Subdiaphragmatic vagotomy blocks the sleep- and fever-promoting effects of interleukin-1β

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Hansen, Michael K., and James M. Krueger. Subdiaphragmatic vagotomy blocks the sleep- and fever-promoting effects of interleukin-1β. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R1246–R1253, 1997.—The mechanism by which peripheral cytokines signal the central nervous system to elicit central manifestations of the acute phase response remains unknown. Recent evidence suggests that cytokines may signal the brain via the vagus nerve. To test this possibility, we examined sleep-wake activity and brain temperature (Tbr) after the intraperitoneal administration of saline or three doses (0.1, 0.5, and 2.5 µg/kg) of interleukin-1β (IL-1β) in subdiaphragmatically vagotomized (Vx) and sham-operated (Sham) rats. The lowest dose of IL-1β (0.1 µg/kg) increased non-rapid eye movement sleep (NREMS) and slightly elevated Tbr in Sham rats; both responses were blocked in Vx animals. The middle dose tested (0.5 µg/kg) increased NREMS and Tbr in Sham animals; however, in Vx rats, the increase in NREMS was attenuated and the increase in Tbr was blocked. The highest dose of IL-1β used (2.5 µg/kg) induced increases in NREMS, decreases in rapid eye movement sleep, and a hypothermic response followed by a biphasic fever; these responses were similar in both Sham and Vx rats. These data provide strong evidence that the subdiaphragmatic vagus plays an important role in communicating both sleep and fever signals to the brain. However, there is clearly an alternative pathway by which IL-1 can signal the brain; whether it occurs through activation of other vagal afferents or through direct or indirect actions on the brain remains unknown.

There is considerable evidence linking interleukin-1β (IL-1β) to physiological sleep regulation. Administration of exogenous IL-1β via intraperitoneal, intravenous, or intracerebroventricular routes results in relatively large increases in non-rapid eye movement sleep (NREMS) in rats, rabbits, mice, cats, and monkeys (reviewed in Ref. 19). Inhibition of endogenous IL-1, using the IL-1 receptor antagonist, anti-IL-1β antibodies, or the soluble IL-1 receptor, reduces spontaneous sleep (19) and inhibits sleep rebound after sleep deprivation (35). IL-1β and other members of the IL-1 family of molecules are constitutively expressed in the brain (19). Cat cerebrospinal fluid levels of IL-1 are reported to vary in phase with the sleep-wake cycle (24). Furthermore, there is a diurnal rhythm of IL-1β mRNA in the hypothalamus, hippocampus, and cortex of rats with the highest levels corresponding to peak sleep periods (34). Finally, after sleep deprivation, brain stem and hypothalamic levels of IL-1β mRNA increase (25).

In addition to its role in physiological sleep regulation, IL-1β also appears to play a key role in mediating the various facets of the acute phase response, such as loss of appetite, social withdrawal, fever, and excess sleep, which occur during infectious disease. Indeed, administration of exogenous IL-1β elicits all of these illness responses (17). In contrast, the administration of antibodies or antagonists to IL-1β blocks illness responses induced by agents such as lipopolysaccharide (LPS) (17, 18) or muramyl dipeptide (36). Although it is clear that IL-1β and other products of the immune system, such as tumor necrosis factor-α, have far-ranging effects on central nervous system functions, it is still unclear how such molecules, whether systemically released or experimentally injected, gain access to the brain because most are relatively large and hydrophobic peptides that are not expected to readily cross the blood-brain barrier.

Various hypotheses have been proposed to address this issue, including entry into the brain at sites where the blood-brain barrier is deficient, e.g., through circumventricular organs, and active transport into the brain (1, 3). Although each hypothesis has its supporting data, it is uncertain whether the amounts shown to enter the brain are sufficient to induce sleep and/or fever. Furthermore, peripherally released cytokines induce the synthesis and release of cytokines in the brain, and these locally produced cytokines are likely critical for brain-cytokine actions. For example, an intravenous injection of muramyl dipeptide increases sleep in rabbits; this sleep response is blocked with an intracerebroventricular injection of the IL-1 receptor fragment, an inhibitor of IL-1β (36). Hence, an alternative pathway by which peripheral cytokines can affect central nervous system functions has recently been suggested (reviewed in Refs. 3 and 39): that is, that neural afferents, such as the vagus nerve, are posited to transmit peripheral immune messages to the brain. Indeed, IL-1-induced fever (28, 38), taste aversion (11), and behavioral changes (5, 6), as well as LPS-induced fever (13, 32), gene expression (23, 37), and depression of food-motivated behavior (6) are blocked or attenuated by vagotomy.

In addition to this putative role of the vagal nerve in communicating immune signals to the brain, the vagus nerve is known to play a role in the regulation of vigilance. Vagal nerve stimulation induces electroencephalographic (EEG) synchronization (7) and excess sleep (30). The NREMS-promoting effects of increased food intake are inhibited by vagotomy (M. K. Hansen, L. Kapás, J. Fang, and J. M. Krueger, unpublished data). In addition, viscerosensory activity influences the sleep-wakefulness rhythm. For example, low-frequency stimulation of the small intestine and splanchnic nerve induces EEG activity characteristic of sleep that outlasts the period of stimulation (22), and repetitive intestinal stimulation increases sleep dura-
tion in both starved and satiated cats (21). We hypothesized that the NREMS-promoting effects of intraperitoneal IL-1ß are dependent on an intact vagal nerve and that the role of the vagal nerve may vary with differing doses of IL-1. To test this hypothesis, subdiaphragmatically vagotomized (Vx) and sham-operated (Sham) rats were injected with three doses of IL-1ß, and the resultant effects on sleep-wake activity and brain temperature (Tbr) were evaluated.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (250–275 g at purchase; Harlan Sprague Dawley, Indianapolis, IN) were used in this study. The animals were housed individually and maintained on a light-dark cycle of 12:12 h (lights on at 0600) and at an ambient temperature of 25 ± 1°C. Food and water were continuously available.

Surgical Techniques

Vagotomy and pyloroplasty. Subdiaphragmatic vagotomy and pyloroplasty were performed on rats as previously described (M. K. Hansen, L. Kapás, J. Fang, and J. M. Krueger, unpublished data). Briefly, after an overnight fast, rats were anesthetized using ketamine-xylazine (87 and 13 mg/kg ip, respectively). The stomach and lower esophagus were visualized from an upper midline laparotomy. The stomach was gently retracted down beneath the diaphragm to clearly expose both vagal trunks. Each vagal trunk was ligated, and at least 1 cm of the visible vagal nerve was dissected. In addition, all neural and connective tissue surrounding the esophagus immediately below the diaphragm was removed to transect all small vagal branches. The vagotomy was supplemented with pyloroplasty to prevent gastric stasis. An incision was made parallel to the axis of the pylorus, through the pyloric sphincter, and then the pylorus wall was reconstructed by sutures perpendicular to the pylorus axis. The stomach was returned to its normal position, and the incisions were closed. Sham animals were also prepared, subjected only to pyloroplasty.

It has been suggested that the lack of responsiveness in Vx rats may be due to their poor health and malnutrition (31). Thus, in an attempt to monitor the health of the animals, body weight was measured daily in both Vx and Sham animals for 2 wk after surgery. Vx rats initially lost more weight than their Sham controls; however, they began to gain weight at a similar rate as Sham rats (Fig. 1). Furthermore, the body weight did not differ significantly when experimental testing was begun (Sham 377 ± 5 g; Vx 370 ± 7 g).

Sleep surgery. Three weeks after either Vx or Sham surgery, the animals were implanted with cortical EEG and nuchal electromyographic (EMG) electrodes and a brain thermometer to measure Tbr, as previously described (20). Briefly, EEG electrodes were placed over the frontal and parietal cortices, and a thermistor (model 44008; Omega Engineering, Stamford, CT) was placed on the dura over the parietal cortices, and a thermistor (model 44008; Omega Engineering, Stamford, CT) was placed on the dura over the parietal cortex. Insulated leads from the EEG and EMG electrodes and thermistor were routed to a Teflon pedestal (Plastics One, Roanoke, VA) and cemented to the skull with dental adhesive (3M, St. Paul, MN). After a 1-wk recovery period, the animals were placed into individual, sound-attenuated, sleep-recording cages for adaptation to the experimental conditions.

Recordings

EEG, EMG, and Tbr were recorded by computer. EMG activity served as an aid for determining the vigilance states and was not further quantified. EEG was filtered below 0.1 and above 40 Hz. The amplified signals were digitized at a frequency of 128 Hz for EEG and EMG and 2 Hz for Tbr. Single Tbr samples were saved on hard disk in 10-s intervals. Average Tbr values were calculated in 1-h time blocks. The vigilance states were determined off-line in 10-s epochs. EEG, EMG, and Tbr were displayed on the computer monitor in 10-s epochs and also simultaneously in a more condensed form in 12-min epochs. Wakefulness, NREMS, and rapid eye movement sleep (REMS) were distinguished as described before in detail (20). Briefly, the criteria for vigilance states are as follows (NREMS: high-amplitude EEG slow waves, low-level EMG activity, and declining Tbr on entry; REMS: highly regular theta activity in the EEG, general lack of body movements with occasional twitches, and a rapid rise in Tbr at onset; wakefulness: low-amplitude, fast EEG activity, high EMG activity, and a gradual increase in Tbr after arousal). Time spent in each vigilance state was calculated for 2-h intervals. On-line fast Fourier analysis of the EEG was performed in 10-s intervals on 2-s segments of the EEG in 0.5-Hz bands of the 0.5–4.0 Hz frequency range. The EEG power density values in the delta frequency range were summed for each 10-s epoch of NREM sleep, and average activities in 2-h intervals were calculated for the NREM periods. The delta activity during NREMS (also called slow-wave activity, SWA) is often regarded as a measure of sleep intensity.

Experimental Protocol

Pyrogen-free saline (0.9% NaCl) was obtained from Abbott Laboratories (North Chicago, IL), and recombinant human IL-1ß was obtained from R&D Systems (Minneapolis, MN). IL-1ß was dissolved in pyrogen-free saline and delivered in an injection volume of 2 ml/kg. All injections were given intraperitoneally.

One week after EEG-implant surgery, thus approximately 4 wk after either Vx or Sham surgery, the rats (n = 8 for each group) were attached to recording cables for habitation. During this 7- to 10-day period the animals received daily intraperitoneal injections of saline at the time when the experimental treatments were to be done. Three doses of...
IL-1β were tested (0.1, 0.5, and 2.5 µg/kg). These doses were chosen on the basis of a dose-response curve determined in a pilot study of IL-1β on sleep-wake activity in rats (M. K. Hansen, L. Kapás, and J. M. Krueger, unpublished data). A within-subject experimental design was used; thus the animals were injected with saline on one day (control day) and with one dose of IL-1β on the following day (test day). At least a 1-wk period was allowed between test days. Furthermore, for each rat, recordings were taken on three separate control days. When rats received IL-1β, it was in the order of the lowest dose to highest dose. There were no signs of tolerance to IL-1β in either the pilot study or in this experimental study. All injections were given promptly at dark onset (1800). EEG, EMG, and Tbr were recorded for 23 h beginning at dark onset for each control day (n = 3 for each rat) and each test day.

Verification Procedures

On completion of the experiments the completeness of vagotomy was assessed using two independent approaches. The first test is based on the satiety effect of cholecystokinin (CCK, Ref. 33). Saline or CCK (4 µg/kg; Peninsula Laboratories) was injected intraperitoneally after 20 h of food deprivation, and food intake was measured after 1 h. The second test is based on the stimulation of gastric acid secretion via the vagus nerve by 2-deoxy-D-glucose (2-DG, Ref. 8) and was performed as previously described (M. K. Hansen, L. Kapás, J. Fang, and J. M. Krueger, unpublished data). Briefly, gastrotomy was performed along the greater curvature in anesthetized rats, the mucosa was exposed, and the bleeding points were ligated. A moistened gauze sponge was placed over the gastric mucosa, and 2 ml of 5% 2-DG were injected intravenously via the femoral vein. This was followed, after a period of 10 min, by 1 ml of a 1% solution of neutral red. The moistened sponge was periodically examined for the presence of a purple color. The neutral red, which is secreted in conjunction with gastric acid, appears purple on the sponge in those rats with an intact vagus; all Vx rats failed this test.

Statistical Analysis

The effects of IL-1β on sleep, SWA, and Tbr were determined by two-way analysis of variance (ANOVA) for repeated measures across the 23-h recording period. The first independent variable was the treatment (saline vs. IL-1β) and the second independent variable was time. When ANOVA indicated significant effects, the Student-Newman-Keuls (SNK) test was used to reveal where the significant effect had occurred. In all tests an α-level of P < 0.05 was taken as an indication of statistical significance.

RESULTS

Vagotomy Blocks Satiety Effect of CCK

CCK significantly inhibited food intake in Sham rats (F(1,14) = 32.748, P < 0.0001; SNK q(4,14) = 14.35, P < 0.01), but not Vx rats, thereby confirming the role of the vagus nerve in CCK-induced satiety (33). Food intake was decreased by about 50% in CCK-injected Sham rats compared with saline-injected Sham rats (3.25 ± 0.40 vs. 6.46 ± 0.4 g, respectively). In contrast, CCK did not significantly decrease food intake in Vx rats compared with saline injection (4.90 ± 0.7 vs. 5.55 ± 0.78 g, respectively).

Vagotomy Blocks Effects of 0.1 µg/kg IL-1β

In Sham rats 0.1 µg/kg IL-1β increased NREMS (Fig. 2, Table 1). On the control day Sham rats spent 61 ± 3 min in NREMS during the first 4 h compared with 90 ±
6 min on the test day [SNK q(6,35) = 9.307, P < 0.01]. In addition, this dose of IL-1β significantly increased Tbr in hour 2 [SNK q(4,154) = 5.40, P < 0.01]. In contrast, this dose of IL-1β failed to induce significant changes in NREMS or Tbr in Vx rats. REMS and EEG SWA were not altered in either group.

Table 1. Effects of intraperitoneal injections of IL-1β on sleep, slow-wave activity, and brain temperature in sham-operated and vagotomized rats: statistical results

<table>
<thead>
<tr>
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<th>0.1 µg/kg</th>
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<th>0.5 µg/kg</th>
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<th>2.5 µg/kg</th>
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<tr>
<td></td>
<td>Sham</td>
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<td>NREMS</td>
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<tr>
<td>Treatment effect</td>
<td>F (1,7) = 9.32*</td>
<td>F (1,7) = 0.129</td>
<td>F (1,7) = 22.6†</td>
<td>F (1,7) = 1.38</td>
<td>F (1,7) = 28.8†</td>
<td>F (1,7) = 22.8†</td>
</tr>
<tr>
<td>Time-treatment interaction</td>
<td>F (5,35) = 7.76‡</td>
<td>F (5,35) = 0.693</td>
<td>F (3,21) = 10.2‡</td>
<td>F (3,21) = 3.75*</td>
<td>F (1,7) = 61.2‡</td>
<td>F (1,7) = 32.8‡</td>
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<td>REMS</td>
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<tr>
<td>Treatment effect</td>
<td>F (1,7) = 0.0826</td>
<td>F (1,7) = 0.690</td>
<td>F (1,7) = 0.000903</td>
<td>F (1,7) = 0.0170</td>
<td>F (1,7) = 1.70</td>
<td>F (1,7) = 3.45</td>
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<td>Time-treatment interaction</td>
<td>F (11,77) = 2.0127*</td>
<td>F (11,77) = 0.645</td>
<td>F (11,77) = 1.225895</td>
<td>F (11,77) = 0.6112</td>
<td>F (5,35) = 8.32‡</td>
<td>F (5,35) = 8.90‡</td>
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<td>SWA</td>
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<td>Treatment effect</td>
<td>F (1,7) = 0.202</td>
<td>F (1,7) = 0.206</td>
<td>F (1,7) = 2.413</td>
<td>F (1,7) = 0.234</td>
<td>F (1,7) = 6.88*</td>
<td>F (1,7) = 14.0‡</td>
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<td>Time-treatment interaction</td>
<td>F (11,77) = 0.949</td>
<td>F (11,77) = 0.212</td>
<td>F (11,77) = 0.953</td>
<td>F (11,77) = 1.954*</td>
<td>F (11,77) = 7.59‡</td>
<td>F (11,77) = 9.60‡</td>
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<tr>
<td>Tbr</td>
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<tr>
<td>Treatment effect</td>
<td>F (1,7) = 0.145</td>
<td>F (1,7) = 0.0462</td>
<td>F (1,7) = 4.42</td>
<td>F (1,7) = 3.246</td>
<td>F (1,7) = 41.10‡</td>
<td>F (1,7) = 18.42‡</td>
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<tr>
<td>Time-treatment interaction</td>
<td>F (22,154) = 2.374†</td>
<td>F (22,154) = 0.4515</td>
<td>F (22,154) = 1.84*</td>
<td>F (22,154) = 0.997</td>
<td>F (22,154) = 8.92‡</td>
<td>F (22,154) = 4.93‡</td>
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Each animal in sham-operated (Sham) and vagotomized (Vx) groups received 3 different doses of interleukin-1β (IL-1β) and 3 separate saline injections. Effects of IL-1β on non-rapid eye movement sleep (NREMS), rapid eye movement sleep (REMS), electroencephalographic (EEG) slow-wave activity (SWA), and brain temperature (Tbr) were analyzed by 2-way ANOVA for repeated measures across 23-h recording period. F values are given for treatment effect (saline vs. IL-1β) and for time-treatment interaction. When ANOVA indicated significant effects Student-Newman-Keuls multiple comparison test was used to determine where significant effects had occurred. *P < 0.05; †P < 0.005; and ‡P < 0.0005.

Vagotomy Attenuates NREMS-Inducing Effects of 0.5 µg/kg IL-1β

The intraperitoneal injection of 0.5 µg/kg IL-1β increased NREMS and Tbr in Sham rats (Fig. 3, Table 1). NREMS was increased in the first 6 h [SNK q(4,21) =
9.596, \( P < 0.01 \), and \( T_{br} \) was increased in hours 1 and 2 \([\text{SNK (hour 1)} q(3,154) = 3.75, \ P < 0.05; \ (\text{hour 2}) \ q(10,154) = 5.56, \ P < 0.01\]). In Vx rats NREMS was also significantly increased \([\text{SNK q(3,21)} = 4.829, \ P < 0.01]\); however, this response was significantly attenuated in Vx rats compared with Sham rats \( (t_{14} = 4.09, \ P < 0.002) \). NREMS was increased by about 58 min in Sham rats compared with about 22 min in Vx rats during this time period. The increase in \( T_{br} \) was completely blocked in Vx animals. REMS was not affected in either group, and there was a slight, but not significant, decrease in EEG SWA in both Sham and Vx rats.

**Vagotomy Does Not Block Effects of 2.5 µg/kg IL-1β**

The highest dose of IL-1 tested, 2.5 µg/kg, resulted in similar effects in both Sham and Vx rats (Fig. 4, Table 1). IL-1 significantly increased NREMS in the first 12-h time period \([\text{SNK (Sham) q(2,7)} = 13.39, \ P < 0.01; \ (\text{Vx}) q(2,7) = 10.53, \ P < 0.01]\). In Sham rats IL-1 increased NREMS by about 91 min (42%); in Vx rats IL-1 increased NREMS by about 74 min (35%). There was a decrease in REMS in both Sham and Vx rats. A significant suppression occurred in the first 4 h postinjection \([\text{SNK (Sham) q(5,35)} = 7.766, \ P < 0.01; \ (\text{Vx}) q(2,35) = 7.952, \ P < 0.01]\). EEG SWA was significantly inhibited in the first 2-h time period \([\text{SNK (Sham) q(14,77)} = 9.24375, \ P < 0.01; \ (\text{Vx}) q(16,77) = 9.5792, \ P < 0.01]\). This was followed by an increase in SWA for 4 h and then a suppression for most of the remaining recording time. IL-1 significantly increased \( T_{br} \). In both Sham and Vx rats, an initial hypothermic response was followed by a biphasic fever.

**Vagotomy Does Not Affect Normal Sleep-Wake Activity or \( T_{br} \)**

To compare sleep-wake activity and \( T_{br} \) in Sham and Vx rats, the data on the 3 control days for each group were averaged. Confirming a previous report (M. K. Hansen, L. Kapás, J. Fang, and J. M. Krueger, unpublished data), vagotomy does not significantly alter sleep-wake activity or \( T_{br} \) (Fig. 5). In both Sham and Vx rats the distribution of the states of vigilance followed a normal diurnal pattern with high percentages of sleep during the day. Maximum durations of NREMS and REMS occurred during the first and second portions of the light period, respectively. Furthermore, \( T_{br} \) varied with the diurnal cycle, being higher during the dark period (the behaviorally active period of rats).

**DISCUSSION**

The present results demonstrate that the vagus is indeed a crucial component in the pathway by which peripheral IL-1β signals the central nervous system to elicit various components of the acute phase response. However, the importance of the subdiaphragmatic vagus varies greatly depending on the dose of IL-1β used. Thus at low doses both IL-1β-induced NREMS and fever were completely abolished by subdiaphragmatic vagotomy. These results are consistent with the find-
IL-1β also triggers sleep and thermoregulatory mechanisms that are not dependent on intact subdiaphragmatic vagi. It is expected that after the intraperitoneal administration of high doses, significant quantities of IL-1β may enter the systemic circulation. When plasma levels of IL-1β are relatively high, they may then be able to reach intact vagal afferents in other peripheral sites, such as in the lung. In support of this, mice inoculated with influenza virus exhibit symptoms of the acute phase response, yet there is no increase in the circulating levels of cytokines (9). Significant elevations of cytokine activity were, however, found in the lung medullary vagi. It is expected that after the intraperitoneal administration of high doses, significant quantities of IL-1β may enter the systemic circulation. When plasma levels of IL-1β are relatively high, they may then be able to reach intact vagal afferents in other peripheral sites, such as in the lung. In support of this, mice inoculated with influenza virus exhibit symptoms of the acute phase response, yet there is no increase in the circulating levels of cytokines (9). Significant elevations of cytokine activity were, however, found in the lung medullary vagi. It is expected that after the intraperitoneal administration of high doses, significant quantities of IL-1β may enter the systemic circulation. When plasma levels of IL-1β are relatively high, they may then be able to reach intact vagal afferents in other peripheral sites, such as in the lung. In support of this, mice inoculated with influenza virus exhibit symptoms of the acute phase response, yet there is no increase in the circulating levels of cytokines (9). Significant elevations of cytokine activity were, however, found in the lung
and EEG SWA. For example, IL-1β induces the release of growth hormone-releasing hormone, another well characterized sleep-promoting substance that also enhances EEG SWA (19). In contrast, intraperitoneal administration of IL-1β increases brain norepinephrine (NE) turnover rate; activation of brain NE systems is known to suppress EEG SWA (2). Therefore, it is likely that the enhancing and suppressing effects of IL-1β on EEG SWA are mediated by different molecular pathways and that these mechanisms are independent of those responsible for duration of NREMS.

It has been suggested that the lack of effects in Vx animals may be due to poor health (31). In the present study, it is very unlikely that the unresponsiveness of Vx rats to low and intermediate doses of IL-1β was due to malnutrition because the body weights of each group of rats were similar, and high doses of IL-1β were capable of inducing both sleep and fever in the same rats. Secondly, the fact that Vx rats had normal sleep patterns at the time of experimental testing indicates that the rats were not seriously distressed; it is well known that any distress seriously affects sleep. Finally, the finding that Vx rats respond to central injections of IL-1β (4) suggests that vagotomy itself does not impair the direct sensitivity of the brain to immune signals. The current data clearly demonstrate that the vagal nerve is an important element in the pathway by which peripheral cytokines signal the central nervous system to elicit various facets of the sickness syndrome.

Perspectives

Much evidence supports the hypothesis that brain IL-1 is critical for immune-cytokine interactions. The central administration of anti-IL-1 antibodies, the IL-1 receptor antagonist, or the IL-1 receptor fragment inhibits sleep (36) and behavioral responses (17), as well as fever (18), in response to peripherally injected immune stimuli. Furthermore, peripheral immune stimuli induce cytokine expression in the brain. Subdia phragmatic vagotomy blocks the induction of IL-1β mRNA in the hippocampus and hypothalamus of LPS-treated mice (23). This evidence therefore suggests that the induction and subsequent release of IL-1β in the brain may be a final and critical step in the pathway by which vagally mediated immune signals result in centrally controlled symptoms of the acute phase response.

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REFERENCES


