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Ghrelin and hypothalamic NPY/AgRP expression in mice are affected by chronic early-life stress exposure in a sex-specific manner

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Highlights

- Ghrelin levels are more prominently affected by chronic early-life stress in neonatal female mice compared to males
- Early-life stress induced alterations in total ghrelin are largely attributed by the desacyl form of ghrelin and not acyl ghrelin
- Hypothalamic NPY and AgRP expression are similarly increased after early-life stress exposure in two-week-old male and female mice

Abstract

Early-life stress (ES) is a risk factor for metabolic disorders (e.g. obesity) with a notoriously higher prevalence in women compared to men. However, mechanisms underlying these effects remain elusive. The development of the hypothalamic feeding and metabolic regulatory circuits occurs mostly in the early sensitive postnatal phase in rodents and is tightly regulated by the metabolic hormones leptin and ghrelin. We have previously demonstrated that chronic ES reduces circulating leptin and alters adipose tissue metabolism early and later in life similarly in both sexes. However, it is unknown whether chronic ES might also affect developmental ghrelin and insulin levels, and if it induces changes in hypothalamic feeding circuits, possibly in a sex-dependent manner. We here show that chronic ES, in the form of exposure to limited nesting and bedding material from postnatal day (P)2 to P9 in mice, affects ghrelin levels differently, depending on the form of ghrelin (acylated vs desacylated), on age (P9 vs P14) and on sex, while insulin levels were similarly increased in both sexes after ES at P9. Even though ghrelin levels were more strongly affected in ES-exposed females, hypothalamic neuropeptide Y (NPY) and agouti-related peptide (AgRP) fiber density at P14 were similarly altered in both sexes by ES. In the paraventricular nucleus of the hypothalamus, both NPY and AgRP fiber density were