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Chronic vagus nerve stimulation for treatment-resistant depression decreases resting ventromedial prefrontal glucose metabolism

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ABSTRACT

Vagus nerve stimulation (VNS) is used as an adjunctive therapy for treatment-resistant depression (TRD). Its mechanism of action is not fully understood. Longitudinal measurement of changes in brain metabolism associated with VNS can provide insights into this new treatment modality. Eight severely depressed outpatients who were highly treatment-resistant underwent electrical stimulation of the left vagus nerve for approximately one year. The main outcome measures were resting regional brain glucose uptake measured with positron emission tomography (PET) and the 24-item Hamilton Depression Scale. The most significant and extensive change over one year of chronic VNS localized to the ventromedial prefrontal cortex extending from the subgenual cingulate to the frontal pole. This region continued to decline in metabolism even toward the end of the study. Clinically, this cohort showed a trend for improvement. No correlations surfaced between change in glucose uptake and depression scores. However, the sample size was small; none remitted; and the range of depression scores was limited. Chronic VNS as adjunctive therapy in patients with severe TRD produces protracted and robust declines in resting brain activity within the ventromedial prefrontal cortex, a network with dense connectivity to the amygdala and structures monitoring the internal milieu.

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Introduction

Depression is a clinical syndrome defined as a decline in function associated with at least two weeks of sustained depressed mood or loss of interest or pleasure (First et al., 2004). Criteria include persistent evidence of at least five of a number of symptoms including diminished interest, feelings of sadness, and physical effects. These symptoms must not result from a medical condition (e.g., hypothyroidism, anemia); or a medication (e.g., reserpine, interferon); or uncomplicated bereavement.

Different patients show considerable variability in response to treatments for depression. Depression is frequently considered to have remitted or responded fully when the level of symptoms has decreased to a low level, a threshold usually defined a priori. Patients are considered to have responded to treatment, or improved clinically, when there is 50% or greater reduction in symptoms as assessed with a depression rating scale.

The definition of treatment-resistant depression (TRD) varies across studies depending on the number of failed medication trials, psychotherapies, or electroconvulsive treatments. Conventional antidepressant therapies are unsuccessful in achieving a full response (i.e., remission) in about 36% of patients (Fava and Davidson, 1996). However, TRD should be distinguished from treatment-nonresponse. Treatment-nonresponse is simply a failed adequate trial of a treatment, whereby another drug or modality could readily induce a response. On the other hand, TRD is a failure to respond to multiple treatment modalities and drugs despite adequate trials, i.e., appropriate doses and length of treatment. Treatment-intolerance occurs when the patient

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cannot conclude a trial because of side effects. Non-compliance with taking the prescribed medication can often appear as treatment-nonresponse and requires checking serum drug levels to ensure that the medication was taken or that the patient did not have extremely rapid metabolism of the drug because of their P450 genotype.

TRD has high morbidity and mortality and consumes a major share of both direct and indirect healthcare costs. When TRD patients are tracked over two years with treatment according to the current standard of care (i.e., "treatment as usual" such as medications with augmentation strategies, psychotherapy, electroconvulsive therapy), over 65% do not respond at anytime, while 81% do not remit (Dunner et al, 2006). These figures are particularly worrisome when considering that men with severe impairment from depression have a suicide rate of approximately 4.9% (Hirschfeld, 2000). Overall, depression is the leading cause of suicide.

VNS is an adjunctive therapy for TRD in adults. The treatment employs a device similar to an externally programmable pacemaker that sends electrical impulses up the left vagus nerve at the neck to the nucleus of the solitary tract (NTS) in the dorsal medulla. The vagus nerve, through the NTS, provides widespread neuromodulatory control of subcortical and cortical structures (George et al., 2005; Rush et al., 2005a; Henry, 2002).

The NTS projects directly to the amygdala (Rogers and Fryman, 1988) which plays an essential role in affective processing, particularly through interactions with the ventromedial prefrontal cortex (VMPFC). Functionally, amygdala activity tracks with activity in the VMPFC during tasks using interroceptive and exteroceptive feedback (Hurliman et al., 2005); during the resting default-mode of brain function (Kilpatrick et al., 2006); during script-driven imagery in remitted PTSD patients (unpublished observation); and during treatments for depression (Pardo et al., 2007b). However, negative correlations can occur depending on the task and on the direction of influence between the amygdala and VMPFC (Ochsner et al., 2004; Stein et al., 2007; van Reekum et al., 2007). The NTS also projects directly to the locus coeruleus (van Bockstaele et al., 1999), the principal source of cortical noradrenergic innervation. It indirectly projects to raphé nuclei that provide widespread cortical serotonergic innervation. Furthermore, the NTS projects densely to the parabrachial nucleus (PBN) that receives afferents from the amygdala, hypothalamus, and cortex (insula, infralimbic and lateral prefrontal regions; Moga et al., 1990).

The parabrachial nucleus is a complex, heterogeneous, autonomic integration network, particularly involved in processing visceral afferent information. It projects to the hypothalamus, periaqueductal grey, amygdala, thalamus (including intralaminar neurons which in turn project densely to the VMPFC; Hsu and Price, 2007), bed nucleus of the stria terminalis, NTS, and zona incerta (Bianchi et al., 1998). The PBN, through its connections to the hypothalamus, innervates orexin neurons that project throughout the cortex and brain stem (Mieda and Yanagisawa, 2002). In particular, orexin neurons in the lateral hypothalamus, through actions upon the ventral tegmental area (and plausibly other sites with orexinergic innervation such as the extended amygdala and the mesocortical limbic system), have been implicated in reward processing: reward-seeking, food and drug preferences, drug relapse, and addiction (Harris and Aston-Jones, 2006; Harris et al., 2007). Considerable evidence indicates that depression involves dysfunctional reward processing which may result from dopaminergic deficits (Dunlop and Nemeroff, 2007).

Consistent with this anatomy, chronic VNS has been shown to increase locus ceoeruleus and dorsal raphé firing in animals (Groves et al., 2005; Dorr and Debonnel, 2006). Elements of the circuitry reviewed above have been implicated during chronic VNS in diverse effects. For example, VNS over 2 years induced weight loss in TRD patients that was linearly dependent on the initial weight and was not correlated with changes in depression symptoms (Pardo et al., 2007a). VNS for epilepsy improved mood irrespective of the degree of seizure control (Elger et al., 2000; Harden et al., 2000). Also, chronic VNS can worsen respiration during sleep (Marzec et al., 2003).

Nevertheless, VNS's mode of action remains incompletely understood, especially because the antidepressant effects continue to accrue over at least one year, a phenomenon not seen with other traditional antidepressant treatments (Rush et al., 2005b; Nahas et al., 2005; Sackeim et al., 2007). A recent publication has reviewed plausible mechanisms of VNS in TRD (Nemeroff et al., 2006).

Functional neuroimaging provides insights into the mode of action of treatments for depression, including some changes that correlate with clinical improvement (Drevets et al., 2002; Drevets 2003; Seminowicz et al., 2004; Goldapple et al., 2004). However, few studies specifically target TRD (Pardo et al., 2007b). Some argue that evidence may be insufficient to consider TRD as a specific subtype of depression (Fagiolini and Kupfer, 2003). To our knowledge, there is no PET study identifying the resting metabolic abnormalities (i.e., biomarkers) associated with unmedicated TRD. Some studies have examined metabolic correlates of those without TRD for whom a particular treatment was unsuccessful (e.g., Little et al., 2005) or of those with TRD during experimental treatments such as deep brain stimulation (e.g., Mayberg et al., 2005; Schlaepfer et al., 2007). Recently, several groups have reported on neuroimaging studies of TRD patients under treatment with VNS.

Zobel et al. (2005) measured blood flow using SPECT with ^{99m}Tc-hexamethyl-propylene amine oxime immediately after a sequence of VNS stimulations in 12 TRD patients. All patients were taking mirtazipine or citalopram for at least 6 weeks before entering into the imaging study. The patients were studied once before implantation and after 4 weeks of VNS treatment while resting with eyes closed in the supine state. The tracer was injected about 20–30 min immediately following a stimulation sequence. They reported a decline of flow in an extensive network including amygdala; hippocampus; thalamus; putamen; caudate; brainstem; subgenual, ventral anterior, posterior, and dorsal anterior cingulate cortex; and orbital, ventrolateral, and dorsolateral prefrontal cortex. The only focus of increased flow arose in the middle frontal gyrus.

Subsequently, Conway et al. (2006) used ^{15}O-water PET to study four TRD women treated with VNS for 3 weeks. The patients were on complex regimens of psychoactive medications including antidepressants, atypical neuroleptics, hormones, benzodiazepines, and dopaminergic agents. The medications were not changed during the 3 week trial. All were studied in the supine state. Before imaging, the device was turned off for 30 min. The patients were scanned during the four subsequent blood flow scans in an "off-on–off-on" design. During the "on" scans, 90 s of VNS stimulation occurred immediately before tracer injection. During active stimulation, blood flow increased in the orbitofrontal cortex (BA 11, 47); dorsal