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※內毒素對大白鼠肺迷走感覺神經受器活性的影響及其機轉※

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英文名稱：Effects of endotoxin on the afferent activity of lung vagal sensory receptors and the underlying mechanisms

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一、中文摘要

在許多的研究中發現內毒素所引發呼吸性的反應中似乎與活化肺迷走感覺神經受器有關。但是，現今對於內毒素血症產生時，是否可影響呼吸系統中的肺迷走感覺神經受器的活性仍不清楚。本實驗是採用六十四隻麻醉、開胸、人工輔助呼吸的大白鼠為實驗動物，以單根神經記錄方式，記錄肺 C 纖維、快適應性受器、持續性的肺牽扯性受器和間歇性的肺牽扯性受器活性之變化。實驗結果顯示，以靜脈注射的方式給予內毒素(50 毫克／公斤)後，在八個所記錄的肺 C 纖維中，有七個肺 C 纖維的放電頻率增加；另在八個所記錄的快適應性受器中，也皆可刺激全部的快適應性受器。至於在所記錄的八個持續性肺牽扯性受器中，內毒素可造成其中的四個受器的活性增加，但在另四個受器的活性卻不受明顯地影響；然而於八個間歇性的肺牽扯性受器反應中，發現內毒素則無法有效地影響其放電頻率。此外，內毒素刺激肺迷走感覺神經之開始時間約在給予內毒素後的三至十六分鐘，並且此刺激作用之時間仍持續至所記錄的九十分鐘。在內毒素刺激 C 纖維和快適應性受器的過程中，其神經活性的增加與呼吸週期的節律並不相關，是呈現一個不規律的放電狀態；但持續性肺牽扯性受器的刺激作用卻具有與呼吸週期相關的型態。再者，若給予生理食鹽水，在我們所觀察的九十分鐘內，皆不會明顯地影響所記錄的神經受器的活性。此外，給予內毒素可明顯地增加全肺阻力、降低動態之肺順應性及降低動脈血壓。根據以上的實驗結果，可知以靜脈注射的方式給予內毒素造成內毒素血症時可刺激肺迷走感覺神經受器，藉此神經受器活性的增加可扮演一偵測與調節肺功能的重要角色。

關鍵詞：內毒血症、肺 C 纖維、快適應性受器、肺牽扯性受器

Abstract

Several endotoxin-induced pulmonary responses are linked to the activation of lung vagal sensory receptors. However, the effects of circulatory endotoxin on lung vagal afferent activity are not clear. We recorded afferent activity arising from vagal pulmonary C fibers (CFs), rapidly adapting receptors (RARs), tonic pulmonary stretch receptors (T-PSRs), and phasic pulmonary stretch receptors (P-PSRs) in 64 anesthetized rats. Intravenous injection of endotoxin (50 mg/kg; lipopolysaccharide) stimulated 7 of the 8 CFs, 8 of the 8 RARs, and 4 of the 8 T-PSRs studied, while having no effect on the 8 P-PSRs tested. The stimulation started 3-16 min after endotoxin injection and lasted until the end of the 90-min observation period. The evoked discharge of either CFs or RARs was not in phase with the ventilatory cycle, whereas that of T-PSRs showed a respiratory modulation. Injection of a saline vehicle caused no significant change in the discharge of these receptors. Additionally, endotoxin significantly produced an increase in total lung resistance, and decreases in dynamic lung compliance and arterial blood pressure. Our results demonstrate that a majority of lung vagal sensory receptors are activated by intravenous endotoxin, and support the notion that these receptors may function as an important afferent system during endotoxemia.

Keywords: endotoxemia; pulmonary C fibers; rapidly adapting receptors; pulmonary stretch rceptors

Introtruction

Systemic endotoxemia has been recognized as one of the leading causes of the acute respiratory distress syndrome and is known to induce various pulmonary pathophysiological consequences (1). Vagal sensory receptors located in the

airways and lungs are believed to play an important role in detecting pulmonary pathophysiological conditions and to elicit resultant respiratory reflexes (2, 3). However, the effects of circulatory endotoxin on lung vagal afferent activity are still not clear.

There are three major types of vagal sensory receptors serving the major afferent system of the airways and lungs: C-fiber nerve endings (C fibers), rapidly adapting receptors (RARs), and pulmonary stretch receptors (PSRs) (2, 3). PSRs can be further categorized as tonic and phasic PSRs whose activity fires throughout the respiratory cycle and in phase with inflation, respectively (2, 3). Lung C fibers, while possessing the highest sensitivity to chemical stimuli (e.g., chemical mediators), are the least sensitive to mechanical stimuli (e.g., bronchoconstriction) among the three receptor types (2, 3). RARs appear to be sensitive to both mechanical and chemical stimuli (2, 3). PSRs are very sensitive to mechanical stimuli, but relative insensitive to chemical stimuli as compared to C fibers and RARs (2, 3). Tonic PSRs have a lower threshold to increased transmural pressure as compared to phasic PSRs (4). Endotoxemia is known to cause the local release of various chemical mediators in lung tissues including histamine (5), arachidonate metabolites (6, 7), oxygen radicals (7, 8), and cytokines (9), and produces a number of pulmonary responses such as bronchoconstriction, increased lung stiffness, and tissue edema (1). It is thus possible that these endotoxin-induced consequences may serve as chemical and mechanical stimuli to activate lung vagal sensory receptors. Several investigators (10-14) have suggested that various local or reflex pulmonary responses to endotoxin are linked to the stimulation of lung vagal sensory receptors. Additionally, activation of vagal afferents have been recently proposed as the neural mechanism in brain signalling of peripheral endotoxin (15, 16). However, direct electrophysiological evidence to support this hypothesis is still lacking.

In this study, we recorded afferent activity arising from vagal pulmonary C fibers, RARs, tonic PSRs, and phasic PSRs in anesthetized rats to determine whether these sensory receptors are activated following intravenous injection of endotoxin.

Methods

General Preparations

Sprague-Dawley rats (weight 323 ± 2 g; n = 64) of either sex were anesthetized with an intraperitoneal injection of chloralose (100 mg/kg; Sigma Chemical, St. Louis, MO, USA) and urethan (500 mg/kg; Sigma Chemical). A polyethylene catheter was inserted into the jugular vein and advanced until the tip was close to the right atrium for intravenous administration of pharmacological agents. The right femoral artery was cannulated for measuring arterial blood pressure. During the course of the experiments, supplemental doses of chloralose (20 mg/kg/hr) and urethan (100 mg/kg/hr) were administered to maintain abolition of pain reflexes induced by pinching the animal's tail. During the recording of vagal action potentials, the rats were paralyzed with pancuronium bromide (0.05 mg/kg, i.v.; Orgnon Teknika, Boxtel, Holland). Periodically, the effect of pancuronium was allowed to wear off so that the depth of anesthesia could be checked. Body temperature was maintained at ~ 36 ℃ throughout the experiment by means of a servo-controlled heating blanket. All protocols were in accordance with the recommendation in the Guide for the Care and Use of Laboratory Animals published by the National Institute of Health, Bethesda, MD, USA and were approved by the Committee of the National Science Council, Taipei, Taiwan, ROC.

The rats were tethered in a supine position, and the trachea was cannulated below the larynx with a short tracheal tube via a tracheotomy. A mid-line thoracotomy was performed and the edges of the rib cage were retracted. The lungs were ventilated by a rodent respirator (Harvard 683; South Natick, MA, USA) at a constant volume of 2 ml. The frequency of the respirator was set at 60-65 breaths/min and was kept constant

in each experiment. The expiratory outlet of the respirator was placed under 3-4 cm of water to maintain a near normal functional residual capacity. Respiratory flow was measured with a pneumotachograph (Fleisch 4/O; Richmond, VA, USA) coupled with a differential pressure transducer (Validyne MP45-12; Northridge, CA, USA). The flow signal was integrated to give tidal volume (V_T). Tracheal pressure (transpulmonary pressure in open-chest preparation) was monitored with a pressure transducer (Validyne MP45-28) via a side tap of the tracheal cannula. Total lung resistance (R_L) and dynamic lung compliance (C_{dyn}) were determined by using the subtraction method. All physiological signals were recorded by a thermal array recorder (Gould TA11; Cleveland, OH, USA) and also recorded on tape (Neurocorder DR-890; New York, NY, USA) for later analysis.

Recording of Afferent Activity

Afferent activity arising from lung vagal sensory receptors was recorded using techniques described elsewhere (17). Briefly, a fine afferent filament was split from the desheathed nerve trunk of the right vagus and placed on a platinum-iridium recording electrode. Action potentials were amplified (Grass P511K; Quincy, MA, USA), monitored with an audio monitor (Grass AM8), and displayed on an oscilloscope (Gould 420). The fine nerve filament was subdivided until activity from only 1 or 2 units were obtained. The strategies to search for different types of lung vagal sensory receptors have been well described previously (18-20). In brief, the lungs were hyperinflated in a step-like manner to 4 x VT or by constant pressure inflation (~ 20 cmH_2O), which was maintained for 10 - 15 s. Vagal pulmonary C fibers could be activated by lung hyperinflation to a relatively high volume (e.g., 4 x VT), whereas RARs and PSRs could be activated by a relatively low volume (e.g., 1 x V_T) (2, 3). Once the presence of a suspected single C-fiber unit was detected, capsaicin (1-2 μg/kg; Sigma Chemical), a potent chemical stimulant of C fibers, was injected as a bolus into the vein. The capsaicin solution was made from a refrigerated stock solution (5 mg/ml) which was prepared by dissolving capsaicin in 10% ethanol, 10% Tween 80, and 80% saline. Only C-fiber units showing stimulation within 2 s after the injection were studied. Once the presence of a suspected single RAR unit was detected, the RAR response to lung deflation was also studied by exposing the expiratory outlet of the respirator to atmospheric pressure for a period of 8 - 10 s. This was performed because a majority of RARs can be activated by lung deflation (2, 3). Furthermore, units displaying an adaptation index to maintained lung inflation > 70% and < 50% were regarded as RARs and PSRs, respectively (21). For PSRs, units that fired throughout the respiratory cycle and in phase with inflation were regarded as tonic and phasic PSRs, respectively. Finally, the conduction velocity of the afferent fibers of the pulmonary receptor was measured by a method described previously (22). Prior to the end of each experiment, the general locations of the receptors studied were identified within the lung structure by gently probing the tissues with a polyethylene rod (diameter = 2 mm).

Experimental Procedures

In total, 64 rats were evenly divided into 8 groups. Four groups of animals received an intravenous injection of saline vehicle, while the other four received an intravenous injection of endotoxin (E. coli lipopolysaccharide; 50 mg/kg, Sigma Chemical). Each of the four groups receiving vehicle or endotoxin injection was used to study one type of lung vagal sensory receptors, and only one receptor was recorded in each animal. Endotoxin or vehicle solution at a volume of 0.6 - 0.7 ml was slowly injected into the vein over a period of 1 min. Each test period included continuous recording of neural activity of lung vagal sensory receptors for 10 min before and at least 90 min after the endotoxin or vehicle injection. To confirm that the receptors remained active, intravenous injection of capsaicin (1-2 μg/kg) or lung hyperinflation (4 x V_T) was

performed at the end of the test period. Results were discarded for those receptors that had become inactive during the test and/or were unresponsive to capsaicin or hyperinflation at the end of the test period.

Data Analysis and Statistics

Neural activity of vagal sensory receptors, RL, Cdyn, mean arterial blood pressure, and heart rate were measured at 1-s intervals or on a breath-by-breath basis, and were averaged over 1-min periods. Baseline data of these physiological parameters were calculated as the average values over the 5-min period immediately preceding intravenous injection of the vehicle or endotoxin. Peak response was defined as the maximal or minimal value averaged over 5 min after vehicle or endotoxin injection. Pulmonary C fibers and RARs were judged to be activated by endotoxin when the peak afferent response exceeded its baseline activity by at least 0.5 impulses/s. PSRs were judged to be activated by endotoxin when their activities increased by at least 20% of their baselines. These physiological parameters were analyzed using a computer equipped with an analog/digital convertor (Gould DASA 4600) and software (BioCybernatics 1.0; Taipei, Taiwan). Data obtained from the computer analysis were routinely checked for accuracy with those calculated manually. Results were evaluated by Student's t-test or a two-way mixed factorial analysis of variance followed by Duncan's test when appropriate. $P < 0.05$ was considered significant. All data are presented as mean ± SE.

Results

The baseline activity of the pulmonary C fibers studied was irregular and sparse (0.07 ± 0.02 impulses/s; n = 16). These nerve endings were stimulated by hyperinflating the lungs up to 3 or 4 x V_T and by bolus intravenous injection of capsaicin (Fig. 1A). The average baseline activity of RARs studied was also sparse (0.08 ± 0.02 impulses/s; n = 16). Three receptors exhibited a baseline activity in phase with ventilatory cycles, while the others had irregular or no baseline activity. The evoked discharge of these RARs in response to maintained lung inflation adapted rapidly (Fig. 1D) and the mean adaptation index reached 89.5 ± 1.4% (range: 80.0 - 99.0%; n = 16). A majority (14 of 16) of these RARs were also activated by lung deflation. All the PSRs studied exhibited baseline activity in phase with ventilatory cycles (Fig. 2). The average baseline activities of these tonic and phasic PSRs were 49.4 ± 3.1 and 16.2 ± 2.5 impulses/s; n = 16), respectively. The evoked discharge of these PSRs in response to maintained lung inflation adapted slowly, and the mean adaptation indices of tonic and phasic PSRs reached only 18.8 ± 2.3% (range: 7.0 - 35.0%; n = 16) and 12.6 ± 1.3% (range: 3.0 - 22.0%; n = 16), respectively. The mean conduction velocities of the afferent fibers conducting impulses from these pulmonary C fibers, RARs, tonic PSRs, and phasic PSRs were 1.2 ± 0.1 m/s (range 0.6-1.8 m/s), 14.7 ± 1.2 m/s (range 6.0 - 23.1 m/s), 18.4 ± 1.2 m/s (range 11.5 - 27.8 m/s), and 16.9 ± 1.0 m/s (range 10.4 - 25.1 m/s), respectively. All the lung vagal sensory receptors studied were localized within the lung structure, and their physiological properties were consistent with those reported in rats (18-20, 22) and in other species (2, 3).

Intravenous injection of endotoxin stimulated 7 of the 8 pulmonary C fibers (Fig. 1B) and activated all 8 RARs studied (Fig. 1E). The stimulation of pulmonary C fibers (Figs. 1B and 3A) and RARs (Figs. 1E and 3B) started 3 - 10 min and 5 - 16 min, respectively, after endotoxin injection and both lasted until the end of the observation period. When stimulated, both types of lung vagal sensory receptors fired irregularly, and the evoked discharge was not in phase with the ventilatory cycle (Fig. 1). Throughout the observation period, the afferent responses of both types of lung vagal sensory receptors constantly alternated between strong and weak stimulation (Fig. 1). On average, the activity of pulmonary C fibers and RARs increased from their baselines to peaks of 1.48 ± 0.37 impulses/s (n = 8) and 3.56 ± 0.67 impulses/s (n = 8),

respectively, after endotoxin injection. In contrast to the effects of endotoxin, intravenous injection of the saline vehicle caused no significant changes in the neural activity of these two types of lung vagal sensory receptors during the same observation period (Fig. 3). On average, the peak evoked discharge of pulmonary C fibers and RARs reached only 0.11 ± 0.04 impulses/s (n = 8) and 0.18 ± 0.07 impulses/s (n = 8), respectively, after vehicle injection. As a result, the afferent response of either pulmonary C fibers (Fig. 3C) or RARs (Fig. 3D) to endotoxin was significantly greater than those to vehicle injection.

Endotoxin injection mildly stimulated 4 of the 8 tonic PSRs (Fig. 2C and 2D) and did not cause any significant change in the neural activity of the other 4. Additionally, the saline vehicle injection failed to affect the neural activity of all 8 tonic PSRs studied (Fig. 4A). The stimulation of tonic PSRs started 4 - 8 min after endotoxin injection and lasted until the end of the observation period (Figs. 2 and 4A). When stimulated, the evoked discharge occurred mainly during the inflation phase (Fig. 2C). On average, the peak evoked discharge of tonic PSRs after endotoxin injection reached 120.4 ± 4.0% (n = 8) of its baseline, which was significantly greater than that after saline injection (Fig. 2C). On the other hand, either endotoxin or saline injection did not significantly alter the neural activity of all 8 phasic PSRs during the entire observation period (Figs. 2 and 4B). As a result, the afferent response of phasic PSRs to endotoxin did not significantly differ from that to saline injection (Fig. 4D).

In saline-treated animals, RL did not change significantly, yet Cdyn progressively and mildly declined during the observation period (Fig. 5). In endotoxin-treated animals, R_L slightly increased and Cdyn decreased (Fig. 5). RL began to increase within 2-3 min, reached its peak in 5 - 7 min after endotoxin injection, and declined to a level higher than its baseline (Fig. 5A). Cdyn displayed an initial step-like drop within 2-3 min after endotoxin injection, followed by a progressive decline until the end of the observation period (Fig. 5B). Statistical analysis revealed that the peak R_L measured after saline injection did not differ from its corresponding baseline, whereas the peak R_L measured after endotoxin injection was significantly greater than its corresponding baseline (Fig. 5C). Additionally, the maximal reductions in Cdyn measured after saline and endotoxin injection were significantly smaller than their corresponding baselines, and the latter was significantly smaller than the former (Fig. 5D).

In saline-treated animals, mean arterial blood pressure slightly decreased from a baseline of 90.0 ± 2.9 mmHg to a maximal reduction of 86.5 ± 3.1 mmHg ($p < 0.05$; n = 32) at the end of the observation period. However, the heart rate did not change significantly throughout the observation period (baseline vs. after injection, 406 ± 5 vs. 400 ± 5 beats/min; $p > 0.05$, n = 32). In endotoxin-treated animals, mean arterial blood pressure significantly decreased from a baseline of 90.2 ± 3.7 mmHg to a maximal reduction of 36.5 ± 1.8 mmHg ($p < 0.05$; n = 32) within 3-5 min (Figs. 1 and 2), and subsequently returned to a level of 73.3 ± 3.2 mmHg ($p < 0.05$; n = 32) at 12-18 min after endotoxin injection. During this initial hypotensive period, the mean heart rate decreased from a baseline of 409 ± 7 beats/min to a peak of 363.1 ± 18.8 beats/min, and returned to a level of 378 ñ 10 beats/min ($p < 0.05$; n = 32). For the rest of the observation period, arterial blood pressure and heart rate did not change further. As a group, mean arterial blood pressure and heart rate were maintained at a level of 72.1 ± 3.8 mmHg and 387 ± 7 beats/min (n = 32), respectively, at the end of the observation period.

Discussion

Results of this study demonstrate that intravenous endotoxin stimulated 87.5% of the vagal pulmonary C fibers, 100% of the RARs, and 50% of the tonic PSRs studied, whereas it failed to activate phasic PSRs. The stimulation of these lung vagal sensory receptors was not due to the vehicle of endotoxin or the progressive changes in

receptor activity that might occur spontaneously under our experimental conditions because no detectable responses were found in the receptors studied as the vehicle/time control. These results demonstrate that a majority of lung vagal sensory receptors are activated by circulatory endotoxin, and suggest that lung vagal sensory receptors may function as an important afferent system during endotoxemia.

The possibility that lung C fibers are associated with endotoxin-induced pulmonary responses has been suggested. Tang et al. (10) demonstrated that the tachypneic response to intravenous endotoxin in rats is largely prevented by either bilateral cervical vagotomy or a procedure to selectively block the conduction of vagal C fibers. Orr et al. (11) reported that intravenous infusion of endotoxin in cats evokes apnea followed by rapid, shallow breathing, a set of ventilatory responses that is thought to originate from lung C fibers. Several investigators (12, 13) indicated that tachykinins, a family of neuropeptides released from C-fiber nerve endings when stimulated, are involved in producing airway hyperreactivity, brochoconstriction, and airway plasma extravasation in response to administration of endotoxin. Long et al. (14) showed that the presence of C fibers attenuates the pulmonary inflammatory response to intratracheal endotoxin and postulated that respiratory reflexes, such as cough, arising from C fibers may protect the lungs from the insult of endotoxin. Taken together, these observations lead to the notion that lung C fibers are stimulated following endotoxin challenge. The present findings provide a direct electrophysiological evidence to support this notion. On the other hand, the contributions of RARs and PSRs to endotoxin-induced pulmonary responses have not been studied. However, stimulation of RARs and PSRs may evoke a number of airway responses. For example, stimulation of RARs produces bronchoconstriction and excitatory effects on breathing, whereas activation of PSRs causes bronchodilation and inhibitory effects on breathing (2, 23). It is known that hyperventilation and bronchoconstriction occur as consequences of endotoxemia (1, 10, 24). Therefore, in addition to C-fiber functions, it is plausible that stimulation of RARs may promote the elicitation of these endotoxin-induced airway responses, whereas activation of PSRs may provide afferent signals to restrain these responses.

The mechanisms by which lung vagal sensory receptors are stimulated following systemic administration of endotoxin remain unclear. In general, chemical and mechanical stimulation are two modes of activation of these sensory receptors (2, 3). Endotoxin can cause increased release of a wide array of chemical mediators and may produce a variety of pulmonary responses (1, 5-13), many of which have been shown to be able to stimulate lung vagal sensory receptors. For example, histamine (25), cyclooxygenase products (18, 19, 25-27), leukotriene (28), and hydroxyl radicals (18, 19, 27), either administered exogenously or formed endogenously, may stimulate lung C fibers and/or RARs. Additionally, pulmonary edema excites both lung C fibers and RARs (29), while bronchoconstriction activates both RARs and PSRs (30, 31). Furthermore, increased lung stiffness stimulates RARs (2). In this study, we found that intravenous endotoxin produced a small increase in RL, and decreases in Cdyn, arterial blood pressure, and heart rate, all of which are clinical signs of endotoxemia (24). These observed responses may have resulted from the effects of various chemical mediators released following endotoxin challenge, such as cyclooxygenase products or oxygen radicals (1). It is unlikely that pulmonary C fibers were stimulated by the observed bronchomotor responses because they are relatively insensitive to mechanical stimuli (2, 3), and because their evoked discharges did not show respiratory modulation. In contrast, the increase in RL may have contributed to the mechanical stimulation of RARs and tonic PSRs because these sensory receptors are sensitive to contraction of the airway smooth muscle (30,

31), and because the onset time of afferent responses correlated well with that of the bronchomotor responses. The decrease in Cdyn is an especially effective mechanical stimulus for RARs (32), but not for PSRs (33). However, since the evoked discharges of RARs following endotoxin injection were also not in phase with respiratory cycles, the involvement of chemical mediators in RAR stimulation should be considered. The effects of low arterial blood pressure on the activity of lung vagal sensory receptors has not been investigated, and accordingly, the possible contribution of the observed hypotension to the afferent responses to endotoxin remains speculative. Collectively, owing to its widespread effects, it is conceivable that intravenous endotoxin stimulates multiple types of lung vagal sensory receptors through multifarious mechanisms.

Tonic PSRs differ from phasic PSRs not only in their patterns of discharge, but also in their locations in the airways and in their sensitivities to increased transmural pressure. Tonic PSRs generally have a low threshold to a certain increase in transmural pressure, whereas phasic PSRs usually have a high threshold (4). The mechanical sensitivities differ probably because tonic PSRs are mainly located in the larger extrapulmonary airways, where mechanical factors suggest that the same transmural pressures result in a greater stimulus to these receptors due to a larger circumferential tension (3). Hence, the inability of intravenous endotoxin to alter the discharge of phasic PSRs in this study could be due to the fact that the evoked bronchomotor responses were not great enough to activate them.

Recent investigations have demonstrated that transection of the vagus below the level of the diaphragm abolished or largely reduced several brain-mediated illness responses to peripheral administration of endotoxin, including fever (34), hyperalgesia (35), and activation of the hypothalamic-pituitary-adrenal axis (36), suggesting the essential role of abdominal vagal afferents in producing these responses. An immunolabeling study (37) revealed that intravenous endotoxin induces the expression of Fos marker in the vagal sensory ganglia and that vagotomy abrogates this expression, indicating the functional activation of vagal afferent by endotoxin. Cytokine interleukins are thought to be the chemical mediators responsible for this afferent activation (15, 16, 38). This vagal afferent pathway has been recognized as the link between brain signaling and the peripheral endotoxin (15, 16, 34-38). Evidently, stimulation of vagal sensory receptors by endotoxin is not unique to the airways and lungs. Although properties of lung and abdominal vagal sensory receptors and chemical mediators responsible for their activation may not be the same, results of this study have provided the first electrophysiological evidence demonstrating the activation of vagal sensory receptors by circulatory endotoxin. Future studies can be directed at investigating the role of chemical mediators, such as cytokines, in the activation of lung vagal sensory receptors during exdotoxemia.

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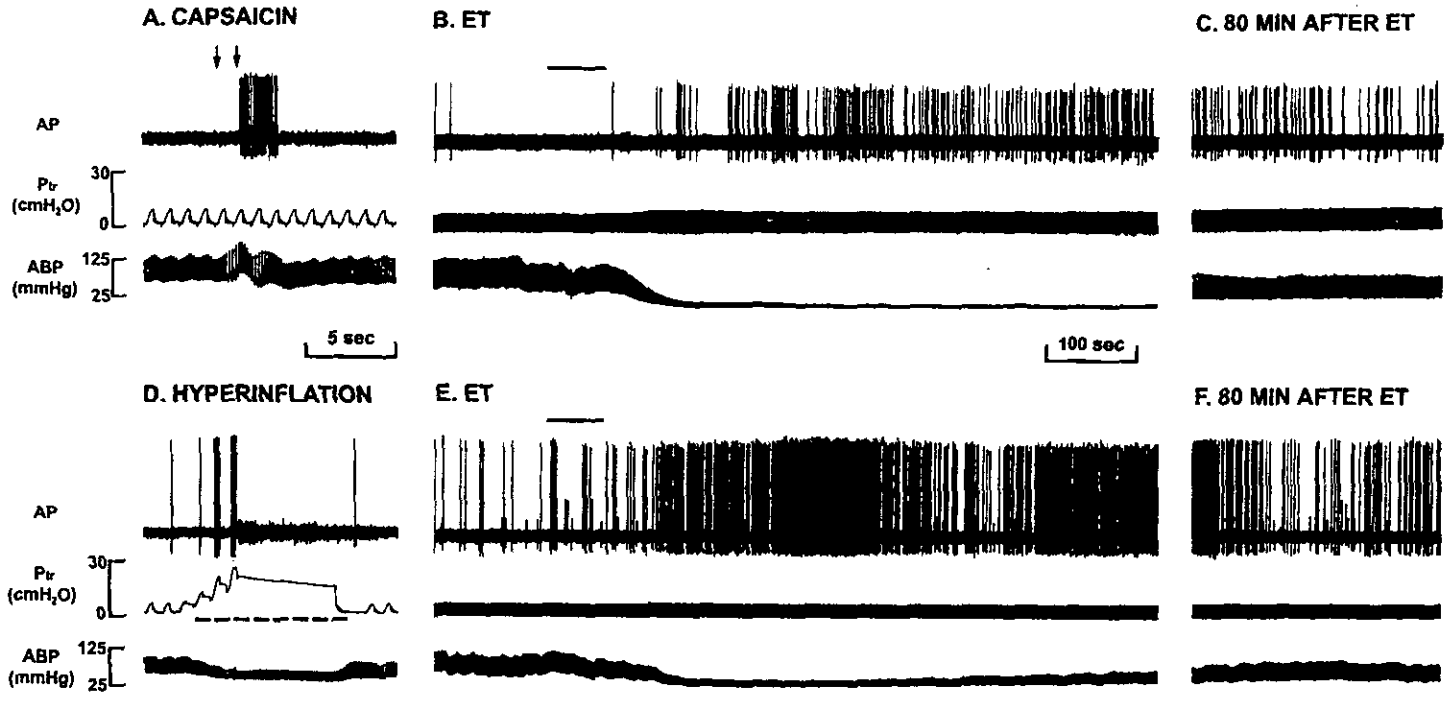

Fig. 1. Afferent responses of a pulmonary C-fiber nerve ending (A, B, and C) and a rapidly adapting receptor (D, E, and F) to capsaicin or lung hyperinflation, and to intravenous endotoxin (ET). A: capsaicin (1 μg/kg) was injected into catheter at first arrow and flushed into vein at second arrow. D: the lungs were hyperinflated to 4 times tidal volume as indicated by dashed line. B and E: 50 mg/kg endotoxin was slowly injected into the veins over a period of 1 min as indicated by solid lines. C and D: receptor responses 80 min after endotoxin injection. Twenty min elapsed between capsaicin injection and endotoxin injection, and 10 min elapsed between lung hyperinflation and endotoxin injection. Ptr, tracheal pressure; AP, action potential; ABP, arterial blood pressure. Note that time scales of A and D differ from those of B, C, E, and F.

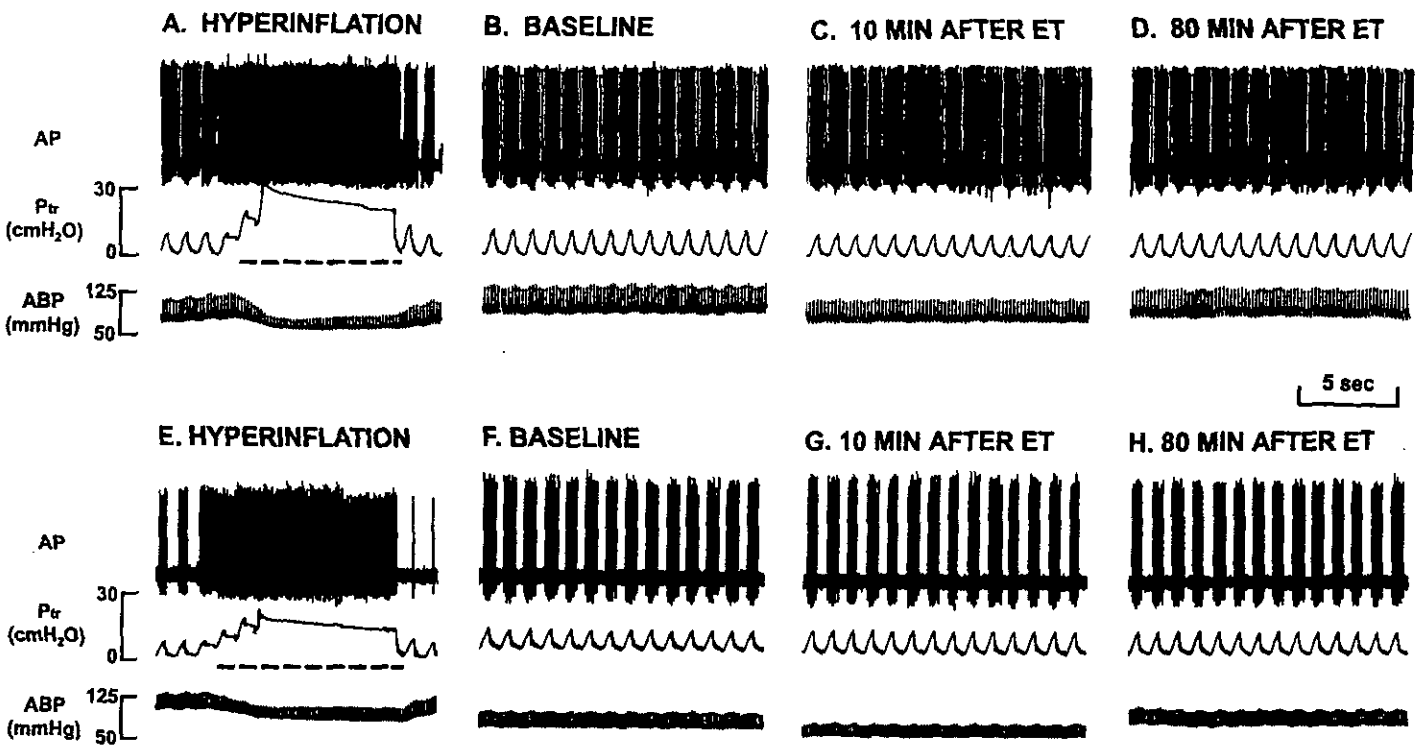

Fig. 2. Afferent responses of a tonic pulmonary stretch receptor (A, B, C, and D) and a phasic pulmonary stretch receptor (E, F, G, and H) to lung hyperinflation and to intravenous endotoxin (ET). A and E: the lungs were hyperinflated to 3 or 4 times tidal volume indicated by dashed lines. B and F: baseline discharge. C and G: responses 10 min after endotoxin injection. D and H: responses 80 min after endotoxin injection. Ten min elapsed between lung hyperinflation and endotoxin injection. Ptr, tracheal pressure; AP, action potential; ABP, arterial blood pressure.

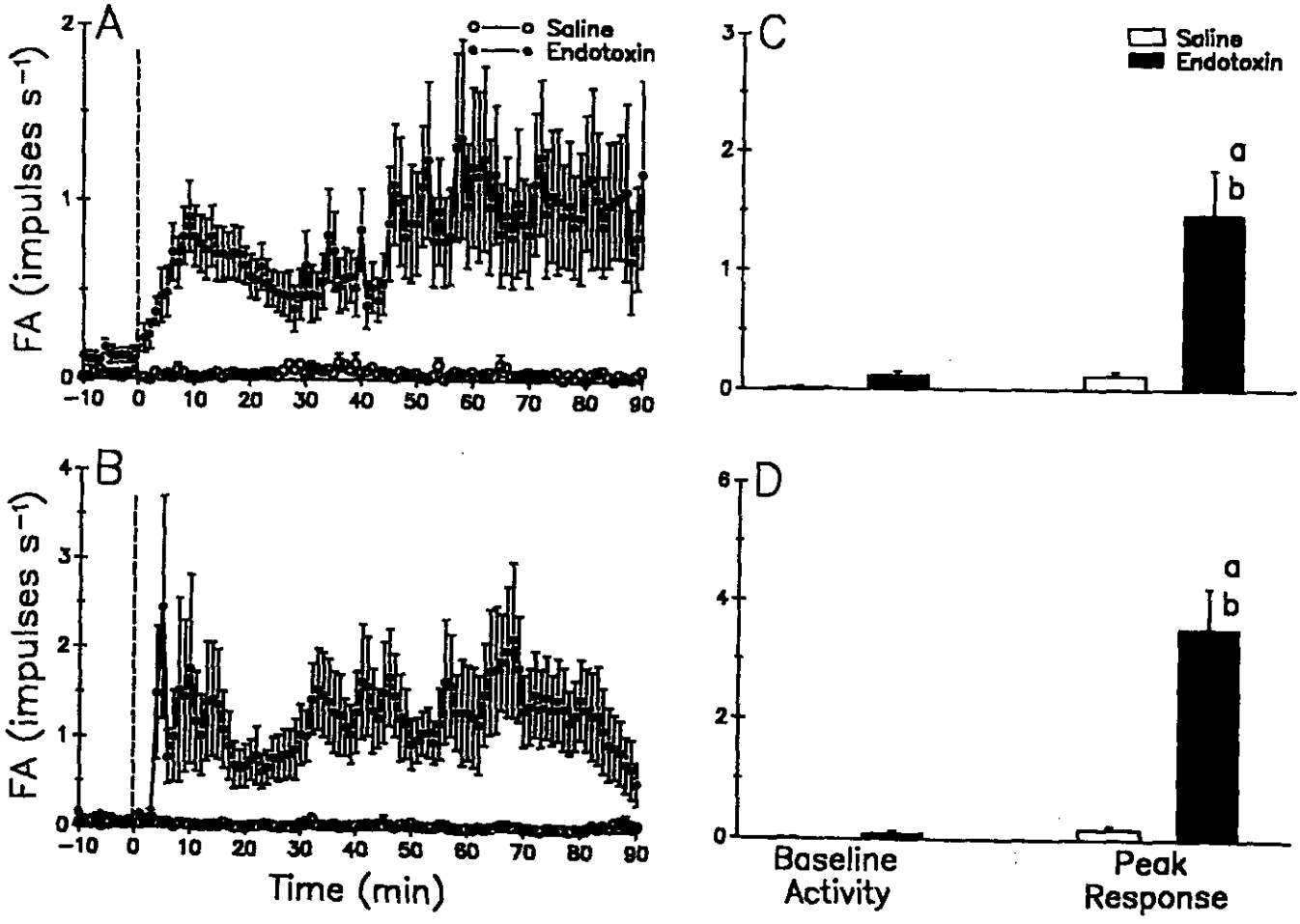

Fig. 3. Mean afferent responses of pulmonary C-fiber nerve endings (A and C) and rapidly adapting receptors (B and D) to intravenous injection of saline vehicle or endotoxin in four groups of rats. In panels A and B, vertical dashed lines indicate onset time of saline or endotoxin injection. FA, fiber activity; a, significantly different from corresponding baseline activity; b, significantly different from responses to saline. Data in each group are mean ± SE of 8 animals.

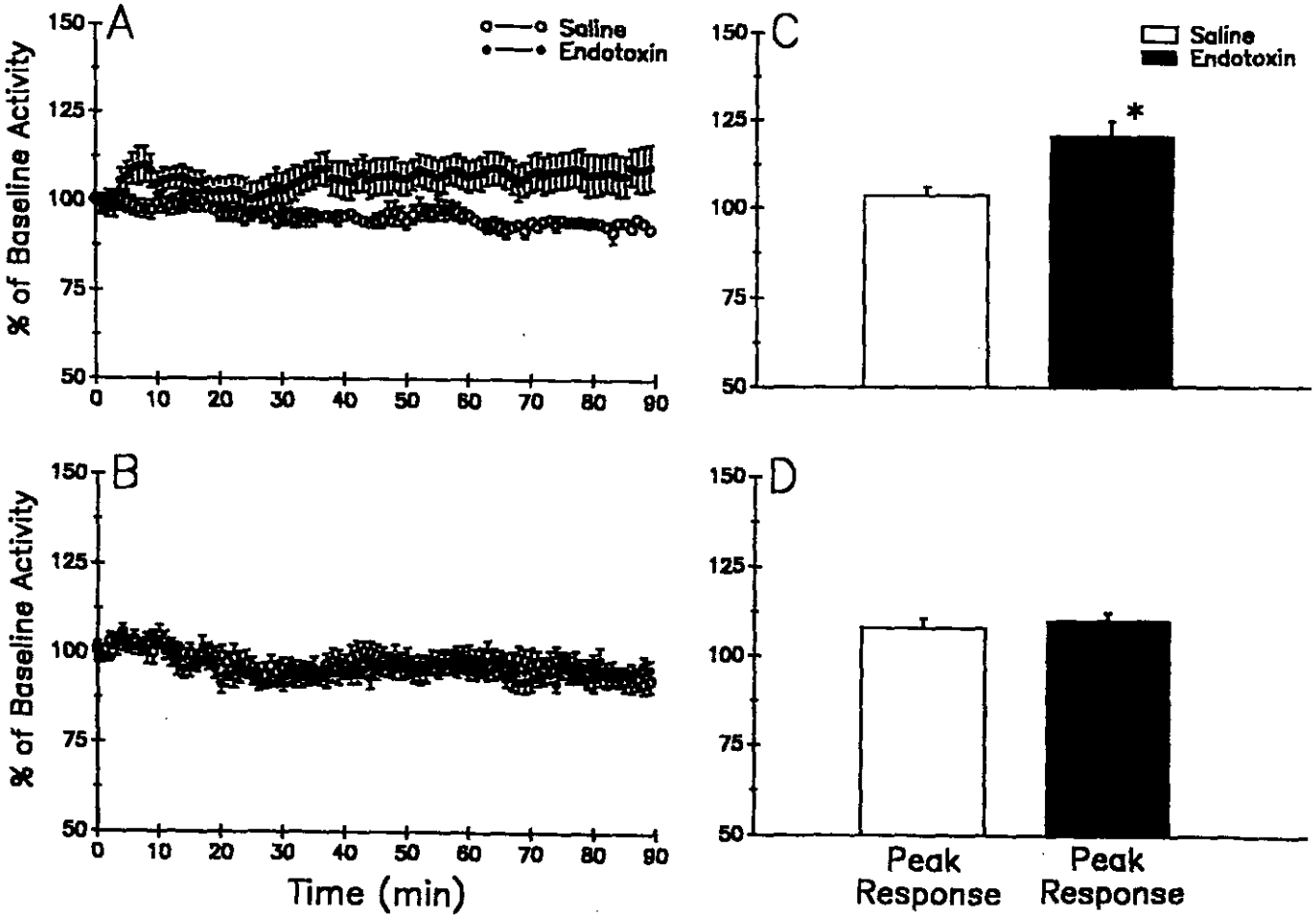

Fig. 4. Mean afferent responses of tonic (A and C) and phasic (B and D) pulmonary stretch receptors to intravenous injection of saline vehicle or endotoxin in four groups of rats. Saline or endotoxin was injected at time 0. *, significantly different from responses to saline. Data in each group are mean ± SE of 8 animals and are expressed as percentage of baseline activity.

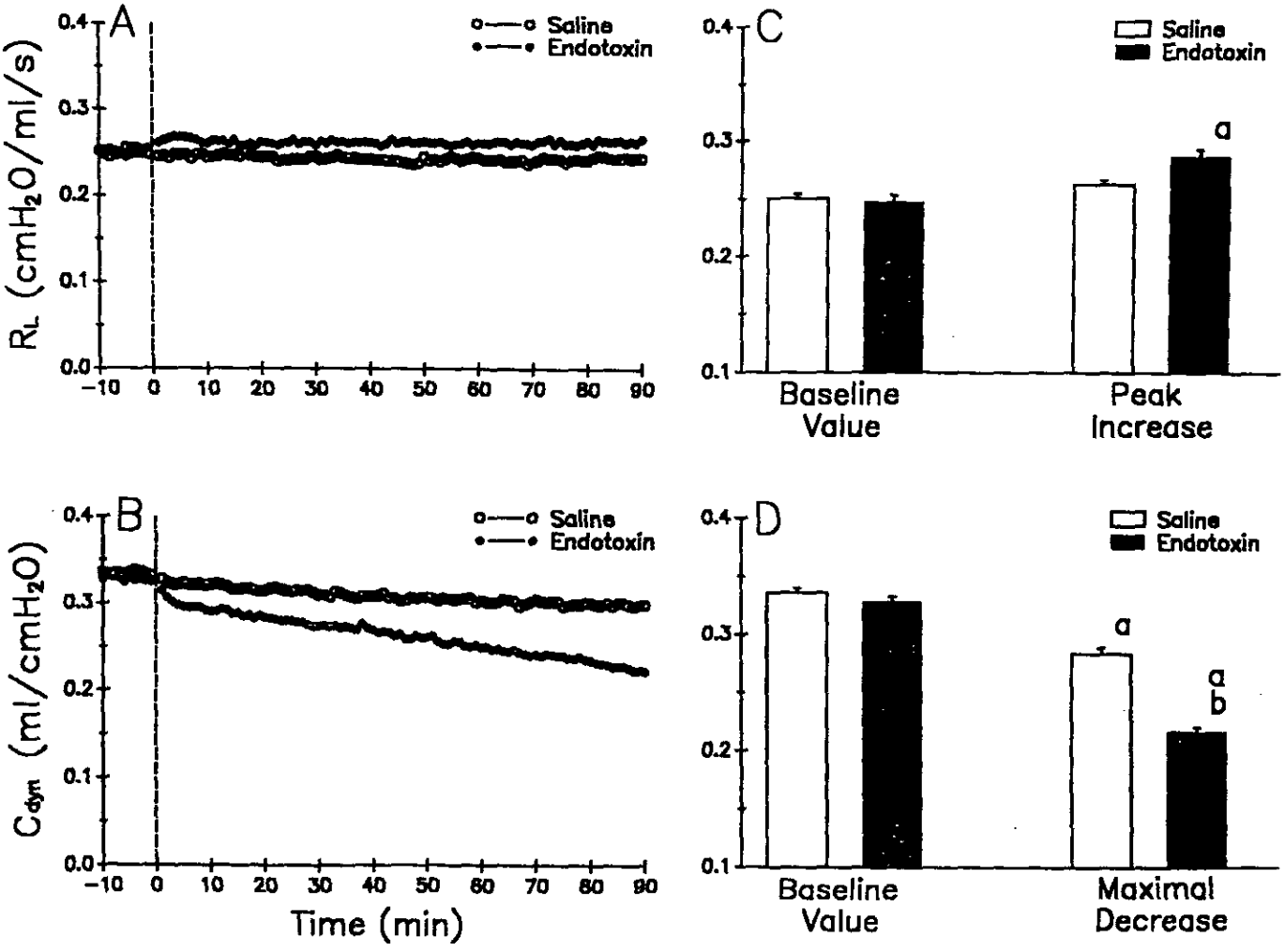

Fig. 5. Mean bronchomotor responses to intravenous injection of saline vehicle or endotoxin in all animals studied. In panels A and B, vertical dashed lines indicate onset time of saline or endotoxin injection. R_L, total lung resistance; C_{dyn}, dynamic lung compliance; a, significantly different from corresponding baseline value; b, significantly different from responses to saline. Data in each group are mean ± SE of 32 animals.