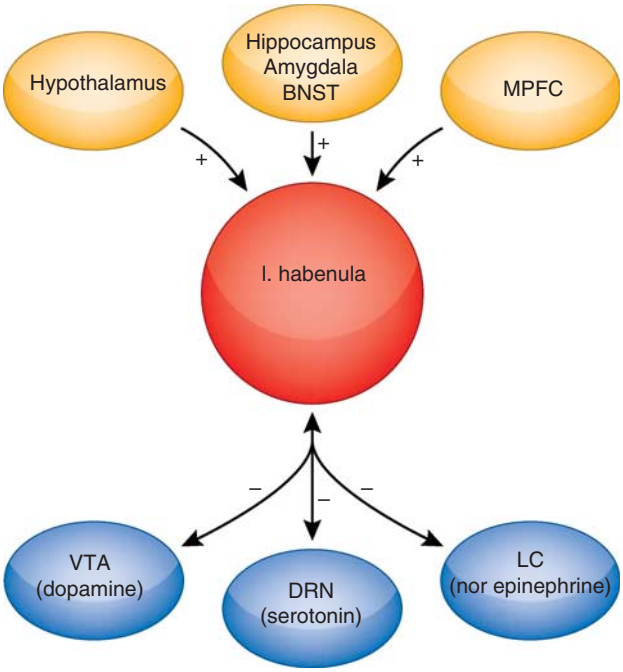

Figure 1. Principal inputs and outputs of the l. habenula crossroad in the circuit mediating depression.

1997), which feed back further increasing l. habenular activity. The l. habenula receives strong inputs from both the limbic system, through the basal nucleus of the stria terminalis, which carries information from the amygdala related to anxiety and from the mPFC, which may be related to the cognitive aspects of depression (Li *et al*, 2011) and sends its output to the midbrain aminergic nuclei.

Because it appears the l. habenula functions as a control center that regulates the reward center, modulating cortical, and limbic areas, it might be an ideal target for deep brain stimulation in cases of intractable, treatment-resistant depression. This has been utilized for a single patient and resulted in a total remission (Sartorius *et al*, 2010) that rapidly reversed when the stimulator was disconnected and returned after the stimulation was reinstated. The time course for the remission after initiating stimulation is slow, weeks for full remission, suggesting that structural changes underlie this effect. High frequency and high voltage stimulation inhibit l. habenula slice activity (Li *et al*, 2011) supporting the concept that inhibition occurs through DBS and this may well be the mechanism through which DBS acts (Figure 1).

Glutaminergic over activity in the mPFC drives the over activation of the l. habenula (Li *et al*, 2011) in the chronically helpless line of animals, allowing the development of a depressive state mediated, in part, by altered monoaminergic function. Excess cortical glutamate in the mPFC, resulting from stress, leads to decreases in cortical synapses, a well-documented effect that can be reversed by ketamine. Chronically helpless animals show a 40% loss of synapses, suggesting enhanced stress sensitivity. The excess glutamate appears to be sustained through decreased astrocytic glutamate transporter in these learned helpless animals (Zink *et al*, 2010), suggesting that astrocytic dysfunction may be a fundamental step in the pathophysiology of depression.

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DISCLOSURE

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Update on Corticotropin-Releasing Factor Pharmacotherapy for Psychiatric Disorders: A Revisionist View

The identification of corticotropin-releasing factor (CRF) in 1981 was followed by the discovery of three CRF paralogs (urocortins 1, 2, and 3) and two CRF/urocortin receptors (CRF_1, CRF_2; Bale and Vale, 2004). Because preclinical studies showed that CRF_1 receptors mediate endocrine, behavioral, and autonomic responses to stress, the pharmaceutical industry developed blood–brain barrier-penetrating CRF_1 receptor antagonists. We and others previously surveyed the pharmacology of non-peptide CRF_1 receptor antagonists and the therapeutic rationale of CRF_1 antagonists for major depression, anxiety disorders, and addiction (see Koob and Zorrilla, 2010; Zorrilla and Koob, 2010, for references). Yet, CRF_1 antagonists have still not yielded positive Phase III clinical trials, prompting the current revisionist view of the

neurotherapeutic potential of CRF_1 antagonists. Our hypothesis is that CRF antagonists may be valuable in specific psychiatric disorders in which stress is a dynamic rather than chronic condition. More explicitly, we suggest that CRF_1 antagonists in psychiatry may particularly be useful in post-traumatic stress disorder (PTSD), panic disorder, and addiction.

Non-peptide CRF_1 antagonists consistently produce anxiolytic-like effects in certain animal models, such as conditioned freezing, defensive burying, acoustic startle responding, the open field, the elevated plus maze, the light–dark box, the defensive withdrawal test, and the social interaction test. A CRF_1 antagonist (R317573/JNJ19567470/CRA5626) also recently showed activity in rodent (Shekhar *et al*, 2011) and human (Bailey *et al*, 2011) panic models. These models reflect a dynamic, active response to an acute stressor and, from a face validity perspective, may reflect more the symptoms of specific subtypes of anxiety disorders rather than of generalized anxiety disorder. Indeed, CRF_1 antagonists exhibited weak activity in punished drinking and punished crossing conflict models, unlike γ-aminobutyric acid anxiolytics. Despite initial positive results, small-molecule CRF_1 antagonists have not consistently shown efficacy in animal models of antidepressant activity (Zorrilla and Koob, 2010).

CRF_1 antagonists also reduce the activation of brain stress systems in models of addiction, supporting the therapeutic potential of CRF_1 antagonists for drug dependence. Hypothalamic-pituitary adrenl-axis and extrahypothalamic CRF systems are activated during acute withdrawal from all major substances of abuse in animals. CRF antagonists blocked anxiogenic-like responses to withdrawal from cocaine, alcohol, nicotine, cannabinoids, and palatable food and blocked the development of or reduced already escalated drug self-administration in addiction models (for details and references, see Koob and Zorrilla, 2010; Boyson *et al*, 2011). CRF_1 antagonists also blocked stress-induced reinstatement of heroin-, cocaine-, nicotine-, alcohol-, and palatable food-seeking behavior and stress-induced reactivation of conditioned place preference for opioids and cocaine (Koob and Zorrilla, 2010).

No CRF_1 antagonist has successfully completed a Phase III trial. R121919 and PF-00572778 were abandoned due to liver enzyme elevations (NCT00580190). The development of ONO-2333 Ms (NCT00514865) and CP-316,311 were halted because of negative efficacy in double-blind, placebo-controlled trials for major depression (Zorrilla and Koob, 2010). Verucerfont (GSK561679) also lacked efficacy in a major depression trial (Protocol # CRS106139). Pexacerfont (BMS-562086) was ineffective against generalized anxiety disorder (Coric *et al*, 2010). Trials of verucerfont and emicerfont for social anxiety disorder have been completed with undisclosed results (NCT00555139). Relevant to the hypothesis proposed herein, Glaxo SmithKline and NIH are currently evaluating verucerfont against startle in healthy women (NCT01059227), in women with PTSD (NCT01018992), and against stress-induced alcohol craving in anxious women (NCT 01187511). A trial for pexacerfont has likewise been initiated in anxious alcoholics by Bristol Myers Squibb and NIAAA (NCT01227980). Several other candidates are earlier in the pipeline, or their status has not been publicly updated by the pharmaceutical industry (eg, GSK586529 [NCT01059227], SSR125543 [NCT01034995], antalarmin). Should results from these trials concur that CRF_1 antagonists are ineffective for chronic anxiety and depression, a re-evaluation should be considered with emphasis on certain anxiety disorders, such as PTSD and possibly panic disorder, and on addiction disorders.

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DISCLOSURE

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Update on Omega-3 Polyunsaturated Fatty Acids in Early-Stage Psychotic Disorders

Polyunsaturated fatty acids (PUFAs) are the major constituents of cell membrane phospholipids. As such, they have