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SHORT COMMUNICATION

Does obesity affect febrile responsiveness?

AI Ivanov[1]*, VA Kulchitsky[2] and AA Romanovsky[1,2]

[1]*Trauma Research, St Joseph's Hospital and Medical Center, Phoenix, Arizona, USA; and* [2]*Thermoregulation Laboratory, Legacy Holladay Park Medical Center, Portland, Oregon, USA*

BACKGROUND AND OBJECTIVE: A decreased resistance to infection and impairments of immunity are common in obese humans and in rodents with hereditary obesity. Since brown fat thermogenesis is also suppressed in obese rodents, we hypothesized that obesity leads to a decreased febrile responsiveness.
METHODS: We compared the fever responses to intravenous *E. coli* lipopolysaccharide (10 μg/kg) between Zucker *fa/fa* (obese due to a defective leptin receptor) and *Fa/?* (lean) rats and between Otsuka Long–Evans Tokushima Fatty (OLETF; obese due to the lacking cholecystokinin-A receptor) and Long-Evans Tokushima Otsuka (lean) rats. Obesity of Zucker *fa/fa* and OLETF rats was verified by increased body mass and fat content, hypertriglyceridemia and hypercholesterolemia.
RESULTS: Neither *fa/fa* nor OLETF animals exhibited a decreased febrile responsiveness; if anything, their fevers tended to be higher than those in their lean counterparts.
CONCLUSION: Obesity *per se* does not lead to antipyresis.
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Introduction

A high incidence of and a decreased resistance to infections have been demonstrated in obese humans[1,2] and experimental animals.[3,4] Does obesity impair the febrile response, a common and prominent sign of infection? A decreased thermogenic capacity of obese animals[5,6] suggests that thermal responses, including fever, may be decreased in obesity. However, three studies[7–9] that were aimed at measuring the febrile response in obese Zucker (*fa/fa*) rats gave contradictory results. Zucker (*fa/fa*) rats have a defective receptor to leptin,[10] an interleukin (IL)-6-like, adipocyte-derived cytokine, that serves as a food intake-inhibiting signal from the adipose tissue to the brain.[11] In *fa/fa* rats, this signal is interrupted and, as a result, hyperphagia and obesity develop. Rosenthal *et al*[7] have found that the early stage of the febrile response to intramuscular (im) lipopolysaccharide (LPS) is attenuated in *fa/fa* rats, as compared to their lean (*Fa/?*) counterparts, but that the late stages are unaffected. Dascombe *et al*[8] reported attenuated fevers after intrabrain cytokine IL-1*β*. Plata-Salamán *et al*[9] showed an exaggeration of the febrile response to intrabrain IL-1*β* in *fa/fa* rats.

In the present study, we investigated the febrile responses to LPS in two Long–Evans-derived rat strains with hereditary obesity, *viz*. Zucker fatty (*fa/fa*) and Otsuka Long–Evans Tokushima Fatty (OLETF) rats. The latter strain lacks the cholecystokinin (CCK)-A receptor[12] and develops hyperphagia and obesity, presumably due to the interruption of a CCK-A-mediated satiety signal.[13]

Materials and methods

Eight male Zucker fatty (*fa/fa*) and eight lean (*Fa/?*) rats were purchased from Harlan (Indianapolis, IN). Seven male OLETF rats and six of their lean counterparts (Long-Evans Tokushima Otsuka, LETO) were a gift from Otsuka Pharmaceutical (Tokushima, Japan). At an age of ~9 weeks, each animal had a catheter implanted into the right jugular vein and was subsequently taken into two experiments (on days 4 and 9 postsurgery). For the experiments, the animal was placed in its individual stock and transferred to an environmental chamber (Forma Scientific, Marietta, OH) set to a neutral ambient temperature of 29.5°C. Half of the animals received an intravenous (i.v.) injection of 10 μg/kg of *Escherichia coli* 0111:B4 LPS (Sigma, St Louis, MO) in 1.0 ml/kg of pyrogen-

*Correspondence: AI Ivanov, Trauma Research, St Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013, USA.
E-mail: aivanov@chw.edu
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free saline (PFS) during the first experiment; during the second experiment, these animals received PFS alone. The second half of the animals received the same treatments in reversed order. All i.v. injections were made through the jugular catheter from the outside the chamber, without disturbing the animals. Colonic temperature (T_c; 9 cm from the anus) was measured with a copper–constantan thermocouple.[14] To evaluate the thermal response, the fever index (FI) was calculated. For this, deviations of T_c from the preinjection level (ΔT_c) were found for both LPS and PFS tests ($\Delta T_{c\text{-LPS}}$ and $\Delta T_{c\text{-PFS}}$, respectively) in each animal, and the difference between $\Delta T_{c\text{-LPS}}$ and $\Delta T_{c\text{-PFS}}$ was integrated over 0–360 min postinjection. Each rat was allowed to recover from the experiments for 3 weeks (*fa/fa* and *Fa/?*) or 6 weeks (OLETF and LETO), anesthetized with ketamine (10 mg/kg, i.v.), had 3 ml of blood withdrawn by heart puncture, and killed with sodium pentobarbital (20 mg/kg, i.v.). The retroperitoneal (including pararenal) and epididymal fat (collectively termed 'visceral' fat) was removed and weighed. The serum samples were sent to a clinical laboratory to determine the total triglycerides and total cholesterol concentrations. Statistical analyses were performed using Student's unpaired *t*-test. The protocol was approved by Legacy Institutional Animal Care and Use Committee.

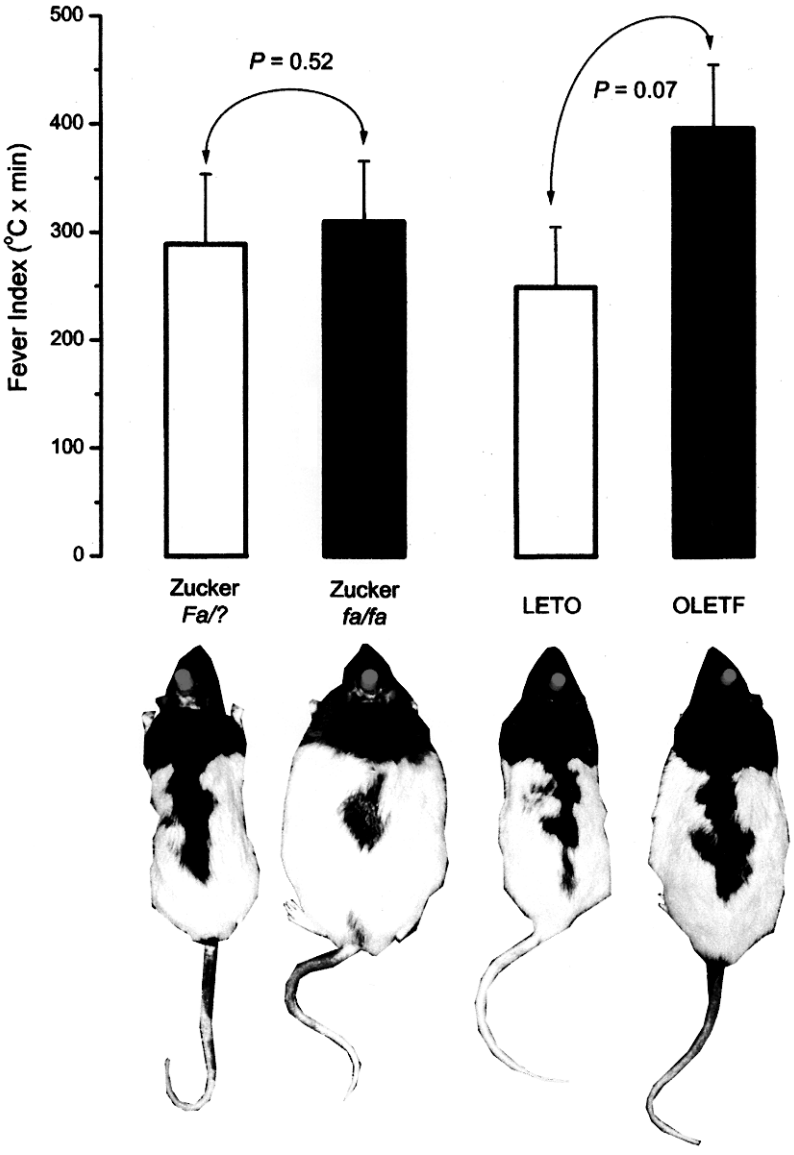

Figure 1 The febrile response to LPS (10 μg/kg, i.v.) in genetically obese rats carrying a defective leptin receptor (Zucker *fa/fa*) or lacking the CCK-A receptor (OLETF) and in their lean counterparts (Zucker *Fa/?* and LETO, respectively). In the photos, all rats have a similar age (~14 weeks) and are shown to the same scale.

Table 1 Verification of obesity in leptin receptor-deficient (Zucker fatty) and CCK-A receptor-deficient (OLETF) rats

	Rat strain			
Obesity index	*Zucker lean*[a] (n = 8)	*Zucker fatty*[a] (n = 8)	*LETO* (n = 5)[b]	*OLETF* (n = 6)[b]
Body mass (g)	305 ± 5	460 ± 10*	415 ± 15	520 ± 15*
Visceral fat (percentage body mass)	1.4 ± 0.1	7.2 ± 0.4*	2.4 ± 0.2	4.7 ± 0.4*
Serum triglycerides (mg/dl)	107 ± 6	400 ± 92*	73 ± 16	157 ± 6*
Serum cholesterol (mg/dl)	65 ± 2	107 ± 8*	92 ± 3	110 ± 5*

[a]14 week old.
[b]17 week old.
*$P < 0.01$; in comparison with the lean counterparts.

Results

The strains tested responded to LPS with polyphasic fevers that resembled the febrile response of the progenitor strain, Long–Evans,[15] except that the third febrile phase was more prominent in OLETF and practically absent in LETO rats. By using the FI as an integrative measure of the febrile response, we found that, within each lean-obese pair compared, the obese animals exhibited no decrease in the febrile responsiveness; if anything, their fevers tended to be higher than fevers in their lean counterparts (Figure 1). The response of Zucker fatty rats (FI 310 ± 56°C min) was similar to that of Zucker lean animals (289 ± 65°C min; $P = 0.52$), and the FI of obese OLETF rats (396 ± 59°C min) did not significantly differ from that of lean LETO animals (249 ± 56°C min, $P = 0.07$). In agreement with their phenotypes (Figure 1), Zucker *fa/fa* and OLETF rats had higher body mass and fat content in comparison with their respective lean counterparts (Table 1). Zucker *fa/fa* rats exhibited severe hypertriglyceridemia and hypercholesterolemia, whereas OLETF rats presented marked hypertriglyceridemia with marginal hypercholesterolemia.

Discussion

The present study demonstrates that neither Zucker nor OLETF obese rats show any decrease in their febrile responsiveness to LPS, thus contradicting Rosenthal *et al,*[7] who reported a suppression of the early febrile response to LPS in Zucker *fa/fa* rats. However, the authors of the latter study administered LPS via an acute i.m. injection, which is unavoidably accompanied by handling and pain, whereas in our study the animals were injected i.v. through a preimplanted catheter, without being handled or needle pricked. In fact, Rosenthal *et al* reported that their injection procedure resulted in a marked stress hyperthermia, and that this hyperthermia was inhibited in the obese animals. Since hyperthermia from injection and fever often overlap,[14,16] the attenuation of the early febrile response in the study by Rosenthal *et al* can reflect a lower stress response of Zucker fatty rather than a depression of the febrile response *per se*.

Another piece of experimental evidence that seemingly contradicts our results is deficient brown fat thermogenesis of *fa/fa* rats.[5,6] Since the brown adipose tissue is the major source of heat production in the rat,[17] Zucker obese rats could have been expected to respond to LPS with low T_c rises. This, however, was not the case in our study, which was conducted at a neutral ambient temperature of 29.5°C. Although brown fat thermogenesis is crucial for thermoregulation in a cold environment, it loses its primary role at neutral temperatures. Under thermoneutral conditions, skin vasoconstriction is the earliest effector to be recruited in the febrile response;[18] often vasoconstriction alone is sufficient to mount the febrile response, and no activation of heat production occurs.[19]

In view of the methodological issues discussed, the literature data do not shed light on the fever mechanisms *per se* in obese animals, but rather demonstrate their decreased thermogenic capacity and stress reactivity. The present study, which was conducted under nonstressful, thermoneutral conditions, shows that obesity *per se* does not decrease the febrile responsiveness. This conclusion is based on the data from two different rat models of hereditary obesity, viz. Zucker *fa/fa* (has a defective receptor for leptin) and OLETF (lacks the CCK-A receptor).

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