PARKINSON DISEASE

Could ghrelin be a novel treatment for PD?

Ghrelin acting outside the hypothalamus has an important role in preserving the production and release of dopamine by the substantia nigra, according to a new study. This finding suggests that this compound could be used therapeutically in patients with Parkinson disease (PD) to slow neurodegeneration, improve appetite, prevent weight loss, and perhaps even reduce symptoms of depression. "I am very keen to convince clinicians in the PD field, particularly those with translational interests, to move ghrelin forward in human studies," stresses the senior author of the study, Tamas Horvath (Yale University School of Medicine, New Haven CT, USA).

Horvath points out that compounds with proven safety records and optimal pharmacokinetics in humans are immediately available for trials in cohorts of patients with PD. "Multiple ghrelin mimetics have already been tested clinically for metabolic disorders such as cachexia," he explains.

> "Ghrelin increases the firing rate of neurons in the substantia nigra..."

The researchers demonstrated that ghrelin binds to cells in the substantia nigra pars compacta, where it electrically activates dopamine production. Ghrelin increases the firing rate of neurons in the substantia nigra, which in turn increases the level of dopamine in the dorsal striatum, thereby protecting neurons from damage caused by a lack of this neurotransmitter. This effect is complemented by alterations in mitochondrial respiration, production of reactive oxygen species and biogenesis that depend on uncoupling protein 2. These mechanisms all serve to render the neurons in this area of the brain considerably less susceptible to cellular stress.

Although several recent studies have shown that ghrelin is neuroprotective, the present study is broader in its approach. The findings suggest that ghrelin probably influences physiological activity within the nigrostriatal dopamine system at the level of electrical activation, as well as at the level of the mitochondria. Ghrelin could, therefore, prevent the onset of neurodegeneration and might also boost the amount of dopamine that is produced by the cells that remain viable. "Therapeutically, I envision that ghrelin could be used to ameliorate existing symptoms in PD patients and also to slow the progression of their disease," concludes Horvath.

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Original article Andrews, Z. B. *et al.* Ghrelin promotes and protects nigrostriatal dopamine function via a UCP2-dependent mitochondrial mechanism. *J. Neurosci.* **29**, 14057–14065 (2009)