### Interaction between cholecystokinergic and opioidergic mechanisms of the lateral parabrachial nucleus in the control of NaCl intake

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Bilateral injections of proglumide, a cholecystokinin (CCK) antagonist, into the lateral parabrachial nucleus (LPBN) increase 1.8% NaCl intake induced by sc furosemide (FURO, 10 mg/kg of body weight) combined with captopril (CAP, 5 mg/kg). The opioidergic agonist beta-endorphin into the LPBN induces 1.8% NaCl intake in satiated and normovolemic rats, an effect abolished by the opioidergic antagonist naloxone. In the present study we investigated the effects of naloxone alone or combined with proglumide into the LPBN on water and 1.8% NaCl intake induced by FURO + CAP. Male Holtzman rats ($n = 10$) with cannulas implanted bilaterally in the LPBN were used. Bilateral injections of proglumide (50 μg/0.2 μl) into the LPBN increased FURO + CAP-induced 1.8% NaCl intake ($23.2 \pm 3.5$ ml/2 h vs. veh.: $9.9 \pm 1.8$ ml/2 h), while naloxone (40 μg/0.2 μl) alone into the LPBN did not change NaCl intake. Naloxone into the LPBN partially reduced the effect of proglumide on FURO + CAP-induced 1.8% NaCl intake ($16.6 \pm 3.3$ ml/2 h). Proglumide or naloxone alone or combined into the LPBN did not change FURO + CAP-induced water intake. The results suggest that the increase in FURO + CAP-induced sodium intake produced by the blockage of CCK receptors in the LPBN is partially dependent on the activation of opioidergic mechanisms in the same area.

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### SNP analyses of postprandial responses in (an)orexigenic hormones and feelings of hunger reveal long-term physiological adaptations to facilitate homeostasis

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Food intake regulation was previously shown to be partly under genetic control. This study aimed to determine whether the postprandial responses in plasma peptide YY (PYY), glucagon-like peptide 1 (GLP-1) and ghrelin levels as well as feelings of hunger and satiety are associated with single nucleotide polymorphisms (SNPs) in relevant genes ($N = 103$; age $31 \pm 14$ years; body mass index (BMI) $25.0 \pm 3.1$ kg m$^{-2}$). Dietary restraint, disinhibition and perceived hunger were determined using the three-factor eating questionnaire (TFEQ). The postprandial response in plasma ghrelin was associated with SNPs in *PYY* and *LEPR* ($P < 0.01$), and in plasma PYY with SNPs in *GHRL* and *GHSR* ($P < 0.05$). The postprandial response in feelings of hunger was characterized by a SNP–SNP interaction in *LEPR* and *NPY2R* ($P < 0.05$). Dietary restraint and disinhibition were associated with a SNP in *GHSR*, perceived hunger with SNPs in *GHSR* and *NPY* ($P < 0.05$). Surprisingly, subjects genetically vulnerable to overeating or a high BMI showed SNP associations with postprandial hormone concentration changes counterbalancing their genetic predisposition. These physiological adaptations facilitate homeostasis. Reinforcements of direct genetic effects were observed as well. SNP–SNP interactions in addition to the conventional single-SNP associations elucidated findings that were otherwise inexplicable.

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### Mapping of G-protein coupling reveals a critical area for mu-opioid receptors in the medial shell of the nucleus accumbens in modulating intake of standard and palatable food

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Mu-opioid receptors (MOPRs) within the nucleus accumbens (NAcc) have been regarded as modulators of the affective aspect of food intake. Within this heterogeneous region, MOPRs are reported to be especially involved in the hedonic evaluation of energy-dense, presumably palatable foods. Here, we aim to determine the effect of MOPR blockade on food intake using the MOPR antagonist, β-funaltrexamine (β-FNA). We administer β-FNA (3.2 nmol/0.2 μl/side or 8 nmol/0.5 μl/side) into different coronal levels of the NAcc medial shell of rats. Furthermore, we compare the effect of β-FNA within a single region of the NAcc medial shell on consumption of standard chow and a highly palatable diet containing sucrose and fat. B-FNA decreased consumption of the palatable diet only within a confined rostrocaudal region of the NAcc. In contrast, MOPR-stimulated G-protein coupling measured by [$^{35}$S]GTPγS autoradiography was decreased in all coronal groups. Thus, although β-FNA decreased coupling in the Nacc medial shell across the entire rostrocaudal axis, this effect was only associated with decreased feeding in a restricted rostrocaudal region. Moreover, β-FNA's hypophagic effect was not diet selective within this region. β-FNA decreased the intake of standard and palatable chow suggesting the anorectic effect of MOPR blockade is not sensitive to the diet's sensory properties. Thus, NAcc MOPRs may be involved in a more general role in the consumption of all foods.

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### Programmed alteration of hypothalamic leptin and insulin signaling pathways contributes to reduced anorexigenic responses in IUGR offspring

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**Objective:** Maternal food restriction (FR) results in IUGR newborns that develop hyperphagia and adult obesity. Central anorexigenic *basal* leptin and insulin signal molecules are downregulated in IUGR newborns. Leptin acts via JAK-STAT3 and insulin-PI3K pathways. We studied the response of hypothalamic leptin/insulin signal molecules to peripheral leptin. **Method:** Rats received ad libitum food (Control) or were 50% FR during pregnancy (i.e. 10–21). One-day-old males received saline or leptin (1 μg/g, i.p.). Hypothalamic protein expression was determined at 15, 30 and 45 min of total STAT3, phosphorylated STAT3 (pSTAT3), inhibitor of leptin signal (SOCS3), insulin substrate (IRS2), AKT and pAKT. Data is compared between leptin and saline treatments. **Result:** In response to peripheral leptin, IUGR newborns show marked dysfunction in hypothalamic signaling responses. (1) JAK-STAT3: Leptin-treated Controls show progressively increased pSTAT3 with initial suppression of SOCS3 than saline-treated controls. In leptin-treated IUGR, there is sustained decline in pSTAT3 level with failure to downregulate SOCS3. (2) PI3K: Leptin-treated Controls show significantly reduced IRS2 and pAKT than saline-treated Controls. However, leptin-treated IUGR newborns exhibit a paradoxical increased IRS2 and pAKT. **Conclusion:** IUGR offspring show reduced pSTAT3 response in conjunction with enhanced SOCS3 response. The persistent increase in insulin responses indicates a dysfunction in dynamic signaling, leading to altered anorexigenic response and development of programmed obesity.

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