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Review

The antidepressant mechanism of action of vagus nerve stimulation: Evidence from preclinical studies

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ABSTRACT

Vagus nerve stimulation (VNS) is a proposed neuromodulatory treatment for medically refractory major depression. Although VNS is already used in clinical practice, the underlying mechanism of action remains unknown. The present review provides an overview of the preclinical VNS studies in view of two major hypotheses in depression research: the monoaminergic and the neural plasticity hypothesis of depression.

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1. Introduction

The World Health Organization estimates that by 2020, major depressive disorders (MDD) will become the second largest cause of global disease problems in the world, only behind ischemic heart disease (Murray and Lopez, 2001). The lifetime prevalence for MDD is reported to be as high as 17% and the 12-month prevalence is estimated to be 4–8% (Alonso et al., 2004; Kessler, 2003). Despite the availability of a variety of antidepressant agents and improved tolerance of new antidepressant medications, up to 20% of patients fail to respond adequately to standard antidepressant treatments (Berlim et al., 2007). This relative lack of efficacy significantly interferes with the psychosocial functioning and quality of life of refractory patients. In addition, it is well recognized that the failure to reach full clinical remission after antidepressant treatment involves a high risk of relapse and recurrence in patients suffering from MDD (Mendlewicz, 2008). The lack of success with current

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pharmacological interventions highlights the importance of optimizing non-pharmacological treatments for refractory patients.

Among other neuromodulation modalities for refractory MDD, vagus nerve stimulation (VNS) is the electrical stimulation of the left vagus nerve at the cervical level, by means of implanted electrodes and a programmable pulse generator. It is also a well-established, safe and effective add-on therapy for refractory epilepsy (Ben-Menachem, 2002). The initial rationale for using VNS for the treatment of refractory depression, resulted from mood improvements in epilepsy patients treated with VNS, irrespective of the presence or absence of beneficial effects on seizure frequency (Harden, 2002; Elger et al., 2000; Klinkenberg et al., 2012). A recent study from our laboratory confirmed the antidepressant effect of VNS in the kainic acid rat model for temporal lobe epilepsy and comorbid depression (Grimonprez et al., 2014). Of interest, MDDs are the most common type of psychiatric comorbidity in patients suffering from refractory epilepsy (Kanner and Balabanov, 2002; Kanner, 2003, 2012).

The therapeutic effect of chronic VNS for treatment resistant depression has been assessed in several clinical studies (Rush et al., 2005a, 2005b, 2000; Sackeim et al., 2001; Nahas et al., 2005; Schlaepfer et al., 2008; Bajbouj et al., 2010; George et al., 2005; Marangell et al., 2002; Cristancho et al., 2011; Nierenberg et al., 2008; Aaronson et al., 2013; Muller et al., 2013; Conway et al., 2012, 2013). VNS demonstrated steadily increasing improvement of depressive symptoms with full benefit after 6–12 months, sustained for up to 2 years. These studies reported response rates of 30–40% and remission rates of 15–17% after 3–24 months of treatment (Holtzheimer and Mayberg, 2012). Furthermore, a recent meta-analysis comparing 'VNS with treatment as usual' ($n = 1035$) versus 'treatment as usual alone' ($n = 425$), revealed that 'VNS with treatment as usual' results in greater response and remission rates that are more likely to persist in the long-term (Berry et al., 2013).

Although VNS has proven to be effective in reducing depressive symptoms in several clinical trials, the optimal stimulation parameters and the mechanism of action remain elusive. A retrospective analysis by Muller et al. (2013) revealed that VNS at low-strength/high-frequency stimulation parameters is effective in reducing depressive symptoms, while VNS at high-strength/low-frequency stimulation parameters is not. Furthermore, a randomized, double-blind, multicenter VNS dosing study by Aaronson et al. compared the safety and effectiveness of different stimulation parameters, i.e. low, medium or high dose VNS. The results from the study showed that VNS induces significant, durable antidepressant effects, irrespective of the applied stimulation parameters. However, higher electrical dose parameters were shown to be associated with response durability (Aaronson et al., 2013). Concerning the mechanism of action, functional brain imaging studies in humans have demonstrated that VNS causes immediate and longer-term changes in brain regions implicated in neuropsychiatric disorders. The regions affected by VNS include the thalamus, cerebellum, prefrontal cortex, limbic system, hypothalamus and medulla (Conway et al., 2012, 2013; Kosel et al., 2011).

Further unraveling the antidepressant mechanism of action of VNS may support the optimization of stimulation parameters and the identification of biomarkers to predict therapeutic response. The present review discusses the putative antidepressant mechanisms of VNS, in the context of two major hypotheses in depression research: the monoaminergic and the neural plasticity hypothesis of MDD.

2. VNS and the monoaminergic hypothesis of MDD

The last 50 years of depression research have been dominated by the monoaminergic hypothesis. The main assumption in this

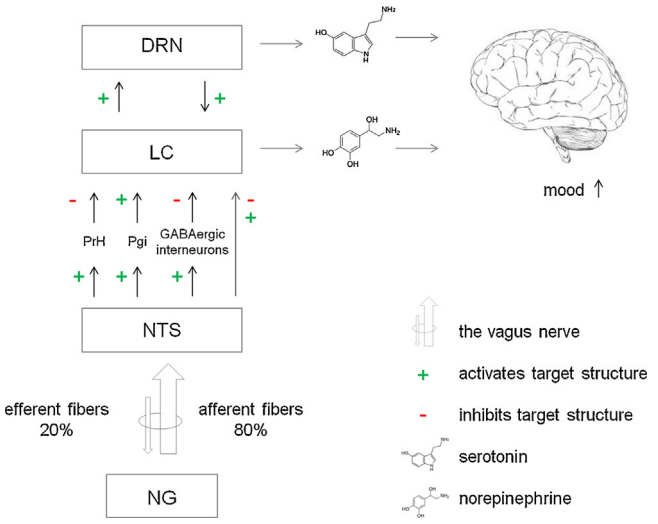

Fig. 1. The afferent projections of the vagus nerve. Nodose ganglion, NG; nucleus tractus solitarius, NTS; locus coeruleus, LC; nucleus prepositus hypoglossi, PrH; nucleus paragigantocellularis, Pgi; dorsal raphe nucleus, DRN.

hypothesis is that depression is caused by an impairment of central monoaminergic functioning. Monoamines are neurotransmitters containing one amino group that is connected to an aromatic ring by a two-carbon chain (Maximino and Herculano, 2010). These neurotransmitters affect a wide range of normal brain functions related to mood control, such as sleep, motivation and hedonic state (Millan, 2004). Decreased activity of the monoamines, due to decreased availability, impaired postsynaptic receptors and/or reduced sub-cellular messenger activity, is a pivotal pathogenic mechanism of depressive disorders and represents the main target for the development of antidepressant therapy (Kanner and Balabanov, 2002; Millan, 2004; Gronli et al., 2005). Almost all currently available antidepressant drugs that reverse depressive symptoms are based on enhancing the monoaminergic neurotransmission, primarily the noradrenergic and/or serotonergic system. Most antidepressant agents increase the concentration of noradrenaline and/or serotonin in the synaptic cleft via (1) reuptake inhibition, (2) antagonism of inhibitory presynaptic autoreceptors or (3) inhibition of monoamine oxidases, which are the enzymes for monoamine degradation (Millan, 2004; Moret and Briley, 2011). Research on the antidepressant actions of drugs has mainly focused on the locus coeruleus (LC) and the dorsal raphe nucleus (DRN) due to their role in noradrenaline and serotonin release, respectively. In the next paragraphs, we will describe how VNS can theoretically enhance the noradrenergic and serotonergic neurotransmission in the brain areas important in mood regulation such as the prefrontal cortex, the amygdala and the hippocampus. This will be based on the neuroanatomical connections from the vagus nerve to the LC and the DRN and on evidence from experimental animal studies.

The vagus nerve is best known for its efferent parasympathetic actions, such as autonomic control and regulation of the heart and the gastrointestinal system (Park et al., 2007). However, the nerve comprises approximately 80% afferent fibers, carrying information from the body to the brain (see Fig. 1, for a detailed review on the anatomy of the vagus nerve, see (Ruffoli et al., 2011)). These fibers have their cell bodies in the nodose ganglion and predominantly project to the nucleus tractus solitarius, an important gateway nucleus for many primary afferents from cardiovascular, respiratory, gastrointestinal and other visceral sensory receptors (Andresen and Kunze, 1994). In turn, the neurons of the nucleus tractus solitarius project to the LC through three disynaptic pathways: (i) GABAergic inhibitory neurons localized in the nucleus prepositus hypoglossi, acting primarily on the $GABA_A$ receptor