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Effect of Age on Fever and Acute-Phase Response of Rats to Endotoxin and *Salmonella typhimurium*

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Age-related effects on endogenous pyrogen-mediated febrile and acute-phase responses to endotoxin and *Salmonella typhimurium* challenge were investigated in young adult and aged Fisher 344 rats. After injection of endotoxin, the febrile response over 6 h and the fall in plasma iron and zinc after 6 h were determined in 14 young adult and 14 aged rats in their thermoneutral zone (26°C) and in 14 young adult and 14 aged rats maintained in a cold environment (15°C). Although at 26°C aged rats showed only a slightly diminished febrile response compared with that of young adult rats, at 15°C they had a markedly diminished febrile response compared with that of young adult rats. At both 26 and 15°C, the injection of endotoxin led to a fall in iron and zinc concentrations in the plasma of both young adult and aged rats. The intact trace metal response diminished but febrile response suggest that aged rats are able to produce endogenous pyrogen but have a reduced capacity to respond to this substance. In 22 aged and 22 young adult rats maintained at 26°C and challenged with *S. typhimurium*, the febrile response was significantly less in the aged rats but the survival rate was virtually identical. When 10 young adult and 10 aged rats were placed at a temperature of 15°C after injection with *S. typhimurium*, the febrile response in the aged rats was significantly lower than that in the young adult rats at only one time point, and the survival rate did not differ between the two age groups. Survival after challenge with *S. typhimurium* was not influenced adversely by the diminished febrile response.

Elderly persons experience an increased number of bacterial infections than do younger people, and the mortality rate from these infections is higher in elderly people (12, 29). The reasons for this increase in the number and severity of infections in the elderly have not been clearly elucidated. Retrospective clinical data suggest a diminished febrile response in elderly patients with infections (11, 28). A reduced febrile response to endotoxin has been documented in aged rabbits and aged squirrel monkeys (4, 9). An impaired febrile response could partially explain a higher mortality rate from infection in the elderly, since many studies showed that fever benefits the infected host (18, 25).

The generation of fever occurs via the production of a small-molecular weight protein, endogenous pyrogen (EP), which appears to be identical with or very similar to interleukin-1 and leukocytic endogenous mediator (6, 21). EP, which is released from a variety of phagocytic cells in response to bacteria, viruses, fungi, and other substances, induces a rise in the hypothalamic set point, thereby causing fever, and initiates a series of other "acute phase" responses, including a fall in the iron and zinc concentrations in plasma (16).

It is possible that an age-related decline in the nonspecific defense mechanisms triggered by EP occurs. An inability to give a febrile response to an infection could reflect a defect in EP production or a reduced ability of the hypothalamus to respond to EP. A diminished febrile response in elderly people may also be caused by a decreased ability to raise the metabolic rate, to peripherally vasoconstrict, or to shiver. As a result, an elderly individual may be able to raise his thermoregulatory "set point" but not to be able to elevate body temperature.

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In this study, we used aged Fisher rats as an animal model to elucidate the possible site of impairment of the EP-mediated response to infection. Fever and changes in iron and zinc concentrations in plasma were compared in young adult and aged rats after injection with *Escherichia coli* endotoxin; fever and survival rate were measured after injection with live *Salmonella typhimurium*.

MATERIALS AND METHODS

Animals. Specific-pathogen-free young adult (2 to 4 month; 170 to 220 g) and aged (24 to 28 months; 375 to 425 g) Fisher 344 male rats were obtained from Charles River Breeding Laboratories, Inc., Portage, Mich. The Fisher 344 strain has a 50% mortality by 22 months; some animals live as long as 36 months. Before the experiment, rats were housed in individual cages and maintained under 12 h of light and 12 h of darkness each day at an ambient temperature of 26 ± 1°C. Tap water and rodent chow were provided ad libitum. In an attempt to include only healthy aged rats in the study, any aged rats with palpable tumors, skin ulcerations, weight loss, or diarrhea were excluded from the study.

Determination of body temperature. Body temperature was measured by battery-operated biotelemetry devices (Mini-Mitter, Inc., Sun River, Oreg.) implanted intraperitoneally into each rat two or more days before the experiments began. Output (clicks) from each transmitter was monitored by an AM radio receiver held outside each cage. The rate of discharge of each transmitter was proportional to the temperature of its environment; the time elapsed for 50 clicks from each transmitter (to the nearest 0.01 s) was determined with a stopwatch. A temperature calibration curve established for each transmitter device before implantation allowed calculation of the body temperature of each animal.

Trace metal measurements. Rats were anesthetized with methoxyfluorane, and 0.6 ml of whole blood was collected

by cardiac puncture or orbital sinus bleed into heparinized microcentrifuge tubes. After centrifugation, 0.1 ml of plasma was drawn off, diluted to 1.0 ml with distilled water, and frozen at −20°C for zinc analysis. For determination of the level of iron in plasma, 0.2 ml of plasma was drawn off, mixed with 0.2 ml of 1.22 M trichloroacetic acid, and heated at 90°C for 15 min to denature the proteins; 0.2 ml of distilled water was added, the sample was centrifuged, and the supernatant was frozen at −20°C. Concentrations of zinc and iron in plasma were determined with an atomic absorption spectrophotometer (Varian, Inc., Park Ridge, Ill.). Sample concentrations were determined by comparing absorbance values with a standard curve (10).

Endotoxin and *S. typhimurium*. Lyophilized *E. coli* endotoxin 0111:B4 (Difco Laboratories, Inc., Detroit, Mich.) was reconstituted in 0.9% saline to a concentration of 50 μg/ml immediately before each experiment. *S. typhimurium* ATCC 15277, stored in glycerol at −20°C, was grown at 37°C on tryptic soy agar with 5% sheep blood. An overnight growth of organisms was suspended in phosphate-buffered saline at a concentration of ca. 6×10^8 to 7×10^8 CFU/ml. Actual CFU were determined by serial dilutions and pour-plate counts.

Response to endotoxin. To determine differences in the ability of young adult and aged rats to develop fever and changes in zinc and iron concentrations in plasma in response to an inducer of EP, a total of 28 young adult and 28 aged rats were injected intravenously with 50 μg of endotoxin per kg. As a control, the same rats were injected with equal volumes of 0.9% endotoxin-free saline. Experiments were conducted with groups of 6 to 8 rats; half received endotoxin and half received saline on any given day. Body temperature was recorded every 30 min, beginning 1 h before injection of endotoxin or saline and continuing for 6 h post-injection. At 6 h post-injection, blood was collected for analysis of iron and zinc in the plasma. These experiments were conducted in two phases to investigate the possibility of impairment of the thermoregulatory effector response to EP in aged rats. In the first part, 14 young adult and 14 aged rats received endotoxin or saline while maintained in their thermoneutral zone of 26°C. In the second part, a second group of 14 young adult and 14 aged rats that had been placed in a temperature-controlled chamber at 15°C for 1 h received endotoxin or saline and were maintained at 15°C for the next 6 h. This cold stress was used to accentuate differences in the thermoregulatory capacity of young adult and aged rats to respond with a febrile response to EP. Previous studies showed that both young adult and aged rats maintained their body temperature in the normal range (36.9 to 38.1°C) when housed at 15°C for 6 h.

Survival studies. The febrile response and survival rate in young adult and aged rats infected with *S. typhimurium* were compared. In the first part of the experiment, 22 young adult and 22 aged rats each received an intravenous injection of 1.2×10^8 to 1.6×10^8 CFU of *S. typhimurium*; the rats were maintained in their thermoneutral zone (26°C) during the experiment. In the second part, 10 young adult and 10 aged rats each received an intravenous injection of 1.3×10^8 CFU of *S. typhimurium*; they were placed at an ambient temperature of 15°C immediately after injection of the bacteria and maintained at that temperature during the experiment. The number that survived was recorded every 12 h for 6 days. Temperature was recorded four times daily for the first 3 days and then once daily for the next 3 days. Markedly hypothermic readings (<30°C) immediately before death were excluded from the analysis.

Data analysis. Values reported are the mean ± standard error of the mean. Febrile response and zinc and iron concentrations in plasma were compared in the young adult and aged rats by using the Student *t* test. Survival data were analyzed by the chi-square test.

RESULTS

The febrile responses over 6 h in the young adult and aged rats injected with saline or endotoxin and maintained at either 26 or 15°C are shown in Fig. 1. At 26°C, the young adult rats showed a maximum increase in temperature of 1.7°C by 4.5 h after endotoxin injection, whereas the aged rats showed a smaller, slower rise in body temperature, with a maximum increase of 1.5°C by 5.5 h post-injection. The differences in febrile responses between young adult and aged rats were amplified at 15°C. At this ambient temperature, both groups of rats had a smaller increase in body temperature in response to the endotoxin. This was most evident in the aged rats, which showed no rise in temperature until after 3.5 h, and even at 6 h had a significantly lower

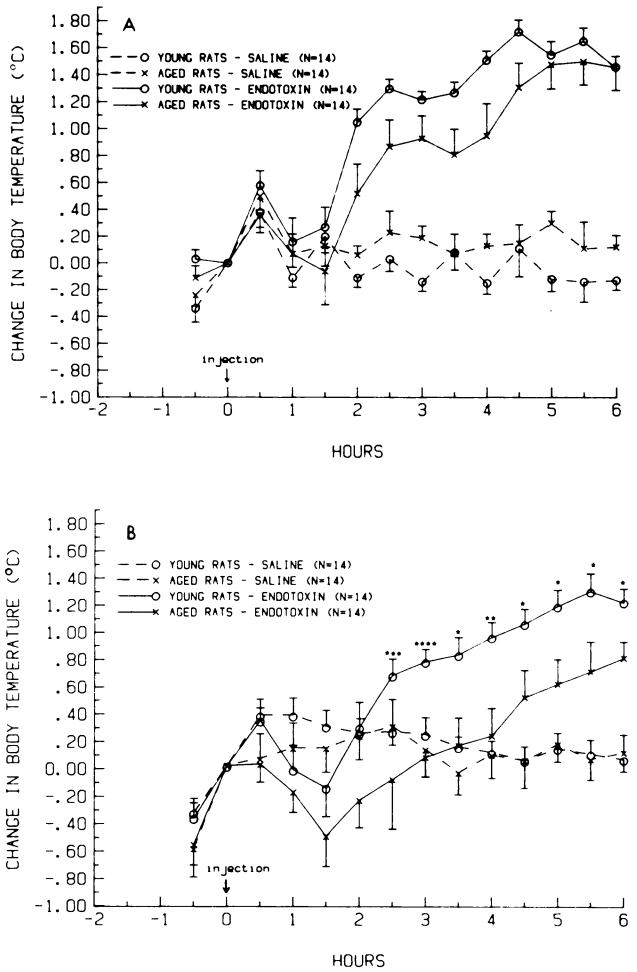

FIG. 1. Febrile response of young adult and aged rats injected intravenously with 50 μg of *E. coli* endotoxin per kg or 0.9% saline and maintained (A) in their thermoneutral zone (26°C) or (B) in a cold environment (15°C). The response of young adult rats was compared with that of aged rats by the Student *t* test. Symbols: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$; ****, $P < 0.001$.

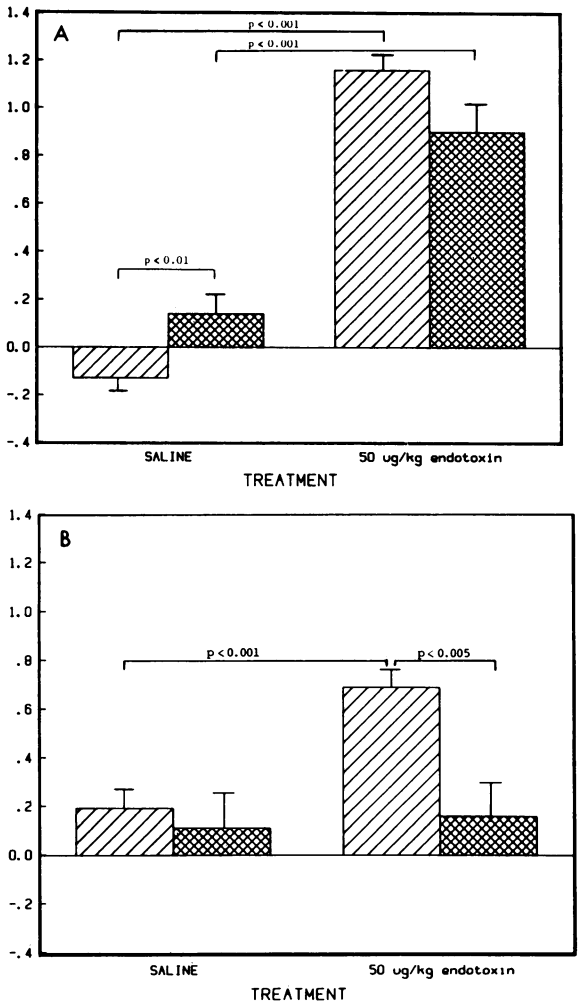

FIG. 2. Average fever over 6 h (ΔT_6) in young adult and aged rats injected intravenously with 50 μg of *E. coli* endotoxin per kg or 0.9% saline and maintained (A) in their thermoneutral zone (26°C) or (B) in a cold environment (15°C). Data were analyzed by the Student *t* test. Symbols: ▨, Young adult rats (n = 14); ⊠, aged rats (n = 14).

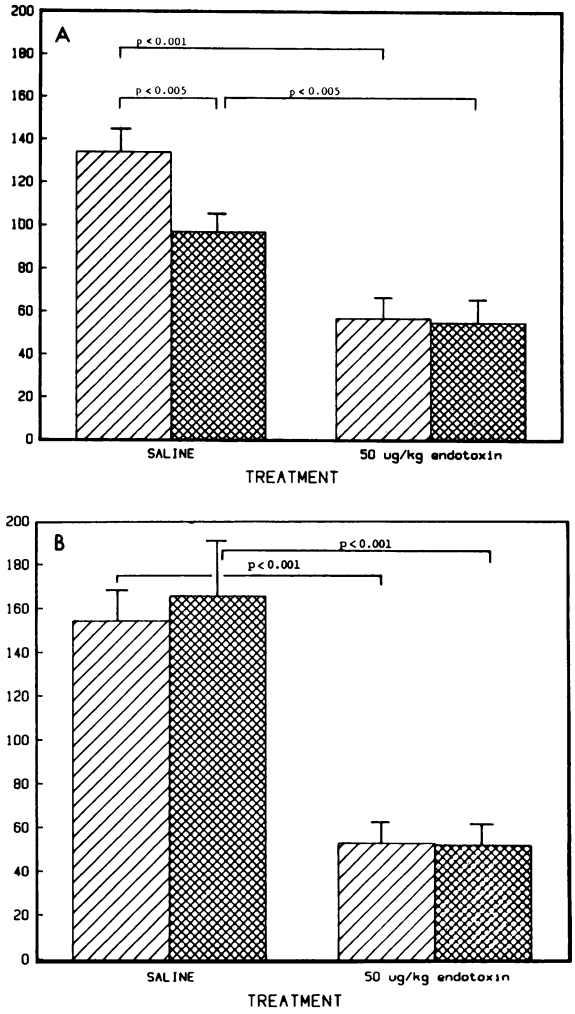

FIG. 3. Iron concentrations in plasma at 6 h post-injection in young adult and aged rats injected intravenously with 50 μg of *E. coli* endotoxin per kg or 0.9% saline and maintained (A) in their thermoneutral zone (26°C) or (B) in a cold environment (15°C). Data were analyzed by the Student *t* test. Symbols: ▨, Young adult rats (n = 14); ⊠, aged rats (n = 14).

temperature than the young adult rats. All animals showed a small, transient rise in body temperature immediately after injection of saline or endotoxin; this was presumably due to the injection procedure itself and was clearly distinguished from the febrile response to the endotoxin.

Expressing these data as the average temperature rise over 6 h (ΔT_6) clarified the differences between young adult and aged rats (Fig. 2). At 26°C, the aged rats showed a slightly depressed, although not significantly different, febrile response from the young adult rats. In both young adult and aged rats, the febrile response to endotoxin was significantly greater than the response to saline ($P < 0.001$). At 15°C, the febrile response in aged rats was significantly more depressed than that of the young adult rats ($P < 0.005$). The injection of endotoxin led to a significant increase in body temperature when compared with the injection of saline ($P < 0.001$) only in young adult rats; in aged rats there was no difference in the febrile response to endotoxin or saline over 6 h.

Figures 3 and 4 show the iron and zinc concentrations in plasma samples of young adult and aged rats injected 6 h earlier with endotoxin or saline and maintained at 26 or 15°C. At both 26 and 15°C, iron concentrations in plasma were significantly lower in the endotoxin-treated rats than in the saline-treated rats, regardless of age (Fig. 3). Likewise, zinc levels in plasma were significantly lower in the endotoxin-treated rats than in the saline-treated rats, regardless of age or ambient temperature (Fig. 4).

At 26°C, the febrile response of the aged rats to *S. typhimurium* challenge was significantly less than that of the young adult rats (Fig. 5). When the rats were maintained under cold stress conditions at 15°C for 6 days after *S. typhimurium* challenge, the febrile response of young adult and aged rats was significantly different only at 20 h post-injection. During infection, temperatures varied widely from animal to animal when they were kept in a cold environment.

The survival rate was virtually identical for young adult and aged rats infected with *S. typhimurium* (Fig. 6). When the rats were maintained at 26°C, overall mortality was 64% in the aged rats and 73% in the young adult rats; at 15°C, overall mortality was 60% in the aged rats and 70% in the young adult rats.

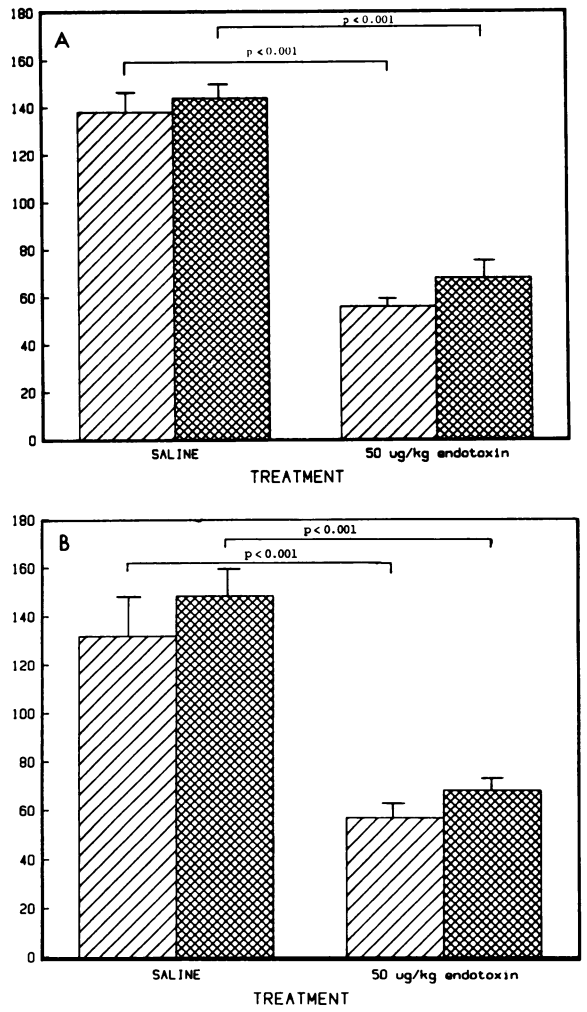

FIG. 4. Zinc concentrations in plasma at 6 h post-injection in young adult and aged rats injected intravenously with 50 μg of *E. coli* endotoxin per kg or 0.9% saline and maintained (A) in their thermoneutral zone (26°C) or (B) in a cold environment (15°C). Data were analyzed by the Student *t* test. Symbols: ▨, Young adult rats (n = 14); ▩, aged rats (n = 14).

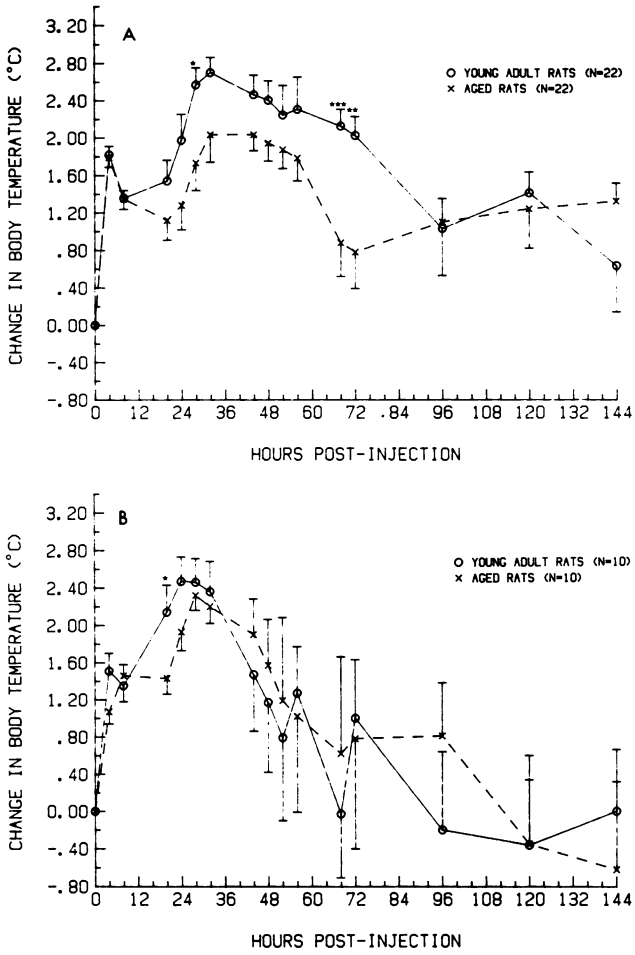

FIG. 5. Febrile response of young adult and aged rats infected with *S. typhimurium* and maintained (A) in their thermoneutral zone (26°C) or (B) in a cold environment (15°C). Young adult rats were compared with aged rats by the Student *t* test. Symbols: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$.

DISCUSSION

Our data support the hypothesis that aged rats have a reduced febrile response to pyrogenic stimuli. In their thermoneutral zone, aged rats showed a febrile response to *E. coli* endotoxin, but there was a tendency for the fevers to be lower than those in young adult rats. When the aged rats were injected with endotoxin in a cold environment, they were able to maintain normal body temperature but unable to produce a significant rise in body temperature. Since animals placed in an environment below their thermoneutral zone must, by definition, increase their metabolic heat production to maintain a constant body temperature, there does not appear to be a defect in the ability of aged rats to generate adequate heat; however, the ability to generate further heat, as occurs after a pyrogenic stimulus, appears to be impaired. The decreased febrile response of aged rats to endotoxin at 15°C, a mild cold stress, suggests that a defect may be present in the effector side of thermoregulation.

Young adult and aged rats showed similar reduction of iron and zinc levels in plasma in response to injection with endotoxin at both 26 and 15°C. Several studies have shown that the febrile response can be eliminated by pharmacological or anatomical manipulation of the hypothalamus while maintaining normal decreases in iron and zinc concentrations in plasma in response to injection of endotoxin or EP (2, 26, 27). Similarly, our observation that the body temperature of aged rats did not significantly increase in a cold environment in response to endotoxin but a fall in zinc and iron concentrations was triggered confirmed the dissociation of hypoferremia from the febrile response, even though both are mediated by EP.

Since iron and zinc concentrations in plasma fell normally in aged rats injected with endotoxin, we concluded that aged rats were able to produce circulating EP, the mediator of zinc and iron redistribution during infection. These data, in conjunction with the attenuated fever observed in the aged rats, suggests several possibilities. (i) Aged rats may have an intact EP-producing system but a reduced capacity to respond to EP at the level of the central temperature integrator, the hypothalamus. (ii) Aged rats may have an intact EP-producing system but a reduced peripheral thermoeffector ability to generate sufficient heat by shivering or non-

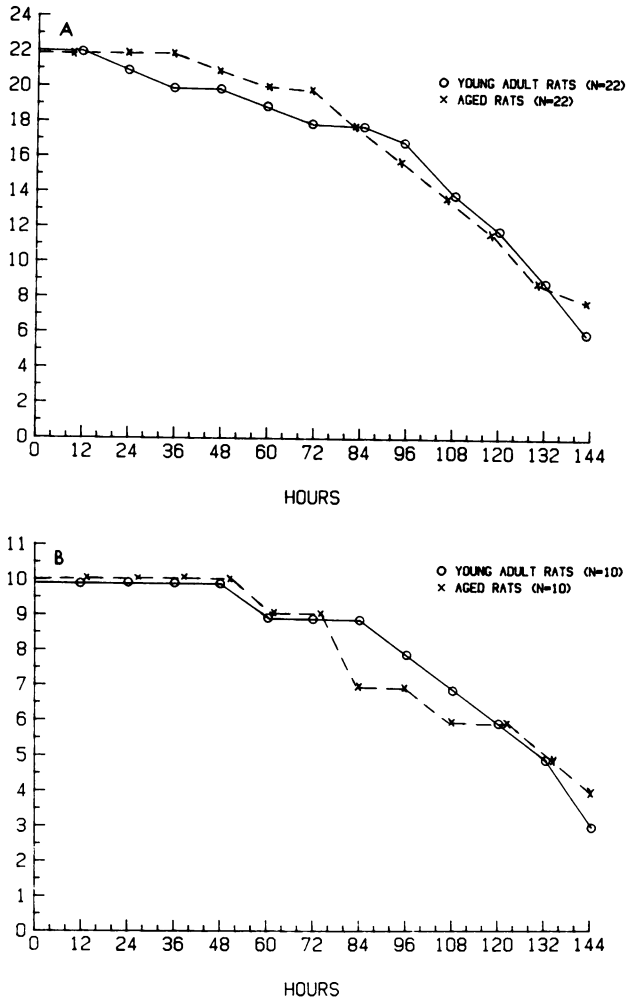

FIG. 6. Survival of young adult and aged rats infected with *S. typhimurium* at time zero and maintained (A) in their thermoneutral zone (26°C) or (B) in a cold environment (15°C).

shivering thermogenesis or to retain sufficient heat by peripheral vasoconstriction. (iii) It is possible that in aged rats a higher concentration of EP is required to induce a fever than to stimulate a fall in the level of trace metals in plasma. Therefore, the aged rats may have a slightly reduced EP-producing capacity, which attenuates the febrile response but not the trace metal response, and this attenuation in fever is further accentuated by a mild cold stress (15°C). (iv) Finally, it is possible that endotoxin, through a direct or indirect effect on blood vessels, is able to overcome the heat-conserving mechanisms of aged rats and that the response to EP does not result in an overall rise in body temperature.

Previous work supports several of the above possibilities. We found that healthy elderly people produced only slightly less EP than young controls, a difference which was not statistically significant (15). Studies in aged mice of the B6 strain have noted a slightly diminished production of interleukin-1 (3). As in our studies in humans, studies in aged squirrel monkeys suggested that these animals produced normal amounts of EP but had an abnormal central (hypothalamic) response to endotoxin injection (4). Likewise, Lipton and Ticknor found decreased sensitivity of the hypothalamus of aged female rabbits to EP injection (19). Some elderly persons have been shown to have defective thermoeffector capabilities in a cold environment (5). However, no studies have assessed the thermoeffector capabilities of elderly people in response to a pyrogenic stimulus, such as endotoxin.

Since fever has been shown to be beneficial during infection (18, 25), studies were undertaken to see whether a reduction in febrile response in the aged rats correlated with a reduction in survival after treatment with a live gram-negative bacterium, *S. typhimurium*. Several studies have shown aged mice to be more susceptible than young mice to infection with *S. typhimurium*, *Listeria monocytogenes*, and *Staphylococcus aureus* (7, 20, 22), although others have noted no differences in mortality rates in young and aged mice infected with *L. monocytogenes*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* (8, 20). We found no significant difference in survival between young adult and aged rats maintained at either 26 or 15°C. It was of interest that the febrile response to *S. typhimurium* was not markedly diminished in the aged rats kept at 15°C, even though the response to endotoxin was significantly affected by exposure to a cold environment. However, there was marked individual variation in the febrile response in animals kept at 15°C after challenge with *S. typhimurium*; this variability was not noted in the endotoxin experiments.

An important consideration in the increased susceptibility to infection in elderly people is the underlying state of health of aged individuals and how that differs from the health of younger individuals. The increased susceptibility to infection noted in retrospective studies in elderly patients may have been due to poor nutrition in hospitalized elderly patients, rather than to the aging process itself (1). Diminished EP has been noted in protein-deprived rabbits and in protein–calorie-malnourished hospitalized patients (13, 14, 17; C. A. Kauffman et al., unpublished observations). Furthermore, several other host defense parameters in the elderly (neutrophil phagocytosis and killing, opsonization, and complement activation) were normal in healthy elderly volunteers but abnormal in hospitalized elderly patients (23, 24). In our study assessing the febrile response, the fall in trace metal concentrations, and the resistance to infection in rats, we were careful to compare only healthy aged animals with healthy young adults. Aging alone may not cause a decreased host response to infection; future studies evaluating the diminished response of elderly people and animals to infection should consider multiple factors associated with aging, rather than chronological age alone.

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