

## **VAGUS NERVE STIMULATION LIKE ANTIDEPRESSANT DRUGS ENHANCES NOREPINEPHRINE RELEASE AND BDNF GENE EXPRESSION IN THE RAT BRAIN**

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The mechanisms underlying the pathophysiology of depression are still poorly understood. Most antidepressant treatments increase the levels of serotonin and/or norepinephrine (NE), suggesting that biochemical imbalances within these two monoaminergic systems may underlie the pathogenesis of this disorder. Nevertheless, although different antidepressant drugs as well as other treatments such as electroconvulsive therapy and vagus nerve stimulation (VNS) induce a rapid increase in extracellular levels of monoamines, the onset of an appreciable clinical effect is usually not immediate. This observation suggests the existence of slower neurochemical and molecular mechanisms that could induce synaptic remodeling through neuronal plasticity. Accordingly, several studies have shown that a plastic and trophic brain is necessary to reduce human vulnerability to both mental and neurodegenerative diseases suggesting the involvement of neurotrophic factors in the pathophysiology of depression. This contention has been strongly supported by studies showing that stress or depression can lead to atrophy and cell loss in limbic brain structures involved in mood modulation. Conversely, antidepressants may reverse neuronal atrophy and cell loss, thereby contributing to the therapeutic actions of these treatments. The goal of our present study was to compare the effects of VNS with those of different classes of antidepressant drugs on NE release and BDNF gene expression in the rat brain, by means of microdialysis, RNase protection assay and western blot respectively. Our results demonstrated that selective antidepressant drugs like the selective serotonin reuptake inhibitor fluvoxamine and the selective noradrenergic reuptake inhibitor reboxetine were effective in increasing BDNF gene expression while the antidepressant mirtazapine, able to enhance both serotonergic and noradrenergic transmission, was less effective. Moreover, we found that VNS, the recently approved treatment for drug-resistant depression, also increased the gene expression of BDNF as well as NE release. The findings of this study demonstrate that different classes of antidepressant drugs are not equally effective in increasing BDNF gene expression suggesting the involvement of discrete target neuronal populations in which antidepressant drugs can specifically activate this gene. They also highlight a possible link among VNS efficacy, NE release and neurotrophic factors gene expression, a phenomenon that may play a key role in morphological and functional changes associated with neuronal plasticity, as suggested also for antidepressant drug treatments.