Altered frequency responses of sympathetic nerve discharge bursts after IL-1β and mild hypothermia

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Altered frequency responses of sympathetic nerve discharge bursts after interleukin-1β (IL-1β) and mild hypothermia. J Appl Physiol 93: 280–288, 2002. First published April 5, 2002; 10.1152/japplphysiol.01250.2001.—Although interleukin-1β (IL-1β) administration produces nonuniform changes in the level of sympathetic nerve discharge (SND), the effect of IL-1β on the frequency-domain relationships between discharges in different sympathetic nerves is not known. Autospectral and coherence analyses were used to determine the effect of IL-1β and mild hypothermia (60 min after IL-1β, colonic temperature from 38°C to 36°C) on the relationships between renal-interscapular brown adipose tissue (IBAT) and splenic-lumbar sympathetic nerve discharges in chloralose-anesthetized rats. The following observations were made. 1) IL-1β did not alter renal-IBAT coherence values in the 0- to 2-Hz frequency band or at the cardiac frequency (CF). 2) Peak coherence values relating splenic-lumbar discharges at the CF were significantly increased after IL-1β and during hypothermia. 3) Hypothermia after IL-1β significantly reduced the coupling (0–2 Hz and CF) between renal-IBAT but not splenic-lumbar SND bursts. 4) Combining IL-1β and mild hypothermia had a greater effect on renal-IBAT SND coherence values than did mild hypothermia alone. These data demonstrate functional plasticity in sympathetic neural circuits and suggest complex relationships between immune products and SND regulation.

By generating nonuniform changes in efferent nerve outflow, the sympathetic nervous system plays an important role in mediating physiological responses to acute stressors. At least two types of heterogeneous sympathetic nerve response profiles have been described. First, directionally opposite changes in the level of activity in sympathetic nerves innervating different targets have been observed during numerous experimental interventions (3, 14, 17, 18, 23, 34, 45, 47). Second, sympathetic nerve discharge (SND) bursts in nerves innervating different targets can uncouple (i.e., reduced coherence) during various experimental interventions (2, 20, 23, 26, 28), providing evidence for stress-induced selectivity in the SND bursting pattern. Importantly, it is known that the pattern of sympathetic nerve stimulation can influence neurotransmitter release and peripheral vasoconstrictor responses (30, 37, 39) and that pattern transformation is one strategy used by the sympathetic nervous system for mediating sympathoexcitation to acute heat stress (22).

Recent studies have established that interleukin-1β (IL-1β) provides a signaling pathway to sympathetic neural circuits (16, 19, 36, 38, 42, 43). Important relative to the present study, IL-1β administration produces nonuniform changes in the level of efferent SND (36, 42). Specifically, intravenous IL-1β in chloralose-anesthetized rats increases splenic and lumbar SND but does not significantly change the level of renal and interscapular brown adipose tissue (IBAT) SND (42), whereas in urethane-anesthetized rats intravenous IL-1β increases splenic and adrenal SND but decreases renal SND (36). However, the effect of IL-1β on the frequency-domain relationships between discharges in sympathetic nerve pairs is not known. This is a critical omission because synchronized discharges in sympathetic nerve pairs can uncouple in response to selected experimental interventions (2, 20, 23, 26, 28), thereby providing, in addition to nonuniform changes in the level of nerve activity, an important strategy by which the nervous system can exert selective control over efferent SND.

In the present study, we used coherence analysis to determine the effect of IL-1β administration followed by acute cold stress (60 min after IL-1β administration, internal body temperature reduced from 38 to 36°C) on the frequency-domain relationships between discharges in renal-IBAT and splenic-lumbar sympathetic nerve pairs. Because IL-1β alters efferent sympathetic nerve outflow (36, 42) and because the sympathetic nervous system can generate differential patterns of efferent sympathetic nerve outflow (34), we hypothesized that the discharges in renal-IBAT and splenic-lumbar sympathetic nerve pairs would uncouple in response to IL-1β alone or to acute cold stress after
intravenous IL-1β. Recordings were made from splenic-lumbar and renal-IBAT nerve pairs because IL-1β increases splenic and lumbar SND but has no effect on renal and IBAT nerve activity (42).

Why use an experimental protocol that includes both IL-1β and acute cold stress? IL-1β administration increases internal body temperature (31–33) and produces physiological responses that are consistent with increasing internal body temperature, including increased oxygen consumption (4), increased brown adipose tissue blood flow (4), and reduced firing rate of warm-sensitive neurons (44, 48) and increased firing rate of cold-sensitive neurons in the preoptic area of the anterior hypothalamus (48). In contrast, intravenous IL-1β administration does not increase IBAT SND in chloralose-anesthetized rats (21), despite the fact that activation of this nerve enhances heat production through nonshivering thermogenesis (10, 11, 13, 29). However, increases in IBAT SND to mild hypothermia are significantly higher in IL-1β-treated rats compared with saline-treated rats (21), demonstrating that IL-1β pretreatment sensitizes IBAT SND responses to acute cold stress. This enhanced cold defense response would likely be beneficial during febrile conditions in defending colonic temperature (\(T_c\)) against reductions in ambient temperature because increased \(T_c\) during the acute phase reaction is generally thought to be an adaptive response, facilitating host defenses (25, 40). Therefore, the fact that IL-1β administration alters the level of efferent SND (36, 42) and enhances sympathetic nerve cold defense responses (21) provides rationale for studying the combined effect of IL-1β and mild hypothermia on the frequency components of SND.

METHODS

General procedures. The Institutional Animal Care and Use Committee approved the surgical procedures and experimental protocols used in the present study. Male Sprague-Dawley rats (320–370 g) were initially anesthetized with methohexital sodium (Brevital, 50–60 mg/kg ip) (20–24). Catheters were placed in the femoral vein for administration of alpha-chloralose (50 mg/kg initial dose and 35 mg·kg\(^{-1}\)·h\(^{-1}\) maintenance doses) (20–24), maintenance doses of methohexital sodium (10–20 mg/kg during surgical interventions) (20–24), and IL-1β or saline. The rats were intubated, paralyzed with gallamine triethiodide (5–10 mg/kg iv initial dose; 10–15 mg·kg\(^{-1}\)·h\(^{-1}\) maintenance dose) (20–24), and artificially ventilated. Femoral arterial pressure and heart rate (HR) were recorded, with the use of standard procedures. \(T_c\) was measured with a thermistor probe inserted ∼5 cm into the colon and was kept at 38°C during surgical interventions by a temperature-controlled table.

Neural recordings. Activity was recorded (from the central end of cut sympathetic nerves) biphasically with a platinum bipolar electrode after preamplification (band pass 30–3,000 Hz). The splenic, renal, and lumbar nerves were isolated after a lateral incision (20–24), and the IBAT nerve was isolated after visualization of the IBAT after a nape incision (12). Nerve-electrode preparations were covered with dental acrylic to avoid exposure to room air. Sympathetic nerve potentials were full-wave rectified and integrated (time constant 10 ms) and were corrected for background noise after ganglionic blockade (trimethaphan camsylate, 15 mg/kg) or nerve crush (20–24). Renal sympathetic nerve activity was recorded because the sympathetic neural innervation to the kidney influences renal blood flow, renin release, and salt and water retention by the renal tubules (5), responses that are a part of the integrative physiological changes to hypothermia and sickness behavior. Splenic SND was recorded because the sympathetic neural innervation to this organ provides a direct link between the central nervous system and splenic lymphocytes and modulates immune function (9, 35, 46). Lumbar SND recordings provided information about sympathetic nerve outflow to the tail and to hindlimb skeletal muscle and skin vasculatures. IBAT nerve recordings were completed because activation of this nerve increases heat production through nonshivering thermogenesis (10, 11, 13, 29).

Experimental protocols. After completion of the surgical interventions, the chloralose-anesthetized rats were allowed to stabilize for up to 60 min before initiation of the experimental protocols. Mean arterial pressure and SND (renal-IBAT, \(n = 5\); splenic-lumbar, \(n = 8\)) were continuously recorded before (control) and for 60 min after IL-1β administration (290 ng·kg\(^{-1}\) iv). Because elevations in internal body temperature provide a potent stimulus to SND (22), \(T_c\) was maintained at 38°C during the 60-min period after IL-1β to ameliorate any potential confounding influence of increased \(T_c\). SND recordings were performed under conditions in which \(T_c\) was decreased from 38 to 36.0°C (0.2°C/min) by use of externally cooled (10°C) water that was recirculated through a perfusion pad (21, 23). The effect of acute cold stress alone (no prior IL-1β administration) on renal-IBAT SND frequency-domain relationships was determined in five experiments. After a 30- to 60-min control period (saline, 300 μl iv administered at the beginning of the control period), \(T_c\) was decreased from 38 to 36.0°C (0.2°C/min) by using the same cooling protocol as described above. Control experiments (\(n = 5\)) were completed in which SND was recorded before and for 60 min after the intravenous administration of physiological saline (300 μl).

Data and statistical analyses. Autospectra and coherence analyses of the arterial pulse and SND bursts were computed by using the methods and programs described previously (20, 27). Fast Fourier transform was performed on 12 contiguous windows of data that were 5 s in duration. Autospectra (relative power vs. frequency) and coherence functions were computed over a frequency band of 0–15 Hz. The amplitudes of the autospectra were autoscaled to the highest peak (20, 27). The frequency resolution was 0.2 Hz/bin. Spectral analyses provide the following information (27). The autospectrum of a signal shows the relative power present at each frequency. The coherence function (normalized cross spectrum) provides a measure of the strength of linear correlation of two signals as a function of frequency. The squared coherence value (referred to as coherence value) is 1.0 in the case of a linear system undisturbed by noise and 0 if the two signals are completely unrelated. The coherence value is >0 but <1 when 1) the two signals arise from common and uncommon sources, 2) noise is present in the system, and/or 3) the system relating the two signals is nonlinear.

Results were analyzed by use of ANOVA techniques with a repeated-measures design. The significance of ANOVA main effects and simple effects at the \(P < 0.05\) levels were identified. Results are presented as means ± SE. Experiments included in the present study demonstrating the effect of IL-1β and hypothermia on the level (not frequency components) of IBAT and renal SND (not lumbar and splenic SND) are a subgroup of experiments that were published previ
RESULTS

Mean arterial pressure remained unchanged after IL-1β and during mild hypothermia in experiments involving renal-IBAT and splenic-lumbar SND recordings (Table 1). The level of renal and IBAT SND remained unchanged, whereas splenic and lumbar SND were significantly increased from control for 60 min after IL-1β (Table 1). During mild hypothermia, the level of IBAT SND was significantly increased from values recorded during control and at 60 min after IL-1β (Table 1), whereas renal, splenic, and lumbar SND were unchanged from values recorded 60 min after IL-1β but remained increased from control values. Figure 1 shows traces (from two separate experiments) of simultaneously recorded SND slow waves (Fig. 1A, renal-IBAT; Fig. 1B, splenic-lumbar) and pulsatile arterial blood pressure during control (Tc = 38°C), 60 min after IL-1β administration (Tc = 38°C), and during acute cold stress that was initiated 60 min after IL-1β and reduced Tc to 37 and 36°C. During control, the majority of renal and IBAT SND bursts were coupled to the arterial pulse, whereas splenic and lumbar SND contained a mixture of cardiac-related and low-frequency bursts. Sixty minutes after IL-1β administration, the renal and IBAT SND bursting patterns were similar to control, whereas splenic and lumbar SND contained primarily cardiac-related bursts. During cooling (37 and 36°C), renal SND contained cardiac-related bursts, IBAT SND was characterized by the presence of synchronized bursts that were not coupled to the cardiac cycle, and splenic and lumbar SND contained both low-frequency and cardiac-related bursts. Figure 2 shows the results of autospectral and coherence analyses of renal and IBAT SND during control, 60 min after IL-1β (Tc = 38°C), and during acute cold stress that reduced Tc to 37 and 36°C. During control, renal and IBAT SND autospectra (top and middle) contained primary peaks at the frequency of the heart rate (7.2 Hz), and the coherence function (bottom) relating the discharges in these nerves demonstrated a correlation that extended from 0 to 12 Hz, with peaks at 7.2 Hz and at frequencies <5 Hz. Sixty minutes after IL-1β, the renal SND autospectrum contained two peaks [primary peak at the cardiac frequency (CF) and a secondary peak in the 0–2 Hz frequency band], whereas the IBAT SND autospectrum and the renal-IBAT coherence function were similar to those constructed during control. During mild hypothermia (Tc = 37 and 36°C), renal SND autospectra remained unchanged, the cardiac-related peak in the IBAT SND autospectrum was eliminated, and there was reduced coupling between discharges in the renal and IBAT nerves, as evidenced by marked reductions in peak coherence values at frequencies between 0 and 12 Hz. Figure 3 shows the results of autospectral and coherence analyses of splenic and lumbar SND at the same experimental points as shown in Fig. 2. Relative power at the CF (7.3 Hz) in splenic and lumbar SND autospectra was increased 60 min after IL-1β, and this persisted during hypothermia for splenic, but not lumbar, SND. Peak coherence values relating splenic and lumbar SND bursts at the CF were increased after IL-1β and during the initial phase of cooling (Tc = 37.0°C).

Mean SND coherence data from renal-IBAT and splenic-lumbar experiments are summarized in Table 2. Peak coherence values relating low-frequency (0- to 2-Hz) and CF renal-IBAT discharges remained unchanged from control for 60 min after IL-1β but were significantly reduced during hypothermia (37 and 36°C). Peak coherence values relating low-frequency splenic-lumbar discharges remained unchanged from control after IL-1β and during cooling, whereas those relating discharges at the CF were significantly increased from control after IL-1β and during the initial phase of cooling (37°C). Peak coherence values (control: 0–2 Hz, 0.62 ± 0.04; CF, 0.56 ± 0.12/15 min saline: 0–2 Hz, 0.67 ± 0.07; CF, 0.63 ± 0.07/30 min saline: 0–2 Hz, 0.63 ± 0.04; CF, 0.60 ± 0.07/45 min saline: 0–2 Hz, 0.69 ± 0.05; CF, 0.69 ± 0.08/60 min saline: 0–2 Hz, 0.62 ± 0.05; CF, 0.60 ± 0.07) were unchanged from control after saline administration (300 μl iv, n = 5).

The effect of acute cold stress (Tc reduced from 38 to 36°C), without the prior administration of IL-1β, on

Table 1. MAP and SND recorded before (control, Tc = 38°C) and after (15, 30, 45, and 60 min, Tc = 38°C) intravenous IL-1β administration (290 ng/kg) and after acute cold stress that was initiated 60 min after IL-1β and produced mild hypothermia (37 and 36°C)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15-min IL-1β</th>
<th>30-min IL-1β</th>
<th>45-min IL-1β</th>
<th>60-min IL-1β</th>
<th>37°C</th>
<th>36°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>Renal-IBAT</td>
<td>118 ± 7</td>
<td>111 ± 4</td>
<td>110 ± 7</td>
<td>112 ± 7</td>
<td>109 ± 11</td>
<td>107 ± 12</td>
</tr>
<tr>
<td></td>
<td>Splenic-lumbar</td>
<td>86 ± 3</td>
<td>91 ± 4</td>
<td>88 ± 3</td>
<td>84 ± 3</td>
<td>83 ± 3</td>
<td>84 ± 3</td>
</tr>
<tr>
<td>SND, %</td>
<td>Renal</td>
<td>0 ± 0</td>
<td>11 ± 11</td>
<td>-6 ± 3</td>
<td>-12 ± 5</td>
<td>-16 ± 6</td>
<td>-21 ± 15</td>
</tr>
<tr>
<td></td>
<td>IBAT</td>
<td>0 ± 0</td>
<td>24 ± 18</td>
<td>20 ± 15</td>
<td>32 ± 18</td>
<td>23 ± 17</td>
<td>144 ± 42</td>
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<tr>
<td></td>
<td>Splenic</td>
<td>0 ± 0</td>
<td>24 ± 6*</td>
<td>41 ± 9*</td>
<td>53 ± 11*</td>
<td>55 ± 9*</td>
<td>57 ± 9*</td>
</tr>
<tr>
<td></td>
<td>Lumbar</td>
<td>0 ± 0</td>
<td>25 ± 6*</td>
<td>31 ± 5*</td>
<td>32 ± 6*</td>
<td>44 ± 7*</td>
<td>63 ± 20*</td>
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</table>

Values are means ± SE; renal-IBAT, interscapular brown adipose tissue (IBAT), n = 5; splenic-lumbar, n = 8. MAP, mean arterial pressure; SND, sympathetic nerve discharge; Tc, colonic temperature; IL-1β, interleukin-1β. *P < 0.05 compared with control; †P < 0.05 compared with 60-min IL-1β.
renal-IBAT coherence functions was determined in five experiments. Figure 4 shows the results of autospectral and coherence analyses of renal and IBAT SND during control and after $T_c$ had been reduced to 37 and 36°C. In contrast to the coherence functions constructed during mild hypothermia after IL-1β (Fig. 2), renal-IBAT discharges remained prominently coupled during mild hypothermia without IL-1β pretreatment (Fig. 4). Peak coherence values relating low-frequency (0–2 Hz) discharges remained unchanged from control after cooling to 37°C but were significantly reduced at 36°C (Table 3). Peak coherence values relating 0–2 Hz (IL-1β + cooling, 0.28 ± 0.03/cooling; 0.60 ± 0.06, $P < 0.05$) and CF (IL-1β + cooling, 0.14 ± 0.03/cooling; 0.60 ± 0.14, $P < 0.05$) renal-IBAT discharges were significantly lower when $T_c$ was reduced to 36°C after IL-1β compared with when $T_c$ was reduced to 36°C without IL-1β pretreatment. Peak coherence values relating renal-IBAT discharges at 33°C in rats with cooling alone (0–2 Hz, 0.40 ± 0.02; CF, 0.10 ± 0.04) were similar to those observed at 36°C after IL-1β (0–2 Hz, 0.28 ± 0.14; CF, 0.14 ± 0.02).

DISCUSSION

This study examined the effect of IL-1β administration and mild hypothermia on the frequency-domain relationships between discharges in renal-IBAT and splenic-lumbar sympathetic nerve pairs in chloralose-anesthetized rats. The following observations were made. First, peak coherence values relating low-frequency (0–2 Hz) and CF discharges in renal-IBAT sympathetic nerve pairs remained unchanged from control 60 min after IL-1β. Second, peak coherence values relating splenic-lumbar discharges at the CF were significantly increased after IL-1β and during the onset of mild hypothermia, despite the fact that arterial pressure was unchanged from control. Third, induction of acute mild hypothermia 60 min after IL-1β administration significantly reduced the coupling between renal-IBAT but not splenic-lumbar sympathetic nerve discharges. Fourth, the combination of IL-1β and mild hypothermia had a more pronounced effect on renal-IBAT SND coherence values than did mild hypothermia alone.

Because of its capability to produce complex and differential response profiles, the sympathetic nervous system plays a critical role in mediating responses to acute physical stress. The generation of directionally opposite changes in the level of activity in sympathetic nerves innervating different target organs, which is evident after intravenous IL-1β administration (36, 42), provides one strategy for the selective regulation of efferent SND. A second strategy involves reducing the frequency-domain coupling between discharges in sympathetic nerve pairs (2, 20, 23, 26, 28). In the present study, peak coherence values relating SND bursts in renal-IBAT and splenic-lumbar sympathetic nerve pairs were not reduced after IL-1β, demonstrating that uncoupling of discharges in sympathetic nerve pairs is not a strategy employed by sympathetic neural circuits to selectively control efferent nerve outflow after IL-1β administration. In fact, splenic-lumbar coherence values at the CF were significantly increased from control after IL-1β administration. In contrast, peak coherence values relating renal-IBAT (but not splenic-lumbar) discharges were significantly reduced during mild hypothermia after IL-1β, demonstrating
selectivity in renal-IBAT frequency-domain responses to IL-1β + mild hypothermia. Taken together, IL-1β alone or the combination of IL-1β + mild hypothermia is associated with a complex profile of SND responses: nonuniformity in the level of activity in sympathetic nerves innervating different target organs in response to IL-1β alone (42) and IL-1β + mild hypothermia (21), maintained or increased frequency-domain coupling of bursts in different sympathetic nerves in response to IL-1β alone (present results), and reduced coupling between discharges in selective sympathetic nerve pairs in response to mild hypothermia after IL-1β (present results). These results demonstrate functional plasticity in sympathetic neural circuits and suggest the existence of complex interactions between immune products and sympathetic nerve regulation.

The present results along with those from other studies (2, 22, 23) demonstrate that the sympathetic nervous system is capable of generating a complex array of output patterns. Although the functional significance of IBAT SND pattern changes to IL-1β + mild hypothermia is not known, several studies have demonstrated the importance of the SND pattern in physiological regulation. DiBona and Sawin (6) reported that at a constant level of activity (integrated voltage) the pattern of electrical stimulation of the renal sympathetic nerve influences renal functional responses (vasoconstriction and urinary sodium excretion) in anesthetized rats. In addition, the pattern of electrical stimulation of sympathetic nerves has been shown to influence the amount of neurotransmitter released in the pig spleen (39) and the contractile responses of rat mesenteric arteries (37). Kenney et al. (22) demonstrated that hyperthermia-induced SND pattern changes contribute to increasing sympathetic nerve activity during progressive elevations in internal body temperature, establishing pattern formation as a strategy for mediating sympathoexcitation to acute heat stress.

Does IL-1β administration modulate baroreflex regulation of SND? The fact that peak coherence values relating splenic-lumbar discharges at the frequency of the cardiac cycle were significantly in-

Fig. 2. Frequency-domain relationships between renal and IBAT SND bursts during control (Tc = 38°C), 60 min after IL-1β administration (Tc = 38°C), and during acute cold stress that was initiated 60 min after IL-1β and reduced Tc to 37 and 36°C. Top and middle, individual autospectra; bottom, nerve-to-nerve coherence functions. Amplitudes of autospectra are autoscaled to the highest peak.
creased from control after IL-1β administration suggests that this might be the case. Sinoaortic denervation eliminates cardiac-related peaks in SND autospectra and coherence functions in chloralose-anesthetized rats (20, 24), demonstrating that the pulse-synchronous component of efferent SND is dependent on intact arterial baroreceptors. In addition, progressive increases in arterial pressure enhance the cardiac-related rhythmicity of SND bursts (20). Importantly, the enhanced coupling between cardiac-related splenic-lumbar discharges was evident despite the fact that arterial pressure remained unchanged after IL-1β. In addition to enhancing splenic-lumbar coherence, it is worth noting that

Table 2. Peak coherence values relating discharges in sympathetic nerve pairs in the 0- to 2-Hz frequency band and at the CF before (control, Tc = 38°C) and after (15, 30, 45, and 60 min, Tc = 38°C) intravenous IL-1β administration (290 ng/kg), and after acute cold stress that was initiated 60 min after IL-1β and produced mild hypothermia (37 and 36°C)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15-min IL-1β</th>
<th>30-min IL-1β</th>
<th>45-min IL-1β</th>
<th>60-min IL-1β</th>
<th>37°C</th>
<th>36°C</th>
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<tbody>
<tr>
<td><strong>Renal-IBAT</strong></td>
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<td>0-2 Hz</td>
<td>0.69 ± 0.06</td>
<td>0.66 ± 0.02</td>
<td>0.71 ± 0.04</td>
<td>0.71 ± 0.04</td>
<td>0.69 ± 0.05</td>
<td>0.41 ± 0.05††</td>
<td>0.28 ± 0.03††</td>
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<td>CF</td>
<td>0.70 ± 0.10</td>
<td>0.54 ± 0.07</td>
<td>0.55 ± 0.12</td>
<td>0.68 ± 0.06</td>
<td>0.70 ± 0.07</td>
<td>0.24 ± 0.08††</td>
<td>0.14 ± 0.03††</td>
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<tr>
<td><strong>Splenic-Lumbar</strong></td>
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<tr>
<td>0-2 Hz</td>
<td>0.63 ± 0.05</td>
<td>0.74 ± 0.05</td>
<td>0.73 ± 0.05</td>
<td>0.74 ± 0.05</td>
<td>0.73 ± 0.05</td>
<td>0.68 ± 0.08</td>
<td>0.63 ± 0.06</td>
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<tr>
<td>CF</td>
<td>0.59 ± 0.07</td>
<td>0.68 ± 0.12</td>
<td>0.79 ± 0.06*</td>
<td>0.76 ± 0.07</td>
<td>0.81 ± 0.05*</td>
<td>0.83 ± 0.01*</td>
<td>0.75 ± 0.03</td>
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</table>

Values are means ± SE; renal-IBAT, n = 5; splenic-lumbar, n = 8. CF, cardiac frequency. *P < 0.05 compared with control; †P < 0.05 compared with 60 min IL-1β.
IL-1β did not alter the coupling of cardiac-related renal-IBAT bursts although this coupling was eliminated during mild hypothermia after IL-1β, suggesting a complicated relationship between baroreflex regulation of efferent SND, IL-1β, and acute cold stress.

The dose of IL-1β used in the present study is similar to that used in previous studies to determine central neural pathways involved in mediating cytokine-induced effects on neuroendocrine neurons (7, 8) and to document the effects of IL-1β on efferent sympathetic nerve activity (19, 42, 43) and splenic blood flow (41). As discussed previously (21), it is estimated that the dose of IL-1β used in the present study produces peak concentrations of IL-1β that are similar to those observed after intraperitoneal administration of lipopolysaccharide (49), an experimental model for systemic bacterial infection. Although the selective administration of a single cytokine, such as IL-1β, provides an experimental advantage to the administration of a broadly-acting cytokine stimulant like lipopolysaccharide, it is known that IL-1β can influence the release of other cytokines, such as IL-6 (1, 15). With this in mind, the interpretation of the present findings is limited to the fact that substantial changes in SND occur after IL-1β administration and during mild hypothermia after IL-1β; however, these changes may not be caused directly by IL-1β.

Table 3. Peak coherence values relating discharges in renal-IBAT sympathetic nerve pairs in the 0- to 2-Hz frequency band and at the CF before (control, $T_c = 38^\circ$C) and during acute cold stress that reduced $T_c$ to 37 and 36°C

<table>
<thead>
<tr>
<th></th>
<th>Control 37°C</th>
<th>36°C</th>
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<tr>
<td>Renal-IBAT</td>
<td></td>
<td></td>
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<tr>
<td>0-2 Hz</td>
<td>0.70 ± 0.03</td>
<td>0.58 ± 0.07</td>
</tr>
<tr>
<td>CF</td>
<td>0.82 ± 0.05</td>
<td>0.71 ± 0.12</td>
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</table>

Values are means ± SE; $n = 5$. *P < 0.05 compared with control.

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