode of specific tidal volume hyperventilation paralleling challenge-produced and clinical panic.

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Abbreviations: ACTH, adreno-cortico-tropic hormone; BNST, bed nucleus striae terminalis; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DVs, distress vocalizations; ESB, electrical brain stimulation; EtCO₂, end-tidal CO₂; GAD, Generalized Anxiety Disorder; HPA, hypothalamic–pituitary–adrenal; N-L, naloxone-lactate; $p\text{CO}_2$, the partial pressure of CO₂ (the amount of carbon dioxide gas dissolved in the blood); PD, panic disorder; PET, positron emission tomography; POMC, pro-opio-melano-cortin; SAD, separation anxiety disorder; SFA, suffocation false alarm theory.

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1. Introduction

We extend the suffocation false alarm theory (SFA) of Panic Disorder (PD) (Klein, 1993) by hypothesizing that an episodic dysfunction in endogenous opioidergic regulation – a phylogenetically old system that co-regulates breathing as well as social-affiliative behavior – explains this adaptive failure. This makes it possible to integrate separation anxiety disorder, CO₂ and lactate hypersensitivity, and a range of respiratory phenomena and pathology with Panic Disorder.

2. Experimental challenge studies: Lactate infusion and CO₂ inhalation in panic

Panic Disorder is unique among psychiatric disorders in that its salient component, the panic attack, can be reliably incited in laboratory settings by specific chemical challenges as well as having challenges specifically blocked by anti-panic agents, e.g. imipramine. We can experimentally turn panic on and off, producing trenchant causally related data rather than inferences from naturalistic data. These challenge studies, using intravenous lactate infusion and carbon dioxide inhalation led to a number of unexpected laboratory findings that have advanced our understanding of clinical panic pathophysiology (see Klein, 1993 for details).

Patients who panic to CO₂ are a subset of lactate panickers (Klein, 1993). It was the recognition that increasing brain CO₂ and lactate are both harbingers of potential asphyxiation that prompted the suffocation false alarm theory of Panic Disorder. This theory is consonant with many recent observations detailed and expanded below.

3. Air hunger (dyspnea) and Panic Disorder

That panic is distinct from Cannon's emergency fear response (Cannon, 1920) and Selye's General Alarm Syndrome (Selye, 1956) is shown by the prominence of intense air hunger during these attacks. Acute air hunger rarely occurs in acute, external-danger initiated fear (Klein, 1993; Preter and Klein, 1998). Further, PD patients have chronic sighing abnormalities outside of the acute attack. Smoking and pulmonary complaints are independent, multiplicative risk factors for PD, but not for other anxiety disorders (Pohl et al., 1992; Amering et al., 1999). Panic is highly prevalent in lung disease (asthma, chronic obstructive pulmonary disease) and in torture victims who specifically suffered suffocation torture rather than other assaults (Bouwer and Stein, 1999).

Although increasing hypercapnia is the salient indicator of potential suffocation, hypoxia also serves this function. Beck et al. (1999; 2000) showed that panic patients respond with

increased panic symptoms not only to CO₂ inhalation, but also to normocapnic hypoxia, as predicted by SFA. Patients with prominent respiratory symptoms during attacks, showed greater fluctuations in tidal volume during and after the challenge, as well as overall lower levels of end-tidal CO₂ than those whose clinical attack did not include respiratory symptoms. Equivalent increases in anxiety and panic symptoms were noted, although the sample size (seven patients in each group) limits conclusions from this particular null result. These findings support the centrality of the suffocation alarm system as a detector of the range of suffocation predictive data.

4. Pulmonary conditions, suffocation, and panic

PD is a frequently comorbid – if not the most prevalent – psychiatric disorder among patients with pulmonary disease (Goodwin and Eaton, 2003; Goodwin et al., 2004; Katon et al., 2004; Nascimento et al., 2002; Klein, 2001; Roy-Byrne et al., 2006; Valenca et al., 2006; Wingate and Hansen-Flaschen, 1997; Yellowlees and Kalucy, 1990; Yellowlees et al., 1987; 1988). Lung disease, including asthma and COPD may predispose to PD (Craske et al., 2001; Goodwin and Eaton, 2003; Hasler et al., 2005; Karajgi et al., 1990; Perna et al., 1997; Verburg et al., 1995), or present solely with panic symptoms (Edlund et al., 1991; Sietsema et al., 1987).

Asthma and PD are both characterized by acute episodes, salient respiratory symptoms and anxiety with avoidance of situations related to acute attacks (Klein, 1993; Yellowlees and Kalucy, 1990). There is a significantly higher (6.5 to 24%) prevalence of PD in asthmatics (Goodwin et al., 2005; Shavitt et al., 1992; Yellowlees et al., 1987; 1988) than the 1–3% reported in the general population (Kessler et al., 2006; Weissman, 1988). Perna et al. (1997) found a significantly higher prevalence of PD, sporadic panic attacks, and social phobia in asthmatics than the general population. In 90% of asthmatics with PD, asthma appeared first. Panic symptomatology during the asthmatic attack predicted longer hospitalizations in asthmatic patients (Baron et al., 1986; Brooks et al., 1989; Jurenc, 1988).

Serotonergic and tricyclic antipanic compounds may symptomatically benefit asthma (Smoller et al., 1998; Sugihara et al., 1965; Yellowlees and Kalucy, 1990). The antipanic drug, sertraline, was reported useful for comorbid anxiety and depression in COPD (Papp et al., 1995).

5. Cigarette smoking is risk factor for panic

Smoking and PD have been positively associated in several epidemiological studies (Amering et al., 1999; Isensee et al., 2003; Pohl et al., 1992). Breslau and Klein (1999) and Breslau et al. (2004) found that current daily smoking increased the

onset risk for panic attack and PD. Quitting smoking sharply reduces risk of panic onset. Pulmonary complaints in both smokers and non-smokers increased panic risk; however, no significant risk for onset of daily smoking in persons with prior panic attacks or disorder was found. That the risk is unidirectional – from prior smoking to panic attack onset – was confirmed, after controlling for alcohol and drug use, anxiety, depressive disorders during adolescence, and parental smoking (Johnson et al., 2000).

In PD patients grouped by symptom profiles into respiratory and nonrespiratory subtypes (Biber and Alkin, 1999), the respiratory group was significantly more sensitive to 35% CO₂ and smoked more cigarettes.

A large twin study (Reichborn-Kjennerud et al., 2004) found little common genetic liability for Panic Disorder and smoking, whereas “shared or familial environmental factors accounted for 75 % of the association between the phenotypes”. Smoking-induced lung pathology, whether manifest or sub-clinical, impairs gas exchange which may trigger panics in those with a low alarm threshold.

6. Separation anxiety and panic

Klein and Fink (1962) posited a developmental pathophysiological link between separation anxiety and PD and subsequent agoraphobia, since 50% of hospitalized agoraphobics reported severe early separation anxiety that often prevented school attendance. Further, panic, in this group, was frequently precipitated by bereavement, or separation. Therefore the anti-panic drug, imipramine, might be effective in childhood separation anxiety disorder (SAD). This was confirmed (Bernstein et al., 2000; Gittelman-Klein and Klein, 1973). These observations, coupled with attachment theory and ethological views of anxiety (Bowlby, 1973) fostered contemporary anxiety disorder classification.

Separation anxiety correlates with increased familial loading and early onset of PD (Battaglia et al., 1995). Patients highly comorbid for multiple anxiety disorders are particularly likely to recall childhood SAD (Lipsitz et al., 1994). Claims that separation anxiety equivalently antecedes other anxious states (Van der Molen et al., 1989) may be due to diagnostically ambiguous limited symptom attacks and the unreliability of the questionnaire method. However, in the only controlled, long-term, direct, blind, clinical interview follow-up of separation-anxious, school-phobic children, the only significant finding was an increased PD rate (Klein, 1995).

Silove et al. (1996) concluded that “the weight of studies support an association between early SA and adult PD; and SA appears to be linked to PD rather than to agoraphobic symptoms, but the specificity of the link remains unresolved, particularly in relation to the other anxiety and depressive disorders”. Manicavasagar et al. (2000) showed the persistence of separation anxiety symptoms from childhood to adulthood, raising the question of persistent SAD (Manicavasagar et al., 2001; 2003).

Panic Disorder is more frequent in women than men (Gater et al., 1998) and commonly presents with symptoms of air

hunger (Sheikh et al., 2002). The onset of panic is often triggered by separation, loss or bereavement (Faravelli and Pallanti, 1989; Kaunonen et al., 2000; Klein, 1993; Milrod et al., 2004).

Pine et al. (2000; 2005) documented a relationship between respiratory dysregulation and specific childhood anxiety disorders. Respiratory hypersensitivity to 5% CO₂ was significantly present in children with separation anxiety disorder, to a lesser degree in generalized anxiety disorder, but not in social phobia.

7. Panic, cortisol, and challenges

Another basic physiologic distinction between fear and panic is the counter-intuitive lack (possibly suppression) of hypothalamic–pituitary–adrenal (HPA) activation in panic (Sinha et al., 1999).

That the panic of PD does not trigger the hypothalamic–pituitary axis (HPA) may be explained by a deduction from the existence of a suffocation detector. Under suffocation circumstances, since acute HPA activation would counterproductively increase catabolic activity and oxygen demand, the fear response should be modified to allow energy conservative activation for possible swift escape. Relying on vagal withdrawal for rapid enhancement of cardiovascular performance (Cevese and Verlato, 1985) while suppressing HPA release seems appropriate (Porges, 1995).

A test of this idea would be measuring the response to transient hypoxia, under circumstances where fearful apprehension and motor activation is avoided. A trenchant example is provided by withdrawal of nasal continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea. Strikingly, this did not trigger cortisol release despite recurrence of sleep apnea and oxygen desaturation (Grunstein et al., 1996).

Gautier (1996) emphasized that hypoxia is associated with a reduced metabolic rate. This hypometabolism may be accompanied by a lowering of the thermoregulatory set point during hypoxia, both mediated by the hypothalamus. These data stress that metabolic shutdown, rather than activation, may promote survival under specific conditions such as potential suffocation.

Similarly, probands flown to high altitudes, but not stressed by exercise, did not develop hypercortisolemia unless suffering from altitude sickness (Larsen et al., 1997). When exercised, probands had an HPA response, showing that high altitude does not prevent HPA activation. Similarly, chronically hypoxic and hypercapnic patients with chronic obstructive pulmonary disease (COPD) had ordinary levels of cortisol (Hjalmarsen et al., 1996), unless they decompensated into acute respiratory failure.

Two other circumstances where hyperoxidation would be counterproductive are hyperthermia and starvation, where HPA axis activation occurs only if the subject is distressed or cachectic (which requires the lipolytic action of cortisol). In isolation, neither pleasant hyperthermia (sauna) (Kukkonen-Harjula and Kauppinen, 1988; Jokinen et al., 1991) nor brief fasting (Adams et al., 1989) causes HPA activation. Conversely, sudden cold exposure (Hiramatsu et al., 1984) adaptively triggers HPA activation and heat production. Therefore, different stresses

produce appropriately adaptive HPA responses rather than a generic activation. This modular view of brain adaptive systems for specific dangers is supported by Corfield et al. (1995) who showed activation of cingulate gyrus and cerebellar structures in a PET study of CO₂-stimulated breathing in normal subjects. Similarly, PET scan and fMRI neuroimaging data implicate the cerebellum in the hypercapnic production of air hunger (Brannan et al., 2001; Parsons et al., 2001; Evans et al., 2002), a “compelling primal emotion like severe thirst” (Liotti et al., 2001). Parsons et al. (2001) have argued that the cerebellum regulates the overriding emotional activation that occurs under conditions of air, food and water deprivation. Notably, thirst and hunger are generally not considered as alarm systems since mortality is considerably delayed. This is not the case for air deprivation.

8. Opioids as physiologic regulators

Since separation anxiety and CO₂ sensitivity are both under opioidergic control (see below), we hypothesized that PD may be due to an episodic functional endogenous opioid deficit (amplified SFA theory).

The endogenous opioid system was unknown until the early 1970's. Naloxone prevents exogenous opiate effects, but has little effect on normal animals (Akil et al., 1998). This hindered a search for endogenous opioids. However, electrical stimulation of the periaqueductal gray (Mayer et al., 1971) produced naloxone-reversible analgesia, strongly suggesting the existence of an endogenous opioid system.

Opioid molecules are among the oldest evolved signaling substances. Remarkably conserved structurally, they are involved in diverse functions, e.g., pain perception, respiration, homeothermy, nutrient intake and immune response (Stefano et al., 1996). Their reward-signaling function may have evolved from anti-nociceptive properties.

Currently three peptide groups, comprising over a dozen molecules, are identified. All arise from prohormones: Proenkephalin contains Met- and Leu-enkephalin; prodynorphin contains dynorphin A, dynorphin B, and neo-endorphin. Enkephalins and dynorphins may be the predominant central transmitters. β -Endorphin is cleaved from the prohormone, pro-opio-melanocortin (POMC) and co-released with ACTH from the anterior pituitary. It is considered the major circulating endogenous opioid agonist.

The opioids interact with three major classes of receptors, the δ , κ and μ receptors (Reisine, 1995), each with several subtypes (Connor and Christie, 1999). The enkephalins and β -endorphin have a high affinity for the μ and δ receptors, whereas dynorphin A may stimulate the κ receptor. The receptors have different affinities for the prototypical opioid antagonist, naloxone, with the μ receptor exhibiting the highest affinity. Novel opioid receptors and corresponding agonists are still regularly discovered. Morphine and codeine are synthesized by vertebrate species, including humans (Glattard et al., 2006; Stefano and Scharrer, 1994; Stefano et al., 2000; Zhu et al., 2001). Our knowledge of this system is still quite incomplete.

μ Receptor activation has been seen responsible for the analgesic, respiratory and addictive effects of opioids and

opiates, but more recently, δ blockade leading to reversal of μ agonist-induced respiratory depression without loss of analgesia has been described (Su et al., 1998; Verborgh and Meert, 1999). Therefore, the effects of μ active agents may partly depend on δ receptor activation. The dose of naloxone (2 mg/kg) that induced panic-like reactions to lactate in normals (Preter et al., 2007, in preparation; Sinha et al., 2007) is well beyond the point of μ receptor saturation and is at the level required for δ blockade (Sluka et al., 1999).

The cranial nerves and muscles for expressing affect all evolved from the primitive gill arches that extract oxygen from water (Porges, 1997). The extent to which endogenous opioids participate in respiratory control in non-stressed human adults, i.e. under normoxic, normocapnic conditions, remains controversial. However, their role in fetal and neonatal respiration, situations in which even small gas exchange abnormalities may be devastating, is clear (Santiago and Edelman, 1985). Endogenous opioids are activated in hypoxic or hypercapnic respiratory distress (Santiago and Edelman, 1985; Olson et al., 1997) and are inhibitory to CRH release (De Souza and Nemeroff, 1989; Dunn and Berridge, 1990). Opioids decrease respiratory sensitivity (Eldridge and Millhorn, 1981; Iasnetsov et al., 1984; Akiyama et al., 1990) and increase survival under hypoxic and hypercapnic conditions. Opioid modulation of CO₂ sensitivity may be of particular importance during sleep, when plasma CO₂ concentration becomes the primary breathing stimulus.

Dyspnea is modulated by central and peripheral opioid levels in both rodents and humans (Santiago and Edelman, 1985). Mice exposed to severe, intermittent hypoxia prolonged their survival during subsequent lethal suffocation (Mayfield and D'Alecy, 1992). Naloxone blocked this effect, suggesting that endogenous opioids increase adaptability to low-oxygen environments. Opioids lowered body temperature in mice, thus slowing counter-productive metabolic activity during hypoxia (Mayfield and D'Alecy, 1992). Stark et al. (1983), in a placebo-controlled trial in normal human subjects, showed that codeine allows high levels of carbon dioxide to be tolerated during breath holding. Opioid receptors, including ‘non-conventional’ ones, are located throughout the respiratory tract. Nebulized morphine is being investigated as a chronic dyspnea treatment (Baydur, 2004; Bruera et al., 2005; Zebraski et al., 2000).

Polyvagal Theory (Porges, 1995, 1997, 2003, 2007) may add an important structural element to SFA. Porges argues that Cannon unduly emphasized that emergency adaptations were due to sympatho-adrenal excitation. In mammals, the vagus evolved into two separate branches, both involved in the mammalian procreative process (feeding, nursing, copulation etc.). The phylogenetically older, unmyelinated dorsal vagal complex (DVC) regulates digestion and responds to novelty or threat, specifically to hypoxia, by reducing metabolic output. Oxytocinergic hypothalamic projections activate DVC output, whose sensory component monitors circulating neuropeptide levels. Porges hypothesizes that this vagal component has evolved to support, in conjunction with neuropeptide systems, mammalian bonding and attachment.

The ventral vagal complex (VVC), unique to mammals, carries myelinated vagal axons and portions of other branchiomeric

cranial nerves (V, VII, IX, XI). Together, these pathways control facial expression, sucking, swallowing, breathing, crying, and vocalization. Further, the myelinated vagus (VVC) controls resting heart rate by tonic inhibition of the sinoatrial node.

Thus, VVC inhibition provides a rapid response system without the need to immediately activate the metabolically costly sympatho-adrenal system (Porges et al., 1996). The mechanism of acute tachycardia during lactate-induced panic has been attributed to vagal withdrawal (Yeragani et al., 1994) rather than sympathetic discharge. For unknown reasons, the vagal withdrawal response seems excessive in Panic Disorder. For instance, patients with PD show vagal withdrawal on standing in contrast to normal and depressed subjects (Yeragani et al., 1990, 1991).

9. The separation cry and opioids

Following birth, mammalian infants cannot survive independently. Survival requires reliable distress signaling mechanisms to elicit parental care and retrieval. Distress vocalizations (DVs) are a primitive form of audio-vocal communication (Panksepp, 1998). A common neuroanatomy subserving DVs may be shared by all mammals, although substantial functional variations depend on the ontogenetic niche. The latter (West and King, 1987) signifies the ecological and social legacies (“the inherited environment”) in which a given set of genes develops. For instance, isolated altricial (developmentally immature) infants do not emit DVs as much as many other species, since it is not likely they will stray from the nest (Panksepp et al., 1992).

Human infants are born immature and practically never get lost for their first six months. Despite frequent maternal absence, separation anxiety in humans develops only after their motor system matures. Young rats are not specifically attached to their mother, i.e. any mother will do as heater or feeder. Only once mobile do they socially bond, but their responses do not compare with the vigor seen in other species. Rats also differ from other species, including primates, dogs and chicks in their greater DV suppression by benzodiazepines (Kalin et al., 1987; Panksepp et al., 1992; Scott, 1974). Since benzodiazepines differentially alleviate anticipatory fear, social isolation in young rodents, as compared to many other mammals, may activate fear more than separation distress. Thus, when using cross-species analogies, it is important to keep in mind that the type and degree of social separation distress depends on ecological and developmental parameters (Panksepp et al., 1992).

Separation anxiety serves as a biologic leash for the increasingly mobile infant who continually checks for the mother’s presence, becomes acutely distressed on discovering her absence, and immediately attempts to elicit retrieval by crying. In humans, separation anxiety usually wanes around age four when the now verbally skilled child can successfully elicit care even from non-relatives.

Using electrical brain stimulation (ESB), DVs have been elicited in many species from homologous areas, including the midbrain, dorsomedial thalamus, ventral septum, preoptic area, and the bed nucleus striae terminalis (BNST). In some higher species, one can obtain separation calls by stimulating the

central amygdala and dorsomedial hypothalamus. All these sites have high opioid receptor densities and figure heavily in sexual and maternal behaviors (Panksepp, 1998). Cortically, electrical stimulation of the rostral cingulate gyrus in monkeys consistently elicits distress calls (Jürgens and Ploog, 1970; Ploog, 1981). The cingulate cortex, found exclusively in mammals, is particularly well developed in humans and contains high densities of opioid receptors (Wise and Herkenham, 1982).

Naloxone-blockable opioid agonists reduce isolation-induced distress vocalizations (DVs) across mammalian species (Hofer and Shair, 1978; Kalin et al., 1988; Kehoe and Blass, 1986; Panksepp et al., 1978). In beagles (Scott, 1974), the only psychotropic drug that yielded specific DV reduction at non-sedating doses, was imipramine, the classic anti-panic agent. Naloxone given to guinea pigs and young chicks (Panksepp et al., 1978) increased baseline vocalizations (by 600%), but only when the animals were in a group, since isolates already emitted maximum DVs.

Kalin et al. (1988) studied opioid modulation of separation distress in primates, showing morphine (0.1 mg/kg) significantly decreased separation distress vocalizations without changes in autonomic and hormonal activation. Naloxone (0.1 mg/kg) blocked this effect. Sympathetic blockade using the $\alpha(2)$ agonist, clonidine, and the β adrenergic antagonist, propranolol, had no specific effect on separation-induced “coos” in infant rhesus monkeys (Kalin and Shelton, 1988).

10. Sighing, yawning and respiratory chaos

The neural structures necessary for yawning are located near (or identical with) other phylogenetically old, respiratory and vasomotor centers. Anencephalic infants, born with only the medulla oblongata, yawn. Hypothalamic neurons originating in the paraventricular nucleus facilitate yawning by releasing oxytocin at distant sites, such as the hippocampus and pontomedullary structures. Opioids inhibit the yawning response at the level of the paraventricular nucleus by decreasing central oxytocinergic transmission. Conversely, naloxone may increase yawning, a classic sign of opiate withdrawal (Argiolas and Melis, 1998).

Both yawning and sighing are contagious. Observed acute inspirations may be interpreted as tests of increased ambient carbon dioxide or efforts to overcome breathlessness. Thus, observing another’s yawn may incite one’s own yawning test, without any relevant cognition, by activation of a phylogenetically fixed action pattern.

Venerable features of “neurosis” are frequent sighs and yawns. A feeling of respiratory oppression precedes sighing. The deep inspiration of a sigh doubles the normal tidal volume, abruptly lowers $p\text{CO}_2$, and relieves respiratory distress. Although PD and generalized anxiety disorder (GAD) patients were equivalent on baseline anxiety levels, Hegel and Ferguson (1997) demonstrated significantly lower baseline end-tidal CO_2 levels (EtCO_2) in PD compared to GAD and normal controls. Moreover, eight of sixteen panic patients who reported a high level of respiratory symptoms during attacks had the lowest baseline end-tidal CO_2 levels.

Comparing, at rest, Panic Disorder with generalized anxiety disorder (GAD) and normal controls, Wilhelm et al. (2001a) showed marked differences between PD and normals: respiratory rate was lower, tidal volume was higher, end-tidal CO₂ (EtCO₂) was lower, and the number of sighs was higher. In GAD some of these respiratory abnormalities were present in attenuated form.

Wilhelm et al. (2001b) found that panic patients at rest for 30 min sighed more frequently than normals. Episodic sighing, rather than sustained increases in ventilation, accounted for the decreased EtCO₂ in PD. In normals, the precipitous drop in EtCO₂ after a sigh was nullified by an immediate tidal volume decrease, thus raising EtCO₂ levels to baseline. However, panic patients continued to ventilate at an increased tidal volume for a number of post-sigh breaths, maintaining EtCO₂ at a lower level before returning to baseline. This may indicate a defense against a swift EtCO₂ increment that could trigger the suffocation alarm.

Abelson et al. (2001) studied breath-by-breath tidal volume and respiratory rate responses to a doxapram challenge in PD and a normal control group. Half of each group received a cognitive intervention designed to reduce doxapram induced anxiety/distress responses. Compared to normals, PD patients had a characteristic sighing pattern of breathing, thus producing significantly greater tidal volume irregularity. Of note, the cognitive intervention attenuated fearful response, but did not significantly influence doxapram-induced hyperventilation.

11. Opioids and the control of separation, and social-affiliative behavior

The first neurochemical system found to inhibit separation distress was the endogenous opioid system. Originally formulated by Panksepp, the brain opioid theory of social attachment was based on phenomenological similarities between social and narcotic dependence, including the stages of euphoria, tolerance and withdrawal. It predicted that opioid release would result in feelings of comfort and alleviation of emotional distress arising from loss and social isolation (Panksepp, 2003, 2005, Panksepp et al., 1978, 1980). Opiates, mimicking endogenous opioids, artificially create feelings of social comfort but decrease motivation to seek out social contact. Opiate antagonists increase social motivation, but reduce the reward afforded by endogenous opioid release.

This evolutionary, neurobiologic attachment theory has received much empirical support (Nelson and Panksepp, 1998). It is now appears that:

1. the endogenous opioid system is activated by several positive social interactions, ranging from mutual grooming in young animals (Keverne et al., 1989; Knowles et al., 1989) to sexual gratification;
2. opioids attenuate the reaction to social separation;
3. a low (but not a high) basal level of opioids increases motivation to seek social contact.

Panksepp (1998) hypothesizes that certain people become addicted to external opiates because they artificially induce feelings of gratification similar to – and probably above and

beyond – those achieved by the release of endogenous opioids in social interactions.

12. Opioid antagonists in panic

An open pilot study (Sinha et al., 2007) showed preliminary results supporting our hypothesis of a functional endogenous opioid deficit in PD (amplified SFA theory). In 8 of 12 normal subjects, naloxone infusion (2 mg/kg) followed by lactate showed significant tidal volume responses similar to those observed during clinical panic attacks (Martinez et al., 1996). Four of these subjects then received placebo-lactate and did not show this tidal volume increment. The naloxone-lactate effect resembled the non-fearful panic described by Beitman et al. (1990) in patients with attacks of cardiorespiratory distress whose cardiac catheterization was normal. DSM-4 (American Psychiatric Association, 1994) requires either acute fear or distress as necessary panic criteria. The panic patients originally studied were psychiatric inpatients whereas Beitman's patients were found in cardiac and neurological practices.

Following Sinha et al.'s report, we designed a properly controlled experimental study of the interaction of naloxone with lactate in normal subjects (Preter et al., 2007, in preparation), using the LifeShirt as a recording device (Wilhelm et al., 2003). Our initial analyses confirm Sinha et al.'s preliminary findings, lending support to our hypothesis that the endogenous opioid system serves to buffer normal subjects from the behavioral and physiological effects of lactate (Lee et al., in press). Conversely, an episodic opioidergic deficit may underlie the suffocation sensitivity and separation anxiety of panic patients. Independently, Facchinetti et al. (1994, 1998) attributed premenstrual syndrome to periodic opioidergic deficit. Remarkably, this syndrome is also vulnerable to CO₂ and lactate induced panic attacks.

Thus, the naloxone-lactate (N-L) interaction may be an experimental model of the clinical panic attack. However, unless elaborated by a confirmatory, double-blind experiment contrasting the N-L effect in the context of a variety of anti-panic and panic irrelevant drugs, it cannot be considered definitively related to the clinical episode. If this were found to be the case, the N-L probe would afford two useful advances: First, there is currently no specific screening method for testing putative anti-panic drugs except by experimental treatment of Panic Disorder patients. Second, and probably of more ultimate importance, finding support for our theory that an opioidergic dysfunction is the pathophysiological mechanism underlying Panic Disorder allows new theoretical and practical approaches to a range of related illnesses. If opioidergic dysfunction underlies panic pathophysiology, the appropriateness of a new class of therapeutic agents comes into question. Recent work with mixed agonist-antagonists, e.g. buprenorphine (Gerra et al., 2006; Wallen et al., 2006) may be relevant.

Positive results would foster investigations into basic molecular mechanisms. For instance, we note that the dose of naloxone used in our study (2 mg/kg) exceeds that needed for μ opioid receptor (MOR) blockade (Sluka et al., 1999), suggesting a role for the δ opioid receptor (DOR). Investigations of μ

knockout mice and δ knockout mice (Gaveriaux-Ruff and Kieffer, 2002; Nadal et al., 2006) also indicate that the DOR is distinctively related to emotionality. A possible approach is to study lactate and CO₂ sensitivity in DOR knockout mice as compared to other mouse strains and preparations. The expectation would be that lactate and CO₂ would distinctively elicit emotional/respiratory responses in DOR knockout as compared to other mice strains or knockout preparations.

13. Conclusion

Our current model provides a framework connecting PD data to endogenous opioidergic dysfunction, separation anxiety, and respiratory vulnerabilities, thus amplifying the suffocation false alarm theory (Klein, 1993). We propose that panic, separation anxiety and opioid dysfunction-related conditions, such as premenstrual dysphoria, may be due to a disturbance of endogenous opioid systems that adaptively regulate respiration, separation anxiety, consummatory pleasures, and social-affiliative rewards, in addition to pain.

The present review has focused on the possible central role of the opioid receptor in pathological panic as it occurs in PD. One of the necessary limitations of this article is that we have not critically discussed alternative views considering the relevance of other neural systems, e.g. cholinergic (Battaglia, 2002), adrenergic (Charney et al., 1990), amygdalocentric (LeDoux, 1998) etc.

Further SFA refinements are necessary to address the gastrointestinal (Fleisher et al., 2005; Lydiard, 2005) and headache symptomatology of separation anxious children and some adult panic patients. That migraine headaches are highly comorbid with PD (Harter et al., 2003), and bi-directional risk factors for onset (Breslau et al., 2001) may provide clues.

Prospective, longitudinal psychobiological studies of genetic predisposition, separation, divorce, grief, bereavement, abortion, birth and adoption, in the context of challenge and therapeutic approaches offer pointed investigative opportunities. The neuroscience and evolutionary psychobiology frameworks serve as heuristic stimuli.

Our hypotheses are sufficiently concrete that falsifications, amplifications and modifications are possible (Klein, 1969). However, developing stable funding mechanisms to support such complex, longitudinal, person-oriented and physiological-sophisticated studies are a necessary precondition.

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