Dobutamine potentiates arterial chemoreflex sensitivity in healthy normal humans

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Dobutamine potentiates arterial chemoreflex sensitivity in healthy normal humans. We tested the hypothesis that the β1-agonist dobutamine increases peripheral chemosensitivity in a double-blind placebo-controlled randomized and crossover study. In 15 healthy subjects, we examined the effects of dobutamine on breathing, hemodynamics, and sympathetic nerve activity (measured using microneurography) during normoxia, isocapnic hypoxia (10% O2), posthypoxic maximal voluntary end-expiratory apnea, hyperoxic hypercapnia, and cold pressor test (CPT). Dobutamine increased ventilation (7.5 ± 0.3 vs. 6.7 ± 0.2 l/min, P = 0.0004) during normoxia, markedly enhanced the ventilatory (16.1 ± 1.6 vs. 14.4 ± 0.7 l/min, P < 0.0001) and sympathetic (+403 ± 94 vs. +222 ± 5%, P < 0.03) responses at the fifth minute of isocapnic hypoxia, and enhanced the sympathetic response to the apnea performed after hypoxia (+501 ± 107% vs. +291 ± 38%, P < 0.05). No differences were observed between dobutamine and placebo on the responses to hyperoxic hypercapnia and CPT. Dobutamine increases ventilation during normoxia and potentiates the ventilatory and sympathetic responses to hypoxia in healthy subjects. Dobutamine does not affect the responses to hyperoxic hypercapnia and CPT. We conclude that dobutamine enhances peripheral chemosensitivity.

Patients with severe heart failure often have mild oxygen desaturation as a result of chronic lung edema (35). The peripheral chemoreceptors, located in the carotid bodies, respond primarily to hypoxia (6, 9, 10, 21) and exert powerful effects on ventilation and on autonomic cardiovascular control (12, 30). Altered chemoreflex sensitivity to hypoxia could have clinically significant effects on breathing, hemodynamics, and neural circulatory control in patients with heart failure (29, 34). These effects may influence both stability and clinical outcome in patients with cardiorespiratory compromise. There are no studies that have assessed the influence of dobutamine on the ventilatory and sympathetic response to hypoxia in humans.

We tested the hypothesis that dobutamine increases chemoreflex sensitivity to hypoxia using a randomized, crossover, double-blinded, placebo-controlled study design in 15 healthy subjects. We examined the effects of dobutamine on ventilation, hemodynamics, and sympathetic nerve activity (SNA; using microneurography) during normoxia and isocapnic hypoxia (10% O2-90% N2). Because hyperventilation stimulates the thoracic stretch afferents, which will inhibit sympathetic nerve activity (3), we also studied the sympathetic nerve response to the interventions during spontaneous breathing and during voluntary end-expiratory apnea to suppress the inhibitory influence of ventilation and disclose the effects of chemoreflex activation without the confounding effects of ventilation.

In addition, we studied the influences of dobutamine on the responses to the cold pressor test (CPT) and hyperoxic hypercapnia. Effects of dobutamine on the responses to the CPT were examined to ensure that the changes observed were not simply due to nonspecific enhancement of responses to excitatory stimuli by dobutamine (22, 23). Hypercapnia activates the central chemoreceptors, which are located in the brain stem, whereas hyperoxia suppresses the activity of the peripheral chemoreceptors (9, 10, 15, 24, 35, 37). Effects of dobutamine on the responses to hyperoxic hypercapnia were assessed to exclude an influence of dobutamine on the central chemoreceptors.

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DOBUTAMINE INCREASES CHEMOREFLEX SENSITIVITY

METHODS

Subjects

Fifteen healthy subjects (all men, age 23 yr, range: 20–30 yr) with normal physical examination and on no medication were enrolled in the study. The Ethical Committee approved the study protocol, and informed written consent was obtained from each subject.

Measurements

We obtained continuous recordings of minute ventilation (pneumotacometer), end-tidal P CO2 (Dtex, Normocap), O2 saturation (Nellcor), and electrocardiogram (Siemens). Mean arterial blood pressure (MABP; Physiocontrol Colin BP-880 sphygmomanometer) was measured every 3 min during normoxia and every minute during hypoxia, hypercapnia, and the CPT. Muscle SNA (MSNA) was recorded continuously using multunit recordings of postganglionic sympathetic activity, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head (7).

Protocols

The protocol used to test the chemoreflex responses was identical to that used in previous studies (22, 35, 36). Subjects breathed across a low-resistance mouthpiece with a nose clip to ensure exclusive mouth breathing during all the sequences.

Infusions of dobutamine (5 μg·kg−1·min−1 in 5% glucose solution) and placebo (identical volumes of 5% glucose solution) were prepared by a research nurse. Each infusion received a random code. The investigators were unaware of the content of each infusion. A venous catheter was inserted into a basilic vein. We used a randomized, double-blind, crossover study design. We randomized both the order of the placebo and dobutamine infusions as well as the order of the breathing sequences. A recovery period of 20 min was allowed between the two infusions and between the two sequences of gas mixture exposure.

Effect of dobutamine during normoxia and isocapnic hypoxia. Ten minutes after the initiation of the dobutamine or placebo infusion, measurements were taken during a 5-min baseline period of room air breathing and during a period of 5 min of exposure to isocapnic hypoxia (10% O2 in 90% N2, with CO2 titrated to maintain isocapnia, n = 15).

Effect of dobutamine during posthypoxic apneas. Maximal voluntary end-expiratory apneas were performed at baseline and at the end of the 5th minute of hypoxia to eliminate the inhibitory influence of ventilation on chemoreflex-mediated circulatory measurements (n = 15) (3).

Effect of dobutamine during hyperoxic hypercapnia. Eleven subjects were exposed after a 5-min baseline period of room air breathing to hyperoxic hypercapnia (7% CO2 in 93% O2) for 5 min.

Effect of dobutamine on CPT. Seven subjects also underwent a 2-min CPT after a recovery period of 15 min after the last sequence of gas mixture exposure.

Data Analysis

Sympathetic bursts were identified by careful inspection of the mean voltage neurogram (33). The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute and multiplied by mean burst amplitude (in arbitrary units). The sympathetic and heart rate responses to the apneas were calculated during the entire apnea period, divided by the duration of the apnea in seconds, and subsequently multiplied by 60 to express the response in changes per minute (24, 34, 36).

Changes in SNA during hypoxia, hypercapnia, and CPT were expressed as the percentage of change from baseline. Relative increases in sympathetic activity were expressed as percent increases from the 5 preceding minutes for the apneas during normoxia and from the 5th minute of hypoxic breathing for the apneas during hypoxia. This best reflects the dynamic nature of the sympathetic responses while taking into account spontaneous fluctuations in activity.

We could not find an adequate sympathetic nerve recording site or lost the sympathetic nerve recording during one of the dobutamine or placebo sessions in several subjects. We completed technically excellent studies examining the effects of dobutamine and placebo on the sympathetic nerve response to hypoxia in nine subjects and on the responses to hypercapnia in eight subjects. SNA recordings were obtained during the CPT in three subjects (these latter data are not presented due to the small number of subjects).

Statistical Analysis

Results are expressed as means ± SE. A multiple ANOVA for repeated measurements determined whether dobutamine affected the cardiovascular and ventilatory responses to hypoxia, hypercapnia, and the CPT compared with the changes occurring during the infusion of placebo. Other comparisons were performed with Student’s paired t-tests (two tailed). Significance was assumed at P < 0.05.

RESULTS

Effects of Dobutamine During Normoxia and Isocapnic Hypoxia

Dobutamine slightly increased minute ventilation, oxygen saturation, and MABP, but did not change end-tidal P CO2 or heart rate during room air breathing (Table 1). The decrease in MSNA during dobutamine infusion failed to reach statistical significance.

Dobutamine markedly increased the ventilatory (16.1 ± 1.6 vs. 11.4 ± 0.7 l/min at the fifth minute of hypoxia, P < 0.0001 by ANOVA, dobutamine vs. placebo, respectively; Fig. 1) and the MSNA responses to hypoxia (+403 ± 94 vs. +222 ± 5% at the fifth minute of hypoxia, P < 0.03 by ANOVA, dobutamine vs. placebo, respectively; Fig. 2). MABP remained higher during dobutamine administration (99 ± 2 vs. 89 ± 3 mmHg, P = 0.01). Dobutamine did not change the fall in oxygen saturation (89 ± 1% under dobutamine vs.

Table 1. Effects of dobutamine during normoxia

<table>
<thead>
<tr>
<th>Normoxia</th>
<th>Dobutamine</th>
<th>Placebo</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation, l/min</td>
<td>7.5 ± 0.3</td>
<td>6.7 ± 0.2</td>
<td>0.0004</td>
</tr>
<tr>
<td>MABP, mmHg</td>
<td>101 ± 2</td>
<td>93 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>70 ± 3</td>
<td>72 ± 2</td>
<td>0.48</td>
</tr>
<tr>
<td>P CO2, mmHg</td>
<td>37 ± 0.5</td>
<td>38 ± 0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Sa O2 %</td>
<td>97.4 ± 0.1</td>
<td>97.1 ± 0.1</td>
<td>0.008</td>
</tr>
<tr>
<td>MSNA, au</td>
<td>244 ± 87</td>
<td>570 ± 192</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SE; n = 15 subjects except for muscle sympathetic nerve activity (MSNA) measurements, where n = 9 subjects. MABP, mean arterial blood pressure; HR, heart rate; SaO2, arterial O2 saturation.

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Effects of Dobutamine on End-Expiratory Apneas

Apneas with dobutamine were always shorter than those with placebo, both after normoxia (P = 0.02) and after hypoxia (P = 0.01; Table 2). Sympathetic activation during the apnea performed after hypoxia was expressed as the relative change from a heightened sympathetic drive induced by 5 min of sustained hypoxia. Dobutamine enhanced the MSNA response to the apnea after the fifth min of hypoxia (P = 0.04) despite the shorter duration and a lesser reduction in oxygen saturation at the end of the apnea (P = 0.02; Fig. 3).

Effects of Dobutamine During CPT

Dobutamine did not affect the ventilatory, heart rate, or MABP responses to the CPT (P > 0.57 by ANOVA).

Effects of Dobutamine During Hyperoxic Hypercapnia

MABP was higher under dobutamine than under placebo (101 ± 2 vs. 92 ± 1 mmHg, P = 0.0003). Dobutamine did not influence the ventilatory (21.8 ± 1.8 l/min under dobutamine vs. 21.6 ± 2.4 l/min under placebo, P = 0.63 by ANOVA; Fig. 4) and sympathetic responses (+228 ± 8% under dobutamine vs. +235 ± 8% under placebo, P = 0.42 by ANOVA; Fig. 5) to hyperoxic hypercapnia. Heart rate and oxygen saturation were identical under both infusions. The increase in end-tidal PCO₂ was similar under dobutamine and placebo (50 ± 0.7 vs. 51 ± 0.4 mmHg, respectively).

DISCUSSION

The novel finding of this double-blind, randomized, placebo-controlled, cross-over study was that dobutamine enhances arterial chemoreflex sensitivity in healthy subjects. This observation is supported by the following findings. First, dobutamine increased minute ventilation in normoxic healthy subjects. Second, dobutamine increased the ventilatory and sympathetic responses to isocapnic hypoxia in our subjects. Third, dobutamine attenuated their apnea duration and blunted the level of hypoxia that could be maintained during apnea, as evident by lesser falls in oxygen saturation for the apneas during hypoxia performed under dobutamine infusion. Apneas during normoxia were also shorter with dobutamine infusion in our subjects. The enhanced sympathetic response to hypoxia during dobutamine was especially evident during the end-expiratory apneas. This enhanced sympathetic response was evident despite the shorter apnea duration and the attenuated fall in oxygen saturation.

Peripheral arterial chemoreceptors have a significant physiological activity in normoxia, the so-called “resting drive” (2, 14). This “resting” chemoreflex activity was likely enhanced during dobutamine administration in the presence of normal levels of oxygen saturation.
Our data also provide evidence for an effect of dobutamine mediated through the peripheral chemoreflex because 1) dobutamine did not enhance the ventilatory response to the CPT, a nonspecific excitatory stimulus (22, 23); and 2) dobutamine did not affect ventilation when peripheral chemoreceptors were inhibited by 93% O₂ while the central chemoreceptors were activated by 7% CO₂.

These observations indicate that the effects observed under dobutamine infusion cannot be attributed to a nonspecific enhancement of ventilation or to the activation of central chemoreceptors. This permits us to conclude that the dobutamine activates the peripheral chemoreceptors in normal subjects.

The inotropic agent dobutamine raises blood pressure in control subjects (32). Increased blood pressure activates the arterial baroreflex. Baroreflex activation is a powerful inhibitor of the peripheral chemoreflex (12, 30). Remarkably, the potentiated peripheral chemosensitivity during dobutamine was evident despite the dobutamine-related rise in blood pressure and consequent baroreflex activation and chemoreflex restraint in normal subjects (12, 29, 30). Dobutamine has a dose-dependent inhibitory effect on arterial baroreflex sensitivity (32). Thus, although the increased blood
pressure would tend to inhibit the sympathetic response to hypoxia, attenuation of baroreflex sensitivity by dobutamine would reduce this effect. Nevertheless, it is important that the sympathetic response remains manifest despite the dobutamine-induced baroreflex activation. This speaks to the importance of dobutamine in enhancing the chemoreflex response to hypoxia in that the increased sympathetic activation is seen despite the higher levels of blood pressure with dobutamine.

During the apneas, other mechanisms, such as interruption of the inhibitory influence of hypoxia-induced hyperventilation on sympathetic activity (3), and further oxygen desaturation during the apneas that follow hypoxic breathing, are potent sympathetic excitatory triggers, which may further override arterial baroreflex restraint of sympathetic nerve traffic (12, 30) in the presence of an enhanced chemoreflex sensitivity.

During hypoxia, dobutamine increased the sympathetic nerve response but not heart rate response. This could be explained by the fact that dobutamine increased arterial blood pressure (32). Subsequent baroreceptor activation decreases sympathetic activity (Table 1) and limits the rise in heart rate during normoxia and hypoxia. During hypoxia, the higher blood pressure blunts any dobutamine-induced tachycardia. There is preservation of the sympathetic response because of the enhanced chemoreflex drive by dobutamine. Changes in heart rate are also limited because the primary response to hypoxia is bradycardia (4, 5).

Our observation of sensitization of peripheral chemoreceptors with dobutamine contrasts with previous evidence of chemoreflex inhibition by low-dose dopamine infusion (36, 37). Dopamine receptors are present in the carotid body and have a specific inhibitory influence on chemoreflex afferent activity in humans (9, 18, 26). Inhibitory effects of dopamine are selectively mediated by dopaminergic receptors because they are seen only at low-dose dopamine infusion directed at dopaminergic receptor stimulation (3–5 μg·kg⁻¹·min⁻¹), without stimulation of α- or β-adrenoreceptors (36, 37). These effects are not suppressed by α- or β-adrenoceptor antagonist (1, 8, 16, 18, 26–28). Conversely, β-adrenoceptor agonism with larger doses of dopamine (10–12 μg·kg⁻¹·min⁻¹) enhances the ventilatory response to hypoxia through sensitization of the peripheral chemoreceptors (37).

Potential Clinical Implications

There are several reasons to believe that our observations of increased ventilatory and sympathetic responses to hypoxia may be of clinical interest. Dobutamine is widely used in the intensive and critical care settings, particularly in patients with congestive heart failure (CHF) and cardiopulmonary compromise (20, 38). In addition, CHF patients have a high prevalence of central and obstructive apneas (25, 31), and chemoreflex-mediated sympathetic activation and vasoconstriction in response to apneic events are thought to contribute to the pathophysiology and progression of heart failure in patients with disordered breathing (17, 25). These responses to hypoxemia and apnea could be exacerbated by concomitant use of dobutamine and consequent chemoreflex potentiation. Our observations in normal subjects should therefore provide a rationale for additional studies on the effect of dobutamine on chemoreflex control in CHF patients.

In conclusion, dobutamine increases ventilation during normoxia and potentiates the ventilatory and sympathetic responses to hypoxia in healthy subjects. Dobutamine does not affect responses to hyperoxic hypercapnia and the CPT. We conclude that dobutamine enhances peripheral chemosensitivity.

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DISCLOSURES

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