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Effects of Sleep Deprivation on Measures of the Febrile Reaction and the Recovery of Somatovisceral Functions and Sleep in Endotoxemia

K. V. Lapshina and I. V. Ekimova

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Electroencephalographic methods were used to study the effects of total sleep deprivation on thermoregulatory measures of the fever response in pigeons (*Columba livia*): brain temperature, peripheral vasomotor reactions, thoracic muscle contractile activity, and the recovery of somatic functions and the time characteristics of waking and sleep in lipopolysaccharide (LPS)-induced endotoxemia. Sleep deprivation during the period in which the quantity of slow-wave sleep increased on administration of LPS induced decreases in the latent period of fever onset and in the duration of fever, along with more significant increases in brain temperature and the level of muscle contractile activity as compared with the effects of LPS alone. The period after sleep deprivation was characterized by more prolonged recovery of muscle contractile activity and the time characteristics of sleep and waking states, along with more prolonged compensatory "rebound" of slow-wave sleep as compared with the effects of sleep deprivation alone. Thus, sleep deprivation in endotoxemia led to decreases in the latent period of fever onset, exacerbation of fever, and increases in the latent period of recovery of physiological functions.

KEY WORDS: lipopolysaccharide, fever, sleep deprivation, brain temperature, muscle contractile activity, vasomotor reaction, slow-wave sleep.

Fever is defined as a controlled increase in body temperature accompanying the ingress of a variety of foreign agents into the body and directed to protecting the body's internal environments [1, 2]. During this state, reactive changes in the functioning of the immune, nervous, thermoregulatory, endocrine, and other body systems are seen. The development of fever in infectious diseases in humans [19] and after administration of a cell wall component from Gram negative bacteria, i.e., the endotoxin lipopolysaccharide (LPS) in rats and rabbits [14, 22], has been shown to be accompanied by increases in the duration of slow-wave sleep and decreases in the total duration of waking and REM sleep. Inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) have been shown to be responsible for somnogenic action of LPS; these directly or indirectly activate neurons in the preoptic areas of the hypothalamus involved in generating and maintaining slow-wave sleep [14, 17]. However, the function of slow-wave sleep in the mechanisms of development of fever remains unclear. In mammals and birds, slow-wave sleep makes the main contribution to decreases in brain temperature, while waking and REM sleep make the main contributions to increases in brain temperature [5, 11, 20, 21]. It remains possible that slow-wave sleep protects the brain from "overheating" during the development of fever. In addition, published data provide indirect evidence that slow-wave sleep in infectious diseases may be a prognostic indicator. Kruger et al. showed that recovery after administration of *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* endotoxins to rabbits started when the course of illness was characterized by prolonged periods of sleep, while animals lacking this alternation died [26]. Thus, slow-wave sleep may be a component of the

I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, 44 M. Torez Prospekt, 194223 St. Petersburg; e-mail: ksenia.lapshina@gmail.com.

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body's protective reaction against infection and its absence may impair the recovery of the body's physiological functions in endotoxemia. However, the effects of sleep deprivation on the development of the fever reaction and the recovery of the body's physiological functions in endotoxemia remain unknown.

The aim of the present work was to study the effects of total sleep deprivation on thermoregulatory measures of the fever reaction: brain temperature, peripheral vasomotor reactions, thoracic muscle contractile activity, and the recovery of somatic functions and the time characteristics of waking and sleep in endotoxemia induced by lipopolysaccharide (LPS). A particularly interesting study system for these tasks is provided by pigeons, whose body temperature is initially 3–3.5°C higher than that in mammals [5, 7]; after administration of endotoxin, body temperature in pigeons increases further, to 42–43°C [16, 17].

METHODS

Experiments were performed on six pigeons (*Columba livia*) weighing 350–380 g. The experimental chamber consisted of a box insulated against light and sound stimuli, in which cages for the birds were placed. The temperature in the chamber was maintained at 25 ± 1°C with a 12:12 photoperiod. The birds were placed in the chamber for adaptation to the photopheriod 7–10 days before surgery, and were fitted with back packs consisting of a printed circuit board for transmission of electrical signals using a mobile commutator (USA). Birds were provided with unrestricted water and food. The birds were provided with the most comfortable possible conditions while in the animal house and during the experiments. Some 10–12 days before the experiments started, birds were anesthetized with Nembutal (25 mg/kg) and gold-plated electrodes were implanted for recording electroencephalograms from the surface of the hyperstriatum of the right and left hemispheres, electrooculograms, and electromyograms (to assess the level of thoracic muscle contractile activity), along with mini-thermistors (BetaTherm cat 2K7 MCD1, diameter 0.46 mm, resistance 1.5 kΩ, USA) to record brain temperature and leg skin temperature to assess peripheral vasomotor reactions. The experiments used a computer system (SASR 8800, Sleep Analysis System, USA) allowing 24-h recordings. Sleep deprivation was imposed for 5 h (4 h of the light phase and 1 h of the dark phase) using tactile and sound stimulation). The bacterial endotoxin LPS (*Escherichia coli* O111:B4, Sigma Aldrich) was given i.v. at a dose of 5 μg/kg in 0.2 ml 4 h before the onset of the dark phase of the day. Controls received apyrogenic physiological saline (i.v., 0.2 ml). Physiological parameters were analyzed using computer programs developed in our laboratory. Statistical analysis of data was performed using Statistica 6. Appropriate statistical methods were used depending on the type of distribution of a feature and the number of groups being compared for that feature: Student's t test, the Wilcoxon non-parametric test, and ANOVA parametric analysis of variance. The minimal probability taken for statistical significance was $p < 0.05$.

RESULTS

Administration of LPS to pigeons initially induced reductions in brain temperature, which were followed by increases (Fig. 1, *a*). During the hypothermic phase, skin temperature decreased from 36.3 ± 0.3°C (administration of physiological saline, control) to 35.1 ± 0.2°C (administration of LPS) ($p < 0.05$), which is evidence for the development of peripheral vasoconstriction. Mean brain temperature from 4 h to 9 h following administration of physiological saline was 39.8 ± 0.2°C, increasing to 40.4 ± 0.1°C after administration of LPS ($p < 0.05$). Vasodilation was seen during the maximum increase in brain temperature – leg skin temperature increased from 36.4 ± 0.2°C (controls) to 37.4 ± 0.1°C (LPS) ($p < 0.05$). Muscle contractile activity increased by an average of 56% ($p < 0.05$) compared with controls 4 h after endotoxin administration (Fig 1, *b*).

The experiments showed that administration of LPS led to changes in the time characteristics of waking and sleep states. From 1 to 4 h after LPS, there were reductions in the total durations of waking and REM sleep (Fig. 2, *a*; Fig. 3, *b*) and an increase in the total duration of slow-wave sleep (Fig. 3, *a*). The quantity of slow-wave sleep increased by an average of 17% ($p < 0.05$) as a result of increases in the duration of episodes of slow-wave sleep, from 20.3 ± 5.5 to 34.2 ± 5.2 sec ($p < 0.05$), and the number of episodes, from 10.6 ± 2.6 to 26.2 ± 4.7 ($p < 0.05$), compared with controls. Decreases in waking occurred because of decreases in the duration of waking episodes, from 117.8 ± 12.9 to 75.9 ± 12.1 sec ($p < 0.05$), and decreases in REM sleep occurred as a result of decreases in the number of episodes, from 37.4 ± 8 to 21.9 ± 6.5 ($p < 0.05$) (Fig. 2, *a*; Fig. 3, *b*). The total duration of waking and sleep reached control values by 50 h after LPS administration.

The sleep deprivation procedure induced changes in the thermoregulation system in pigeons. Brain temperature increased 2 h before the end of sleep deprivation (Fig. 1, *a*) and peripheral vasodilation occurred, as evidenced by an increase in skin temperature by 1.2 ± 0.4°C ($p < 0.05$). During the whole 5-h period of sleep deprivation, there was an increase in the level of muscle contractile activity, by 220% compared with controls ($p < 0.001$) (Fig. 1, *b*). The increased level of muscle contractile activity persisted for 1 h into the post-deprivation period (Fig. 1, *b*). The sleep deprivation procedure, using tactile and sound stimulation, eliminated drowsiness and sleep (slow-wave sleep and REM sleep) by 95% ($p < 0.001$) (Figs. 2, 3). After the sleep deprivation procedure ended, the animals did not fall asleep immediately; the dominant state during the first hour of the post-

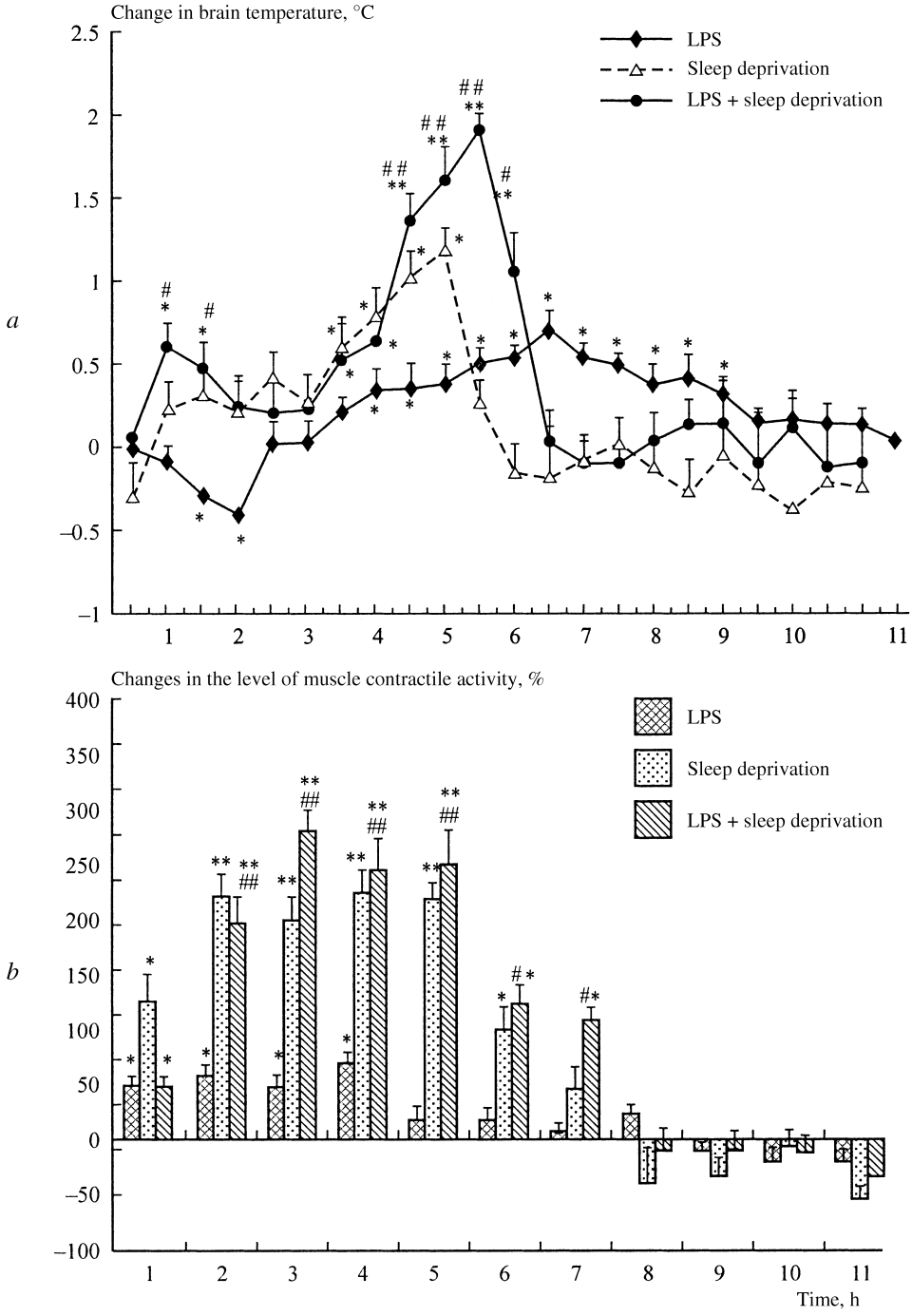

Fig. 1. Changes in brain temperature (*a*) and levels of muscle contractile activity (*b*) in pigeons on exposure to lipopolysaccharide (LPS) and sleep deprivation alone and in combination. The ordinates show changes in brain temperature (*a*) and muscle contractile activity (*b*) relative to controls (null line); the abscissas show time (h) from the moment of administration of LPS/physiological saline. Here and in Figs. 2 and 3: the period of sleep deprivation is the time from 1 to 5 h on the abscissa; the post-deprivation period is from 6 to 11 h. *Significant changes compared with control, $p < 0.05$; **$p < 0.001$. #Significant changes on combined sleep deprivation + LPS compared with LPS, $p < 0.05$; ##$p < 0.001$.

deprivation period was waking (Fig. 2, *a*). The total duration of waking increased mainly because of an increase in the duration of waking episodes, by 49.3 ± 5.8 sec ($p < 0.001$) as compared with controls. The total duration of slow-wave and REM sleep decreased significantly during the first hour of the post-deprivation period (Fig. 3, *a*, *b*). The decrease in

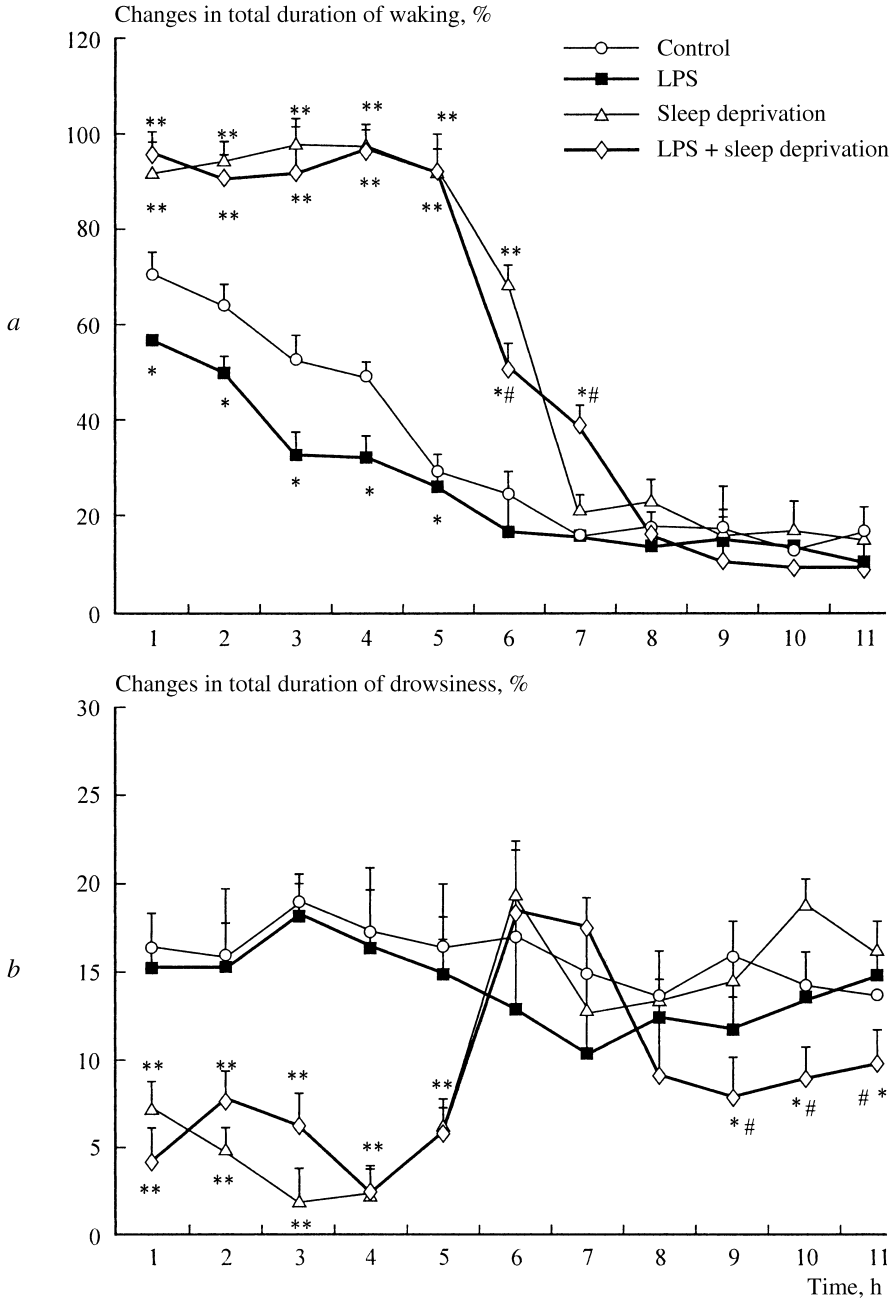

Fig. 2. Changes in total durations of waking (*a*) and drowsiness (*b*) in pigeons in control conditions and on exposure to lipopolysaccharide (LPS), sleep deprivation, and LPS combined with sleep deprivation. Here and in Fig. 3: the ordinates show total durations of each state (%) during each recording hour; abscissas show time (h) from the moment of administration of LPS/physiological saline. *Significant changes compared with controls, $p < 0.05$; **$p < 0.001$. #Significant changes on combined exposure to sleep deprivation and LPS compared with sleep deprivation, $p < 0.05$; ##$p < 0.001$.

the total duration of slow-wave sleep occurred because of reductions in the number of episodes by 18.1 ± 3 ($p < 0.05$) and the duration of episodes by 17.7 ± 4.5 sec ($p < 0.05$); the decrease in REM sleep resulted from a reduction in the number of episodes by 13.9 ± 3.3 ($p < 0.05$) compared with controls. Starting from the second hour of the post-deprivation period, the animals showed prolonged episodes of slow-wave sleep, along with "rebound" of slow-wave sleep. The total duration of slow-wave sleep during this hour increased by 15% ($p < 0.05$) as compared with controls. The increase in the quantity of slow-wave sleep occurred as a result of an increase in the duration of its

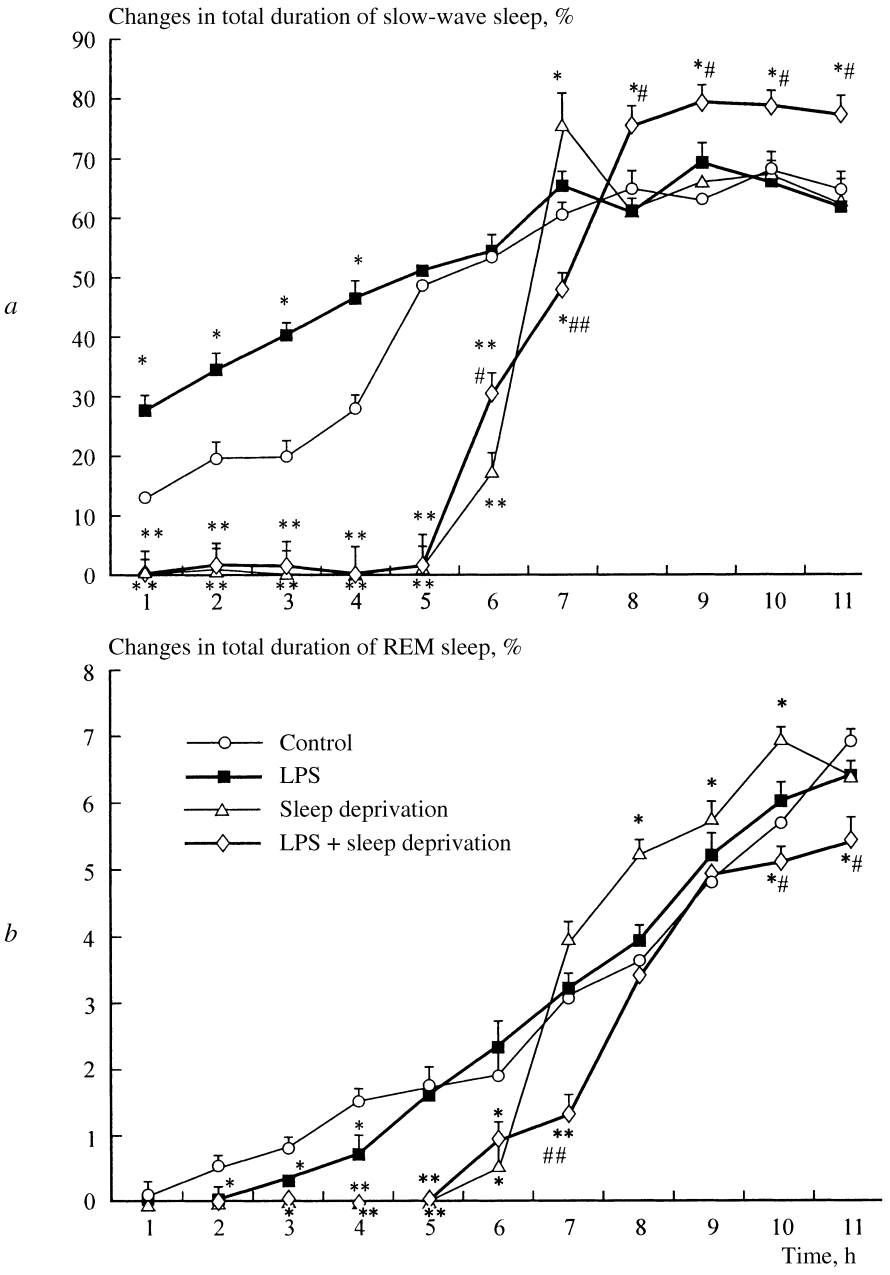

Fig. 3. Changes in total durations of slow-wave sleep (*a*) and REM sleep (*b*) in pigeons in control conditions and on exposure to lipopolysaccharide (LPS), sleep deprivation, and sleep deprivation combined with LPS.

episodes by 14 ± 2.9 sec ($p < 0.05$) as compared with controls. By 3 h into the post-deprivation period, the total duration of slow-wave sleep was no different from that in controls, though the total duration of REM sleep increased. "Rebound" of REM sleep was seen from 3 to 6 h of the post-deprivation period (Fig. 3, *b*). The increase in the total duration of REM sleep during these hours occurred as a result of an increase in the number of episodes by 10.2 ± 3.2 ($p < 0.05$) compared with controls.

Sleep deprivation in endotoxemia led to changes in the thermoregulatory measures of the fever reaction. In these conditions, there was a reduction in the latent period of the increase in brain temperature, with an increase in fever and a reduction in its duration by 3 h (Fig. 1, *a*). The maximum increase in brain temperature in the combination of LPS and sleep deprivation, by 1.2 ± 0.3°C ($p < 0.05$), was greater than the increase in brain temperature on exposure to endotoxin alone. During the maximum increase in brain temper-

ature, there was marked peripheral vasodilation, as evidenced by an increase in leg skin temperature by 1.5 ± 0.3°C ($p < 0.05$). A characteristic feature of fever in this situation was the absence of a hypothermic phase in the change in brain temperature, as well as a lack of peripheral vasoconstriction. Sleep deprivation in endotoxemia also led to a longer-lasting and more significant increase in the level of muscle contractile activity as compared with LPS alone (Fig. 1, *b*). Recovery of the level of muscle contractile activity to control levels during the post-deprivation period occurred 3 h later than on exposure to endotoxin and 1 h later than with sleep deprivation alone (Fig. 1, *b*). Sleep deprivation in conditions of endotoxemia produced more significant changes in the time characteristics of the states of waking and sleep, with later recovery of the sleep-waking cycle as compared with sleep deprivation alone (Figs. 2 and 3). An increased level of waking was seen for a longer period of time (1 h longer) as compared with the effects of sleep deprivation and, during 2 h of the post-deprivation period, the quantity was 20% greater ($p < 0.05$) than the quantity of waking in sleep deprivation (Fig. 2, *a*). The increase in the duration of waking during the second hour occurred as a result of an increase in episode durations by an average of 21.7 ± 3.5 sec ($p < 0.05$) compared with sleep deprivation alone. The total duration of slow-wave and REM sleep decreased significantly during the first 2 h of the post-deprivation period (Fig. 3). The quantities of waking and REM sleep reached control values by the third hour of the post-deprivation period. In conditions of the combined actions of sleep deprivation and LPS, the slow-wave sleep "rebound" was displaced and increased by 2 h as compared with sleep deprivation alone (Fig. 3, *a*). An increase in the quantity of slow-wave sleep occurred from 4 to 7 h of the post-deprivation period and resulted from an increase in the duration of its episodes by 25.3 ± 5.6 sec ($p < 0.001$) and a decrease in the number of episodes by 11.5 ± 1.9 ($p < 0.05$) as compared with controls. The total duration of waking, drowsiness, and sleep decreased during this period (Figs. 2 and 3, *b*) mainly because of reductions in the numbers of episodes by 13 ± 2.6 ($p < 0.05$), 15.8 ± 2.7 ($p < 0.05$), and 14.6 ± 3.1 ($p < 0.05$), respectively, as compared with controls. In sleep deprivation in conditions of endotoxemia, in contrast to the effects of sleep deprivation alone, the period of "rebound" of slow-wave sleep was not followed by a period of "rebound" of REM sleep. On the contrary, from 9 to 11 h of the post-deprivation period, the quantity of REM sleep decreased as compared with sleep deprivation alone (Fig. 3, *b*).

DISCUSSION

These experiments showed that administration of LPS to pigeons during the light phase of the day led to a biphasic change in brain temperature – a decrease followed by an increase. Analysis of published data showed that the changes in brain temperature in our experiments were similar to changes in body temperature in pigeons following i.v. administration of LPS at doses of 5 and 10 μg/kg in the light phase of the day [16, 27]. However, administration of LPS to pigeons in the dark phase of the day led to an immediate increase in body temperature without an initial reduction [16]. These data provide evidence supporting the suggestion that sensitivity to the endotoxin LPS in pigeons differs in the light and dark phases of the day. The initial reduction in brain temperature in our experiments may result from endotoxic shock associated with the greater sensitivity to LPS in the light phase of the day. The further increase in brain temperature on administration of LPS was found to promote the development of peripheral vasoconstriction, hindering heat loss, and a high level of muscle contractile activity, increasing heat production. Thus, in pigeons, as in mammals, (rats, rabbits) [9, 10, 24], one of the main mechanisms leading to the development of fever on administration of LPS is a reduction in heat loss with an increase in contractile thermogenesis. The main characteristics of fever in pigeons are the presence of a hypothermic phase and a longer latent period for the increase in brain temperature in the light phase of the day as compared with mammals. In our experiments, LPS in pigeons, increased slow-wave sleep and decreased REM sleep, as has been demonstrated in laboratory mammals [14, 22]. However, the magnitude of the reduction in the total duration of REM sleep in birds was smaller than that in mammals. The mechanisms underlying the somnogenic effect of LPS in birds have not yet been identified. Published results [14, 15, 17, 18] suggest that in pigeons, as in mammals, lipid A in the endotoxin LPS and endogenous factors of protein nature, i.e., proinflammatory cytokines (IL-1β, IL-6, TNF-α), which are intensely expressed on administration of LPS, may be involved in the mechanisms triggering and maintaining slow-wave sleep and suppressing REM sleep.

The experiments reported here showed that sleep deprivation during the period when the amount of sleep increased after administration of LPS not only reduced the latent period of the increase in brain temperature, strengthened fever, and reduced its duration, but also extended the latent period of recovery of muscle contractile activity and sleep in pigeons. Decreases in the duration of the febrile response in these experiments are probably associated with the more significant (than with LPS alone) dilation of peripheral vessels, increasing heat loss. In our experiments, the increase in fever on combined exposure to sleep deprivation and LPS promoted a more significant increase in the level of muscle contractile activity, increasing heat production as compared with LPS and sleep deprivation alone. In addition, the absence of any contribution from slow-wave sleep to the reduction in brain temperature following the total sleep deprivation procedure played a role in the increase in the febrile response. One of the functions of

slow-wave sleep is a thermoregulatory function [11, 20]. In pigeons, slow-wave sleep makes the main contribution to the reduction in brain temperature, while waking and REM sleep make the main contributions to the increase in brain temperature [5, 21]. Sleep evidently interacts with the thermoregulation system and other homeostatic functions during the development of fever in such a way that impairments in one of these have actions on the others.

The next cause of increases in fever in sleep deprivation may be summation of the temperature effects of LPS and the emotional stress resulting from sleep deprivation. Published data indicate that sleep deprivation, imposed in animals [4, 8, 23] or voluntary in humans [12], is an emotional stress leading to activation of the hypothalamo-hypophyseal-adrenal system. Activation of this system increases blood stress hormone levels, these having calorigenic actions [6], making a significant contribution to the increases in body and brain temperature in sleep deprivation. Increases in endotoxin fever in 4-h sleep deprivation using tactile stimuli were obtained in another study in rabbits [25]. The increase in the febrile response in conditions of total sleep deprivation thus appear also to be characteristic of the body reaction in both birds and mammals.

Our experiments showed that sleep deprivation in endotoxemia affected not only the thermoregulatory parameters of the febrile response, but also the process of recovery of somatic functions and sleep. We observed later recovery of the level of muscle contractile activity and extension of the "rebound" period of slow-wave sleep as compared with LPS and sleep deprivation alone. Ingress into the body of a foreign agent such as the endotoxin LPS leads to the development of intoxication stress in animals [3]. The increase in the latent periods of recovery of muscle contractile activity and sleep in pigeons on combined exposure to sleep deprivation and LPS is probably associated with exacerbation of intoxication stress by the emotional stress induced by sleep deprivation. In these conditions, exposure to stressors of different biological modalities appears to produce more significant activation of the body's hypothalamo-hypophyseal-adrenal, somatoautonomic, thermoregulatory, and immune systems. Our suggestion receives partial support from data from another study, in which the combined action of LPS and pain stress (leading to sleep deprivation) produced increased fever and massive release of corticosterone and adrenocorticotropic hormone into the blood in rats [13]. The greater increase in the total duration of "rebound" slow-wave sleep during the post-deprivation period seen in conditions of sleep deprivation combined with endotoxemia as compared with sleep deprivation alone can be regarded as a compensatory reaction in response to prolonged waking induced by the combined actions of stress factors of different origins on the body.

Thus, sleep deprivation during the period at which sleep increased after administration of LPS induced not only a reduction in the latent period of onset of fever and an increase in fever, but also an increase in the latent period of recovery of somatic functions and sleep.

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