Body temperature, behavior, and plasma cortisol changes induced by chronic infusion of *Staphylococcus aureus* in goats

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First published June 24, 2004; 10.1152/ajpregu.00064.2004.—Most experimentally induced fevers are acute, usually lasting ~6–12 h, and thus do not mimic chronic natural fevers, which can extend over several days or more. To produce a model of chronic natural fever, we infused eight goats (*Capra hircus*) intravenously with 2 ml of $2 \times 10^1$ cell walls of *Staphylococcus aureus* (S. aureus) for 6 days using osmotic infusion pumps ($10 \mu l/h$) while measuring changes in body temperature, behavior, and plasma cortisol concentration. Seven control animals were infused with sterile saline. Abdominal temperature-sensitive data loggers and osmotic infusion pumps were implanted under halothane anesthesia. To compare our new model with existing models of experimental fever, we also administered 2 ml bolus intravenous injections of $2 \times 10^1$ S. aureus cell walls, 0.1 µg/kg lipopolysaccharide (*Escherichia coli*, serotype 0111:B4), and sterile saline in random order to six other goats. Bolus injection of lipopolysaccharide and *S. aureus* induced typical acute phase responses, characterized by fevers lasting ~6 h, sickness behavior, and increased plasma cortisol concentration. Infusion of *S. aureus* evoked prolonged fevers, which lasted for ~3 days, starting on day 4 of infusion (ANOVA, $P < 0.05$), and did not disrupt the normal circadian rhythm of body temperature. However, pyrogen infusion did not cause plasma cortisol concentration to rise (ANOVA, $P > 0.05$) or the expression of sickness behavior. In conclusion, infusion of *S. aureus* produced a fever response resembling that of sustained natural fevers but did not elicit the cortisol and behavioral responses that often are described clinically and during short-term experimental fevers.

osmotic infusion pumps; lipopolysaccharide; circadian rhythm

THE ACUTE PHASE RESPONSE to one-time inoculations of low and moderate doses of lipopolysaccharide, a gram-negative bacterial pyrogen, is well characterized and typically includes fevers, which resolve within 6–12 h and disrupt the circadian rhythm of body temperature, neuroendocrine changes such as increased glucocorticoid and cytokine secretion, and behavioral changes such as anorexia and lethargy (16, 25, 41, 52). In contrast to the relatively consistent, but acute, character of experimentally induced fevers, fevers that occur naturally have a highly variable duration and temperature pattern. Natural fevers may last several hours to several weeks and be characterized by chronic elevation or cyclical febrile peaks of body temperature (8, 20, 31). Also, in the first complete characterization of a spontaneously occurring natural fever, we showed that the pattern of the circadian rhythm of body temperature of free-living antelope is maintained throughout prolonged febrile episodes, including the period of fever genesis and resolution (20). The dichotomous character of the febrile responses seen experimentally and naturally would suggest that the underlying mechanisms of these fevers might differ.

Attempts to mimic the temperature changes observed during natural fevers in the laboratory have been hampered by the tendency of pyrogenic tolerance to develop when either lipopolysaccharide is chronically infused or repeat bolus doses are administered (36, 50, 51). Indeed, only high doses of lipopolysaccharide, which produce a sepsislike state, successfully have mimicked the sustained elevations in body temperature often seen during fevers of natural origin (11, 14, 15, 33, 43, 49). However, other than with cecal ligation (15, 49), which produces remarkably reproducible fevers, the effects of infusing sepsislike doses of lipopolysaccharide on body temperature often are unpredictable (11, 14, 43). Also, although fevers occur during sepsis, sepsis results from an inappropriate exaggeration of the immune response to a pathogen and can be separated from the appropriate immune response seen during more low-grade systemic infections, which also cause fever, but are not accompanied by the severe hypotension, coagulopathy, and multiple organ failure that accompany sepsis (6). The combination of unpredictable body temperature changes and the sepsislike doses of pyrogen required limit the usefulness of these models of endotoxemia as correlates of natural fevers that occur during low-grade infections. Thus the successful development of an experimental model of natural fever, without septic doses of pyrogen, requires the use of pyrogens to which tolerance does not readily develop.

Fever also is induced by gram-positive bacteria, which account for ~30% of infections in nonseptic patients under intensive care hospitalization (1). Experimental fevers induced by gram-positive bacterial pyrogens, such as muramyl dipeptide and *S. aureus* cell walls, are similar to those induced by lipopolysaccharide, but tolerance to gram-positive pyrogens does not readily develop (5, 12, 13, 37, 38). Consequently, we have attempted to produce an experimental correlate of the natural fevers we have observed in free-living antelope (20) by infusing goats, a domesticated ruminant species of similar size to the free-living antelope we described, with cell walls from the gram-positive bacterium *S. aureus* for 6 days while measuring body temperature, behavioral, and neuroendocrine changes. Goats exhibit similar body temperature, leukocyte, and behavioral changes to pyrogens as rats and rabbits do and, as such, have been proposed as useful animals for fever

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research (45, 46). To facilitate comparisons between our model of chronic fever and typical models of acute fever, we also have measured the temperature, behavioral, and neuroendocrine changes induced when lipopolysaccharide or _S. aureus_ cell walls are administered to goats as a single bolus injection.

**MATERIALS AND METHODS**

**Animals**

Twenty-one male goats (_Capra hircus_) aged 2–3 yr and weighing 19–32 kg were obtained from commercial breeders. The animals were housed in pens at ±24°C within the thermoneutral zone of goats of 6–27°C (40). A 12:12-h light-dark cycle (lights on at 0700) was maintained throughout the study, and the animals had free access to food and water. The Animal Ethics Screening Committee of the University of the Witwatersrand approved all experimental protocols (clearance numbers: 2002/66/4 and 2002/8/5).

**Temperature Measurement**

Under general anesthesia, temperature-sensitive data loggers (StowAway TidiBI, Onset Computer) were implanted into the peritoneal cavity of goats through a small incision in the paralumbar fossa, and the wound was sutured closed and sprayed with a topical antibiotic (Necrospary, Centaur Laboratories). Anesthesia was induced by intramuscular injection of 0.04 mg/kg medetomidine (Domitor, Ciba-Geigy) and 2.4 mg/kg ketamine (Anaket-V, Centaur Laboratories) and maintained with halothane (1% *Fluothane*, Zeneca). After surgery, animals received intramuscular injections of 0.2 mg/kg atipamezole (Antisedan, Ciba-Geigy) to reverse the medetomidine and an antibiotic, 5 ml of 5% enrofloxacin (*Baytril*, Bayer).

The operation of the data loggers has been described previously in detail (21). In brief, the data loggers, which have dimensions of 30 × 41 × 17 mm and a mass of ~30 g when covered by an inert, waterproof wax (*Sasol*), recorded abdominal temperature continuously at 5-min intervals. Before implantation, the loggers were calibrated against a high-accuracy quartz thermometer (Quart 100, Heraeus, Hanau, Germany) in an insulated water bath to an accuracy of 0.04°C. Loggers were dry-sterilized in a sealed drum containing formaldehyde tablets for at least 24 h before implantation into goats. The data loggers were implanted 2 wk before the start of any experimentation.

**Behavioral Observations**

In 1-h epochs, observations were made by a single observer for the presence of shivering and the time spent feeding and lying down. For the bolus injection study (see below, _Experiment 1_), behavioral observations were made from 1100 to 1200, 2 h after injection of saline or pyrogen, during the rising phase of the fever. For the infusion study (see below, _Experiment 2_), behavior also was monitored from 1100 to 1200, but on each day of the infusion period. The observer was unaware of which animals had received bacterial pyrogens or pyrogen-free saline.

**Radioimmunoassay for Cortisol**

Plasma cortisol levels were determined by radioimmunoassay according to the manufacturer’s instructions (Coat-A-Count Cortisol kit, Diagnostic Products). In brief, 25 μl of sample or cortisol standard were pipetted into polypropylene tubes coated with antibodies against cortisol. One milliliter of 125I-labeled cortisol was added to all tubes, which were then incubated at 37°C for 45 min before the solution was decanted, and the amount of antibody-bound 125I-labeled cortisol was determined using a gamma counter (Cobra Auto-gamma B5002, Packard). Standard curves were constructed, and plasma levels of cortisol were calculated.

**Experimental Protocols**

_**Experiment 1: bolus injection of pyrogens.**_ In random order, six goats were administered a 2-ml bolus injection of 2 × 10^11_ S. aureus_ cell walls (Sigma), 0.1 μg/kg lipopolysaccharide ( _E. coli_, serotype 0111:B4, Sigma), or pyrogen-free saline, in the jugular vein. All injections were administered at 0900 and spaced at least 2 wk apart. Sixty minutes before and 60 and 180 min after each injection, venous blood samples (4 ml) were collected by venipuncture in chilled propylene tubes containing heparin. Blood samples were immediately centrifuged, and the plasma was stored at −70°C for later determination of plasma cortisol concentrations.

_**Experiment 2: infusion of pyrogens.**_ Two weeks after data logger implantation, Alzet osmotic infusion pumps (2ML1, Alza, Pala Alto, CA) were implanted in a separate group of 15 goats under general anesthesia (see above). The osmotic infusion pumps were implanted subcutaneously in the neck with the tip of a 500-mm-long Portex catheter inserted into the jugular vein and sutured in position. Catheters, which were filled with heparinized saline (100 units/ml), delivered the infusion of pump contents until 24 h after implantation. Pumps were loaded either with 2 μl of sterile saline (n = 7) or 2 × 10^11 S. aureus cell walls (n = 8). The osmotic pumps infused their contents continuously into the jugular vein at a rate of 10 μl/h for 7 days. Forty-eight hours before pumps were implanted and every 2 days thereafter for 6 days after pump implantation, venous blood samples were collected at 0900 for the determination of plasma cortisol levels (see above).

At the end of both experiments, animals were euthanized by intravenous injection of pentobarbital sodium (Eutha-naze, Bayer), data loggers were retrieved, and the data were downloaded. Postmortem observations were performed on all animals in experiment 2, and no signs of secondary infection or pathology that may have affected the infusion were found. Complete delivery of the contents of the osmotic pumps was confirmed by opening each pump and examining the contents of the internal reservoir.

**Data Analysis**

All data are shown as means with SD in parentheses. Body temperature and cortisol data were analyzed using a two-way repeated-measure ANOVA with treatment and time as main effects. To reduce the size of the model, average hourly temperature was used for _experiment 1_ and average daily temperature for _experiment 2_. Mean hourly and daily temperatures were calculated from the original 5-min temperature recordings. A Newman-Keuls post hoc test was used to compare individual means when significant main effects or interactions were detected by the ANOVA. For the infusion study, the daily amplitude of the circadian rhythm of body temperature of each goat was calculated by subtracting the peak temperature from the nadir temperature, whereas the periodicity of the rhythm was determined by establishing the time at which the peak and the nadir occurred. The mean amplitude and period of the circadian rhythm was calculated for each goat over days 4, 5, and 6 of the _S. aureus_ and saline infusion period (the period when the _S. aureus_ infused animals were febrile). Differences between the groups were investigated using paired Student’s t-tests, with Bonferroni correction for multiple comparisons. Because the nadir of the circadian rhythm of body temperature occurred before injection of saline or pyrogens in _experiment 1_, alterations in circadian rhythm were investigated by comparing the average daytime and nighttime temperatures in response to saline, _S. aureus_, and lipopolysaccharide injections using one-way repeated-measures ANOVA with Dunnett’s multiple-comparisons post hoc test with saline as a control. Behavior data were summarized as the percentage of time spent lying down, feeding, or shivering during the periods of observation. Animals were said to have exhibited a behavior if they spent more than 50% of the time during the observation period displaying the behavior. Associations between groups and behavior categories were tested between groups using Fisher’s exact...
test. For the infusion study, only behavioral data on febrile days (days 4, 5, 6) are presented. Data for the 24-h period after infusion pump implantation were excluded from analyses and graphs because they coincided with infusion of the contents of the saline-filled delay line.

RESULTS

Body Temperature

Body temperatures of goats administered bolus intravenous injections of saline, lipopolysaccharide, and \textit{S. aureus} cell walls are shown in Fig. 1. The main effect of time was significant ($F_{6,90} = 37.76$, $P < 0.001$), as was the interaction ($F_{12,90} = 7.03$, $P < 0.001$), but the main effect of group was not significant ($F_{1,15} = 1.06$, $P = 0.372$). Administration of saline thus had no significant effect on body temperature, but injection of lipopolysaccharide and \textit{S. aureus} induced robust fevers, which lasted ~6 h, with peak febrile temperature ~4 h after pyrogen administration. Injection of pyrogens disrupted the normal circadian rhythm of body temperature. Mean daytime body temperature of pyrogen-injected animals was ~0.2°C higher than that of saline-injected animals ($F_{2,2} = 15.1$, $P < 0.001$), but there were no significant differences in the average nighttime temperature of animals that received saline and pyrogen ($F_{2,2} = 0.47$; $P = 0.64$).

Figure 2 shows the effects of continuously infusing goats intravenously with \textit{S. aureus} cell walls or saline on mean daily body temperature (Fig. 2A), and mean 24-h body robust temperature measured at 5-min intervals (Fig. 2B). The main effects of treatment ($F_{1,13} = 5.34$, $P = 0.037$) and time ($F_{7,91} = 2.44$, $P = 0.024$) on mean daily body temperature were significant, as was the interaction ($F_{7,91} = 3.61$, $P = 0.002$). Infusion of \textit{S. aureus} cell walls caused a gradual increase in mean daily body temperature, which became significantly elevated above preinfusion levels of body temperature by day 4 and remained elevated until day 6 of infusion. After day 6 of infusion, body temperature returned to preinfusion levels. This pyrogen-induced elevation in body temperature did not affect the periodicity or the amplitude of the circadian rhythm of body temperature (Fig. 3, t-tests, $P > 0.05$). The amplitude of the rhythm was maintained at ~0.5°C, whereas the nadir and peak of the rhythm remained at about 0800 and 1700, respectively.

Cortisol

The effect of bolus, intravenous injections of saline, lipopolysaccharide, or \textit{S. aureus} cell walls on plasma cortisol concentrations in goats is shown in Fig. 4A. The main effects of treatment ($F_{2,15} = 5.28$, $P = 0.003$) and time ($F_{2,30} = 14.19$, $P < 0.001$) were significant, as was the interaction ($F_{4,30} = 4.73$, $P = 0.004$). Administration of lipopolysaccharide and \textit{S. aureus} produced similar elevations in plasma cortisol concentration 60 and 180 min after pyrogen injection. Changes in plasma cortisol concentrations in goats infused continuously either with saline or \textit{S. aureus} cell walls are shown in Fig. 4B. Neither the main effects of treatment ($F_{1,5} = 0.003$, $P = 0.96$) and time ($F_{4,20} = 0.65$, $P = 0.63$) nor the interaction ($F_{4,20} = 0.28$, $P = 0.89$) was significant. Thus, unlike the bolus injection of \textit{S. aureus}, infusion of the pyrogen had no significant
To compare our new model with previous models of experimentally induced fever, we also measured the temperature, behavioral, and neuroendocrine changes induced by bolus administration of *S. aureus* and the gram-negative pyrogen lipopolysaccharide. We found that chronic infusion of *S. aureus* evoked prolonged fevers that lasted for ~3 days, starting on the 4th day of infusion, but did not disrupt the normal circadian rhythm of body temperature. In contrast, bolus injections of *S. aureus* cell walls and lipopolysaccharide evoked typical, short-duration fevers that lasted ~6 h. Despite the development of a prolonged fever, cortisol concentration remained at basal levels throughout the infusion of *S. aureus*. Bolus administration of the pyrogens induced an increase in cortisol concentration typical of that previously reported in animal fever studies (3, 16). Infusion of *S. aureus* also did not evoke the typical suite of sickness behaviors observed in animals administered bolus injections of *S. aureus* and lipopolysaccharide. Thus, although the behavioral and neuroendocrine responses were different than those typically observed in acute fevers in laboratory animals, we successfully developed a model of sustained natural fever in goats.

However, despite infusion of *S. aureus* eliciting a sustained elevation in body temperature in goats, the fevers were small in magnitude. The small fever magnitude probably was a consequence of the limited pyrogen load that was delivered by the osmotic infusion pumps; pyrogen load was limited by the volume of the pump and restrictions on the maximum concentration of the *S. aureus* solution. Another possibility is that the small fever magnitude resulted from pump failure or the rate of infusion being slowed by blockages. However, we found at the end of the experiment that all pumps had infused their contents, and there were no blockages or kinks in the delay line. The infusion rate specified by the manufacturers of the osmotic pump was confirmed by T. Cartmell (unpublished observation), who used an osmotic pump to infuse a rabbit intravenously with a radio-opaque dye while taking X-rays immediately after surgical implantation of the pump and on a daily basis thereafter to confirm the continuous infusion of the pump’s contents over the stated infusion duration for the pump. Nevertheless, the dead space created by the use of a delay line, to allow the animals time to recover from surgery before the start of pyrogen administration, probably limited the effective infusion period of the pumps contents to 5 days. Occupation of the delay line by *S. aureus* on day 7 of infusion could explain the defervescence that occurred at that time. Alternatively, the development of tolerance to the pyrogen could have occurred at this final stage of infusion.

**Table 1. Behavioral changes induced by injection or infusion of bacterial pyrogens**

<table>
<thead>
<tr>
<th>Percent Time</th>
<th>Infusion (Saline, n = 7; <em>S. aureus</em>, n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus (n = 6)</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
</tr>
<tr>
<td>Lying*</td>
<td>32 (42)</td>
</tr>
<tr>
<td>Feeding</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Shivering</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values represented as mean (SD). Bolus data collected from 1100 to 1200 on day of injection. Infusion data collected from 1100 to 1200 during infusion days 4, 5, and 6. * Animals standing when not lying down. No statistically significant differences were found between any groups.
Repeated administration of gram-negative lipopolysaccharide causes pyrogenic tolerance to develop (for review, see Ref. 51). Tolerance also develops to repeated administration of the gram-positive pyrogen muramyl dipeptide, but only during the first 6 h of the fever (37, 51). Thus the underlying mechanism of tolerance development to pyrogens derived from gram-negative and gram-positive pathogens appears to differ. For example, the development of tolerance to lipopolysaccharide is associated with reduced secretion of proinflammatory cytokines, tumor necrosis factor-α, and interleukin-6 (28, 36, 47), whereas there is no attenuation of cytokine release when tolerance develops to muramyl dipeptide (13, 37). Indeed, tolerance induced by repeated lipopolysaccharide administration can be reversed by administration of gram-positive pyrogens (12, 38). In our study, however, infusion of S. aureus induced a gradual increase in body temperature, so there was no evidence of tolerance development during pyrogen infusion, except possibly on the 7th day of infusion. In support of the concept of no tolerance development to infused S. aureus, Goelst and Laburn (12) also found no attenuation of the fever response to 5 consecutive days of bolus administration of S. aureus. Thus, although muramyl dipeptide, a breakdown product of S. aureus cell walls, probably contributed to the development of fever in our animals, other pyrogenic components of the killed bacterial cells, such as enterotoxins and toxic shock syndrome toxin-1 (9), may also have been responsible for maintaining the fever.

In addition to producing sustained fever, we also wished to mimic the pattern of body temperature change recorded serendipitously in febrile, free-living antelope. The mean daily body temperature of these antelope was elevated ~0.5–1°C above normal for 2–11 days, but throughout these febrile periods, the nadir and peak of the circadian rhythm of body temperature remained unchanged (20). This maintenance of circadian rhythm during infection also has been well documented in febrile humans (26, 31). In this study, the sustained fever induced by S. aureus infusion also was characterized by maintenance of the periodicity and amplitude of the circadian rhythm of body temperature. The periodicity of the rhythm even was preserved during the rising phase of the fever. We therefore have successfully mimicked the temperature profile observed during fevers of natural origin in free-living antelope (20). As far as we are aware, maintenance of the circadian rhythm of body temperature in our animals infused with pyrogen is a novel discovery. Other experiments producing fevers exceeding 24 h have led to elevated body temperatures above those of afebrile animals only during periods of the circadian rhythm when body temperature is at its nadir (15, 33).

Interestingly, the gradual increase in body temperature recorded over the first 3 days of pyrogen infusion was unaccompanied by shivering. Thus unlike the rapidly developing fevers that followed bolus injection with lipopolysaccharide and S. aureus in which shivering was observed, it is unlikely that the development of low-grade fever to S. aureus infusion was the result of increased heat production, but rather reduced heat loss. The rate of rise of body temperature, the magnitude of the fever, and the ambient temperature probably determine whether shivering is employed during fever genesis (17, 18). Thus the low fever magnitude, gradual increase in body temperature, and warm ambient temperatures probably all contributed to the absence of shivering in animals infused with S. aureus. Reductions in heat loss in our animals may have resulted from autonomic changes in skin blood flow and evaporative water loss or from behavioral changes, such as curling up or huddling with other animals to reduce the surface area for heat loss (19). Our animals did not curl up or huddle with other pyrogen-infused animals in their pens, thus reductions in heat loss probably were elicited through autonomic mechanisms.

Other behavioral changes that can occur during infection include sickness behaviors, such as anorexia, lethargy, somnolence, and decreased social interaction, which are hypothesized to reduce the proliferation and spread of pathogens (16, 29). Bolus injection of lipopolysaccharide and S. aureus in our goats elicited other signs of sickness behavior, such as marginal decreases in the time spent feeding, but we observed no such behavioral changes in animals infused with S. aureus. Sickness behavior is mediated by cytokines, principally interleukin-1β and tumor necrosis factor-α (7, 23, 24), which are released during infection. Therefore, differences in the cytokine response to bolus pyrogen injection versus pyrogen infusion may explain the differential expression of sickness behavior in our two experiments. Unfortunately, we do not have cytokine data for our animals, but horses with natural fevers arising from perioperative infection, inflammation, or trauma have low circulating cytokine titers compared with the amounts of cytokines that are detected when bolus injections of gram-positive and gram-negative pyrogens are administered (J. Roth, unpublished observations). Thus the inflammatory response induced during low-grade fevers, as we produced during S. aureus infusion, may be insufficient to elicit the full suite of adaptive responses seen during more substantial infections (for example, when bolus injections of pyrogens are administered), thus dampening the expression of sickness behavior. However, even with elevated cytokine levels, Werling and colleagues (48) showed that food intake was not affected in heifers infused intravenously with lipopolysaccharide. In contrast to our findings and those of Werling et al. (48), O’Reilly and colleagues (33) showed that feeding was reduced in rats infused intraperitoneally with lipopolysaccharide, even after the animals had become tolerant to the pyrogenic effects of the lipopolysaccharide. The cause for these disparate findings is unclear, but may involve differences in the route of pyrogen administration, the dose or rate of pyrogen administration, and the species of animal used. The results of our study and these previous studies (33, 48), however, show that fever and the anorexia associated with infection can occur independently of each other.

In addition to thermoregulatory and behavioral changes, the acute phase response to infection also is characterized by activation of the hypothalamic-pituitary-adrenal axis, in which cytokines, such as interleukin-1β, interleukin-6, and tumor necrosis factor-α, stimulate the secretion of corticotrophin-releasing hormone from the hypothalamus and ultimately cortisol from the adrenal glands (2, 3, 27, 34, 35, 44). The secretion of cortisol then modulates the inflammatory response to pyrogens (10, 30), for example, by inhibiting the production of prostaglandins (42) and inflammatory cytokines (22, 42). We measured the cortisol response during S. aureus infusion and after bolus administration of lipopolysaccharide and S. aureus as a measure of the hypothalamic-pituitary-adrenal axis.
activation. Whereas bolus pyrogen injection induced a typical cortisol response, cortisol levels remained at preinfusion levels when S. aureus was infused. An increase in cortisol secretion has been observed clinically in people with febrile illnesses (32, 39). However, because of innate immune system’s capability to recognize and fight off pathogens, fever still develops. The immunopathogenesis of sepsis. Nature 2002, submitted.


34. Perstein RS, Whitnall MH, Abrams LS, Mougey EH, and Neta R. Synergistic roles of interleukin-6, interleukin-1 and tumor necrosis factor...
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