tobacco dependence and smoking-associated diseases (Bierut *et al*, 2008; Thorgeirsson *et al*, 2008). In particular, a polymorphism in *CHRNA5* (rs16969968) that results in an aspartic acid to asparagine substitution at amino-acid reside 398 (D398N) more than doubles the risk of tobacco dependence in those carrying two copies of the risk allele. Little was known about how nAChRs-containing α5, α3, and/or β4 subunits may contribute to tobacco dependence. However, recent findings suggest that nAChRs containing these subunits play a key role in regulating nicotine reinforcement.

The α3, α5, and β4 nAChR subunits are densely expressed in the medial habenula (MHb) and its major site of projection, the interpeduncular nucleus (IPN) (Salas *et al*, 2009). Our laboratory has recently shown that mice with null mutation in the α5 nAChR subunit gene intravenously self-administer significantly greater quantities of nicotine than their wild-type counterparts, particularly when higher unit doses of the drug are available for consumption (Fowler *et al*, 2011). This enhanced intake in the mutant mice was ameliorated by virus-mediated re-expression of α5 nAChR subunits in the MHb–IPN tract. In addition, we found that IPN neurons were insensitive to nicotine in the mutant mice, reflected in greatly diminished induction of Fos immunoreactivity in response to nicotine injections. Moreover, lidocaine-induced inactivation of the MHb or IPN increased nicotine self-administration in rats, particularly at higher units doses of the drug. Finally, virus-mediated knockdown of α5 nAChR subunits in the MHb–IPN tract did not alter the reward-enhancing properties of lower nicotine doses, but greatly attenuated the reward-inhibiting (ie, aversive) effects of higher nicotine doses in rats (Fowler *et al*, 2011). In keeping with these findings, overexpression of β4 nAChR subunits in the MHb–IPN tract enhanced aversion to nicotine and reduced consumption of the drug in mice (Frahm *et al*, 2011). Moreover, virus-mediated expression in the MHb of a major risk allele of the α5 subunit gene (D398N allele), which decreases the function of α5-containing nAChRs incorporating this risk allele and increases vulnerability to tobacco dependence in humans, reduced aversion to nicotine and enhanced nicotine intake in the β4 subunit-overexpressing mice (Frahm *et al*, 2011). Hence, nAChRs-containing α5 and/or β4 subunits regulate the activation of the MHb–IPN tract in response to nicotine, which signals aversion to the drug. Deficient nAChR signaling in the MHb–IPN tract, which likely occurs in humans carrying risk alleles in the *CHRNA3-CHRNA5-CHRNB4* gene cluster, reduces nicotine aversion and results in greater consumption of the drug. As such, these finding reveal fundamental new insights into the mechanisms of nicotine reinforcement and the neurocircuitry of tobacco dependence.

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DISCLOSURE

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Circuits, Cells, and Synapses: Toward a New Target for Deep Brain Stimulation in Depression

Understanding the pathophysiology of depression requires knowledge of the anatomical pathways that malfunction in this disorder. The anatomy of depression involves limbic and hypothalamic activation mediating stress and anxiety. These interact with cortical areas, primarily the medial prefrontal cortex (mPFC), which appears to mediate the cognitive aspects of depression. The mPFC in turn innervates the thalamus and lateral habenula (l. habenula). The anatomy of melancholia has recently been advanced through an understanding of the role of the l. habenula and incorporation of this structure between the cortical and limbic inputs and the monoaminergic nuclei. The l. habenula controls the midbrain monoaminergic nuclei, whose output pathways interact with each other, as well as providing strong modulatory control of limbic and cortical areas. Recently understanding of how the dopamine system is regulated by the l. habenula in normal (Matsumoto and Hikosaka, 2009) and affectively disturbed states (Li *et al*, 2011) has been investigated. Over activity in the l. habenula is seen in both the learned helplessness model (Li *et al*, 2011) and in patients who express depressive symptoms following tryptophan depletion (Roiser *et al*, 2009). This over activity causes decreased dopaminergic stimulation, suppressing reward signals (Matsumoto and Hikosaka, 2009). It also depresses 5HT signals (Wang and Aghajanian,

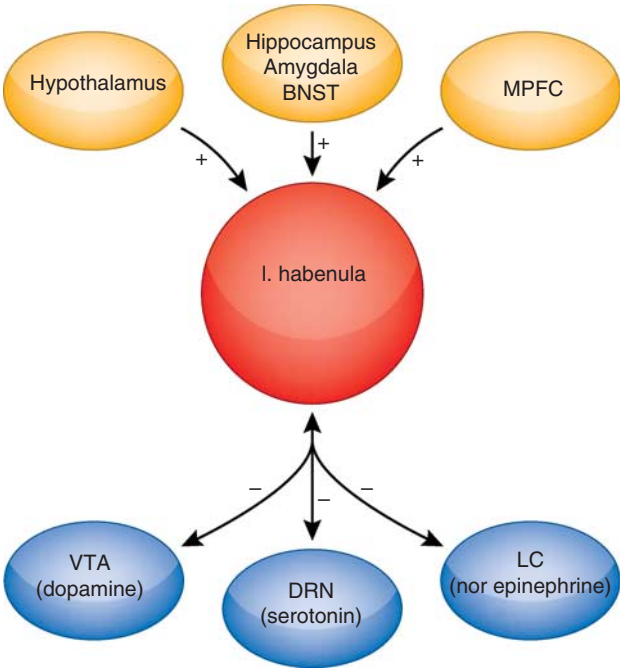

Figure 1. Principal inputs and outputs of the l. habenula crossroad in the circuit mediating depression.

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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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