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Perspective

Dysfunctional oleoylethanolamide signaling in a mouse model of Prader-Willi syndrome

Miki Igarashi[a], Vidya Narayanaswami[a], Virginia Kimonis[b], Pietro M. Galassetti[b], Fariba Oveisi[a], Kwang-Mook Jung[a], Daniele Piomelli[a,c,d,*]

[a] Department of Anatomy and Neurobiology, University of California, Irvine, CA, 92697, USA
[b] Department of Pediatrics, University of California, Irvine, CA, 92697, USA
[c] Department of Biological Chemistry, University of California, Irvine, CA, 92697, USA
[d] Department of Pharmacology, University of California, Irvine, CA, 92697, USA

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ABSTRACT

Prader-Willi syndrome (PWS), the leading genetic cause of obesity, is characterized by a striking hyperphagic behavior that can lead to obesity, type-2 diabetes, cardiovascular disease and death. The molecular mechanism underlying impaired satiety in PWS is unknown. Oleoylethanolamide (OEA) is a lipid mediator involved in the control of feeding, body weight and energy metabolism. OEA produced by small-intestinal enterocytes during dietary fat digestion activates type-α peroxisome proliferator-activated receptors (PPAR-α) to trigger an afferent signal that causes satiety. Emerging evidence from genetic and human laboratory studies suggests that deficits in OEA-mediated signaling might be implicated in human obesity. In the present study, we investigated whether OEA contributes to feeding dysregulation in *Magel2*$^{m+/p-}$ (*Magel2 KO*) mice, an animal model of PWS. Fasted/refed male *Magel2 KO* mice eat more than do their wild-type littermates and become overweight with age. Meal pattern analyses show that hyperphagia in *Magel2 KO* is due to increased meal size and meal duration rather than to lengthening of the intermeal interval, which is suggestive of a defect in mechanisms underlying satiation. Food-dependent OEA accumulation in jejunum and fasting OEA levels in plasma are significantly greater in *Magel2 KO* mice than in wild-type controls. Together, these findings indicate that deletion of the *Magel2* gene is accompanied by marked changes in OEA signaling. Importantly, intraperitoneal administration of OEA (10 mg/kg) significantly reduces food intake in fasted/refed *Magel2 KO* mice, pointing to a possible use of this natural compound to control hunger in PWS.

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1. Introduction

Prader-Willi syndrome (PWS) is the leading genetic cause of obesity. Children with PWS develop a striking hyperphagic behavior that leads, if left unchecked, to morbid obesity, type-2 diabetes, cardiovascular disease and premature death. Mice carrying a deletion of the *Magel2* gene (*Magel2 KO* mice), which is frequently deleted or mutated in individuals affected by the disease, also display a deficit in the ability to regulate food intake [1–3], but the molecular mechanism underlying this dysregulation is unknown.

Oleoylethanolamide (OEA) is a lipid messenger that controls feeding, body weight and lipid metabolism [4–7]. Unlike peptide gastrointestinal hormones (e.g. ghrelin and cholecystokinin), which are stored in and released from enteroendocrine cells, OEA is generated on-demand by small intestinal enterocytes during the digestion of dietary fats [8,9]. The biochemical pathway responsible for OEA formation and deactivation has been elucidated [6]. Its first step is the transfer of a fatty acid, oleic acid, from phosphatidylcholine (PC) to phosphatidylethanolamine (PE). This reaction is catalyzed by the *N*-acyl transferase PLA2G4E [10] and produces various forms of *N*-acyl-phosphatidylethanolamine (NAPE), including the OEA precursor *N*-oleoyl-phosphatidylethanolamine (NOPE).

Abbreviations: PWS, Prader–Willi syndrome; OEA, oleoylethanolamide; PC, phosphatidylcholine; PE, phosphatidylethanolamine; NAT, *N*-acyl transferase; NAPE, N-acyl-phosphatidylethanolamine; NOPE, N-oleoyl-phosphatidylethanolamine; NAPE-PLD, N-acylphosphatidylethanolamine-selective phospholipase D; FAAH, fatty acid amide hydrolase; NAAA, *N*-acylethanolamine acid amidase; PPAR-α, peroxisome proliferator activated receptor-α; PEA, palmitoylethanolamide; FAE, fatty acid ethanolamide; LC–MS, liquid chromatography-mass spectrometry; SIM, selected ion monitoring; ANOVA, analysis of variance.

* Corresponding author at: Department of Anatomy and Neurobiology, University of California, 3216 Gillespie NRF, Irvine, CA, 92697-4625, USA.
E-mail address: piomelli@uci.edu (D. Piomelli).

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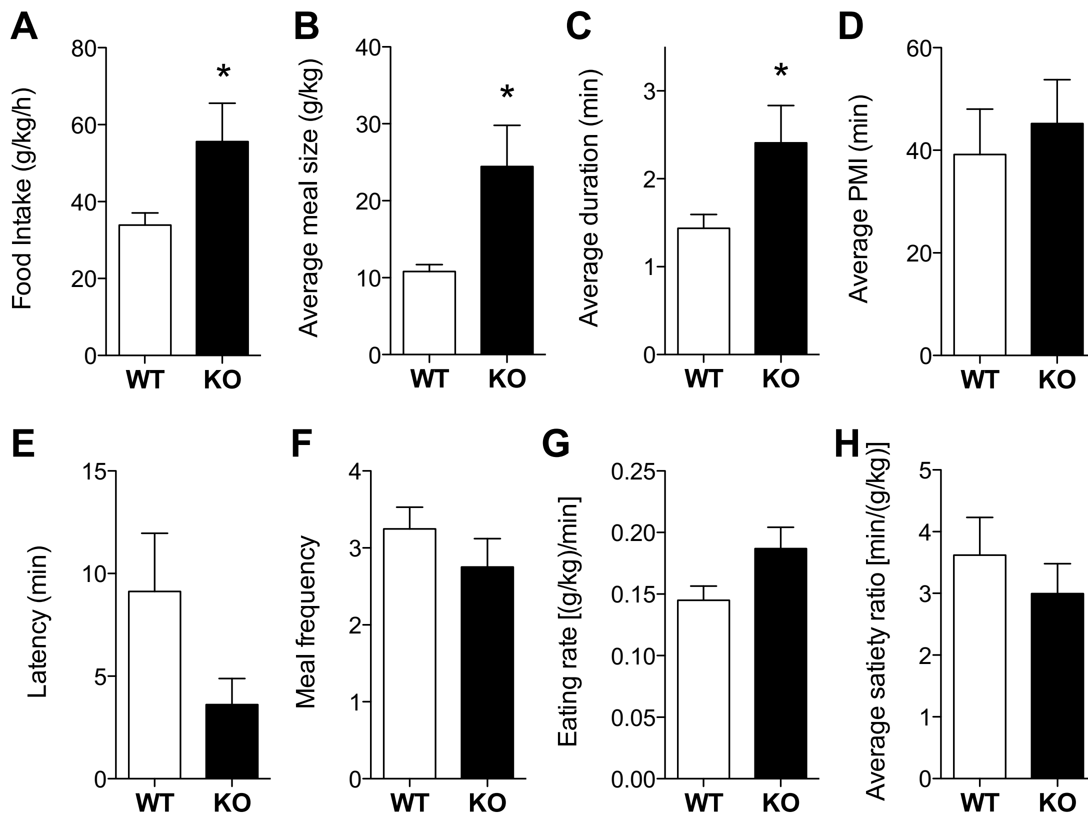

Fig. 1. Satiation deficits in fasted/re-fed *Magel2 KO* mice. (A) Food intake, (B) average meal size, (C) meal duration, (D) post-meal interval (PMI), (E) latency to feed, (F) meal frequency, (G) eating rate, and (H) satiety ratio in male *Magel2 KO* mice and their wild-type (WT) littermates. Meal patterns were measured after 24-h food deprivation. Results are expressed as mean ± SEM.*, $P < 0.05$ by unpaired Student's *t*-test (n = 12 per group).

Next, NOPE is hydrolyzed by *N*-acylphosphatidylethanolamine-selective phospholipase D (NAPE-PLD) to generate OEA [11]. The biological actions of OEA are terminated by enzyme-mediated hydrolysis, which can be catalyzed by either of two intracellular amidases: fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine acid amidase (NAAA) [12–15].

OEA formation in the small intestine is primarily controlled by the animal's feeding status [8,16]. Studies have shown that intake of dietary fat is necessary and sufficient to trigger OEA production, which primarily occurs in duodenal and jejunal enterocytes. Experiments in which individual nutrients were infused separately into the rat duodenum have shown that dietary fat, rather than sugar or protein, is a potent stimulus for jejunal OEA production [9]. Additional investigations have demonstrated that enterocytes lining the lumen of the proximal gut internalize food-derived oleic acid and use it to produce NOPE and OEA [9].

OEA is a potent agonist of type-α peroxisome proliferator activated receptor (PPAR) and activation of this receptor mediates the compound's ability to cause satiety [16–20]. Accordingly, OEA-dependent hypophagia is abolished by PPAR-α deletion, is reproduced by administration of PPAR-α agonists, and is accompanied by changes in the expression of PPAR-α target genes [5]. Furthermore, the concentrations reached by the compound in the jejunum after feeding (300–400 nM) are sufficient to fully activate PPAR-α [8,21,22]. In addition to causing satiety, OEA also stimulates lipolysis in white adipose cells and hepatocytes, increases ketone body production, and enhances fatty acid oxidation in skeletal muscle cells through PPAR-α activation [23,24].

In the current study, we examined whether deficits in OEA-mediated satiety signaling might contribute to food intake dysregulation in *Magel2 KO* mice. Our results indicate that deletion of the *Magel2* gene mice interferes with OEA signaling and that administration of exogenous OEA normalizes feeding behavior in hyperphagic *Magel2 KO* mice.

2. Materials and methods

2.1. Animals

All experimental procedures were approved by the Animal Care and Use Committee of the University of California, Irvine. Male *Magel2*$^{m+/p-}$ (C57BL/6-Magel2tm1Stw/J, *Magel2 KO*) mice and control wild-type mice obtained from the same colony were purchased from Jackson Laboratory (Bar Harbor, ME). The heterozygous *Magel2 KO* mice harbor a maternally inherited imprinted wild-type allele and a paternally inherited *Magel2-lacZ* knock-in allele that was constructed by gene-targeted replacement of the *Magel2* open reading frame with a *LacZ* reporter cassette [25,26]. Upon arrival, animals were acclimated for at least 1 week in our animal facility (temperature, 22 °C; humidity, 30–60%), with a controlled 12 h light/12 h dark cycle (on at 6:30 a.m., off at 6:30 p.m.). Animals were provided with *ad libitum* access to water and food (regular chow, 2020X, Harlan, Madison, WI), except for experiments that involved food deprivation.

2.2. Experimental design for food deprivation and re-feeding studies

Food intake was recorded using an automated monitoring system (Scipro, New York, NY), as described previously [17]. The system consists of 20 cages equipped with food baskets connected to weight sensors. Animals were housed individually in wired-

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