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Fever responses of Zucker rats with and without *fatty* mutation of the leptin receptor

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Ivanov, Andrei I., and Andrej A. Romanovsky. Fever responses of Zucker rats with and without *fatty* mutation of the leptin receptor. *Am J Physiol Regulatory Integrative Comp Physiol* 282: R311–R316, 2002; 10.1152/ajpregu.00376.2001.—Leptin is thought to be involved in febrigenic signaling from the periphery to the brain. Zucker obese rats have a so-called *fatty* mutation in the leptin receptor gene and express a dysfunctional protein. Studies comparing the fever responses of *fatty* (*fa*/*fa*) rats and of their lean (*Fa*/*Fa* and *Fa*/*fa*) counterparts yield contradictory results. To resolve these contradictions, we evaluated the effect of *fatty* mutation on infectious and stress-associated fevers at thermoneutrality (29°C) and in a cool environment (20°C). Zucker *fa*/*fa* and *Fa*/*?* rats were infused with *Escherichia coli* lipopolysaccharide (LPS; 10 μg/kg) through a jugular catheter (infectious fever) or with saline through the catheter (control) or received a painful intramuscular injection of saline (stress fever). At thermoneutrality, the colonic temperature (T_c) responses of *fatty* rats to all stimuli tested were no different from the responses of lean rats. In a cool environment, T_c responses of *fatty* rats to all stimuli were ~0.5°C lower than those of lean rats. The observed attenuation of LPS-induced and stress-associated fevers in Zucker *fatty* rats in the cold agrees with the literature data showing that brown adipose tissue (the major heat production effector) is morphologically and functionally defective in these rats. The normal febrile responses of *fatty* Zucker rats to pyrogenic stimuli at thermoneutrality indicate that *fatty* mutation does not interrupt febrigenic signaling from the periphery to the brain.

infectious fever; stress fever; lipopolysaccharide; endotoxin; thermogenesis; thermoneutrality; cold exposure; obesity

FEVER is a common sign of inflammation, infection, and stress. According to the definition (38), infectious fever is triggered by a variety of exogenous pyrogens, such as bacterial lipopolysaccharide (LPS), and further mediated by endogenous pyrogens, including cytokines [e.g., interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α] and prostaglandins (PGs) of the E series. Stress fever (also known as stress hyperthermia) is evoked by both physical and psychological stimuli such as restraint, foot shock, or exposure to a new environment. Like infectious fever, stress fever is mediated by cytokines and PGs (19, 20). At the effector level, fever is realized via inhibition of heat loss mechanisms and/or activation of heat production mechanisms (34, 36).

Several lines of evidence suggest that mechanisms of LPS- and cytokine-induced fevers involve leptin, an IL-6-like protein produced by adipocytes and responsible for adipose tissue-to-brain signaling (7, 9). Indeed, exogenous (LPS) and endogenous (IL-1 and TNF) pyrogens upregulate expression of the leptin gene and increase the concentration of leptin in the blood (15, 17, 31). LPS-induced leptin expression is mediated by IL-1β (10). Leptin, in turn, stimulates production of pyrogenic cytokines by immunocytes (21, 22). Furthermore, Luheshi et al. (23) demonstrated pyrogenic activity for leptin. The authors found that intracerebroventricular or intravenous administration of leptin to rats causes fever, which is mediated by IL-1β and PGs. It could be expected, therefore, that animals deficient in leptin or its receptor should respond to pyrogens with attenuated fevers.

Zucker obese rats have a missense point mutation (*fatty*) in the primary leptin receptor gene and express a dysfunctional protein with a glycine-to-proline substitution in position 269 of the ligand-binding domain (4, 26). As a result, the receptor-mediated transport and intracellular signaling of leptin are defective in these animals (6, 41). Studies examining the effect of the *fatty* mutation on fever yield contradictory results (3, 8, 27, 30). Rosenthal et al. (30) observed an atten-

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uation of the early, but not late, stages of an intramuscular LPS-induced fever in Zucker *fatty* (*fa/fa*) rats compared with their lean (*Fa/Fa* and *Fa/fa*) counterparts. The authors also reported that the *fatty* rats responded to a painful intramuscular injection of saline with an attenuated stress fever. Dascombe et al. (8) and Busbridge et al. (3) found that the febrile response to intracerebroventricular IL-1β was strongly attenuated in Zucker obese rats. Plata-Salamán et al. (27) found that intracerebroventricular IL-1β-induced fever was not inhibited but, to the contrary, strongly exaggerated in *fa/fa* rats, whereas intracerebroventricular IL-2- and IL-6-induced fevers were suppressed, and intracerebroventricular TNF-α-induced fever was unaffected. The data showing an attenuation of fever in obese rats (3, 8, 27, 30) seem to suggest a functionally important role of leptin receptor in febrigenic signaling; they also suggest a deficiency of this signaling in *fatty* mutants. However, interpretation of these data is convoluted.

All studies reviewed (3, 8, 27, 30) were conducted at an ambient temperature (T_a) of 22–24°C, i.e., under conditions of mild-to-moderate cold exposure. Even 24°C is normally below the lower border of the thermoneutral zone for Zucker rats, both obese and lean (25, 28). At subneutral T_as, the development of the febrile response requires activation of thermogenesis in brown adipose tissue, the major heat production effector in the rat (12). However, brown adipose tissue is morphologically and functionally defective in *fatty* animals, and their thermogenic responses are weak (2, 33). Hence, the observed attenuation of intracerebroventricular IL-1β, IL-2, and IL-6 fevers (3, 8, 27), stress fever (30), and the early stages of intramuscular LPS fever (30) might result from insufficient thermogenesis rather than a deficiency of the hypothesized leptin receptor-mediated febrigenic signaling.

The present study was conducted to evaluate the effect of *fatty* mutation of the leptin receptor on LPS-induced fever and stress fever; the latter was caused by a painful intramuscular injection of saline. The responses were studied at thermoneutrality and in a cool environment. The results suggest that *fatty* mutation leads to a thermogenic insufficiency but does not interfere with febrigenic signaling.

MATERIALS AND METHODS

Animals

Twelve male Zucker *fa/fa* and eleven *Fa/?* rats were purchased from Harlan (Indianapolis, IN). At the time of the experiments, all rats were 9–10 wk old. Initially, the animals were housed three per standard "shoebox"; after surgery, they were caged individually. The room was on a 12:12-h light-dark cycle (lights on from 7:00 AM); T_a was maintained at 22°C. Food (Teklad Rodent Diet W 8604, Harlan Teklad, Madison, WI) and water were available ad libitum. The animals were handled and weighed regularly. They also were habituated (5 training sessions, 4 h each) to a cylindrical stock that limited their back-and-forth movements and prevented them from turning around. The same stocks have been used in our laboratory in the past (29). We learned that rats easily adapt to the stocks and often prefer them to the open space of their home cages; they show no signs of stress and have the same body temperature as their freely moving counterparts would have at the same T_a (42). All experiments were performed during the light phase (measurements started at ~9:00 AM). To prevent the development of tolerance, each animal received LPS only once. At the end of the study, the rats were killed with pentobarbital sodium (20 mg/kg iv). The experiments have been approved by the Institutional Animal Care and Use Committee (Protocol 98–07).

Surgical Preparation

General information. Each rat was subjected to a two-step surgical operation. During the first step, an acrylic platform was secured to the rat's skull. During the second step, a catheter was implanted into the vena cava superior, the free end of the catheter was placed into a hollow pedestal, and the pedestal was affixed to the platform (see below). Before surgery, each rat received a subcutaneous injection of an antibiotic (enrofloxacin, 12 mg/kg) and was anesthetized with an intraperitoneal injection of ketamine-xylazine-acepromazine cocktail (55.6, 5.5, and 1.1 mg/kg, respectively). During surgery, the animal's body was heated with a Deltaphase Isothermal Pad (Braintree Scientific, Braintree, MA). Postoperatively, the animal was allowed to recover from anesthesia under a heating lamp and transferred to its home cage thereafter.

Step 1. The head of an anesthetized rat was placed into a stereotaxic instrument (model 900, David Kopf Instruments, Tujunga, CA), and a 1.5-cm incision was made over the sagittal suture. Subcutaneous tissues were removed, and the bone was cleansed with hydrogen peroxide (3%) and dried with ethanol (98%). Four miniature stainless steel screws were threaded into the bone. The bone and the screws were covered with dental acrylic to form a round platform (~1 cm in diameter) with a flat surface. After the acrylic hardened, the rat was released from the stereotaxic instrument.

Step 2. The animal was then placed on an operating board (Harvard Apparatus, South Natick, MA), and a 1-cm longitudinal incision was made on the ventral surface of the neck, 1 cm to the right of the trachea. The muscles were retracted, and the right jugular vein was exposed. A silicone catheter (ID 0.5 mm, OD 0.9 mm) containing heparinized (50 U/ml) pyrogen-free saline was passed into the vena cava superior through the right jugular vein. The 15-cm free end of the catheter was pulled under the skin to the head. The wound on the ventral surface of the neck was sutured. The free end of the catheter was rolled into a coil and placed into a polypropylene vial (pedestal). The pedestal was affixed to the platform with dental acrylic and protected with a screwed-on cap. The day after surgery and every other day thereafter, the catheter was flushed with heparinized saline.

Experiments

Instrumentation. For an experiment, each rat was placed into its stock and transferred to a climatic chamber (Forma Scientific, Marietta, OH) set to 50% relative humidity and a T_a of either 29.0°C (neutral for Zucker rats; Refs. 25, 28) or 20.0°C (moderate cold exposure). The exteriorized portion of the intravenous catheter was pulled through a wall port and connected to a syringe. Each animal was instrumented with a thermocouple (inserted 9 cm beyond the anus) to measure its colonic temperature (T_c). The thermocouples from multiple animals were connected to a data logger (Dianachart, Rockaway, NJ) and personal computer. After a 1-h stabiliza-

tion period, the measurements were begun, and T_c and T_a were sampled every 2 min for the duration of the test.

Protocol. After the baseline T_c was recorded for 1 h, each animal received either an intravenous injection of saline (saline test), an intravenous injection of LPS (LPS test), or a painful intramuscular injection of saline (stress test). In the LPS test, *Escherichia coli* 0111:B4 LPS (lot no. 35H4086; Sigma, St. Louis, MO; 10 μg/kg) in saline (1 ml/kg) was nonstressfully injected through the catheter from outside the chamber. In the saline test, pyrogen-free saline (1 ml/kg) was injected through the catheter. In the stress test, saline (1 ml/kg) was injected intramuscularly, into the posterior aspect of the thigh (mm. biceps femoris, semitendinosus, and gluteus maximus) with a 23-gauge needle; this injection was associated with unavoidable pain and stress. In each rat, all three tests were conducted. The LPS and saline tests were performed 3 days apart in a counterbalanced order; the stress test was performed 2 wk later. Each test was conducted in a neutral (29°C) or cool (20°C) environment. The rats were observed for 8 h (LPS or saline test) or 2 h (stress test).

Data Processing and Analysis

Measure of the febrile response. Two measures are often used to assess the height of fever: deep body temperature (e.g., T_c) at the peak of the response (T_{max}) and the maximal rise in deep body temperature (ΔT_{max}). The latter is calculated as follows

$$\Delta T_{max} = T_{max} - T_0 \quad (1)$$

where T_0 is T_c at *time 0* (time of the pyrogen injection). *Equation 1* shows that, if two animals have equal T_0s and respond to a pyrogen with equal ΔT_{max}s, their T_{max}s are equal as well. Hence, when animals have the same T_0, their febrile responses can be compared by using either T_{max} or ΔT_{max}, and the results of the comparison are independent of the response measure used. However, when two animals have different T_0s and respond to a pyrogen with equal ΔT_{max}s, their T_{max}s are not equal. In this case, comparison of the two responses gives different results, depending on whether T_{max} or ΔT_{max} is used. In a variety of models [intracerebroventricular PGE_1- or PGE_2-induced fever (11, 24, 35, 37), intracerebroventricular cholecystokinin-8-induced fever (35, 37), intravenous LPS fever (34), and yeast infection-associated fever (18) in rats; intraperitoneal LPS-induced fever and stress fever in hamsters (5)], it has been firmly established that T_{max} represents a consistent characteristic of the febrile response. In contrast, ΔT_{max} varies widely, depending on experimental conditions (different T_0s due to different T_as, day-night variations, etc.), and cannot be used as a reliable measure of fever height. Hence, T_{max} (not ΔT_{max}) is the physiologically justified measure [see Feng et al. (11)]. This measure was used in the present study. For the triphasic LPS-induced fever (see Ref. 29), three T_{max}s were determined, one for each febrile phase. For the monophasic stress fever, one T_{max} was determined.

Data analysis. Different procedures were used to compare curves [T_c(time) functions] and individual points (T_0s and T_{max}s). The T_c curves were randomized between genotypes (separately for each test) and subjected to 10,000 repetitions of the analysis of variance. An empirical distribution of the *F*-statistic was created and compared with the original statistic. The T_{max}s (for stress fever and each phase of LPS fever) and T_0s were determined in individual curves, averaged across the group, and compared between genotypes by Student's *t*-test. The data are presented as means ± SE.

RESULTS

Saline Test

At thermoneutrality (Fig. 1, *left*), Zucker *Fa/?* and *fa/fa* rats had similar T_0s (37.8 ± 0.1 and 38.1 ± 0.2°C, respectively; $P = 0.153$). Saline injection did not affect T_c in either strain and evoked no significant difference between the genotypes ($P = 0.603$). In the cool environment (Fig. 1, *right*), the T_0 of the lean rats (37.9 ± 0.2°C) was substantially higher than that of the *fatty* rats (37.3 ± 0.1°C; $P = 0.010$). Throughout the test, T_c of the lean rats gradually decreased and reached ~37.3°C at the end of the observation period. In the obese rats, T_c decreased in a parallel fashion and remained ~1°C lower than in the lean rats throughout the test ($P = 0.004$).

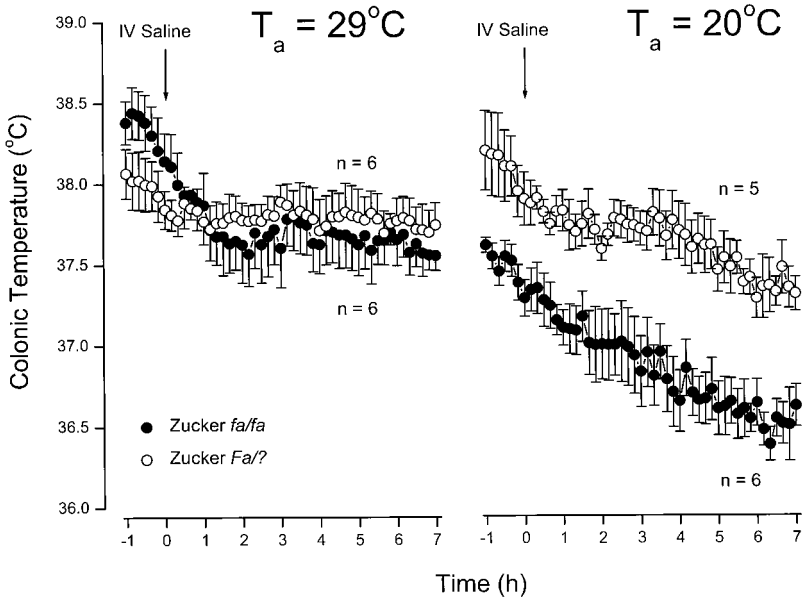

Fig. 1. Thermal responses of Zucker obese (*fa/fa*) and lean (*Fa/?*) rats to a nonstressful infusion of pyrogen-free saline (1 ml/kg iv) via a jugular catheter at thermoneutrality [ambient temperature (T_a) = 29°C; *left*] or in a cool environment (T_a = 20°C; *right*).

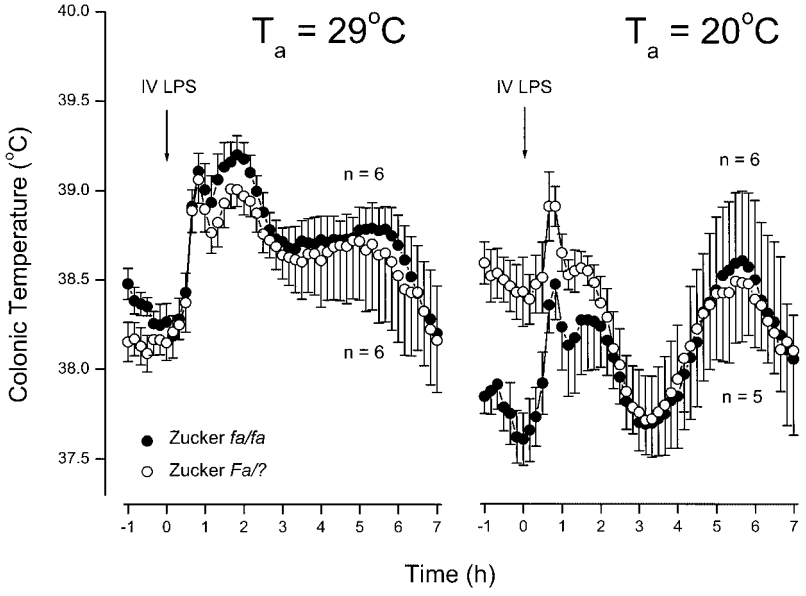

Fig. 2. Infectious fever in Zucker rats. Thermal responses of obese (*fa/fa*) and lean (*Fa/?*) rats to a pain-free infusion of *Escherichia coli* lipopolysaccharide (LPS; 10 μg/kg iv) via a jugular catheter at thermoneutrality (T_a = 29°C; *left*) or in a cool environment (T_a = 20°C; *right*).

LPS Test

At the neutral T_a (Fig. 2, *left*), T_0s of the lean and obese rats were 38.1 ± 0.1 and 38.3 ± 0.1°C, respectively (P = 0.089). Both genotypes responded to LPS with triphasic fevers. These fevers had a relatively high first phase (lean: T_{max} = 39.1 ± 0.1°C; obese: T_{max} = 39.1 ± 0.1°C; P = 0.721) and a relatively low third phase (lean: T_{max} = 38.8 ± 0.3°C; obese: T_{max} = 39.0 ± 0.1°C; P = 0.638), which is typical for Long-Evans and Long-Evans-derived rat strains (16, 29). No febrile phase differed significantly between the genotypes. In the cool environment (Fig. 2, *right*), the T_0 of the lean rats (38.4 ± 0.2°C) was substantially higher than that of the obese animals (37.6 ± 0.1°C; P = 0.003). The first phase of the triphasic LPS fever was suppressed in the obese rats (T_{max} = 38.5 ± 0.2°C) compared with the lean (T_{max} = 39.0 ± 0.1°C; P = 0.026), but neither the second phase (lean: T_{max} = 38.6 ± 0.1°C; obese: T_{max} = 38.3 ± 0.3°C; P = 0.325) nor the third phase (lean: T_{max} = 38.6 ± 0.3°C; obese: T_{max} = 38.6 ± 0.4°C; P = 0.934) was affected.

Stress Test

At the neutral T_a (Fig. 3, *left*), T_0s of the lean and obese rats were 37.7 ± 0.1 and 37.9 ± 0.2°C, respectively (P = 0.206). Both genotypes responded to the painful intramuscular injection of saline with rapid rises in T_c; no significant intergenotype differences were found (lean: T_{max} = 38.5 ± 0.1°C; obese: T_{max} = 38.5 ± 0.1°C; P = 0.920). In the cool environment (Fig. 3, *right*), the T_0 of the lean rats (37.9 ± 0.1°C) was substantially higher than that of the obese animals

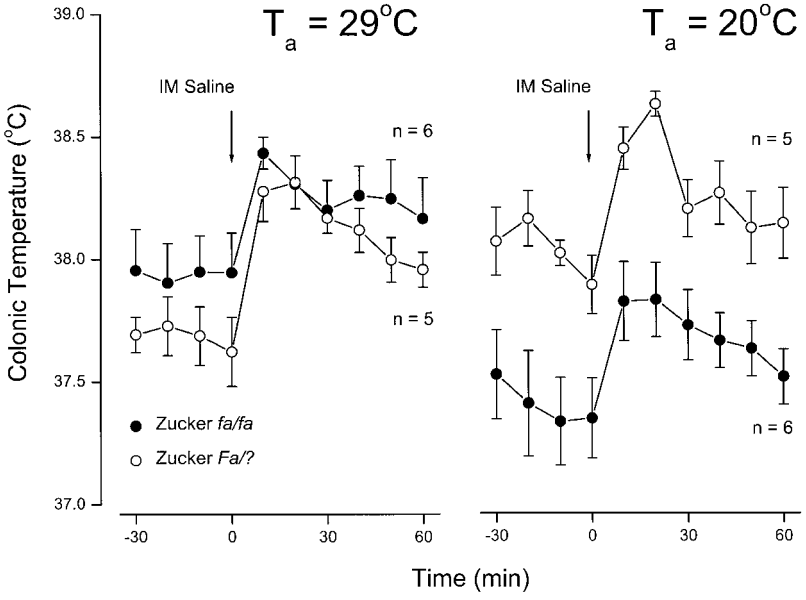

Fig. 3. Stress fever in Zucker rats. Thermal responses of obese (*fa/fa*) and lean (*Fa/?*) rats to a stressful, painful injection of pyrogen-free saline (1 ml/kg im) at thermoneutrality (T_a = 29°C; *left*) or in a cool environment (T_a = 20°C; *right*).

(37.3 ± 0.2°C; $P = 0.015$). The stress fever was suppressed in the obese rats (T_{max} = 38.1 ± 0.2°C) compared with their lean counterparts (T_{max} = 38.8 ± 0.1°C; $P = 0.012$).

DISCUSSION

To test the hypothesis that *fatty* mutation of the leptin receptor impairs febrile responsiveness, we studied LPS fever (a model of infectious fever) and stress fever in Zucker *fa*/*fa* and *Fa*/*?* rats. At thermoneutrality, the two genotypes had comparable T_cs and responded with similar T_c rises to the febrigenic stimuli used, i.e., an intravenous injection of LPS and a mild stressor (intramuscular injection of saline). These findings represent the first attempt to measure the febrile response of *fatty* rats at a neutral T_a. They demonstrate that the *fatty* mutation-associated defect in the primary leptin receptor affects neither LPS-induced nor stress-associated fever.

In a cool environment, the T_0 of *fatty* rats was substantially lower than that of lean rats. These data support previous studies showing that leptin receptor-deficient rats have a defective response to cold and are prone to hypothermia at subneutral T_as (8, 27, 39). Both LPS fever and stress fever were attenuated in the mutants. These findings are consistent with data by others who also used T_c (not ΔT_c; see *Data Processing and Analysis*) as a response measure and showed that stress fever (30), intramuscular LPS-induced fever (30), and intracerebroventricular IL-1β fever (3, 8) were all attenuated in *fatty* Zucker rats at subneutral T_as. In contrast, the only study that used ΔT_c found a variable effect of *fatty* mutation on the febrile response to intracerebroventricular cytokines, from inhibition to no effect to exaggeration (27). However, T_0 of the obese rats was 0.6°C lower than that of the lean rats (27). When T_0s are different, an attenuation of the T_c response may correspond to any change of the ΔT_c response, from inhibition to no effect to exaggeration. Hence, most reports (3, 8, 30) support our finding that febrile responsiveness of Zucker *fatty* rats is inhibited in the cold, while the only remaining study (27) neither supports nor refutes it.

Why is the febrile response of *fatty* rats normal at thermoneutrality but inhibited in the cold? Fever occurs because of a decrease in heat loss (the predominant autonomic mechanism is skin vasoconstriction) and/or an increase in heat production (the predominant autonomic mechanism is thermogenesis in brown adipose tissue). Energetically inexpensive effector mechanisms (skin vasoconstriction) are recruited first; if their activation is insufficient to produce an adequate response, then the expensive effectors (thermogenesis) are activated (36). At neutral and supraneutral T_as, skin vasoconstriction is always used by rats to mount a fever; moreover, at these T_as, rats respond to a pyrogen [e.g., intravenous LPS (34), intracerebroventricular PGE_1 (37), or intracerebroventricular cholecystokinin-8 (37)] often by using skin vasoconstriction alone, without activation of heat production. At subneutral T_as, skin vasculature is already constricted; no further constriction is possible (28, 34), and rats depend on brown fat thermogenesis to produce the febrile response. Yet, the brown adipose tissue is morphologically and functionally defective in Zucker *fatty* animals, and their thermogenic responses are weak (2, 33). Therefore, the impaired thermogenesis in Zucker *fa*/*fa* rats is likely to account for the inhibition of their febrile responsiveness at subneutral T_as (3, 8, 30, and present data). At neutral T_as, the role of thermogenesis is less important, and its deficiency leads to no change in the fever response.

We conclude that attenuation of the febrile response observed in *fatty* Zucker rats at subneutral T_as probably reflects impaired thermogenesis in brown adipose tissue. When studied at thermoneutrality, LPS-induced and stress-associated fevers of *fatty* rats are no different from the responses of lean rats. These data indicate that *fatty* mutation of the leptin receptor does not interrupt febrigenic signaling.

Perspectives

The present results show that *fatty* mutation does not interrupt the mediatory cascade of fever. Nevertheless, they do not rule out the possibility that the febrigenic cascade involves the leptin receptor. Until recently, *fatty* mutation was thought to attenuate or even to prevent leptin receptor-mediated signaling completely in various experimental tests (1, 6, 14, 32, 41). However, recent studies (13, 40) show that this mutation may permit normal functioning of the leptin receptor, at least in some experimental paradigms. Hence, negative results obtained in *fatty* mutants should be viewed with caution. Further investigations involving pharmacological blockade or genetic deletion of the leptin receptor are warranted.

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REFERENCES

1. **Al-Barazanji KA, Buckingham RE, Arch JR, Haynes A, Mossakowska DL, Holmes SD, McHale MT, Wang XM, and Gloger IS.** Effect of intracerebroventricular infusion of leptin in obese Zucker rats. *Obes Res* 5: 387–394, 1997.
2. **Bing C, Pickavance L, Wang Q, Frankish H, Trayhurn P, and Williams G.** Role of hypothalamic neuropeptide Y neurons in the defective thermogenic response to acute cold exposure in *fatty* Zucker rats. *Neuroscience* 80: 277–284, 1997.
3. **Busbridge NJ, Carnie JA, Dascombe MJ, Johnston JA, and Rothwell NJ.** Adrenalectomy reverses the impaired pyrogenic responses to interleukin-1β in obese Zucker rats. *Int J Obes* 14: 809–814, 1990.
4. **Chua SC, White DW, Wu-Peng XS, Liu SM, Okada N, Kershaw EE, Chung WK, Power-Kehoe L, Chua M, Tartaglia LA, and Liebel RL.** Phenotype of *fatty* due to Gln269Pro mutation in the leptin receptor (Lepr). *Diabetes* 45: 1141–1143, 1996.

5. **Conn CA, Borer KT, and Kluger MJ.** Body temperature rhythm and response to pyrogen in exercising and sedentary hamsters. *Med Sci Sports Exerc* 22: 636–642, 1990.
6. **Crouse JA, Elliott GE, Burgess TL, Chui L, Bennett L, Moore J, Nicolson M, and Pacifici RE.** Altered cell surface expression and signaling of leptin receptor containing the *fatty* mutation. *J Biol Chem* 273: 18365–18373, 1998.
7. **Dallongeville J, Fruchart JC, and Auwerx J.** Leptin, a pleiotropic hormone: physiology, pharmacology, and strategies for discovery of leptin modulators. *J Med Chem* 41: 5337–5352, 1998.
8. **Dascombe MJ, Hardwick A, Lefeuvre RA, and Rothwell NJ.** Impaired effects of interleukin-1β on fever and thermogenesis in genetically obese rats. *Int J Obes* 13: 367–373, 1989.
9. **Elmquist JK, Maratos-Flier E, Saper CB, and Flier JS.** Unraveling the central nervous system pathways underlying responses to leptin. *Nat Neurosci* 1: 445–450, 1998.
10. **Faggioni R, Fantuzzi G, Fuller J, Dinarello CA, Feingold KR, and Grunfeld C.** IL-1β mediates leptin induction during inflammation. *Am J Physiol Regulatory Integrative Comp Physiol* 274: R204–R208, 1998.
11. **Feng JD, Price M, Cohen J, and Satinoff E.** Prostaglandin fevers in rats: regulated change in body temperature or change in regulated body temperature? *Am J Physiol Regulatory Integrative Comp Physiol* 257: R695–R699, 1989.
12. **Foster DO.** Quantitative contribution of brown adipose tissue thermogenesis to overall metabolism. *Can J Biochem Cell Biol* 62: 618–622, 1984.
13. **Fox AS and Olster DH.** Effect of intracerebroventricular leptin administration of feeding and sexual behaviors in lean and obese female Zucker rats. *Horm Behav* 4: 377–387, 2000.
14. **Glaum SR, Hara M, Bindokas VP, Lee CC, Polonsky KS, Bell GI, and Miller RJ.** Leptin, the obese gene product, rapidly modulates synaptic transmission in the hypothalamus. *Mol Pharmacol* 50: 230–235, 1996.
15. **Grunfeld C, Zhao C, Fuller J, Pollack A, Moser A, Friedman J, and Feingold KR.** Endotoxin and cytokines induce expression of leptin, the *ob* gene product, in hamsters. *J Clin Invest* 97: 2152–2157, 1996.
16. **Ivanov AI, Kulchitsky VA, and Romanovsky AA.** Role of cholecystokinin A receptor (CCK Ar) in fever. *Soc Neurosci Abstr* 26: 1740, 2000.
17. **Janik JE, Curti BD, Considine RV, Rager HC, Powers GC, Alvord WG, Smith J, Gause BL, and Kopp WC.** Interleukin 1α increases serum leptin concentrations in humans. *J Clin Endocrinol Metab* 82: 3084–3086, 1997.
18. **Kent S, Price M, and Satinoff E.** Fever alters characteristics of sleep in rats. *Physiol Behav* 44: 709–715, 1988.
19. **Kluger MJ, O'Reilly B, Shore TR, and Vander AJ.** Further evidence that stress hyperthermia is a fever. *Physiol Behav* 39: 736–766, 1987.
20. **LeMay LG, Vander AJ, and Kluger MJ.** The effect of psychological stress on plasma interleukin-6 activity in rats. *Physiol Behav* 47: 957–961, 1990.
21. **Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD, and Diehl AM.** Leptin regulates proinflammatory immune responses. *FASEB J* 12: 57–65, 1998.
22. **Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, and Lechler RI.** Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 394: 897–901, 1998.
23. **Luheshi GN, Gardener JD, Rushforth DA, Loudon AS, and Rothwell NJ.** Leptin actions on food intake and body temperature are mediated by IL-1. *Proc Natl Acad Sci USA* 96: 7047–7052, 1999.
24. **Malkinson TJ, Cooper KE, and Veale WL.** Physiological changes during thermoregulation and fever in urethane-anesthetized rats. *Am J Physiol Regulatory Integrative Comp Physiol* 255: R73–R81, 1988.
25. **Megirian D, Dmochowski J, and Farkas GA.** Mechanism controlling sleep organization of the obese Zucker rats. *J Appl Physiol* 84: 253–256, 1998.
26. **Phillips MS, Liu Q, Hammond HA, Dugan V, Hey PJ, Caskey CT, and Hess JF.** Leptin receptor missense mutation in the *fatty* Zucker rat. *Nat Genet* 13: 18–19, 1996.
27. **Plata-Salamán C, Peloso E, and Satinoff E.** Cytokine-induced fever in obese (*fa/fa*) and lean (*Fa/Fa*) Zucker rats. *Am J Physiol Regulatory Integrative Comp Physiol* 275: R1353–R1357, 1998.
28. **Romanovsky AA, Ivanov AI, and Shimansky YP.** How to determine whether a given environment is thermoneutral for a given animal. *Soc Neurosci Abstr* 27: 2506, 2001.
29. **Romanovsky AA, Simons CT, and Kulchitsky VA.** "Biphasic" fever often consists of more than two phases. *Am J Physiol Regulatory Integrative Comp Physiol* 275: R323–R331, 1998.
30. **Rosenthal M, Roth J, Störr J, and Zeisberger E.** Fever response in lean (*Fa/−*) and obese (*fa/fa*) Zucker rats and its lack to repeated injections of LPS. *Physiol Behav* 59: 787–793, 1996.
31. **Sarraf P, Friderich RC, Turner EM, Ma G, Jaskowiak NT, Rivet D, Flier JS, Lowell BB, Fraker DL, and Alexander HR.** Multiple cytokines and acute inflammation raise mouse leptin level: potential role in the inflammatory anorexia. *J Exp Med* 185: 171–175, 1997.
32. **Seeley RJ, van Dijk G, Campfield LA, Smith FJ, Burn P, Nelligan JA, Bell SM, Backin DG, Woods SC, and Schwartz MW.** Intraventricular OB protein (leptin) reduces food intake and body weight of lean rats but not obese Zucker rats. *Horm Metab Res* 28: 664–668, 1996.
33. **Seydoux J, Benzi RH, Shibata M, and Girardier L.** Underlying mechanisms of atrophic state of brown adipose tissue in obese Zucker rats. *Am J Physiol Regulatory Integrative Comp Physiol* 259: R61–R69, 1990.
34. **Székely M and Szelényi Z.** Endotoxin fever in the rat. *Acta Physiol Hung* 53: 265–277, 1979.
35. **Szelényi Z, Barthó L, Székely M, and Romanovsky AA.** Cholecystokinin-octapeptide (CCK-8) injected into a cerebral ventricle induces a fever-like thermoregulatory response mediated by type B CCK-receptor in the rat. *Brain Res* 638: 69–77, 1994.
36. **Szelényi Z and Székely M.** Comparison of the effector mechanisms during endotoxin fever in the adult rabbit. *Acta Physiol Hung* 54: 33–41, 1979.
37. **Szelényi Z, Székely M, and Romanovskii AA (Romanovsky AA).** The central thermoregulatory action of cholecystokinin-8 and prostaglandin E_1. *Fiziol Zh* 78: 94–101, 1992 (in Russian).
38. **The Commission for Thermal Physiology of the International Union of Physiological Sciences (I.U.P.S. Thermal Commission).** Glossary of terms for thermal physiology: third edition. *Jpn J Physiol* 51: i–xxxvi, 2001.
39. **Trayhurn P, Thurlby PL, and James WP.** A defective response to cold in the obese (*ob/ob*) mouse and the obese Zucker (*fa/fa*) rat (Abstract). *Proc Nutr Soc* 35: 133A, 1976.
40. **Wang T, Hartzell DL, Flatt WP, Martin RJ, and Baile CA.** Responses of lean and obese Zucker rats to centrally administered leptin. *Physiol Behav* 65: 333–341, 1998.
41. **Yamashita T, Murakami T, Iida M, Kuwajima M, and Shima K.** Leptin receptor of Zucker *fatty* rat performs reduced signal transduction. *Diabetes* 46: 1077–1080, 1997.
42. **Yang Y and Gordon CJ.** Ambient temperature limits and stability of temperature regulation in telemetered male and female rats. *J Therm Biol* 21: 353–363, 1996.