Being overweight during the peripubertal period modifies the hypothalamic metabolic response to leptin in female rats

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The authors have nothing to diclose

Introduction

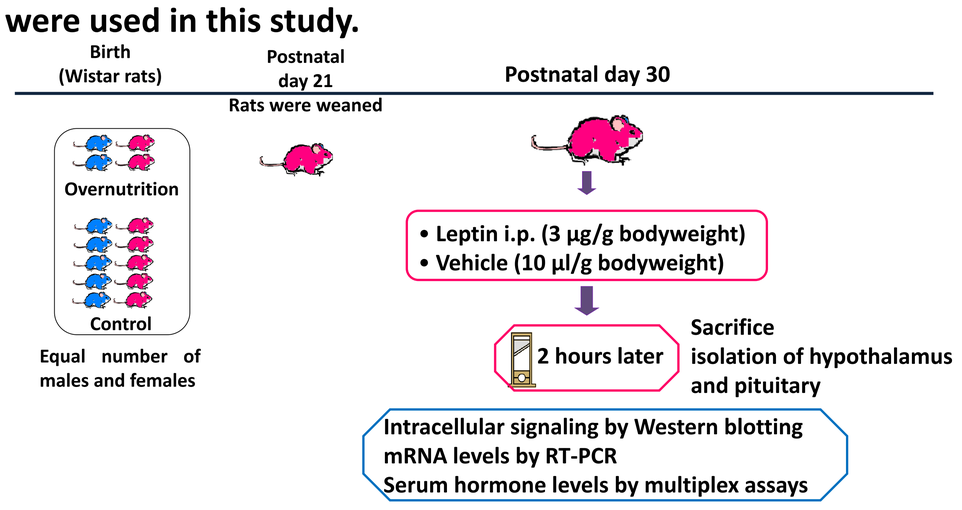
Leptin is suggested to be a permissive factor for the onset of puberty by signaling at the level of the hypothalamus to indicate adequate energy stores. Overweight female rats due to increased neonatal nutrition have been shown to develop puberty before normal weight rats. Being overweight after puberty is associated with decreased leptin sensitivity, suggesting that this would result in a decreased effect of leptin on the reproductive axis in these subjects. However, the effect of being overweight on central leptin sensitivity during the peripubertal period has not been thoroughly studied.

Hypothesis

We hypothesized that the permissive effect of leptin on puberty may be due not only to increased leptin levels, but also to increased hypothalamic sensitivity to this hormone before pubertal onset.

Materials and methods

On the day of birth Wistar rats were arranged into litters of 4 (neonatal overnutrition, NO) or 12 (control, Ct) pups and weaned on postnatal day (PND) 21. On PND30 all rats remained prepubertal although NO rats weighed more than Ct rats and had higher serum leptin levels. They then received an intraperitoneal injection of leptin (3 µg/g bodyweight) or vehicle and were sacrificed 2 hours later. Only female pups were used in this study.



Results

Rats with NO ate more than Ct throughout the study (A). NO rats also gained more weight (B) and were longer (C). Leptin treatment induced a rise in serum leptin levels (D) in both groups, but at 2 hrs levels were higher in NO rats. Both Ct and NO rats had a rise in hypothalamic phosphorylated (p)STAT3 levels, but this rise was significantly greater in NO rats (E; $p<0.05$). There was no effect on pERK1 (F), but pERK2 was reduced by leptin with this effect being greater in Ct (G; $p<0.01$). Leptin reduced pAkt only in Ct rats (H; $p<0.05$). SOCS3 levels were induced by leptin in both groups (I). PTP1B levels in the membrane were reduced by leptin in NO rats (J; $p<0.01$), with no effect on cytoplasmic PTP1B (K) or pPTEN (L) levels. Basal hypothalamic NPY mRNA levels were higher in NO rats, with levels decreasing in both Ct and NO rats in response to leptin, with a greater decline in NO rats (M; $p<0.05$). No differences in AgRP mRNA levels were found (N). POMC mRNA levels were not different at baseline, but the leptin induced rise was greater in NO rats (O; $p<0.01$). Leptin receptor (LepR) mRNA levels were increased by leptin, but only in NO rats (P; $p<0.05$). There were no baseline differences between Ct and NO rats in kisspeptin (Q), Kiss receptor (R) or GnRH (S) mRNA levels and leptin had no significant effect in either group. Pituitary LH (T) and FSH (U) mRNA levels were not affected by NO or leptin treatment.

Results

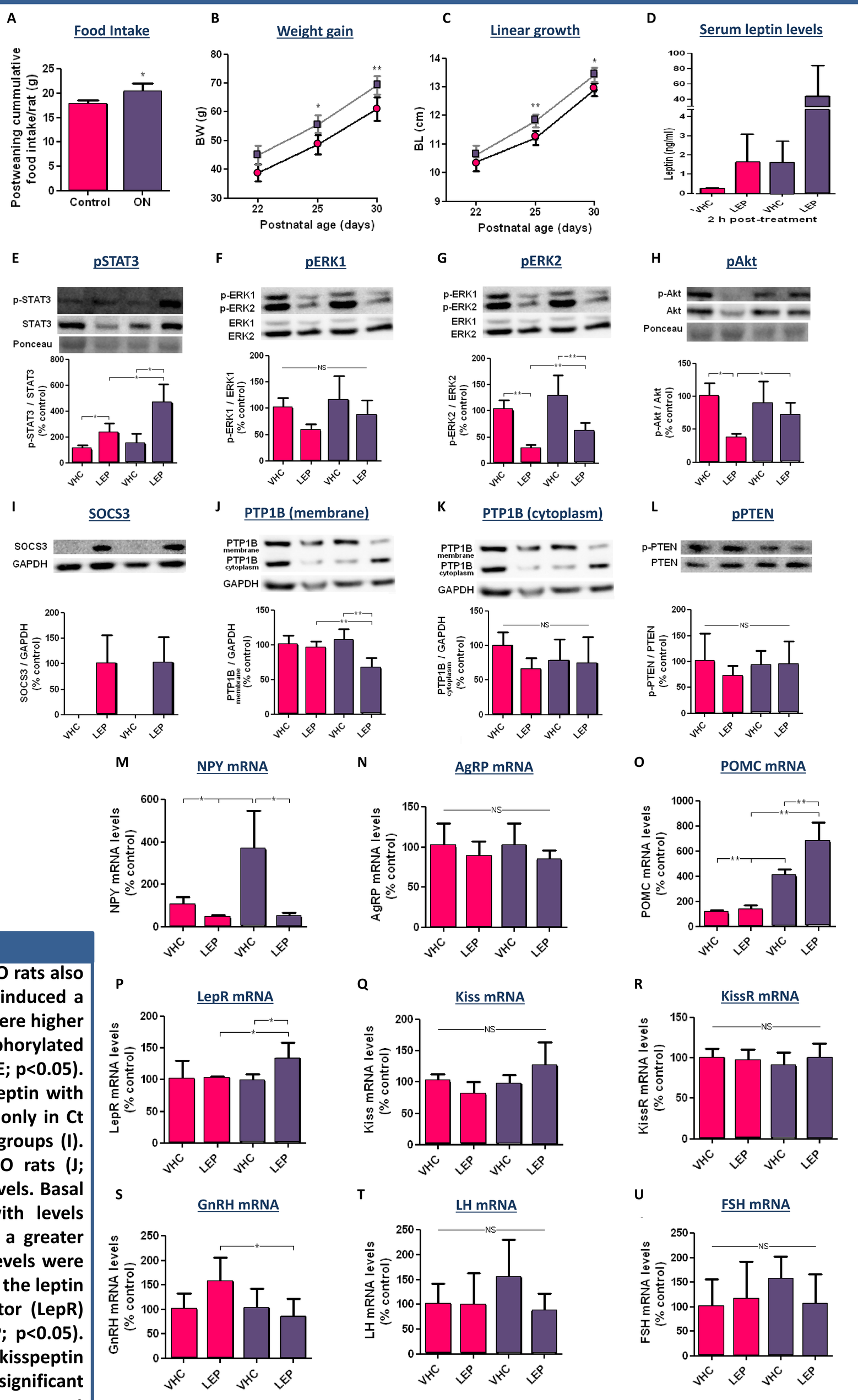


Figure 1. Effects of acute leptin (LEP) treatment or vehicle (VHC) on the activation of intracellular signaling pathways and neuropeptide expression in the hypothalamus and gonadotropin expression in the pituitary.

Conclusion:

There is an increased response of metabolic neuropeptide systems in overweight peripubertal female rats to an acute rise in leptin levels. However, leptin induced no changes in reproductive neuropeptides in control or overweight rats. Thus, during the peripubertal period the response of hypothalamic neuronal systems may be differentially affected by changes in leptin.