

# Ghrelin and Stress

## C137 Deletion of ghrelin alters the response of Edinger-Westphal nucleus to restraint stress in the mouse

Ghrelin is a gut-brain peptide hormone that plays an important role in the control of energy metabolism. In the mouse, the expression of its receptor, growth hormone secretagogue receptor (GHSR), was reported to be highest in two brain regions, the arcuate nucleus (ARC) in the hypothalamus and non-preganglionic Edinger-Westphal nucleus (npEW) in the midbrain. The npEW is also the most dominant site of urocortin 1 (Ucn1) expression in the mammalian brain and the npEW-Ucn1 neurons play an important role in stress adaptation response.

Despite the importance of ghrelin for regulating food intake and body weight, mice lacking ghrelin or GHSR show no, or only a modest metabolic phenotype. Because GHSR mRNA is abundantly present in the stress-sensitive npEW, we hypothesized that ghrelin is not only involved in metabolism control but also in the stress response. To test this we studied the ghrelin-KO mice, under basal non-stressed and acute stressed conditions. Under basal conditions, KO mice have higher activation of npEW-Ucn1 neurons as demonstrated by dual label Ucn-1 and Fos immunohistochemistry. After restraint stress both wild-type (WT) and KO mice revealed an increased activation of the npEW nucleus, but we found that stress recruited Ucn1-ir neurons only in WT, but not in KO mice. We also determined Ucn1 mRNA expression in stressed and non-stressed conditions in KO and WT mice by in situ hybridization and found a strong up-regulation of Ucn1 mRNA in KO than in WT mice. Moreover, KO but not WT mice revealed stress-induced Ucn1 mRNA expression.

Taken together, our data provide evidence for ghrelin actions in stress response. We propose that Ucn1 neurons in the npEW are instrumental in ghrelin's action on the animal's stress adaptation response.

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**PHOENIX PHARMACEUTICALS, INC.**  
330 BEACH ROAD, BURLINGAME CA, 94010, USA  
PHONE: (650) 558-8898 EMAIL: [info@phoenixpeptide.com](mailto:info@phoenixpeptide.com)  
[WWW.PHOENIXPEPTIDE.COM](http://WWW.PHOENIXPEPTIDE.COM)

**PHOENIX EUROPE GMBH**  
VIKTORIASTRASSE 3-5, D-76133 KARLSRUHE, GERMANY  
PHONE: +49-721-1611950 EMAIL: [germany@phoenixpeptide.com](mailto:germany@phoenixpeptide.com)  
[WWW.PHOENIXPEPTIDE.COM](http://WWW.PHOENIXPEPTIDE.COM)