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REVIEW

Adult cyclical vomiting syndrome: a disorder of allostatic regulation?

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Abstract Cyclic vomiting syndrome (CVS) is an idiopathic illness characterized by stereotypic and sudden-onset episodes of intense retching and repetitive vomiting that are often accompanied by severe abdominal pain. Many associated factors that predict CVS attacks, such as prolonged periods of fasting, sleep deprivation, physical and emotional stress, or acute anxiety, implicate sympathetic nervous system activation as a mechanism that may contribute to CVS pathogenesis. Furthermore, adult patients with CVS tend to have a history of early adverse life events, mood disorders, chronic stress, and drug abuse—all associations that may potentiate sympathetic neural activity. In this review, we set forth a conceptual model in which CVS is viewed as a brain disorder involving maladaptive plasticity within central neural circuits important for allostatic regulation of the sympathetic nervous system. This model not only can account for the varied clinical observations that are linked with CVS, but also has implications for potential therapeutic interventions. Thus, it is likely that cognitive behavioral therapy, stress management ("mind–body") interventions, regular exercise, improved sleep, and avoidance of cannabis and opiate use could have positive influences on the clinical course for patients with CVS.

Keywords Cyclic vomiting syndrome-plus · Autonomic dysfunction · Central nervous system · Allostasis · Allostatic load

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Cyclic vomiting syndrome (CVS) is an idiopathic illness that is increasingly recognized in adults (Abell et al. 2008; Boles et al. 2009). The disorder is characterized by its highly dichotomous pattern with often long asymptomatic periods and intermittent, stereotypic, and sudden-onset episodes of intense retching and repetitive vomiting that are often accompanied by severe abdominal pain (Abell et al. 2008). While secondary changes in gastrointestinal structure, such as Mallory Weiss tears, are commonly observed in patients with CVS, no consistent structural or functional changes in the gastrointestinal tract have been identified. Thus, CVS is exclusively diagnosed based on the typical symptom constellation described above (Tack et al. 2006).

Approximately two-thirds of pediatric CVS patients also suffer from chronic migraine headaches, and this strong association suggests that similar pathophysiological mechanisms may contribute to these apparently dissimilar diseases (Abell et al. 2008; Boles et al. 2006, 2009; Cupini et al. 2003). Prior studies in pediatric CVS patients also confirmed a matrilineal inheritance pattern and an overrepresentation of specific mutations in mitochondrial DNA (mtDNA), features which also observed in patients with migraines (Boles et al. 2005, 2006; Rinaldo 1999; Wang et al. 2004; Zaki et al. 2009; Li et al. 2008). However, these same mitochondrial DNA mutations are not strongly associated with adult-onset CVS (Boles et al. 2009), and a minority of adult-onset CVS patients suffer from concurrent migraines. Yet, prolonged periods of fasting are a known trigger for emetic episodes in both pediatric and adult CVS patients. Thus, there may be other mutations in mtDNA associated with adult-onset CVS that could confer a sensitivity to low energy stores, which would be predicted to lead to mitochondrial dysfunction and oxidative stress (Hejazi and McCallum 2011; Boles 2011). Consistent with this proposal, uncontrolled studies have suggested

that coenzyme Q10 supplementation, which would be predicted to improve mitochondrial function, can prevent CVS attacks (Boles et al. 2010; Hejazi and McCallum 2011).

However, whereas fasting may indeed trigger emetic episodes in adult CVS patients, such exacerbations are more frequently linked to other factors, such as sleep deprivation, physical stress, emotional upheaval, or anxiety (Abell et al. 2008; Fleisher et al. 2005). Conversely, many adult patients utilize the calming effects of hot showers or the sedating influences of marijuana or other drugs to stave off attacks (Donnino et al. 2011). The importance of such sedating effects is highlighted by the fact that the most effective interventions to abort a CVS attack involve the administration of opioids and/or benzodiazepines (Fleisher et al. 2005). The acute effect of cannabinoids, opioids and benzodiazepines stands in stark contrast to the sequelae of their chronic use, which has been linked to the onset or worsening of CVS with eventual evolution of disease coalescence (Hejazi et al. 2010; Fleisher 1997). The goal of this review is to integrate these clinical observations into a model that may explain the varied manifestations of this syndrome and can provide a rationale for new treatments to blunt and—more importantly—prevent CVS attacks.

CVS and circadian patterns

One of the conspicuous features of CVS attacks is their distinct circadian pattern—the majority of patients experience an onset of symptoms in the early morning hours (Fig. 1). Physiologically, this time of day is normally associated with increases in cortisol production and increases in sympathetic nervous system activity. In normal diurnal patterns, corticotrophin releasing factor (CRF) secretion by neurons within the paraventricular nucleus of the hypothalamus (PVN) is increased in the early AM hours (Kalsbeek et al. 2012). Increased peripheral CRF levels have inhibitory effects on gastric motility (Taché and Perdue 2004), which may lower the threshold to develop vomiting during this time of day. Thus, the circadian pattern which is observed in CVS attacks could be in part mediated by CRF (Tache 1999), cortisol, and increased sympathetic nervous system activity. These circadian patterns in hypothalamic–pituitary–adrenal (HPA) axis and autonomic function may also alter the susceptibility to develop other disorders across multiple organ systems. For example, analyses of emergency admissions for myocardial infarctions show an overrepresentation of cardiac events with an early morning onset (Muller et al. 1985; Jia et al. 2012;), and the incidence of hypertensive crises, asthma exacerbations, and even seizures may be increased during this time of day (Gupta and Shetty 2005; Grassi et al. 2010; Burioka et al. 2010; Pavlova et al. 2012; Kawano et al. 1994). Basic circadian rhythms and subsequent impact in HPA axis and autonomic function are ultimately driven in large part from activity of neurons in the suprachiasmatic nucleus (SCN). In animal experiments, mild stressors and changes in motor activity can influence SCN neuronal activity (Webb et al. 2010; van Oosterhout et al. 2012). Given the potential role for marijuana use in the development of CVS, it is interesting to note that acute administration of cannabinoids can also impact SCN function (Acuna-Goycolea et al. 2010). Thus, we hypothesize that emotional and/or physical stress and exposure to exogenous cannabinoids may all affect SCN neurons to contribute to the development and phenotypic expression of CVS.

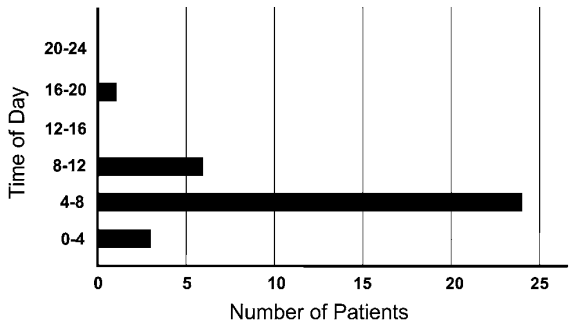

Fig. 1 Emetic episodes in CVS patients display a circadian pattern. The data are derived from 40 consecutive CVS patients seen at the University of Pittsburgh Medical Center. Six patients described random onset of attacks without distinct temporal patterns and are excluded from the graph

CVS and autonomic function

Several of the clinical associations and manifestations of CVS implicate an essential role for aberrant sympathetic nervous system activity in disease pathogenesis. As noted above, the circadian pattern of early morning hour attacks suggests an important role for increased sympathetic tone. Potential triggers for emetic episodes in CVS include prolonged fasting, acute stress, and sleep deprivation (Abell et al. 2008; Hejazi and McCallum 2011; Fleisher et al. 2005; Zhong et al. 2005), all stimuli that drive increased sympathetic activity. Furthermore, CVS attacks often are accompanied by significant sweating, hot flashes, trembling, tachycardia, and elevated blood pressure which in many ways are similar to patterns of generalized sympathetic activation seen in panic attacks (Fleisher et al. 2005). Indeed, several clinical studies have demonstrated a high prevalence of dysautonomia at baseline (between attacks) in both adult and pediatric patients with CVS. Exaggerated heart rate responses to orthostatic challenges are most

commonly observed, which suggest changes in sympathetic efferent pathways (Hejazi and McCallum 2011; Venkatesan et al. 2010; Rashed et al. 1999; Chelimsky et al. 2009; Chelimsky and Chelimsky 2007). These findings are consistent with spectral analysis of heart rate variability and electrogastrograms of CVS patients, which demonstrate changes consistent with enhanced sympathetic drive to the heart and stomach (To et al. 1999; Chong 1999; Namin et al. 2007). Thus, both acute and chronic increases in sympathetic nervous activity may play an important role in the development of CVS.

Central nervous system regulation of autonomic function: allostasis

The traditional view of autonomic control is based on the concept of homeostasis, in which all physiologic parameters are constantly adjusted to meet a defined "set-point." In this model, autonomic nerves are required to fine-tune these physiologic parameters based on negative feedback loops driven by information from sensors located in the periphery. Despite its influence on science and medicine for more than 100 years, the homeostatic model is fundamentally incomplete. It cannot account for anticipatory, feed-forward adjustments in autonomic function that are tuned to match physiologic demands accompanying changes in behavior state (i.e., exercise, or eating) (Sterling 2012). It also cannot account for patterns of associative learning in which physiological responses are linked to stimuli independent of information from autonomic sensory structures (i.e., Pavlovian conditioning). Finally, homeostasis cannot fully explain autonomic changes that accompany purely cognitive and emotional events. A more comprehensive conceptual framework for autonomic control that accounts for these observations is referred to as allostasis (Sterling 2012).

Allostatic regulation requires "central commands" that orchestrate changes in autonomic and motor activity. These central commands may ultimately derive from the cerebral cortex and a network of central nuclei essential for autonomic regulation [the "central autonomic network" (CAN)]. Within the framework of allostatic regulation, cognitive events, anticipation of behavioral changes and physiological needs, and learned associations all shape patterns of autonomic control through changes in neural activity within the CAN. Sleep deprivation, mood disorders, chronic stress, and a history of early adverse life events may lead to disruption of allostatic regulation via maladaptive neural plasticity within various nodes of the CAN. Such maladaptive neural plasticity could then chronically drive abnormal patterns of autonomic and neuroendocrine activity [i.e., "allostatic load" (McEwen and Gianaros 2011; Juster et al. 2010)].

The fact that vomiting and retching during CVS attacks primarily occur when the stomach is completely emptied implies that feed-forward allostatic mechanisms, rather than feedback purely from the periphery, primarily drive CVS attacks. Thus, while ideal allostatic regulation meets upcoming physiological needs, disordered allostatic regulation in CVS patients could result in a decreased threshold to engage vomiting and retching behaviors, independent of physiological need or peripheral input. We propose that this disordered regulation is due to altered plasticity in the central neural circuits that influence autonomic and motor outflow. This neural system could develop abnormally to become broadly activated with low threshold by a variety of mental and/or physiological stimuli. CVS attacks may be characterized by an increased frequency of vomiting and retching compared that seen strictly in response to peripheral factors (i.e., viral gastroenteritis or gastric mucosal irritants). This observation may be analogous to anticipatory patterns of rapid breathing in patients with panic attacks (Blechert et al. 2013). The prediction from this model would be that any factor that acutely relieves stress or anxiety in CVS patients could ameliorate centrally driven patterns of vomiting. For example, it is possible that the therapeutic effect of hot showers during CVS attacks is mediated by mental relaxation, which would be predicted to disengage neural activity in CAN structures important for maintaining the vomiting attack.

This allostasis model could also explain why early adverse life events, chronic stress, sleep deprivation, and mood disorders are associated with autonomic dysfunction observed in patients with CVS and other functional disorders, cardiovascular diseases, and migraines (Fleisher et al. 1997; Van Oudenhove et al. 2008; Drossman 1999; Videlock et al. 2009; Bradford et al. 2012; Berman et al. 2012; Dimsdale 2008; Holm et al. 1997; Borsook et al. 2012;, Meerlo et al. 2008; Chandola et al. 2010; Gori et al. 2005). Thus, unlike in the traditional view of homeostasis which emphasizes peripheral mechanisms of disease, models based on disordered allostasis emphasize brain-driven autonomic dysfunction. Therefore, the brain should be considered the primary target for medical interventions for CVS patients. The important prediction of the model is that cognitive and behavioral interventions may be just as important as pharmacologic interventions in the management of CVS.

Toward a neurobiological model of CVS

As noted above, disordered allostasis and chronic allostatic load provide a model by which sleep deprivation, chronic stress, adverse early life events, and mood disorders may influence the function of the CAN to cause autonomic dysfunction. Chronic allostatic load seen in chronic stress may

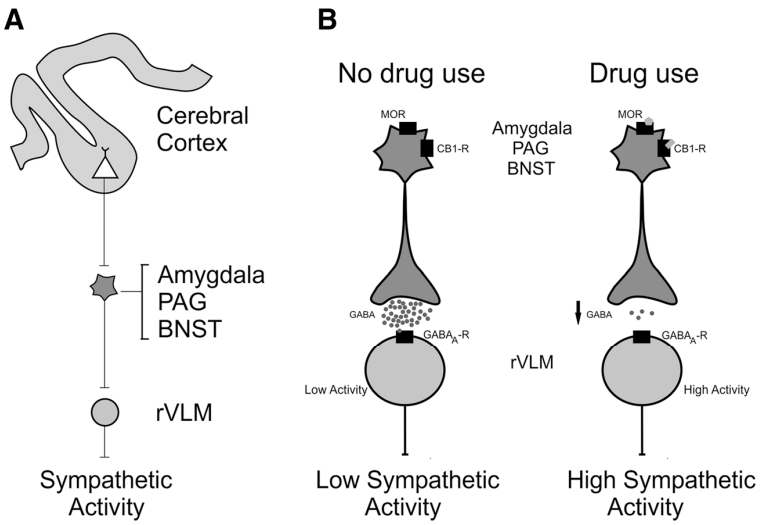

Fig. 2 Schematic diagram showing part of the central autonomic network (**a**) and the impact of cannabis and opiate use on the regulation of sympathetic neural activity (**b**). *BNST* bed nucleus of the stria terminalis, *CB1-R* endocannabinoid-1 receptor, *GABAA-R* GABAA receptor, *MOR* mu-opioid receptor, *PAG* periaqueductal gray, *RVLM* rostral ventrolateral medulla

also be associated with altered neuroendocrine, metabolic, and immune function (Juster et al. 2010, 2011), particularly in relation to circadian patterns and responses evoked by mental events. These functional changes can be captured in a comprehensive panel of biomarkers which interrogate these factors [i.e., the allostatic load (AL) index] (Juster et al 2010, 2011). The primary predication of the allostasis hypothesis for adult CVS is that similar mechanisms play a role in disease pathogenesis. If so, then these same measures of allostatic load could be used as biomarkers for CVS and as outcome measures of therapeutic interventions in CVS patients.

But can allostasis explain some of the unique features of adult CVS, such as the particular association with chronic marijuana and opiate use? Interestingly, cannabinoid use is independently associated with increases in sympathetic outflow (Benowitz et al. 1979; Schmid et al. 2010), as is the chronic exposure to opiates (Napier et al. 1998). These observations imply a specific effect of these compounds on autonomic regulation. Conversely, abrupt cessation of cannabinoids, benzodiazepines, and especially opioids are well known to trigger withdrawal symptoms characterized by autonomic manifestations including severe hypertension, and prominent gastrointestinal complaints with nausea, vomiting, and abdominal pain—all symptoms that significantly overlap with those of CVS (Copersino et al. 2010; Levin et al. 2010; McDonald et al. 1999; Armstrong et al. 2003; Buajordet et al. 2004). The neuroanatomical organization of the CAN provides potentially important mechanistic insight in this context. The CAN is a network of cortical and subcortical neurons that ultimately regulate the neural activity of parasympathetic and sympathetic pre-ganglionic neurons. Some of the key subcortical sites in the CAN, such as the amygdala, periaqueductal gray (PAG), and bed nucleus of the stria terminalis (BNST), receive cortical inputs and send dense projections to sites in the nucleus tractus solitarius (NTS) and rostral ventral medulla (rVLM; Fig. 2a). These descending projections, many of which involve GABAergic inhibitory neurons, form an important neural substrate that can tonically influence sympathetic activity (Price and Amaral, 1981; van der Kooy et al. 1984; Cameron et al. 1995; Bowman et al. 2013). Further, the NTS forms a component of the brainstem "vomiting center." Thus, neural inputs to both the rVLM and NTS could broadly impact autonomic function and vomiting. It is intriguing that both endocannabinoid receptors (CB1) and mu-opiate receptors (MOR) are expressed on GABAergic neurons within several of these CAN nuclei. Thus, cannabinoids and opiates may have a broad influence on autonomic activity by inhibiting the activity of these descending GABAergic neurons (Yan et al. 2013; Beckerman et al. 2013; Wilson-Poe et al. 2012; Puente et al. 2010). Because this descending GABAergic input ultimately inhibits activity of rVLM neurons (Tjen-A-Looi et al. 2009), chronic cannabinoid and opiate inhibition of this input would be expected to increase the activity of target rVLM neurons (Fig. 2b). Decreased GABAergic input to the NTS could lower the threshold to vomit.

These findings may explain the apparent paradox that chronic exposure to apparently sedating agents (cannabinoids and opiates) may result in autonomic arousal (increased sympathetic activity) via impaired GABAA inhibition in brainstem sites critical for autonomic regulation (Fig. 2b). The model also proposes that benzodiazepines, which selectively bind to GABAA receptors, are effective therapies in aborting CVS attacks due in part to direct inhibition of rVLM neurons and NTS neurons whose activity drive sympathetic discharge and vomiting, respectively. Such a model could account for some unique

features of adult forms of CVS. For example, despite their acute antiemetic effects, cannabinoids contribute to the pathogenesis of CVS in up to 50 % of adults with this disorder (Allen et al. 2004; Choung et al. 2012; Donnino et al. 2011). Due to their analgesic and sedating effects, opioids are commonly used to abort acute emetic episodes, but their chronic use has been implicated in the development of coalescent and/or refractory CVS (Abell et al. 2008; Hejazi et al. 2010; Hejazi and McCallum 2011). These observations may reflect the fact that chronic exposure to these drugs can ultimately increase basal sympathetic activity and sensitize the central neural systems important for vomiting, thus predisposing to more frequent CVS attacks.

An alternative framework for CVS

CVS should be viewed as an allostatic disorder with a predominant gastrointestinal phenotype that results from abnormal central regulation of autonomic function. Chronic allostatic load, driven by exposure to adverse early life events, chronic stress, sleep deprivation, mood disorders, and chronic cannabis and/or opiate use, may lead to maladaptive plasticity in central neural structures important for optimal HPA axis and autonomic regulation (McEwen 2012; Danese and McEwen 2012). These neuroplastic changes likely lead to chronically increased sympathetic activity or responsivity, and thus decrease the threshold to develop the marked sympathetic discharges that characterize CVS attacks. Disordered neuroplasticity in the neural circuits that regulate vomiting may act to sensitize the system to factors normally not sufficient to cause emesis. Consistent with this model, sedatives rather than antiemetics are typically needed to terminate the emetic phase of CVS attacks. This model may also explain the apparent paradox that acute interventions with cannabinoids and opiates may help abort CVS attacks (via neural pathways involved in sensations of nausea and pain), but that chronic exposure to these agents may contribute to increased sympathetic activity and sensitivity to develop emesis that contributes to a poor disease trajectory characterized by ever more frequent attacks.

The proposed conceptual model comes with several potential implications. First, biomarkers have been proposed to assess differences in allostatic load between populations of adults (Juster et al. 2010, 2011). While not specific for CVS, these tests could assess the validity of the proposed framework that CVS is characterized by allostatic load, as measured by altered circadian patterns and stress-induced changes in autonomic, neuroendocrine, and even metabolic and immune factors. Secondly, initial experiments suggest that antidepressants may act in part by increasing neurogenesis within brain regions of adults that are affected by allostatic load (such as the hippocampus) (Taupin 2006; Diniz et al. 2013; Lisowski et al. 2013). This observation may provide further mechanistic explanation for the therapeutic effect of tricyclic antidepressants as prophylactic agents in CVS patients (Hejazi et al. 2010; Prakash and Clouse 1999). Finally, if CVS is mediated by maladaptive plasticity within the central neural network that regulates autonomic function and vomiting, then therapeutic strategies that engage neuroplasticity could potentially reverse the dysfunction in these neural circuits. Thus, it is likely that cognitive behavioral therapy, stress management ("mind–body") interventions, regular exercise, improved sleep, and avoidance of cannabis and opiate use could have positive influences on the clinical course for patients with CVS. These simple and risk-free interventions, in addition to standard pharmacological approaches, should form the cornerstone of management of adult CVS patients.

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