

# Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia

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## Abstract

Implanted vagus nerve stimulation (VNS) has been used to treat seizures and depression. In this study, we explored the mechanism of action of noninvasive vagus nerve stimulation (nVNS) for the treatment of trigeminal allodynia. Rats were repeatedly infused with inflammatory mediators directly onto the dura, which led to chronic trigeminal allodynia. Administration of nVNS for 2 minutes decreased periorbital sensitivity in rats with periorbital trigeminal allodynia for up to 3.5 hours after stimulation. Using microdialysis, we quantified levels of extracellular neurotransmitters in the trigeminal nucleus caudalis (TNC). Allodynic rats showed a  $7.7 \pm 0.9$ -fold increase in extracellular glutamate in the TNC after i.p. administration of the chemical headache trigger glyceryl trinitrate (GTN; 0.1 mg/kg). Allodynic rats that received nVNS had only a  $2.3 \pm 0.4$ -fold increase in extracellular glutamate after GTN, similar to the response in control naive rats. When nVNS was delayed until 120 minutes after GTN treatment, the high levels of glutamate in the TNC were reversed after nVNS. The nVNS stimulation parameters used in this study did not produce significant changes in blood pressure or heart rate. These data suggest that nVNS may be used to treat trigeminal allodynia.

**Keywords:** Chronic headache; Glutamate; Migraine; Vagus nerve.

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