Physiology & Behavior, Vol. 47, pp. 773–775. © Pergamon Press plc, 1990. Printed in the U.S.A. 0031-9384/90 $3.00 + .00

BRIEF COMMUNICATION

Stress-Induced Rise of Body Temperature in Rats Is the Same in Warm and Cool Environments

NANCY C. LONG, ARTHUR J. VANDER AND MATTHEW J. KLUGER

Department of Physiology, University of Michigan Medical School, Ann Arbor, MI 48109

Received 27 November 1989

LONG, N. C., A. J. VANDER AND M. J. KLUGER. *Stress-induced rise of body temperature in rats is the same in warm and cool environments*. PHYSIOL BEHAV **47**(4) 773–775, 1990.—Several forms of psychological stress result in a rise in body temperature in rats. In this study, we report that rats housed at a low ambient temperature (11.1°C) develop stress-induced rises in body temperature that do not differ from the responses seen when the animals are kept at a temperature within their thermoneutral zone (24.7°C). These data support the hypothesis that stress-induced "hyperthermia" is a regulated rise in temperature (i.e., a rise in thermoregulatory "set-point," or fever), and is not simply the result of metabolic changes associated with the stress response itself.

Stress-hyperthermia Fever Temperature regulation Metabolic rate

PSYCHOLOGICAL stress has been shown to cause a rapid rise in the body temperature of rats (2–4, 8, 9, 14, 16, 20, 22, 25), rabbits (21,24), and humans (10,17). Exposure to a novel environment, a classic stress paradigm for the rat, causes an average increase in body temperature of about 1.4°C (20). Somewhat milder psychological stress can be induced by simply switching the cages of rats (14).

Previous studies in this and other laboratories have produced data supporting the hypothesis that this elevation in temperature, often called "stress-hyperthermia," is a regulated rise (i.e., a rise in thermoregulatory "set-point"), and hence may be considered to be a true fever. Evidence that stress-hyperthermia is a fever is based upon the following findings: 1) Pretreatment of rats with prostaglandin inhibitors such as sodium salicylate or indomethacin injected either intraperitoneally (IP) or intracerebroventricularly (ICV) blocked more than half of the elevation in temperature due to exposure to psychological stress (4, 14, 20). 2) The injection of antiserum against tumor necrosis factor (TNF), which causes an elevation in the fever due to the injection of lipopolysaccharide (LPS) (15), also results in an increase in the stress-hyperthermia response in rats (16). 3) Although activity increases when rats are cage-switched, the increase that occurs when rats are cage-switched during the day does not correlate with the subsequent increase in temperature. When rats are cage-switched at night, the temperature and activity changes are negatively correlated, suggesting that the rats regulate their activity level to keep their temperatures from going too high (16). All these observations suggest to us that the magnitude of LPS fever and stress hyperthermia are controlled by a common mechanism.

Despite the above data, it is still possible that the rise in body temperature when rats are exposed to novel environments is simply the result of an unregulated increase in temperature caused by an increase in metabolic rate. If the elevation in body temperature seen in rats after cage-switch is a regulated change, then we would expect to see the same rise in body temperature under warm or cool conditions, as occurs during true fever. Alternatively, if stress hyperthermia is not a regulated elevation in temperature, but is simply the result of metabolic changes associated with the stress response itself, then we would expect to see a smaller rise in temperature in rats that are cage-switched while kept at a cool ambient temperature. The rationale for this last assumption is as follows. When rats are kept at a temperature within their thermoneutral zone (ca. 25°C) their metabolic rate tends to be low, their skin blood vessels are peripherally vasodilated (or not tightly vasoconstricted), and they are not employing heat-conserving behaviors. In a cool environment, however, the metabolic rate is elevated as a result of shivering and nonshivering thermogenesis, skin blood vessels are vasoconstricted, and postural changes are employed that decrease heat loss to the environment. An increase in heat production in the cold can be effectively compensated for by increasing skin blood flow (peripheral vasodilation), decreasing shivering and nonshivering metabolism, and

[1]Requests for reprints should be addressed to Matthew J. Kluger, Ph.D.

behavioral changes. If there is no change in thermoregulatory "set-point," then the rat exposed to cage-switch in the cold would compensate for the increased heat production by peripheral vasodilation and behavioral changes, resulting in a smaller increase in body temperature. Therefore, we would expect to see a smaller stress-induced rise in body temperature in a rat exposed to cage-switch while kept in a cool room compared to the response in rats kept in a warm room.

In the current study, we switched the cages of rats while the animals were kept at an ambient temperature within their thermoneutral zone (24.7°C) or at a temperature well below their thermoneutral zone (11.1°C) (11). We then monitored and compared the subsequent changes in body temperature and activity under both conditions, and found that rats housed in a cool environment showed stress-induced rises in body temperature of similar magnitude to those seen when the animals were kept at a temperature within their thermoneutral zone.

METHOD

Animals

Specific pathogen-free male Sprague-Dawley rats weighing 160 to 260 g were used in this study. The rats were housed in individual cages measuring 33 cm (l) × 20 cm (w) × 18 cm (h) in a room initially maintained at 24.7°C, a temperature within the thermoneutral zone for rats, with a photoperiod consisting of 12 hr light:12 hr dark, with lights on at 0600 hr. Tap water and rodent chow (Purina 5001) were provided ad lib.

Body Temperature and Activity Measurement

Body temperature and activity were measured using battery-operated biotelemetry devices (Mini Mitter, Sunriver, OR) implanted intraperitoneally four or more days before experimentation began. Temperature data (frequency in Hz) was monitored by a mounted antenna placed under each animal's cage and fed into a peripheral processor connected to a microcomputer (IBM PC).

This receiver detects activity by recording changes in position of the implanted biotelemetry device. As the animal moves, the orientation of the transmitter changes with respect to the antenna that is mounted under the board. A change in the position of the transmitter alters the strength of the signal that is detected by the antenna. Any change in the signal strength is recorded as a "pulse" of activity. Temperature and activity were monitored and recorded at 5-minute intervals during all experiments [see (19) for a more detailed description].

Stress Paradigms

Psychological stress was induced by a paradigm called cage-switch stress. This stress is evoked by placing a rat into an empty cage previously occupied by another rat. Exposure to the olfactory and visual stimuli associated with this new environment causes a temperature elevation of about 1.0°C over about 30 minutes (16). Care was taken not to disturb the animals before or after the stress exposure. All animals had been conditioned to handling for at least 1 week prior to the experiments. To minimize any confounding effects of the circadian rhythm for temperature, all stress experiments were performed between 1000 hr and 1200 hr.

Experimental Design

Nine rats were used in this study. The rats were implanted with transmitters and allowed 5 days to recover in a room maintained at 24.7 ± 0.01°C. After the recovery period, the rats were exposed to cage-switch stress. Temperature and activity levels were monitored over the next 60-minute period. The temperature of the room was then lowered to 11.1 ± 0.02°C, and the rats were allowed 4 days to adapt to the cooler temperature. The rats were then cage-switched again at the lower room temperature. To confirm that the rats' response to cage-switch had not changed, the temperature of the room was returned to 24.7°C, and, after allowing 4 more days for the animals to adjust to the temperature change, the rats were cage-switched a third time.

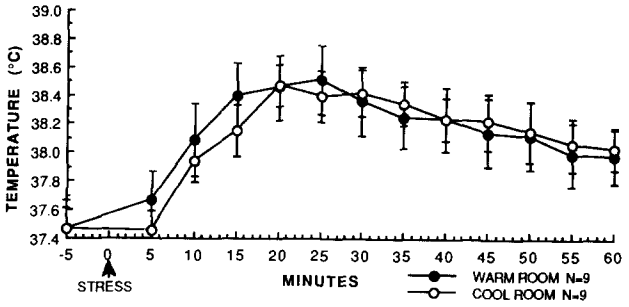

FIG. 1. The time course of the stress-induced change in body temperature in rats after cage-switch in a warm (24.7°C) or cool (11.1°C) room.

Statistical Analysis

The data were analyzed by Student's *t*-test using Statview 512+ on a Macintosh computer.

RESULTS

The stress hyperthermia response of rats exposed to cage-switch at warm and cool room temperatures is shown in Fig. 1. Prior to exposure to stress, the body temperatures of rats at both ambient temperatures did not differ significantly (37.5 ± 0.19 in the warm room vs. 37.5 ± 0.12 in the cool room, $p = 0.84$). When the rats were cage-switched at an ambient temperature within their thermoneutral zone, they showed a peak rise of 1.13 ± 0.10°C within 30 minutes. This did not differ significantly from the rise seen when the animals were cage-switched in a cool room (1.08 ± 0.18°C, $p = 0.67$). When the rats were cage-switched once more at 24.7°C, they showed a peak change in temperature of 1.21 ± 0.20°C within the first 30 minutes. This was not significantly different from the stress-induced elevation in body temperature of the rats after the first cage-switch ($p = 0.61$).

The change in activity of the rats after cage-switch at warm and cool temperatures is shown in Fig. 2. Prior to exposure to cage-switch, there was no significant difference in the activity of

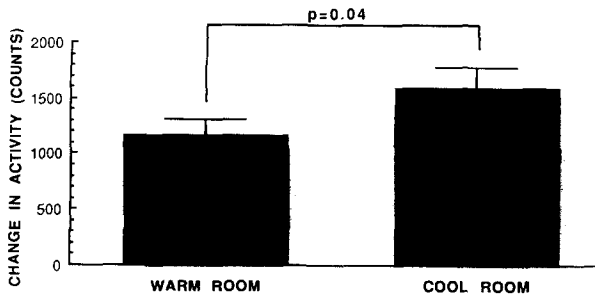

FIG. 2. The change in activity of rats exposed to cage-switch stress in a warm (24.7°C) or cool (11.1°C) room.

the rats (124 ± 58 in the warm vs. 74 ± 19 in the cool room). However, after the rats were cage-switched, they showed a significantly higher change in activity in the cool (1596 ± 185) than they did in the warm room (1165 ± 145; $p = 0.04$).

DISCUSSION

These data are consistent with the hypothesis that "stress-hyperthermia" is a regulated change in temperature (i.e., a true fever). Our finding that rats cage-switched under warm or cool conditions show similar rises in temperature suggests that this change is not simply the result of nonspecific metabolic changes associated with the stress response itself, but is a change in the thermoregulatory "set-point."

The physiological response to psychological stress involves many systems of the body. Researchers in other laboratories have shown that rats exposed to novel environments show increased plasma levels of corticosterone, as well as other hormonal changes (1, 5–7). It is possible that the vasoconstriction and increase in metabolic rate associated with the action of these hormones could be sufficient to cause the elevation in body temperature associated with psychological stress. However, rats kept at 11.1°C would already be vasoconstricted and would have metabolic rates approximately 75% higher than those of rats kept at 24.7°C (11). Therefore, our finding that rats kept under these conditions show a stress-induced elevation in temperature that is virtually identical to those seen when the rats were kept at temperatures within their thermoneutral zone suggests that other mechanisms are probably involved.

Our data comparing the activity change after cage-switch when the rats were kept under warm or cool conditions further supports the hypothesis that stress-induced elevations in body temperature are regulated rises. The fact that rats kept in a cool room showed larger increases in activity than they did when kept in a warm room suggests that the animals increased their activity level in order to elevate their body temperatures.

Since there are considerable data supporting the hypothesis that fever evolved as a host defense response (12, 13, 18), we speculate that stress-induced fevers may also have evolved as an adaptive mechanism that prepares the host for potential tissue injury and infection.

ACKNOWLEDGEMENT

Research supported in part by a grant from the Biomedical Research Council and the Office of the Vice President for Research from the University of Michigan.

REFERENCES

1. Baldwin, D. M.; Columbo, J. A.; Sawyer, C. H. Plasma prolactin, LH, and corticosterone in rats exposed to a novel environment. Am. J. Physiol. 226(6):1366–1369; 1974.
2. Blasig, J.; Hollt, V.; Bauerle, U.; Herz, A. Involvement of endorphins in emotional hyperthermia of rats. Life Sci. 23:2525–2532; 1978.
3. Briese, E.; De Quijada, M. G. Colonic temperatures of rats during handling. Acta Physiol. Latinoam. 20:97–102; 1970.
4. Briese, E.; Cabanac, M. Emotional fever and salicylates. In: Szelenyi, Z.; Szekely, M., eds. Proc. of 28th Intern. Cong. Physiol. Sci., vol. 32 in Advances in Physiological Sciences. Pergamon Press-Adakemiai Kiado; 1980:161–163.
5. Brown, G. M.; Uhlir, I. V.; Seggie, J.; Schaaly, V.; Kastin, A. J. Effect of septal lesions on plasma levels of MSH, corticosterone, GH and prolactin before and after exposure to novel environment: Role of MSH in septal syndrome. Endocrinology 94(4):583–587; 1974.
6. Brown, G. M.; Martin, J. B. Corticosterone, prolactin and growth hormone responses to handling and new environment in the rat. Psychosom. Med. 36(3):241–247; 1974.
7. Clamage, D. M.; Sanford, C. S.; Vander, A. J.; Mouw, D. R. Effects of psychosocial stimuli on plasma renin activity in rats. Am. J. Physiol. 23(4)1290–1294; 1976.
8. Goldstein, A.; Lowery, P. Effect of the opiate antagonist naloxone on body temperature in rats. Life Sci. 17:927–932; 1975.
9. Gollnick, P. D.; Ianuzzo, C. D. Colonic temperature response of rats during exercise. J. Appl. Physiol. 24:747–750; 1968.
10. Hasan, M. K.; White, A. C. Psychogenic fever, entity or nonentity? Postgrad Med. J. 66:152–154; 1979.
11. Herrington, L. P. The heat regulation of small laboratory animals at various environmental temperatures. Am. J. Physiol. 129:123–131; 1940.
12. Kluger, M. J. Fever: Its biology, evolution and function. Princeton, NJ: Princeton University Press; 1979.
13. Kluger, M. J. Is fever beneficial? Yale J. Biol. Med. 59:89–95; 1986.
14. Kluger, M. J.; O'Reilly, B.; Shope, T. R.; Vander, A. J. Further evidence that stress hyperthermia is a fever. Physiol. Behav. 39: 763–766; 1987.
15. Long, N. C.; Kunkel, S. L.; Vander, A. J.; Kluger, M. J. Antiserum against TNF enhances LPS fever in the rat. Am. J. Physiol., in press; 1990.
16. Long, N. C.; Vander, A. J.; Kunkel, S. L.; Kluger, M. J. Antiserum against tumor necrosis factor increases stress hyperthermia in rats. Am. J. Physiol., in press; 1990.
17. Renbourn, E. T. Body temperature and pulse rate in boys and young men prior to sporting contests. A study in emotional hyperthermia, with a review of the literature. J. Psychosom. Res. 4:149–175; 1960.
18. Roberts, N. J., Jr. Temperature and host defense. Microbiol. Rev. 43:241–259; 1979.
19. Scales, W. E.; Kluger, M. J. Effect of antipyretic drugs on circadian rhythm in body temperature of rats. Am. J. Physiol. 253:R306–R313; 1987.
20. Singer, R.; Harker, C. T.; Vander, A. J.; Kluger, M. J. Hyperthermia induced by open-field stress is blocked by salicylate. Physiol. Behav. 36:1179–1182; 1986.
21. Snow, A. E.; Horita, A. Interaction of apomorphine and stressors in the production of hyperthermia in the rabbit. J. Pharmacol. Exp. Ther. 220(2):335–339; 1982.
22. Stewart, J.; Eikelboom, R. Stress masks the hypothermic effect of naloxone in rats. Life Sci. 25:1165–1172; 1979.
23. Vidal, C.; Suaudeau, C.; Jacob, J. Hyper- and hypothermia induced by non-noxious stress, effects of naloxone, diazepam, and gamma-acetylenic GABA. Life Sci. 33:587–590; 1983.
24. Yokoi, Y. Effect of ambient temperature upon emotional hyperthermia and hypothermia in rabbits. J. Appl. Physiol. 21(6):1795–1798; 1966.
25. York, J. L.; Regan, S. G. Conditioned and unconditioned influences on body temperature and ethanol hypothermia in laboratory rats. Pharmacol. Biochem. Behav. 17:119–124; 1982.