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Regulatory Peptides 146 (2008) 176–182
REGULATORY PEPTIDES
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Hypothalamic gene expression following ghrelin therapy to gastrectomized rodents

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Received 7 February 2007; received in revised form 30 August 2007; accepted 5 September 2007
Available online 14 September 2007

Abstract

We investigated whether ghrelin depletion (by gastrectomy surgery) and/or treatment/replacement with the gastric hormone ghrelin alters the expression of key hypothalamic genes involved in energy balance, in a manner consistent with ghrelin's pro-obesity effects. At 2 weeks after surgery mice were treated with ghrelin (12 nmol/mouse/day, sc) or vehicle for 8 weeks. Gastrectomy had little effect on the expression of these genes, with the exception of NPY mRNA in the arcuate nucleus that was increased. Ghrelin treatment (to gastrectomized and sham mice) increased the mRNA expression of orexigenic peptides NPY and AgRP while decreasing mRNA expression of the anorexigenic peptide POMC. Two weeks gavage treatment with the ghrelin mimetic, MK-0677, to rats increased NPY and POMC mRNA in the arcuate nucleus and MCH mRNA in the lateral hypothalamus. Thus, while predicted pro-obesity ghrelin signalling pathways were activated by ghrelin and ghrelin mimetics, these were largely unaffected by gastrectomy.

Keywords: Appetite; Growth hormone secretagogues; GHS-R1a; MK-0677; Melanin-concentrating hormone; Pro-opiomelanocortin; Neuropeptide Y; Agouti-related peptide

1. Introduction

The hormone ghrelin was discovered in 1999 by Kojima et al., who isolated it from the rat stomach [1] where it is produced by the A-like cells of the oxyntic glands [2]. Indeed, the stomach is the major source of circulating ghrelin [2], although small amounts have been detected in other organs [3]. In addition, ghrelin is produced by hypothalamic neurones that regulate the activity of the orexigenic neuropeptide Y (NPY) neurones of the arcuate nucleus [4].

Ghrelin is the first identified endogenous ligand for the growth hormone secretagogue receptor, GHS-R1a, cloned in 1996. This receptor is expressed in several tissues, notably at key CNS sites that regulate fat mass including the arcuate nucleus and ventromedial nucleus of the hypothalamus and the mesolimbic system [5,6]. Ligands for this receptor, the growth hormone secretagogues (GHSs), have been studied for over 20 years and have provided a wealth of information about the mechanism of action of ghrelin. These agents include peptide and orally-active non-peptide GHS-R1a agonists, such as MK-0677 [7]. Although both ghrelin and GHS-R1a agonists induce growth hormone secretion, recent interest largely focuses on their ability to stimulate food intake [8] and fat accumulation [9,10].

The stimulatory effects of ghrelin and GHS-R1a agonists on food intake and fat accumulation are thought to be mediated by an interaction with the hypothalamic circuits that regulate energy balance and also with mesolimbic pathways associated

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0167-0115/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.regpep.2007.09.006

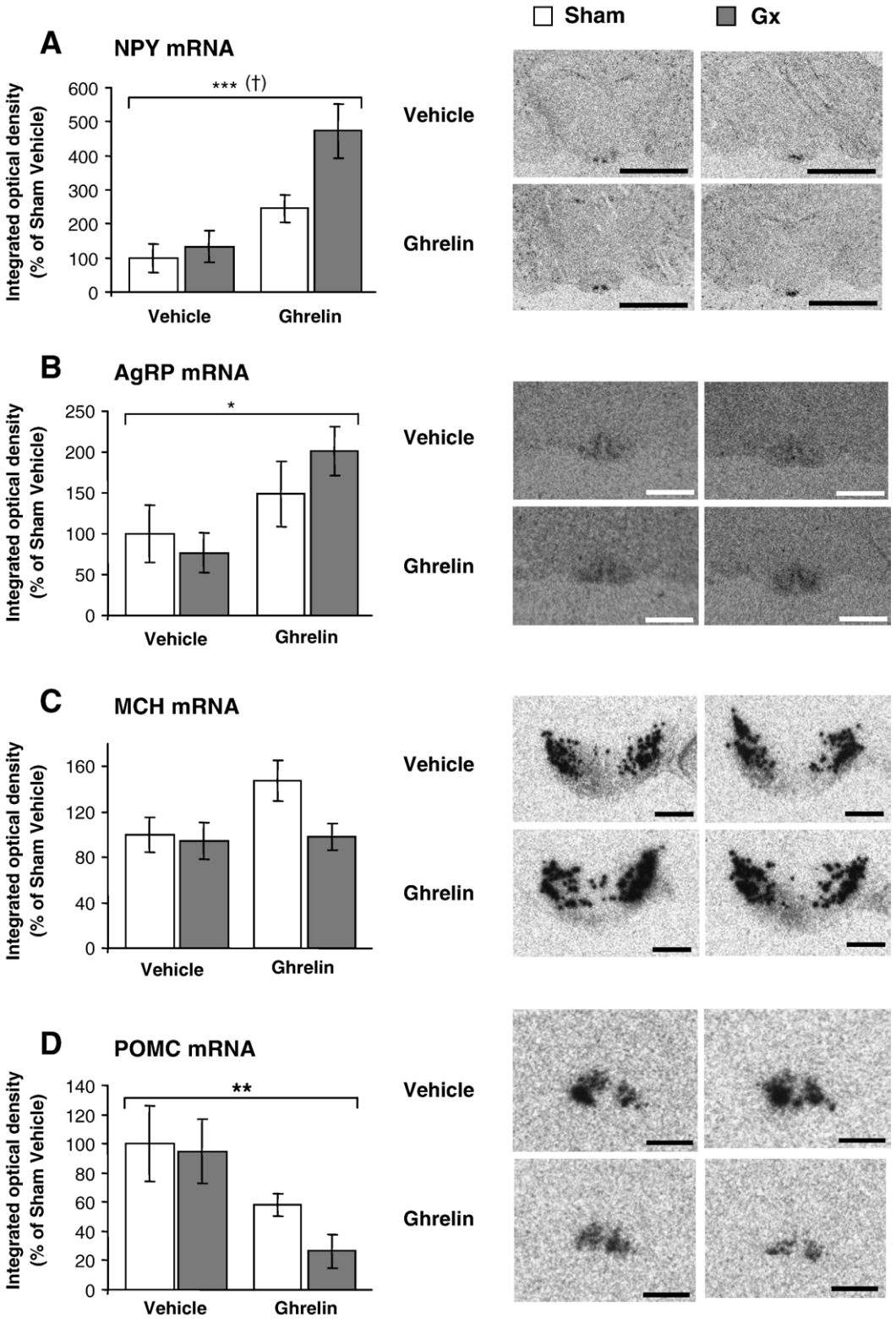

Fig. 1. Integrated optical density, analyzed by *in situ* hybridization, for (A) NPY, (B) AgRP, (D) POMC mRNAs in the arcuate nucleus and (C) MCH mRNA in the lateral hypothalamus of either sham-operated (Sham) and gastrectomized (Gx) mice. The animals were given ghrelin (12 nmol/day) or vehicle by sc injections daily for 8 weeks. Representative bright field photomicrographs of sections incubated with ^{35}S-labeled antisense oligonucleotide for each respective group and neuropeptide. The scale bar represents A) 3 mm, B) 800 μm, C) 500 μm, D) 800 μm, respectively. Values are mean ± SEM (n = 5–6). Statistical comparison was made with a 2-way ANOVA. *P < 0.05 and ***P < 0.001 = significant difference between saline and ghrelin treatment. †P < 0.05 = significant difference between sham and gastrectomy surgery.