CHEST

Original Research

HYPOXIA-RELATED ISSUES

Does Endothelin Play a Role in Chemoreception During Acute Hypoxia in Normal Men?*

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Background: **The peripheral chemoreceptors are the dominant reflex mechanism responsible for the rise in ventilation and muscle sympathetic nerve activity (MSNA) in response to hypoxia. Animal studies have suggested that endothelin (ET) plays an important role in chemosensitivity. Moreover, several human clinical conditions in which circulating ET levels are increased are accompanied by enhanced chemoreflex sensitivity. Whether ET plays a role in normal human chemosensitivity is unknown.**

Methods: **We determined whether bosentan, a nonspecific ET receptor antagonist, would decrease chemoreflex sensitivity in 14 healthy subjects. We assessed the effects of bosentan on the response to isocapnic hypoxia, using a randomized, crossover, double-blinded study design.**

Results: **Bosentan increased mean (± SEM) plasma ET levels from 1.97 ± 0.28 to 2.53 ± 0.23 pg/mL ($p = 0.01$). Hypoxia increased mean minute ventilation from 6.7 ± 0.3 to 8+/0.4 L/min ($p < 0.01$), mean MSNA from 100 to 111 ± 5% ($p < 0.01$), mean heart rate from 67 ± 3 to 86 ± 3 beats/min ($p < 0.01$), and mean systolic BP from 116 ± 3 to 122 ± 3 mm Hg ($p < 0.01$). However, none of these responses differed between therapy with bosentan and therapy with placebo ($p = 0.26$). Bosentan did not affect the mean MSNA responses to the apneas, during normoxia (change from baseline: placebo, 259 ± 58%; bosentan, 201 ± 28%; $p = 0.17$) or during hypoxia (change from baseline: placebo, 469 ± 139%; bosentan, 329 ± 46%; $p = 0.24$). The durations of the voluntary end-expiratory apneas in normoxia and hypoxia, and the subsequent reductions in oxygen saturation, were also similar with therapy using bosentan and placebo ($p = 0.42$).**

Conclusion: **In healthy men, ET does not play an important role in peripheral chemoreceptor activation by acute hypoxia.** ***(CHEST 2007; 131:1467–1472)***

Key words: endothelin; human chemoreceptor; hypoxia; sympathetic nervous system

Abbreviations: ANOVA = analysis of varicance; df = degrees of freedom; ET = endothelin; ETA = type A endothelin receptor; ETB = type B endothelin receptor; HR = heart rate; MSNA = muscle sympathetic nerve activity; SBP = systolic arterial BP

Chemoreception plays an important role in the control of ventilation.[1,2] The peripheral chemoreceptors are located in the carotid bodies and aortic arch[3] and respond primarily to hypoxia.[4,5] The activation of peripheral chemoreceptors leads to an increase in ventilation, muscle sympathetic nerve activity (MSNA), and BP.[6]

Endothelin (ET) is a peptide of 21 amino acids that is produced by many different tissues (including endothelium, brain, lungs, and kidneys) and is represented by three isoforms (ET-1, ET-2, and ET-3). The effects of ET are mediated by two types of receptors (type A ET receptor [ETA] and type B ET receptor [ETB]) in an autocrine and paracrine way. ETAs and ETBs are both present on smooth-muscle cells in the systemic and pulmonary circulation, where they elicit vasoconstriction. ETBs are also found on endothelial cells, and elicit vasodilation via nitric oxide and prostacyclin production.[7] In addition, ET-1 is cleared by ETBs.[8]

Several animal studies[9–15] have suggested that the ET system may play a major role in chemoreceptor sensitivity. ETAs and ETBs are present in chemosensitive tissue of the carotid bodies of cats and rats.[13,15] Moreover, IV administration of ET-1 in rats increases ventilation. This effect is mediated by ETAs and was blocked by specific ETA antagonism and bilateral transection of the carotid sinus nerves.[12] One study[9] in rabbits revealed an increased peripheral chemoreceptor activity during hypoxia in response to ET, independent of its vascular effects. These effects were demonstrated in vascularly perfused cat carotid body preparations but not in superfused carotid body experiments,[14] suggesting a species difference in the effects of ET on carotid body. A role of endogenous ET in the control of ventilation was also evidenced in ET-1-deficient and ETA-deficient mice, in which reflex increases in ventilation due to hypoxia were attenuated.[11]

Human studies have shown an increase in peripheral chemoreceptor sensitivity and sympathetic activity in obstructive sleep apnea,[16] an increase in the sympathetic response to hypoxia in systemic hypertension,[17] and an increase in chemoreceptor sensitivity in heart failure[18–20]; however, the exact mechanism responsible for these observations is incompletely understood. Several studies,[21,22] but not all,[23,24] have shown increased plasma ET levels in patients with obstructive sleep apnea. This condition was also found in patients with heart failure.[25,26] However, whether ET increases chemosensitivity in humans is not known.

We decided to test the hypothesis that endogenous ET plays a role in human chemoreception physiology. We assessed the effects of the nonspecific ET antagonist bosentan (Tracleer; Actelion; Basel, Switzerland) on ventilation, hemodynamics, and MSNA during normoxia and isocapnic hypoxia using a randomized, crossover, double-blinded, placebo-controlled study design. We also determined MSNA during maximal voluntary end-expiratory apneas in order to suppress the confounding effects of ventilation and the stimulation of pulmonary stretch afferents, which inhibit sympathetic nerve activity.[27]

Materials and Methods

Subjects

We were expecting a 25% difference in ventilation and MSNA with an SD of 15% between placebo and bosentan use.[28,29] As a result, we needed to include eight patients to reach a statistical power of 80%. We recruited 14 young healthy subjects (all men; age, 23 years; age range, 20 to 29 years; median age, 23 years; SD, 2.6 years) who were not receiving any medication and had normal findings on physical examination. The Ethical Committee of Erasme Hospital approved the study protocol, and written informed consent was obtained from each subject.

Measurements

We obtained continuous recordings of minute ventilation (pneumotacometer), end-tidal CO_2 (Normocap; Datex-Ohmeda; Madison, WI), O_2 saturation (Nellcor; Pleasanton, CA), heart rate (HR), and ECG (Siemens; New York, NY). Systolic arterial BP (SBP) was measured every minute during normoxia and isocapnic hypoxia (Physiocontrol BP-880 sphygmomanometer; Colin; San Antonio, TX). MSNA was recorded continuously using multiunit recordings of postganglionic sympathetic activity, which was measured from a nerve fascicle in the peroneal nerve posterior to the fibular head.[30]

Interventions

The protocol used to test the chemoreflex responses was identical to that used in previous studies.[19,28] Subjects breathed across a low-resistance mouthpiece with a nose clip to ensure exclusive mouth breathing during each sequence.

Isocapnic Hypoxia

Measurements were made after 5 min of stable baseline recordings with subjects breathing room air, followed by a period of 5 min of peripheral chemoreflex activation achieved by exposure to isocapnic hypoxia (10% O_2 in 90% N_2, with CO_2 titrated to maintain isocapnia).

Apnea

Recordings were also made during a voluntary maximal end-expiratory apnea after the baseline period and after hypoxia to correct for the possible inhibitory influence of ventilation on MSNA.[27] The duration of the apneas was not standardized because this is an important parameter affected by chemoreflex sensitivity.[29]

Measurements were made twice, on two separate days with

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