The hormones leptin and ghrelin act within the brain to coordinate bodily energy status with ingestive and locomotor behaviors, and are crucial mediators of adaptive feeding, energy expenditure, and body weight. Leptin is secreted by adipose cells and is a signal of energy excess. Ghrelin is secreted by cells in the gastrointestinal tract and signals energy deficiency. Distinct populations of neurons within the lateral hypothalamic area (LHA) respond to leptin and ghrelin to modify behavior and resolve energy imbalances. LHA neurons that express the neuropeptide Y (NPY) (NPY) are activated by ghrelin via the growth hormone secretagogue receptor (GHSR) to increase food intake (Leinninger - 2003). Separate LHA neurons express the neuropeptide Neurotensin (Nts), and many of them co-express the long form of Nts (NtsLepRb), which are involved in the control of energy balance. LHA neurons also respond to leptin and ghrelin to resolve energy imbalance. LHA neurons in the lateral hypothalamic area (LHA) respond to leptin and ghrelin to resolve energy imbalance. LHA neurons expressing the neuropeptide Neurotensin (Nts), and many of them co-express the long form of Nts, as well as the NtsLepRb receptor, which are involved in the control of energy balance. LHA neurons also respond to leptin and ghrelin to resolve energy imbalance.

### Figure 1: Leptin Activates NtsLepRb Neurons but Ghrelin Activates OX Neurons

**A**) Male NtsGFP mice were injected with leptin (10 μg, i.p.) or ghrelin (100 μg, i.p.) and brains were immunostained for GFP (Nts), OX and cFos (a marker of neuronal activation). In the LHA ghrelin-induced cFos is present in many OX neurons, but essentially no Nts neurons. **B**) Male LRKO and Control mice (ages 11 – 14 wks) were given a choice of water and a 1% sucrose solution, while Baseline sucrose preference was not different between groups before treatment. **C**) Leptin significantly reduces feeding in control mice, as well as in LRKO mice. *P ≤ 0.01. **D**) In LRKO mice, feeding is restored by leptin, whereas leptin does not significantly affect feeding in Control mice.

### Figure 2: Specific Disruption of LHA NtsLepRb Signaling

**A**) Male LRKO and Control mice (ages 11 – 14 wks) were injected with leptin (10 μg, i.p.) or ghrelin (100 μg, i.p.) and the time of peak cFos expression was determined. **B**) Ghrelin activates LHA OX neurons (OX neurons containing cFos) in Control mice, but not in LRKO mice.

### Figure 3: Disruption of Signaling via LHA Nts Causes Obesity

**A**) Male LRKO and Control mice (ages 11 – 14 wks) were injected with leptin (10 μg, i.p.) or ghrelin (100 μg, i.p.) and the time of peak cFos expression was determined. **B**) Ghrelin activates LHA OX neurons (OX neurons containing cFos) in Control mice, but not in LRKO mice.

### Figure 4: Loss of Adaptive Response to Leptin

**A**) Male LRKO and Control mice (ages 11 – 14 wks) were given a choice of water and a 1% sucrose solution, while Baseline sucrose preference was not different between groups before treatment. **B**) While leptin significantly reduces feeding in control mice, as well as in LRKO mice, **C**) in LRKO mice, feeding is restored by leptin, whereas leptin does not significantly affect feeding in Control mice.

Loss of adaptive response to Leptin in LRKO mice is likely due to loss of functional NtsLepRb signaling in the LHA. Together these data show that loss of leptin signaling via LHA NtsLepRb neurons decreases basal and motivated locomotor activity and energy expenditure, which promotes weight gain.

### Figure 5: Loss of Adaptive Response Pathway Activation

**A**) Loss of adaptive response to Leptin is likely due to loss of functional NtsLepRb signaling in the LHA. Together these data show that loss of leptin signaling via LHA NtsLepRb neurons decreases basal and motivated locomotor activity and energy expenditure, which promotes weight gain.

### Figure 6: Disruption of Motivated Responding

**A**) Loss of adaptive response to Leptin is likely due to loss of functional NtsLepRb signaling in the LHA. Together these data show that loss of leptin signaling via LHA NtsLepRb neurons decreases basal and motivated locomotor activity and energy expenditure, which promotes weight gain.

### Figure 8: Disruption of Leptin-Induced VTA cFos Expression

**A**) Male LRKO and Control mice (ages 11 – 14 wks) were injected with leptin (10 μg, i.p.), or amphetamine (4mg/kg, i.p.), and brains were immunostained for cFos to identify activated neurons.

### Abstract

**Loss of Action through NtsLepRb Neurons Disrupts Adaptive Energy Balance**

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The hormones leptin and ghrelin act within the brain to coordinate bodily energy status with ingestive and locomotor behaviors, and are crucial mediators of adaptive feeding, energy expenditure, and body weight. Leptin is secreted by adipose cells and is a signal of energy excess. Ghrelin is secreted by cells in the gastrointestinal tract and signals energy deficiency. Distinct populations of neurons within the lateral hypothalamic area (LHA) respond to leptin and ghrelin to modify behavior and resolve energy imbalances. LHA neurons that express the neuropeptide Y (NPY) (NPY) are activated by ghrelin via the growth hormone secretagogue receptor (GHSR) to increase food intake (Leinninger - 2003). Separate LHA neurons express the neuropeptide Neurotensin (Nts), and many of them co-express the long form of Nts (NtsLepRb), which are involved in the control of energy balance. LHA neurons also respond to leptin and ghrelin to resolve energy imbalance.

**Introduction:**

The hormones leptin and ghrelin act within the brain to coordinate bodily energy status with ingestive and locomotor behaviors, and are crucial mediators of adaptive feeding, energy expenditure, and body weight. Leptin is secreted by adipose cells and is a signal of energy excess. Ghrelin is secreted by cells in the gastrointestinal tract and signals energy deficiency. Distinct populations of neurons within the lateral hypothalamic area (LHA) respond to leptin and ghrelin to modify behavior and resolve energy imbalances. LHA neurons that express the neuropeptide Y (NPY) (NPY) are activated by ghrelin via the growth hormone secretagogue receptor (GHSR) to increase food intake (Leinninger - 2003). Separate LHA neurons express the neuropeptide Neurotensin (Nts), and many of them co-express the long form of Nts (NtsLepRb), which are involved in the control of energy balance. LHA neurons also respond to leptin and ghrelin to resolve energy imbalance.