Published in final edited form as:

J Burn Care Res. 2009 ; 30(6): 993–1001. doi:10.1097/BCR.0b013e3181bf7b4.

Effects of Burn Injury on Markers of Hypermetabolism in Rats

Maria-Louisa Izamis, MS, Korkut Uygun, PhD, Basak Uygun, PhD, Martin L. Yarmush, MD, PhD, and François Berthiaume, PhD

Center for Engineering in Medicine/Surgical Services, Massachusetts General Hospital, Harvard Medical School, Boston; and the Shriners Hospitals for Children, Boston, Massachusetts

Abstract

The basic metrics of hypermetabolism have not been thoroughly characterized in rat burn injury models. We examined three models expected to differ in sensitivity to burn injury to identify that which group(s) exhibited the most clinically relevant metabolic response. Six and 12 weeks old male CD (6 week mCD and 12 week mCD) rats, and 12 weeks old female Fischer (12 week fFI) rats received a 20% total body surface area burn, followed by saline resuscitation. Activity, core body temperature, heart rate (via implanted telemetry devices), body weight, food and water intake, and fecal output were measured daily for 1 week before and after burn. Rats lost weight initially postburn but resumed weight gain by 1 week, except for 12 week mCD rats. Core body temperature increased above normal 2 days postburn and returned to baseline by 1 week. Food intake, normalized to body weight, remained unchanged postburn for 12 week mCD rats, but decreased in 6 week mCD rats and increased in 12 week fFI rats. Heart rate in the 12 week mCD and 12 week fFI rats remained at 10 to 15% above baseline, whereas, in 6 week mCD, heart rates returned to baseline after 4 days. Activity levels were unchanged for 12 week fFI and 6 week mCD rats postburn, but decreased for 12 week mCD rats. Postburn hypermetabolism was most significant and sustained in 12 week mCD rats, of least consequence and brief in 6 week mCD rats, and intermediate in 12 week fFI rats. The disparate responses indicate that the choice of animal model should be carefully considered in hypermetabolism studies.

Hypermetabolism is a complex clinical state characterized by an increase in resting energy expenditure, a febrile response, and a hyperdynamic circulation. Hypermetabolism typically occurs after severe trauma, such as burns or major surgery, and in certain critical illnesses, such as cancer, and that persists in parallel to, or beyond, the original pathology as an often-fatal comorbidity.^{1,2} The long-term consequence of hypermetabolism is a severe depletion of the patient's resources by the combined effects of neurohormonal dysfunction, immune compromise, and autocatabolism. Although various therapeutic approaches have been shown to ameliorate hypermetabolism,^{2–9} it has never successfully been eliminated by clinical intervention.

Several human studies have demonstrated differences in the long-term outcome after burn injury as a function of age and genetic constitution.^{8,10–14} Children were found to tolerate and survive large burns better than adults, whereas in adults, increased muscle catabolism

was primarily a function of increasing age, weight, and delay in surgical attention.¹⁵ Mouse and rat models of burn injury are potentially useful to assess these variables at the preclinical level. Previous studies have shown that survival and wound-healing rates vary significantly depending on strain, gender, and age,^{16–19} and genetic differences may account for some of the variations observed.¹⁷ In these studies, however, there was little information on the impact of these factors on the basic metrics of the hypermetabolic response (resting energy expenditure, heart rate, and core body temperature). This information could substantially facilitate a better understanding of the role of hypermetabolism on postburn survival and subsequently enable optimized models and treatment strategies.

In this study, we asked the question whether different rat models subjected to the same severity of burn injury [a nonlethal 20% total body surface area (TBSA) burn] would exhibit different responses with respect to the classical markers of hypermetabolism. In previous studies, we have described in detail the hepatic and hindquarter metabolic response after a well-defined and nonlethal 20% TBSA burn in 150 to 200 g (and, thus, 6–7 weeks old) male CD rats.^{20–22} Rapaport et al¹⁹ demonstrated that this strain of rat (at 250–300 g or roughly 8–9 weeks old) had an “intermediate” sensitivity to burn. We subsequently created a group of 6-week-old male Sprague Dawley rats (6-week mCD) and compared them with a group twice their age and more than three times their body size (12-week mCD) and with a “susceptible” group of 12-week-old female Fischer rats (12-week fFI), who were the same age as the 12-week mCD rats, but of similar weight as the 6-week mCD rats at time of burn. The results show that all rats exhibited a distinctive but varied hypermetabolic response. The 6-week mCD group was least affected, whereas slightly older 12-week mCD rats exhibited significantly different responses. Rats in the 12-week fFI group demonstrated a similar though milder response to burn than the age-matched 12-week mCD group, suggesting that genetic variations also impact on the hypermetabolic response. These results highlight the critical importance of characterizing the hypermetabolic response in animal models of burn injury.

METHODS

Animals

Animal procedures were performed in accordance with National Research Council guidelines, and the experimental protocol was approved by the Subcommittee on Research Animal Care, Committee on Research, Massachusetts General Hospital. Three types of rats were obtained from Charles River Labs, Inc. (Wilmington, MA): 12-week-old male CD (12-week mCD), 6-week-old male CD (6-week mCD), and 12-week-old female Fischer/CDF F-344 (12-week fFI).

On arrival, animals were individually housed in metabolic cages (Rat Metabolic Cage 150–300 g; Ancare Corp., North Bellmore, NY), where they were provided water and food ad libitum. After an acclimatization period of at least 2 days, the animals were subsequently weighed at the same time daily, and their 24-hour food and water consumption, as well as fecal output, were recorded for the entire duration of the experiment (2 weeks).

Implantation of Telemetry Device and Burn Injury Model

Rats within groups (n = 8 per group) were randomized, and half from each group (n = 4 per group) received implantable telemetry devices (PhysioTel CTA-F40 Small Animal Transmitter; Data Sciences International, St. Paul, MN) that continuously measure heart rate, core body temperature, and body motion/ activity. Rats were anesthetized with isoflurane, and under aseptic conditions, a 2-cm midline incision was made through the abdominal muscle, followed by two 4-mm incisions distal to the incision in the abdominal muscle. The implant was placed in the abdominal cavity, and the leads were passed out through the 4-mm incisions. The muscle layer was sutured back in place, securing the implant through suture rings to the abdominal wall. The leads were passed through blunt dissection between skin and fascia to the right armpit and left groin area and sewn in place. Finally, the abdominal skin incision was closed. All animal weights measured postimplant were corrected for the weight of the implant (5 ± 0.5 g).

One week postimplant, at which point the animals had recovered their normal weight gain rates, animals were anesthetized with a mixture of ketamine (62.5 mg/kg of body weight) and xylazine (12.5 mg/kg of body weight). The dorsum of each rat was shaved with clippers and marked for an area equivalent to 20% of the calculated TBSA according to a computer-generated template.²³ The marked dorsal area was immersed in boiling water for 10 seconds as previously described.^{22,24} Animals were then immediately resuscitated with an intraperitoneal saline injection (3 ml/kg/%TBSA) and returned to their cages. Their progress was followed for 1 week, after which they were killed. At that time, the burn wound and implant site were examined for possible signs of infection. This study design provided two periods of observation: postimplant/preburn with no-implant control and postburn.

Food Mass Balance

Daily food intake and fecal output were recorded, and the data were used in a simple mass balance equation that we developed as follows:

$$\text{Food Mass Intake} - \text{Fecal Mass Output} - \text{Body Weight Gain} = \text{OE} \quad [1]$$

The difference between daily food consumption, fecal production, and weight gain, is referred to as mass for other energy (OE)-requiring processes that include basal metabolism and activity. This equation makes the following four assumptions: 1) a direct correlation exists between daily food intake, fecal output, and body weight gain; 2) water homeostasis—intake and loss through urine/evaporation—in a normal rat has a negligible impact on this correlation; 3) any extraneous mass losses, such as hair, nails, or skin, also has a negligible impact; and 4) OE values in a normal rat are constant in the time frame of this study (2 weeks). Subsequently, if OE values decreased postburn, this could be because of a decline in food intake, an increase in fecal mass output, and/or an increase in body weight gain. Conversely, an increased OE suggestive of greater activity and basal metabolism would be because of increased food consumption, reduced fecal output, and/or less weight gain. Food consumption, fecal output, and body weight gain were measured postburn, and this mass balance equation was used to estimate OE.

Next, the average preburn value for OE was used to predict the expected daily body weight gain postburn for the amount of food consumed. Rearranging Eq. (1) and using $OE_{PreBurn}$ yields Eq. (2) for the expected body weight gain. Expected Body Weight Gain

$$\text{Expected Body Weight Gain} = \text{Food Intake} - \text{Fecal Mass Output} - OE_{PreBurn} \quad [2]$$

The values of expected weight gains were compared with the measured preburn values to assess how well the correlation fit the data over that time period. On finding a good correlation, it could be determined that if the postburn values of expected weight gains matched the actual measured values, this would imply that there was no change in OE and that any differences in trends were purely behavioral. A decrease in body weight gain compared with the expected, however, would suggest that, in burn rats, a greater amount of net food intake was being used for OE requiring processes rather than growth.

Caloric and Water Intake

Rats consumed Prolab RMH 3000 5P00 chow (Lab-Diet/Purina), which comprises 78.8% digestible nutrients and 3.2 metabolizable kcal/g. Weight of daily food consumption was calculated as the difference between food from the day previous and that remaining on the day of measurement and, subsequently, converted into caloric intake. It was then normalized to the concurrent weight of the rat. Water consumption was similarly measured as the daily volume consumed.

Activity, Heart Rate, and Core Body Temperature

The telemetry device signals were acquired on a continuous basis and measured activity, heart rate, and core body temperature. Activity was reported as arbitrary “counts” as determined by movement of the telemetry device in the animal relative to the fixed receiver. Heart rate was measured by the device leads that pick up the electrocardiogram using proprietary software (Dataquest A.R.T. 4.1; Data Sciences International). Core body temperature was measured by the device transmitter itself located in the peritoneal cavity. These measurements were performed every 10 seconds and averaged over daily 24-hour periods.

Statistics

The results of continuous sampling of heart rate, temperature, and activity data were averaged daily spanning 24-hour periods. The SD of each measurement was propagated through to reflect an average error per group per day using the summation of sample variances. A paired Student's *t*-test was conducted to compare variables for each rat for differences between preburn and postburn. Analysis of variance was used to determine the significance of differences among groups of rats. Differences were deemed significant when $P < .05$.

RESULTS

Body Weight Gain, Food, and Water Intake Profiles

The telemetry implants demonstrated no significant impact on the body weight gain of rats either before or after burn injury (Table 1). Therefore, we could reasonably assume that the burn-induced responses were not significantly affected by the presence of the telemetry implants.

Rats in the 12-week mCD group (Figure 1A) gained weight before burn at a nearly constant rate of 6.0 ± 3.7 g/d. There was a transient period of weight loss after burn until postburn day 3, after which the body weight stabilized to an unchanging value of 378 ± 31 g until the end of the experiment. Rats in the 6-week mCD group (Figure 1B) gained weight at a constant rate of 8.5 ± 2.0 g/d in the preburn phase. This rate decreased to 2.5 ± 0.9 g/d after burn injury until postburn day 3 and, then, increased to 6.8 ± 1.5 g/d by postburn days 5 through 7, suggesting recovery towards near-normal weight gain within a week of thermal injury. Rats in the 12-week fFI group 12F (Figure 1C) showed a fairly constant though slow weight gain of 0.6 ± 1.6 g/d before burn. These animals continued to gain weight at this rate until postburn day 2, after which they experienced a 4.7 ± 1.5 -g/d weight loss by postburn day 3, which tapered to a 0.4 ± 1.5 -g/d weight loss by postburn day 5. By postburn day 6, the rate of weight gain reached 0.63 ± 1.5 g/d.

The daily caloric intake normalized to the weight of each rat (Figure 2A) demonstrates that, before burn, 6-week mCD rats consumed on average 0.31 ± 0.02 kcal/g/d, which is significantly more than 12-week mCD rats, which consumed 0.19 ± 0.02 kcal/g/d ($P < .05$). The 12-week fFI rats consumed 0.18 ± 0.03 kcal/g/d before burn, which is similar to 12-week mCD rats despite major differences in size and daily body weight gain between these two groups. Preburn and postburn values differed significantly, except in the 12-week mCD group. Rats in the 12-week mCD group decreased their caloric intake to 0.08 ± 0.03 kcal/g/d on postburn day 1, but returned to preburn levels by postburn day 3, ie, 0.19 ± 0.05 kcal/g/d. Rats in the 6-week mCD group decreased their caloric intake to 0.15 ± 0.02 kcal/g/d on postburn day 1 and remained ~10% below preburn values ($P < .05$) for the remainder of the experiment, with an overall average intake of 0.28 ± 0.03 kcal/g/d from postburn day 2 onwards. Rats in the 12-week fFI group decreased their intake to 0.06 ± 0.02 kcal/g/d on postburn day 1 and subsequently increased their intake to 0.21 ± 0.03 kcal/g/d by postburn day 2, which was about 12% above preburn levels ($P < .001$).

Water intake normalized to rat body weight was monitored as well (Figure 2B). Comparison of preburn and postburn average values shows that water intake increased by 20 to 25% after burn injury in the 12-week mCD (from 111 ± 16 to 138 ± 24 mL/kg/d; $P < .05$) and 12-week fFI groups (from 152 ± 12 to 183 ± 28 mL/kg/d; $P < .05$), whereas there was no significant change in the 6-week mCD rats (from 196 ± 31 to 215 ± 22 mL/kg/d).

The ratio of fecal mass to food intake did not change after burn injury and was found to be constant for all rats before and after burn, although it differed amongst groups. Table 2 presents that the most efficient absorption of food occurred amongst the 12-week fFI rats, followed by the 6-week mCD rats, whereas the 12-week mCD rats lost essentially half their

food intake to fecal waste. This suggests that burn injury did not significantly impact the degree of absorption of food.

Values for food intake, fecal output, and actual weight gain were used in conjunction with Eq. (1) to estimate the mass “lost” because of OE-requiring processes, including basal metabolism and activity. OE values are shown as a function of time in Figure 3 and averages preburn and postburn are summarized in Table 2. OE values are relatively constant in all groups before burn but increased significantly postburn. The average preburn values of OE were then used in Eq. (2) to predict the expected body weight gain based on daily food consumption and fecal output measured after burn. Figure 4 compares the predicted vs actually measured body weight gain values as a function of time, and averaged pre and postburn values are summarized in Table 2. As expected, the correspondence between predicted and measured values was excellent before burn injury. However, after burn injury, predicted body weight gain was significantly higher than actually observed in all groups ($P < .05$), suggesting that less of the food absorbed was used towards growth of the animal, and more towards OE-requiring processes.

Animal Activity, Heart Rate, and Core Body Temperature

The average daily activity as determined by the telemetry device was compared for the 7-day periods before and after burn injury (Figure 5). Rats in the 12-week mCD group showed a 37% drop in activity postburn ($P < .05$), whereas the other groups showed no changes.

Heart rate was averaged over the week preburn for each group and then used to normalize postburn values. As shown in Figure 6, rats in the 12-week mCD group exhibited an increased heart rate within the first 24 hours of postburn, when the average was 1.11 ± 0.00 times baseline (356 ± 16 bpm), and by 48 hours, it was 1.18 ± 0.01 . Overall, the postburn value averaged 1.16 ± 0.03 for the remainder of the experiment, which was significantly higher than baseline ($P < 10^{-9}$). Rats in the 6-week mCD group showed a slight increase in heart rate, reaching up to 1.03 ± 0.01 times baseline (491 ± 11 bpm) on postburn day 1 and dropping back to baseline within postburn day 4; note that, this time point also corresponds to return to a normal rate of body weight gain (Figure 1). Overall, the average postburn heart rate in this group was 1.01 ± 0.01 , which was not significantly different from baseline ($P < .02$). Rats in the 12-week fFI group showed a decline in heart rate to 0.97 ± 0.00 times baseline (408 ± 15 bpm) during the first 24-hours postburn, followed by an elevation to 1.12 ± 0.00 at 48 hours. The average heart rate in the postburn phase was 1.08 ± 0.05 , which was significantly above baseline ($P < .003$).

Core body temperature dropped significantly in all groups on postburn day 1 and rose significantly ($P < .05$) above preburn levels on postburn day 2 (Figure 7). The most significant elevation was seen in the 6-week mCD group, with a rise of $0.33 \pm 0.05^{\circ}\text{C}$ above preburn, followed by a gradual descent to near preburn levels by day 7. Rats in the 12-week mCD group showed a maximal elevation of $0.22 \pm 0.11^{\circ}\text{C}$ increase above preburn also by postburn day 2, and their body temperature remained at least 0.1°C above baseline for the remainder of the experiment. Data for the 12-week fFI group also showed maximal elevation above normal on day 2 at $0.31 \pm 0.1^{\circ}\text{C}$, but this group returned to baseline by day 4.

DISCUSSION

In this study, we characterized the hypermetabolic response after a 20% TBSA burn injury in three different groups of rats. All animals exhibited an increase in heart rate and core body temperature. By using a correlation between body weight gain and food intake established before burn, body weight gain was significantly less than expected in all groups after burn, suggesting an increase in energy used for purposes other than body growth or activity. Significant variations in response amongst the groups were also observed. Most interesting were variations in body weight gain: Six-week mCD rats, which were rapidly gaining weight before burn, experienced only a very transient decrease in body weight gain after burn. By contrast, the older 12-week mCD rats lost weight early after burn and failed to regain a positive growth profile during the period of observation. The 12-week fFI rats also lost weight after burn but demonstrated compensatory weight gain by the end of the period of observation. It is also noteworthy that the 12-week mCD rats had a decreased level of activity after burn—in other words, became more lethargic compared with their preburn state—whereas the other groups showed no change. Taken together, these results suggest that the 12-week mCD group fared worse than the others after burn injury.

To estimate semiquantitatively the changes in resting energy expenditure, we used a simple mass balance approach that compares the body weight gain and the food intake minus fecal output [Eq. (1)] before burn. We then derived a correlation to predict postburn weight gain based on measured food intake [Eq. (2)]. In all groups, we found that the measured weight gain after burn was less than that predicted based on the intake of food, suggesting that more of the food was used to sustain energy-requiring processes other than body growth. These other processes likely represent maintenance and resting energy expenditure. In this estimation, we did not take into account the effect of fluid shifts that likely to be resulted from the burn injury, such as fluid retention in the burn wound area or water loss because of evaporation. All groups seemed to experience some weight loss early postburn despite saline resuscitation, which would tend to increase body weight. Previous published data generally indicate that the excess fluids given are subsequently eliminated by increased urine production within 2 to 3 days postburn.^{25,26} Thus, although fluid retention may have artificially increased body weight in the first 2 to 3 days postburn, it is not likely to have affected body weight changes at later time points. Furthermore, because predicted weight gain postburn was always higher than the actual measured value, any water retention that did occur would have minimized this difference. Finally, significant dehydration leading to weight loss is unlikely in these animals because of their high water intake, which is comparable to human equivalent rehydration recommendations of 4 to 6 ml/kg/%TBSA burn.^{27,28} Thus, the elevated predicted weight gain postburn compared with the actual weight gain is strongly suggestive of increased energy expenditure.

An interesting observation in this study was the differential response between the 6-week mCD and 12-week mCD groups, which are significantly different in body size but of identical strain and in a similar age group (using a conversion of rat to human time of 10.5 rat days to 1 human year,²⁹ these animals are 4 and 8 human years old, respectively). This difference was most dramatic when comparing the rate of body weight gain postburn, which was barely affected in the 6-week mCD rats, whereas the 12-week mCD rats had their

growth stunted (Figure 1). In addition, the 6-week mCD rats did not experience a reduction in activity level, unlike the 12-week mCD rats (Figure 5), and they exhibited a much more muted heart rate increase after burn (Figure 6). It is noteworthy that the 6-week mCD rats ate at least 50% more food per body weight (Figure 2) and absorbed 10% more of it (Table 2) than the 12-week mCD rats. They also had an 11-fold smaller OE value before burn, which increased 11-fold postburn, while 12-week mCD rats doubled their OE values postburn (Table 2). Whether the greater dependence on food rather than body fat/muscle reserves for energy and being in a state of rapid growth helps to reduce the impact of the hypermetabolic response is unknown; further studies on the effect of these factors are warranted.

The 12-week fFl group was similar in age to the 12-week mCD group and similar in size to the 6-week mCD group at the time of burn. However, their basal metabolic pattern differed from the other groups, because the rate of body weight gain was much lower than the other groups before burn (Figure 1). Furthermore, the mass balance analysis showed that as much as 70% of their food intake was used for OE-requiring processes, compared with 30% or less for the other groups (Table 2). This is most apparent when one considers that although the food intake, expressed in kcal/g/rat/d, was about the same for the 12-week fFl and 12-week mCD groups (Figure 2), the 12-week fFl rats gained weight at a rate that was only about 10% of the rate observed in the 12-week mCD rats (Table 2). After burn injury, 12-week fFl rats gained weight for the first 2 days postburn, which could reflect fluid retention, then lost weight for the two following days, after which they started to regain weight at rates equal to or even higher than preburn values (Figure 1). Core body temperature was elevated early after burn but returned to baseline within 4 days (Figure 7), and activity level was not affected by burn injury in this group (Figure 5). The only parameter that reflected a hypermetabolic state at that point was heart rate, which remained above baseline until the end of the study period (Figure 6). Taken together, these results suggest that 12-week fFl rats respond to the 20% TBSA burn to an intermediate degree compared with the other two groups. The effects of strain¹⁹ could be further investigated as a function of gender,^{8,30} as well as body size and percent fat mass composition.^{31,32}

In conclusion, we showed that a 20% TBSA burn injury elicits widely dissimilar hypermetabolic responses in different groups of rats. The 6-week mCD group was least affected, while slightly older 12-week mCD rats exhibited significantly more profound and sustained responses. Rats in the 12-week fFl group demonstrated a similar though milder response to burn than the age-matched 12-week mCD group, suggesting that genetic variations also impact on the hypermetabolic response. These results highlight the critical importance of characterizing the hypermetabolic response in animal models of burn injury and motivate further studies to dissect the roles of age, sex, and strain on these differences. A judicious choice of these parameters when using rat models in the future will be important to perform clinically relevant studies of burn pathology and treatment on one hand and to provide opportunities to study these factors in greater detail on the other hand.

Acknowledgments

Supported by the Shriners Hospitals for Children grants 8640, 8450, 8460, 8490, for this work, and Shriners Hospitals for Children Fellowships 8496 (to K.U.) and 8503 (to B.U.).

REFERENCES

1. Delano MJ, Moldawer LL. The origins of cachexia in acute and chronic inflammatory disease. *Nutr Clin Pract.* 2006; 21:68–81. [PubMed: 16439772]
2. Gore DC, Wolf SE, Sanford AP, Herndon DM, Wolfe RR. Extremity hyperinsulinemia stimulates muscle protein synthesis in severely injured patients. *Am J Physiol Endocrinol Metab.* 2004; 286:E529–E534. [PubMed: 14665444]
3. Gore DC, Chinkes DL, Hart DW, Wolf SE, Herndon DN, Sanford AP. Hyperglycemia exacerbates muscle protein catabolism in burn-injured patients. *Crit Care Med.* 2002; 30:2438–2442. [PubMed: 12441751]
4. Przkora R, Barrow RE, Jeschke MG, et al. Body composition changes with time in pediatric burn patients. *J Trauma.* 2006; 60:968–971. [PubMed: 16688056]
5. Cochran A, Davis L, Morris SE, Saffle JR. Safety and efficacy of an intensive insulin protocol in a burn-trauma intensive care unit. *J Burn Care Res.* 2008; 29:187–191. [PubMed: 18182920]
6. Suman OE, Herndon DN. Effects of cessation of a structured and supervised exercise conditioning program on lean mass and muscle strength in severely burned children. *Arch Phys Med Rehabil.* 2007; 88:S24–S29. [PubMed: 18036977]
7. Arbabi S, Ahms KS, Wahl WL, et al. Beta-blocker use is associated with improved outcomes in adult burn patients. *J Trauma.* 2004; 56:265–269. [PubMed: 14960966]
8. Jeschke MG, Przkora R, Suman OE, et al. Sex differences in the long-term outcome after a severe thermal injury. *Shock.* 2007; 27:461–465. [PubMed: 17438449]
9. Pereira C, Jeschke M, Herndon DN. Beta-blockade in burns. *Novartis Found Symp.* 2007; 280:238–248. [PubMed: 17380798]
10. Barber RC, Chang LY, Purdue GF, et al. Detecting genetic predisposition for complicated clinical outcomes after burn injury. *Burns.* 2006; 32:821–827. [PubMed: 17005325]
11. Barber RC, Diaz-Arrastia R, Purdue GF. Searching for alleles associated with complicated outcomes after burn injury. *J Burn Care Res.* 2007; 28:205–211. [PubMed: 17351434]
12. Finnerty CC, Jeschke MG, Herndon DN, et al. Temporal cytokine profiles in severely burned patients: a comparison of adults and children. *Mol Med.* 2008; 14:553–560. [PubMed: 18548133]
13. Mlcak RP, Jeschke MG, Barrow RE, Herndon DN. The influence of age and gender on resting energy expenditure in severely burned children. *Ann Surg.* 2006; 244:121–130. [PubMed: 16794397]
14. Moreau AR, Westfall PH, Cancio LC, Mason AD Jr. Development and validation of an age-risk score for mortality prediction after thermal injury. *J Trauma.* 2005; 58:967–972. [PubMed: 15920410]
15. Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery.* 2000; 128:312–319. [PubMed: 10923010]
16. Gill TJ III, Kunz HW, Rapaport FT. A genetic model for the control of host resistance to thermal injury. *J Surg Res.* 1989; 47:433–437. [PubMed: 2811357]
17. Radojici C, Andri B, Simovi M, Duji A, Marinkovi D. Genetic basis of resistance to trauma in inbred strains of mice. *J Trauma.* 1990; 30:211–213. [PubMed: 2304117]
18. Khalil Z, Helme R. Sensory peptides as neuromodulators of wound healing in aged rats. *J Gerontol A Biol Sci Med Sci.* 1996; 51:B354–B361. [PubMed: 8808984]
19. Rapaport FT, Bachvaroff RJ, Grullon J, Kunz H, Gill TJ III. Genetics of natural resistance to thermal injury. *Ann Surg.* 1982; 195:294–304. [PubMed: 6977344]
20. Banta S, Vemula M, Yokoyama T, Jayaraman A, Berthiaume F, Yarmush ML. Contribution of gene expression to metabolic fluxes in hypermetabolic livers induced through burn injury and cecal ligation and puncture in rats. *Biotechnol Bioeng.* 2007; 97:118–137. [PubMed: 17009336]

21. Lee K, Berthiaume F, Stephanopoulos GN, Yarmush ML. Profiling of dynamic changes in hypermetabolic livers. *Biotechnol Bioeng*. 2003; 83:400–415. [PubMed: 12800135]
22. Yamaguchi Y, Yu YM, Zupke C, et al. Effect of burn injury on glucose and nitrogen metabolism in the liver: preliminary studies in a perfuse liver system. *Surgery*. 1997; 121:295–303. [PubMed: 9092130]
23. Schmidt-Nielsen, K. *Scaling: why is animal size so important?*. New York: Cambridge University Press; 1991.
24. Carter EA, Derojas-Walker T, Tami S, Tannebaum SR, Yu YM, Tompkins RG. Nitric oxide production is intensely and persistently increased in tissue by thermal injury. *Biochem J*. 1994; 304:201–204. [PubMed: 7528006]
25. Carlson RG, Miller SF, Finley RK Jr, et al. Fluid retention and burn survival. *J Trauma*. 1987; 27:127–135. [PubMed: 3820349]
26. Carlson RG, Finley RK Jr, Miller SF, Jones LM, Morath MA, Alkire S. Fluid retention during the first 48 hours as an indicator of burn survival. *J Trauma*. 1986; 26:840–843. [PubMed: 3746960]
27. Mitra B, Fitzgerald M, Cameron P, Cleland H. Fluid resuscitation in major burns. *ANZ J Surg*. 2006; 76:35–38. [PubMed: 16483293]
28. Sheridan RL. Burns. *Crit Care Med*. 2002; 30:S500–S514. [PubMed: 12528792]
29. Quinn R. Comparing rat's to human's age: how old is my rat in people years? *Nutrition*. 2005; 21:775–777. [PubMed: 15925305]
30. Jeschke MG, Mlcak RP, Finnerty CC, et al. Gender differences in pediatric burn patients: does it make a difference? *Ann Surg*. 2008; 248:126–136. [PubMed: 18580216]
31. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000; 232:455–465. [PubMed: 10998644]
32. Ireton-Jones C. Comparison of the metabolic response to burn injury in obese and nonobese patients. *J Burn Care Rehabil*. 1997; 18:82–85. [PubMed: 9063794]

Figure 1.

Body weight as a function of time before and after burn injury (administered on day 0). Twelve-week-old male CD rats (A), 6-week-old male CD rats (B), and 12-week-old female Fischer rats (C). Data shown are means $\pm$ SD of four animals per group.

Figure 2.

Food (A) and water (B) intake normalized to body weight as a function of time before and after burn injury (administered on day 0). Data shown are means $\pm$ SD of four animals per group.

Figure 3.

Estimated body weight lost because of other energy-requiring processes, including basal metabolism and activity, from a simple mass balance of food intake minus fecal output and body weight gain [Eq. (1)]. Burn injury was administered on day 0. A, Twelve-week-old male CD rats; B, 6-week-old male rats; and C, 12-week-old female Fischer rats. Data shown are means $\pm$ SD of four animals per group.

Figure 4.

Comparison between measured and estimated body weight gain as a function of time before and after burn injury (administered on day 0). Estimated values are based on Eq. (2) and measured daily food uptake. A, Twelve-week-old male CD rats; B, 6-week-old male CD rats; and C, 12-week-old female Fischer rats. Data shown are means $\pm$ SD of four animals per group.

Figure 5.

Effect of burn injury on the average level of activity for each group of rats. Data shown are means $\pm$ SD of four animals per group. *Significantly different from before burn ($P < .05$).

Figure 6.

Average heart rate in the postburn phase normalized to preburn values in each group. Data shown are time averages over 24 hours. Means $\pm$ SD of four animals per group were then calculated. Baseline values were 356 ± 16 beats per minute (bpm) for 12-week mCD rats, 491 ± 11 bpm for 6-week mCD rats, and 408 ± 15 bpm for 12-week fFI rats.

Figure 7.

Core body temperature fluctuations after burn injury for $n = 4$ per group. Measurements were recorded every 10 seconds and averaged over 24 hours. Values shown are deviations from baseline measured preburn. Preburn body temperatures were $37.6 \pm 0.1^\circ\text{C}$ for 12-week mCD rats, $37.8 \pm 0.3^\circ\text{C}$ for 6-week mCD rats, and $37.4 \pm 0.1^\circ\text{C}$ for 12-week fFI rats.

Table 1

Effect of implant and burn injury on average body weight gain *

	Before Burn		After Burn	
	No Implant (N = 4)	Implant (N = 4)	No Implant (N = 4)	Implant (N = 4)
12 wk mCD	6.0 ± 3.7	5.3 ± 2.6	-1.0 ± 6.1	-3.2 ± 5.7
6 wk mCD	8.5 ± 2.0	7.6 ± 2.1	4.8 ± 2.4	5.2 ± 2.7
12 wk fFI	0.6 ± 1.6	-1.6 ± 5.6	-0.48 ± 2.4	1.2 ± 3.2

* Values shown are 7-day averages ± SD before and after burn expressed in g/d. There were no significant changes because of implant.

Table 2

Whole Body Mass Balance Parameters Before and After Burn Injury

	Food Intake (g/d)	Fecal Output (g/d)	Fecal Output		Calculated Other Energy (g/d)	Measured Weight Gain (g/d)	Predicted Weight Gain (g/d)
			Food	Intake			
12 wk mCD							
Preburn	28.5 ± 3.6	14 ± 3.1	0.51 ± 0.12		8.7 ± 2.7	5.5 ± 4.3	5.5 ± 4.1
Postburn	29.6 ± 4.9	14 ± 4.5	0.48 ± 0.14		16.3 ± 5.1 [*]	-1.6 ± 5.7 [*]	7.6 ± 6.1 [†]
6 wk mCD							
Preburn	16.3 ± 4.6	6.0 ± 1.3	0.41 ± 0.21		0.75 ± 1.8	8.2 ± 1.1	6.5 ± 3.0
Postburn	22.6 ± 2.1 [*]	8.5 ± 1.3 [*]	0.38 ± 0.06		8.1 ± 3.3 [*]	5.39 ± 2.6	12.7 ± 2.3 ^{*,†}
12 wk ffI							
Preburn	10.5 ± 1.6	2.9 ± 0.7	0.28 ± 0.07		7.0 ± 2.2	0.58 ± 1.7	0.98 ± 1.5
Postburn	12.1 ± 1.6 [*]	3.2 ± 0.6	0.27 ± 0.05		9.3 ± 2.2 [*]	-0.5 ± 2.1 [*]	2.2 ± 1.4 [†]

^{*} $P < .05$ for values of preburn vs postburn.[†] $P < .05$ for values of predicted weight gain vs actual weight gain.