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Letter to the Editor

Vagus Nerve Stimulation, Depression, and Inflammation

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Sir

Both acute and long-term studies suggested that vagus nerve stimulation (VNS) is of benefit in the therapy for treatment-resistant depression. VNS therapy acts via innervation of the nucleus tractus solitarius, with secondary projections to limbic and cortical structures that are involved in mood regulation, including brainstem regions that contain serotonergic and noradrenergic perikarya that project to the forebrain. Mechanisms that mediate the beneficial effects of the procedure of stimulation of vagus nerve for treatment of resistant depression remains obscure (Nemeroff *et al*, 2006). I propose that the procedure of stimulation of vagus nerve for treatment of depression works by suppressing the production of proinflammatory cytokines: interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), HMGB1 (high mobility group box 1), and macrophage migration inhibitory factor (MIF) (Bernik *et al*, 2002; Guarini *et al*, 2003).

Proinflammatory cytokines may cause depressive illness. This is based on the observations that: (a) activation of the immune system, and administration of endotoxin (LPS) or IL-1 to experimental animals induces sickness behavior, which resembles depression; (b) activation of the immune system is observed in many depressed patients; (c) depression is more frequent in those with medical disorders associated with immune dysfunction; (d) treatment of patients with cytokines can produce symptoms of depression; (e) chronic treatment with antidepressants inhibits sickness behavior induced by LPS; (f) proinflammatory cytokines activate the hypothalamo–pituitary–adrenocortical axis, which is activated in depressed patients; (g) cytokines activate cerebral noradrenergic systems that is known to occur in depressed patients; and (h) several proinflammatory cytokines activate brain serotonergic systems, which have been implicated in major depressive illness and its treatment (Schiepers *et al*, 2005; O'Brien *et al*, 2004; Dunn *et al*, 2005; Castanon *et al*, 2002; Sluzewska *et al*, 1996; Basterzi *et al*, 2005). These results imply that depression could be a low-grade systemic inflammatory condition.

Central nervous system regulates the production of proinflammatory cytokines: TNF, IL-1, HMGB1, IL-6, and MIF through the efferent vagus nerve (Borovikova *et al*, 2000; Ulloa, 2005). Acetylcholine, the principal vagus neurotransmitter, inhibits the production of proinflammatory cytokines through a mechanism dependent on the α7 nicotinic acetylcholine receptor subunit. Thus, vagus nerve stimulation controls the production of proinflammatory cytokines.

As VNS is of benefit in depression, vagus inhibits the production of proinflammatory cytokines, and patients with depression have elevated plasma and cerebrospinal fluid concentrations of these cytokines (Levine *et al*, 1999; Suarez *et al*, 2003), I propose that the beneficial effect of VNS in depression is owing to its (VNS) inhibitory action on the production of proinflammatory cytokines. This can be verified by estimating plasma levels of various proinflammatory cytokines before and after VNS therapy and response. I also suggest that failure of VNS therapy, in some, could be due to its inability to suppress production of proinflammatory cytokines either because duration and/or strength of VNS is not sufficient. Thus, if this idea is true, correlation of VNS, depression, and plasma and cerebrospinal fluid cytokine profile may in turn be an interesting tool as suitable biomarkers to predict response and adequacy of VNS, and for screening of populations under risk for depression.

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REFERENCES

Basterzi AD, Aydemir C, Kisa C, Aksaray S, Tuzer V, Yazici K *et al* (2005). IL-6 levels decrease with SSRI treatment in patients with major depression. *Hum Psychopharmacol* **20**: 473–476.

Bernik TR, Friedman SG, Ochani M, DiRaimo R, Ulloa L, Yang H *et al* (2002). Pharmacological stimulation of the cholinergic antiinflammatory pathway. *J Exp Med* **195**: 781–788.

Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR *et al* (2000). Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* **405**: 458–462.

Castanon N, Leonard BE, Neveu PJ, Yirmiya R (2002). Effects of antidepressants on cytokine production and actions. *Brain Behav Immun* **16**: 569–574.

Dunn AJ, Swiergiel AH, de Beaurepaire R (2005). Cytokines as mediators of depression: what can we learn from animal studies? *Neurosci Biobehav Rev* **29**: 891–909.

Guarini S, Altavilla D, Giuliani D, Bigiani A, Marini H, Squadrito G *et al* (2003). Efferent vagal fibre stimulation blunts nuclear factor-kappaB activation and protects against hypovolemic hemorrhagic shock. *Circulation* **107**: 1189–1194.

Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V (1999). Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology* **40**: 171–176.

Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR *et al* (2006). VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Pscychoneuropharmacology* **31**: 1345–1355.

O'Brien SM, Scott LV, Dinan TG (2004). Cytokines: abnormalities in major depression and implications for pharmacological treatment. *Hum Psychopharmacol* **19**: 397–403.

Schiepers OJ, Wichers MC, Maes M (2005). Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry* **29**: 201–217.

Sluzewska A, Rybakowski J, Bosmans E, Sobieska M, Berghmans R, Maes M *et al* (1996). Indicators of immune activation in major depression. *Psychiatry Res* **64**: 161–167.

Suarez EC, Krishnan RR, Lewis JG (2003). The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. *Psychosom Med* **65**: 362–368.

Ulloa L (2005). The vagus nerve and the nicotinic anti-inflammatory pathway. *Nat Rev Drug Discov* **4**: 673–683.