Título: Ghrelin signaling mediates fasting-induced activation of the hypophysiotropic CRF neurons via recruitment of the NPY/AGRP/GABA neurons.

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Ghrelin is a stomach-derived hormone that acts on thegrowth hormone secretagogue receptor (GHSR). Plasmaghrelin increases under fasting, when it promotesappetite and activation of the hypothalamic? pituitary? Adrenal (HPA) via its action on corticotropin-releasing factor(CRF) neurons of the paraventricular nucleus (PVN). The neuronal circuits by which ghrelin regulates these actionsare unclear. Here, we tested in male mice with pharmacologicalor genetic blockage of GHSR the effect of 48 hfasting on the PVN CRF neurons and on the neuropeptideY (NPY)/agouti-related protein (AgRP)/GABA neurons ofthe arcuate nucleus (ARC), which sense plasma factorsand regulate the PVN. Results: As compared to fedmice, fasted mice had an increase of the number of PVNCRF cells (3.57±0.22 fold increase, p≤0.05, T-test) and ofthe NPY/AgRP-fiber intensity (NPY-fibers: 0.09±0.02 vs0.17±0.02 OD; AgRP-fibers:3428±754 vs 10783±1490intensity; GFP-fibers: 8558±965 vs 16799±1771 intensityin mice expressing GFP in NPY neurons, p≤0.05, T-test).As compared to wild-type (WT) mice, GHSR-deficientmice had lower levels of plasma corticosterone and themarker of neuronal activation, c-Fos, in the PVN (corticosterone:204±30 vs 113±30 ng/ml; c-Fos: 44±9 vs13±6 cells/side, p≤0.05, 2-way ANOVA). Similarly, fastedmice with pharmacological blockage of GHSR showedlower c-Fos and of NPY-fiber intensity in the PVN (c-Fos:119±19 vs 177±13 cells/side; NPY-fiber: 0.21±0.01 vs0.45±0.04 OD, p≤0.05, T-test). Fasted mice expressingtdTomato fluorescent protein in GABA neurons had moretdTomato fibers in PVN (1.36±0.08 fold increase, p≤0.05vs fed mice, T-test). As compared to fed mice, PVN explantsof fasted mice had a reduction of the basal andKCl-stimulated GABA release (basal: 4.5±0.3 vs 3.1±0.5and KCl: 6.1±0.3 vs 4.3±0.8 % of total incorporated tracer,p≤ 0.05, 2-way ANOVA). Current results indicate thatghrelin signaling mediates fasting-induced activation ofthe hypophysiotropic CRF neurons via recruitment of the NPY/AGRP/GABA neurons.