Genes & Diseases (2015) 2, 255–260

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SHORT COMMUNICATION

Platelet-activating factor receptor affects food intake and body weight

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Received 15 May 2015; accepted 16 June 2015
Available online 24 June 2015

KEYWORDS
Behavior;
Food intake;
Obesity;
Physical activity;
Platelet-activating factor

Abstract "Let's Move!" is a comprehensive initiative, launched by the First Lady, Michelle Obama, dedicates to solving problems of obesity, which is growing in child. The life behaviors do affect obesity; however, the mechanistic insight in molecular level is still not clear. In this study, by continually monitoring mouse body weight under chow and high fat western diets as well as metabolic, physical activity and food intake behaviors assessed in a CLAMS Comprehensive Lab Animal Monitoring System, we demonstrated that the platelet-activating factor receptor (PTAFR) contributes to modification of life behaviors. PTAFR does not affect metabolism of ingested dietary fat and carbohydrate in young animals; however, *Ptafr* ablation dramatically increased weight gain without affecting adipose tissue accumulation. *Ptafr*$^{-/-}$ mice possess new habits that increased food intake and decreased movement. Our studies suggest that regulation of PTAFR activity may be a novel strategy to control obesity in children or young adults.

Introduction

Obesity is a growing worldwide health problem that is associated with an increased risk of cardiovascular diseases, type II diabetes as well as cancer, and is positively correlated with the presence of inflammatory factors.[1] This population is becoming young and children obesity has been a serious public health concern to be solved. Platelet-activating factor (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine, PAF) is a potent autocoid—locally signaling hormone—that initiates

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Peer review under responsibility of Chongqing Medical University.

http://dx.doi.org/10.1016/j.gendis.2015.06.002

and localizes acute inflammation.[2] PAF initiates signaling after engagement of a G-protein coupled receptor, the PAF receptor (PTAFR), with exceedingly high affinity.[3–5] PTAFR is expressed by most cells of the innate immune and vascular systems, but is absent on hepatocytes.[6] PTAFR is unique in recognizing PAF to the exclusion of other physiologic phospholipids, although a range of phospholipids generated by unregulated oxidative truncation of polyunsaturated choline phospholipids are PTAFR agonists and are biologically active.[7]

Despite the widespread roles of PAF and PTAFR in cell activation *ex vivo*, genetic ablation of *Ptafr* does not interfere with birth or viability, nor even induce marked changes to the inflammatory system in the absence of overt stimulation.[3,4] We employed *Ptafr*$^{-/-}$ mice to assess circulating PAF and PAF-like oxidized phospholipids in blood of older animals,[8] and noted that most of these aged mice were significantly obese when compared to age-matched wild type C57BL6 mice (WT) or *Apoe* null mice (data not shown). This phenotype was found in both genders. Our findings are identical to the recent studies which reported that loss of PTAFR increases adiposity over time, although the mechanism for this weight gain is not fully elucidated.[9,10] In this study, we provide additional evidence and mechanistic insights regarding the role of PTAFR in obesity. We found young *Ptafr* null mice were "couch potatoes" that ingested significantly more food and moved significantly less frequently. We conclude PTAFR signaling contributes to behavior control in early life through the dual actions of enhanced movement and feeding suppression separate from a metabolic role, implicating PTAFR signaling in behavior modification.

Material and methods

All procedures and manipulations of mice have been approved by the Institutional Animal Care and Use Committee (IACUC) of The Cleveland Clinic in accordance with the United States Public Health Service *Policy on the Humane Care and Use of Animals*, and the NIH *Guide for the Care and Use of Laboratory Animals*. WT mice were purchased from Jackson Laboratories. *Ptafr*$^{-/-}$ mice, which have been back-crossed to the C57/BL6 mouse more than 10 times, were from Jeffery Travers (University of Indiana) with permission of the strain's originator Takao Shimizu (University of Tokyo). Animals were identified by ear tags and fed *ad libitum* with regular chow (CD, 8604 Teklad Rodent Diet) with the calorie contributions from protein, fat, and carbohydrate being 32%, 14% and 54%, respectively. Harlan TD.88137 "Western diets" (WD) was used to accelerate gain of body weight and the calorie contributions from protein, fat, and carbohydrate were 15.2%, 42% and 42.7%. TD.88137 also includes 0.2% cholesterol by weight. Mice were weighed weekly.

Behavior and metabolism assessment

Mouse metabolism was assessed using an Oxymax Lab Animal Monitoring System: CLAMS Comprehensive Lab Animal Monitoring System (Columbus Instruments, Columbus, OH). This system can continuously monitor food intake as well as movement detection by interruption of triple axis infrared beams. Interruption of a beam in any dimension accrues as a single "count". This system also continuously monitors the volume of oxygen consumed and carbon dioxide exhaled, which can be used to calculate the energy content of the foodstuff utilized by the mouse. Mice were placed in individual isolator cages and allowed to acclimate to the environmental chamber for two days prior to data collection. The data were collected over a two-day period after acclimation.

Body composition

At the end of experiments, the mice were weighted and anesthetized with Ketamine/Xylazine (100/10 mg/kg, IP injection). The abdominal cavity was opened via middle incision and then abdominopelvic fat was isolated from gonadal organs, and its wet weight measured. Liver was isolated from surrounding tissue, all visible ligaments and vessels were removed, and then the wet weight was immediately measured. Data are presented as ratio of the weight of abdominopelvic fat or liver to the body weight.

Statistical analysis

Statistical analyses were performed using Prisim4 (GraphPad) software. One-way ANOVA (Bonferroni/Dunn) was used to determine the differences among groups. Unpaired *t* test was used to determine differences between groups. Data are presented as the mean ± SEM, with $p < 0.05$ considered significant.

Results and discussion

Ptafr$^{-/-}$ mice excessively gain weight irrespective the type of diet

PAF is a potent inflammatory mediator,[5] but PTAFR also participates in non-inflammatory events. PAF modulates complex physiologic events including blood pressure regulation,[11] matrix production by renal tubulointerstitial epithelial cells,[12] vascular permeability in kidney,[13] and reproduction.[4] A western diet (WD) induces chronic and low level of inflammation,[14,15] so to determine if potential diet-mediated inflammation contributes to *Ptafr*-null-mediated gain of body weight, we fed the WT and *Pafr*$^{-/-}$ mice with control diet (CD) or WD and body weight were monitored continually up to 8 weeks. The study was initiated in 8-week-old mice as at this moment there is no difference in body weight was found between the two strains. The body weight of the 8-week-old WT mice ingesting CD increased linearly and reached a final weight of approximately 27 g after 8 weeks feeding period (Fig. 1A), and gain about 4 g body weight (Fig. 1B). As predicted, when WT mice were fed WD, they gained weight at a greater rate than that of CD-fed mice (Fig. 1A), and the difference became significant from week two of the trial, and increased over time without achieving a constant value. Ultimately, these WD-fed WT mice gained almost 10 g of weight over the eight weeks feeding period (Fig. 1B). *Ptafr*$^{-/-}$ mice ingesting CD