Evidence that the renin decrease during hypoxia is adenosine mediated in conscious dogs

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Höhne, Claudia, Martin Otto Krebs, Willehad Boemke, Elisabeth Arntz, and Gabriele Kaczmarczyk. Evidence that the renin decrease during hypoxia is adenosine mediated in conscious dogs. J Appl Physiol 90: 1842–1848, 2001.—This study investigated whether adenosine mediates the decrease in plasma renin activity (PRA) during acute hypoxia. Eight chronically tracheotomized, conscious beagle dogs were kept under standardized environmental conditions and received a low-sodium diet (0.5 mmol·kg body wt⁻¹·day⁻¹). During the experiments, the dogs were breathing spontaneously via a ventilator circuit: first hour, normoxia (21% inspiratory concentration of O₂); second and third hours, hypoxia (10% inspiratory concentration of O₂). Each of the eight dogs was studied twice in randomized order in control and theophylline experiments. In theophylline experiments, theophylline, an A₁-receptor antagonist, was infused intravenously during hypoxia (loading dose: 3 mg/kg within 30 min, maintenance: 0.5 mg·kg⁻¹·h⁻¹). In theophylline experiments, PRA (5.9 ± 0.8 ng·ANG·I·ml⁻¹·h⁻¹) and ANG II plasma concentration (15.9 ± 2.3 pg/ml) did not decrease during hypoxia, whereas plasma aldosterone concentration decreased from 277 ± 63 to 132 ± 23 pg/ml (P < 0.05). In control experiments, PRA decreased from 6.8 ± 0.8 during normoxia to 3.0 ± 0.5 ng·ANG·I·ml⁻¹·h⁻¹ during hypoxia, ANG II decreased from 13.3 ± 1.9 to 7.3 ± 1.9 pg/ml, and plasma aldosterone concentration decreased from 315 ± 50 to 70 ± 13 pg/ml (P < 0.05). Thus infusion of the adenosine receptor antagonist theophylline inhibited the suppression of the renin-angiotensin system during acute hypoxia. The decrease in aldosterone occurred independently and is apparently directly related to hypoxia. In conclusion, it is likely that adenosine mediates the decrease in PRA during acute hypoxia in conscious dogs.

angiotensin II; aldosterone; theophylline

IN PREVIOUS STUDIES FROM OUR laboratory, performed on conscious, resting dogs kept under standardized environmental and dietary conditions, plasma renin activity (PRA) decreased regularly during acute hypoxia, despite cardiovascular signs of sympathetic stimulation (11). The underlying mechanisms are unknown. Adenosine, however, would be a possible mediator for the decrease in PRA. Adenosine is a nucleoside that was shown to increase during hypoxia (20). As discussed by Jackson (9), adenosine inhibits the adenylcyclase via the A₁ receptors located on juxtaglomerular cells and may, via this mechanism, act as a “molecular brake” on renin release (cAMP pathway = “adenosine-brake hypothesis”). In agreement with this finding, an intrarenal infusion of adenosine decreased PRA in anesthetized dogs (23).

The present study examines whether the inhibition of the A₁ receptor by a low dose of theophylline would inhibit the decrease in PRA during acute hypoxia in healthy, conscious dogs. The degree of hypoxia applied (10% inspiratory oxygen concentration) was comparable to an altitude of ~5,000 m. If food intake is uncontrolled or rich in sodium, PRA values are often very low. To prestimulate the renin-angiotensin system before the experiments, i.e., to increase PRA levels, the dogs received a low-sodium diet. Using this procedure, changes in PRA due to hypoxia and/or theophylline infusion were expected to become more apparent.

MATERIALS AND METHODS

Animals, maintenance, and diet. Eight purebred female beagle dogs (12.2 ± 0.7 kg body wt) were used for 16 experiments, i.e., two experiments were conducted on each dog. The dogs were obtained from the Central Animal Facilities of the Humboldt University in Berlin. Permission to perform the experiments was obtained from the Governmental Animal Protection Committee (AZ 0183/97).

The dogs were selected for their social behavior and tolerance to urinary bladder catheterization, as well as intravascular cannulas. They were trained for 4–5 wk to lie quietly on their right side on a padded animal table for at least 4 h. The environmental conditions were standardized: air-conditioned animal room during the day and individual kennels during the night (21°C, 55% humidity). General status, body temperature, and body weight were checked daily.

The dogs were fed a standardized low-sodium diet beginning 5 days before the experiments. The diet consisted of minced beef (12 g) and boiled rice (58 g). It contained 91 ml water, 0.5 mmol sodium, and 3.5 mmol potassium (all values given per kg body wt and day). The calories supplied with this diet (277 kJ·kg body wt⁻¹·day⁻¹) were sufficient to keep

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the dogs’ body weight constant. The food mash was offered once a day at 2:00 PM, and the intake was finished by all dogs within 1 h.

Seven days before an experiment, 150 ml of the dog’s own blood were collected via puncture of a foreleg vein and stored in a blood bag at 4°C (Biopack, Biotrans, Dreieich, Germany). Intervals between the two experiments in the same dog were at least 10 days.

**Surgical procedure for tracheotomy.** Anesthesia was induced with methohexital sodium (~8 mg/kg body wt iv) and, after tracheal intubation, maintained with isoflurane (0.8–1.5%) and nitrous oxide-oxygen (2:1). A permanent tracheotomy was performed according to a method described by others (4) with minor modifications. Antibiotic prophylaxis with 1.5 g flucloxacillin and 240 mg gentamycin per day was continued for 3 days. Postoperative analgesia was provided by 2–4 mg xylazine hydrochloride (2% Rompun; Bayer, Leverkusen, Germany). On completion of surgery, the dogs were given at least 3 wk to recover. Barking and breathing were not impaired by the tracheotomy.

The dogs received theophylline (Bronchoparat, Klinge Pharma, Harsefeld, Germany) at 3 mg/kg body wt iv) and, after tracheal intubation, with isoflurane (2%–4% 0.8–1.5%) and nitrous oxide-oxygen (2:1). A permanent tracheotomy was performed according to a method described by others (4) with minor modifications. Antibiotic prophylaxis with 1.5 g flucloxacillin and 240 mg gentamycin per day was continued for 3 days. Postoperative analgesia was provided by 2–4 mg xylazine hydrochloride (2% Rompun; Bayer, Leverkusen, Germany). On completion of surgery, the dogs were given at least 3 wk to recover. Barking and breathing were not impaired by the tracheotomy.

**Experimental protocols.** Preparation of the dogs for the experiments started at 8 AM. Body temperature and body weight were recorded. Thereafter, a self-retaining bladder catheter was inserted through the urethra. A foreleg vein was punctured, and an infusion of creatinine was started (priming dose: 1.4 g for 30 min, maintenance infusion: 4.7 mg/min). With the use of local anesthesia (1% lidocaine; Braun, Melsungen, Germany), a pulmonary artery catheter (5 F, no. 132F5; Baxter, Unterschleissheim, Germany) was inserted via the right external jugular vein, and an arterial line (20 G, no. 4235–8; Ohmeda, Erlangen, Germany) was advanced into the abdominal aorta via the femoral artery for continuous blood pressure monitoring and blood sampling. After catheter insertion, the dogs were placed on the padded animal table and positioned on their right side. The pressure transducers were adjusted to the level of the right atrium. The distance between transducer and table was recorded and also used for the next experiment in this individual dog. Finally, the tracheal tube was inserted, blocked, and connected to the ventilator set to continuous positive airway pressure mode. We used the widest tube that would fit the tracheostoma (mostly 8-mm ID) to decrease respiratory resistance. When smaller tubes are used, dead space ventilation might increase because of higher respiratory rates.

Each of the eight dogs underwent two protocols in randomized order: control experiments and theophylline experiments.

In control experiments, the dogs breathed room air (21% O2-79% N2; normoxia) for 1 h, followed by breathing of a gas mixture containing 10% O2 and 90% N2 for 2 h (hypoxia).

In the theophylline experiments, after 1 h of normoxia, the dogs received theophylline (Bronchoparat, Klinke Pharma, Munich, Germany; loading dose: 3 mg/kg body wt within 30 min, maintenance dose: 0.5 mg/kg body wt−1·h−1) during the 2 h of hypoxia.

Heart rate (HR), mean arterial blood pressure (MAP), central venous pressure, and pulmonary artery pressure (PAP) were measured continuously, and data were stored on a computer (Vectra 486, Hewlett Packard). Cardiac output was measured by using the thermodilution technique (5-ml injection volume at 5–10°C). Five consecutive measurements were performed. The highest and lowest values were rejected. The mean cardiac output was calculated from the remaining three determinations and taken for calculation of systemic and pulmonary vascular resistance (PVR) by standard formulas.

At the end of each experimental hour, blood samples were taken to determine arterial blood gases, plasma electrolytes, creatinine, and hormones. In the theophylline experiments, plasma levels of theophylline were measured. The blood withdrawn was immediately replaced with an equal amount of the dog’s own stored blood using a blood filter (TNSB-3, Biotest, Alzenau, Germany).

At hourly intervals, renal sodium, water, potassium, and creatinine excretions were measured after complete evacuation of the urinary bladder (air washout). Exogenous creatinine clearance was calculated by the standard formula to assess glomerular filtration rate (GFR).

**Assays.** Blood samples for hormone analysis were collected into precooled Na-EDTA vials and centrifuged at 4°C. The plasma was separated and stored at −22°C until analysis. Commercially available radioimmunoassay kits were used to measure PRA, ANG II, plasma aldosterone concentration (PAC), atrial natriuretic peptide (ANP), arginine vasopressin (AVP), and angiotensin-converting enzyme (ACE) activity (for details see Ref. 11). In plasma and urine, sodium, and potassium were measured by flame photometry (Photorometer Eppendorf, Hamburg, Germany), and creatinine by a creatinine analyzer (modified Jaffe reaction; Beckmann Instruments, Brea, CA). The theophylline assay utilized a fluorescence polarization immunoassay technology (Abbott Laboratories, Axysm-System, Wiesbaden, Germany). The sensitivity of the test was 0.82 ng/l.

**Statistical analysis.** All values are given as means ± SE (n = 8). Intergroup comparison, i.e., control vs. theophylline during the respective normoxia and hypoxia period, was performed using Student’s t-test. For intragroup comparison (time course), a general linear model of ANOVA for repeated measures was used (SPSS 7.5, Chicago, IL). Post hoc testing of means was performed with Student’s t-test with Bonferroni correction for multiple comparisons. Statistical significance was considered at P < 0.05.

**RESULTS**

**Minute ventilation, arterial blood gases, pH, and plasma values.** During hypoxia, arterial O2 tension decreased from ~95 to 35–38 Torr in both protocols (P < 0.05) (Table 1). During hypoxia, the arterial carbon dioxide tension decreased from 34 to 24–27 Torr in both protocols (P < 0.05), caused by an 0.8–1.4 l/min increase in minute ventilation (P < 0.05). Bicarbonate concentration (19.9–20.4 mmol/l), base excess (−5.2 to −5.7), plasma sodium concentration (141–144 mmol/l), and plasma osmolality (299–305 mosmol/l) were not different between both protocols and remained unchanged during hypoxia. Plasma potassium concentration decreased slightly during hypoxia in both control and theophylline experiments (P < 0.05).

**Plasma hormones.** PRA decreased in control experiments during hypoxia (P < 0.05) (Fig. 1). In theophylline experiments, PRA remained unchanged. The same applied to ANG II concentrations. PAC decreased in control as well as in theophylline experiments during hypoxia. Plasma concentrations of ANP (37–39 pg/ml), ACE (45–46 U/l), and AVP (0.3–1 pg/ml) were similar.
in both protocols and did not change during hypoxia in either protocol.

**Hemodynamics.** During hypoxia, MAP increased in both protocols \((P < 0.05)\) (Fig. 2). HR did not change in the control experiments but did increase in the theophylline experiments during hypoxia \((P < 0.05)\). During hypoxia, cardiac output increased by 10–20\% in both control and theophylline experiments \((P < 0.05)\) (Table 2). Central venous pressure and systemic vascular resistance were similar in both protocols and remained unchanged throughout the experiments. Mean PAP and PVR increased during hypoxia in both protocols \((P < 0.05)\).

**Renal function data.** Urine volume \((P < 0.05)\) and urinary potassium excretion increased \(-50\%\) during hypoxia in the control experiments (Table 3). In the theophylline experiments, urine volume and urinary potassium excretion \((P < 0.05)\) increased during hypoxia. Urinary sodium excretion and GFR did not change during hypoxia in either protocol.

**Theophylline plasma concentrations.** In the theophylline experiments, plasma theophylline concentrations at the end of the first and second hour of hypoxia were found to be in the same range \((4.1 \pm 0.4 \text{ mg/l})\).

**DISCUSSION**

The purpose of this study was to determine whether the decrease in PRA during acute hypoxia, which was regularly found in one of our laboratory’s previous studies \((11)\), is mediated by the nucleoside adenosine. Experiments were performed on eight trained, conscious beagle dogs. In a 3-h protocol, the dogs breathed room air during the first hour and, thereafter, a hypoxic gas mixture for the next 2 h. The results demonstrated that the decrease in PRA and ANG II during hypoxia is inhibited by administration of the adenosine receptor antagonist theophylline, whereas the PAC decreases during hypoxia independently of whether theophylline is administered or not.

The present study describes some basic physiological and pathophysiological events during acute hypoxia in conscious dogs with all of their regulatory mechanisms intact. The significance of the results obtained is a matter of speculation. A decrease in PRA and ANG II

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**Table 1. Arterial blood gases, pH, plasma potassium concentration, and minute ventilation during control and theophylline experiments**

<table>
<thead>
<tr>
<th></th>
<th>Normoxia, 1st h</th>
<th>Hypoxia, 2nd h</th>
<th>Hypoxia, 3rd h</th>
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<tbody>
<tr>
<td>(\text{Pao}_2), Torr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>95 \pm 2</td>
<td>38 \pm 2*</td>
<td>38 \pm 2*</td>
</tr>
<tr>
<td>Theophylline</td>
<td>96 \pm 2</td>
<td>36 \pm 1*</td>
<td>35 \pm 1*</td>
</tr>
<tr>
<td>(\text{Paco}_2), Torr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>34 \pm 1</td>
<td>27 \pm 1*</td>
<td>27 \pm 1*</td>
</tr>
<tr>
<td>Theophylline</td>
<td>34 \pm 1</td>
<td>25 \pm 1*</td>
<td>24 \pm 1*</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>7.35 \pm 0.01</td>
<td>7.43 \pm 0.01*</td>
<td>7.46 \pm 0.01*</td>
</tr>
<tr>
<td>Theophylline</td>
<td>7.37 \pm 0.01</td>
<td>7.45 \pm 0.01*</td>
<td>7.46 \pm 0.01*</td>
</tr>
<tr>
<td>Plasma potassium concentration, mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.8 \pm 0.1</td>
<td>3.6 \pm 0.1*</td>
<td>3.5 \pm 0.1*</td>
</tr>
<tr>
<td>Theophylline</td>
<td>3.7 \pm 0.1</td>
<td>3.7 \pm 0.1</td>
<td>3.4 \pm 0.1*</td>
</tr>
<tr>
<td>Minute ventilation, l/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.9 \pm 0.2</td>
<td>3.9 \pm 0.2*</td>
<td>4.3 \pm 0.4*</td>
</tr>
<tr>
<td>Theophylline</td>
<td>2.9 \pm 0.2</td>
<td>3.6 \pm 0.2*</td>
<td>4.1 \pm 0.2*</td>
</tr>
</tbody>
</table>

Values are means \(\pm \text{SE}; n = 8\). \(\text{Pao}_2\), arterial \(\text{O}_2\) tension; \(\text{Paco}_2\), arterial \(\text{CO}_2\) tension. Values were measured during 1 h of normoxia \((21\% \text{ inspiratory } \text{O}_2\text{ concentration})\) and 2 h of hypoxia \((10\% \text{ inspiratory } \text{O}_2\text{ concentration})\). *\(P < 0.05\) vs. normoxia.
receptor was identified in the renal cortex and medulla of the rat (28), but a connection to the renin-angiotensin-aldosterone system has not yet been demonstrated.

In the rat kidney, the A₁-receptor mRNA was localized in juxtaglomerular cells (25), i.e., the renin-secretion. Stimulation of the A₂ receptors on juxtaglomerular cells still requires evidence.

Adenosine has a considerably higher affinity to the A₁ receptor (nanomolar range) than to the A₂ receptor (micromolar range) (19). Hypoxia (8% inspiratory O₂) suppressed the renin-angiotensin system, may facilitate sodium and water excretion during hypoxia and improve oxygen transport by the resulting hemoconcentration.

During acute hypoxia, increases as well as decreases in PRA have been reported in humans as well as in animals (e.g., Refs. 10, 16, 21). However, often sodium and water intake was not controlled (21), or it was not differentiated between resting states and exercise (16). In a previous study by our laboratory in conscious dogs kept on a normal sodium diet, a decrease in PRA was regularly observed during hypoxia (11). We speculated that the underlying mediator might be adenosine.

There are basically three adenosine receptors known to date (A₁, A₂, A₃). Stimulation of the A₁ receptor decreases (8, 12), whereas stimulation of the A₂ receptors increases renin release from the kidney (3). An A₃ receptor was identified in the renal cortex and medulla of the rat (28), but a connection to the renin-angiotensin-aldosterone system has not yet been demonstrated.

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rabbit within the nanomolar range (17). Thus it seems unlikely that $A_2$ receptors are regularly involved in the control of renin release under hypoxic conditions.

Because of its very short half-life (1–3 s) (20), it is very cumbersome to determine adenosine concentrations correctly in arterial and venous renal blood of conscious animals (which would otherwise be the preferred procedure to demonstrate an increase in adenosine and a decrease in PRA during acute hypoxia). That is why we used an indirect approach to test our hypothesis. We chose theophylline, a methylxanthine, to inhibit the cell membrane-bound $A_1$ receptors (27). When theophylline is administered at a low dose, as in our experiments (plasma levels ~4 mg/l), theophylline penetration of cell membranes and consequently intracellular effects, like the inhibition of phosphodiesterase (26) or induction of renin release (9) due to an increase in intracellular calcium concentrations (27), should not become effective. The occurrence of intracellular effects has been demonstrated to be dose dependent, and a large number of studies suggest that intracellular effects of theophylline become effective only at plasma concentrations ranging between 8 and 20 mg/l (7).

PRA. By blocking the $A_1$ receptor with theophylline, the decrease in PRA and ANG II during hypoxia was abolished.

The magnitude of PRA levels is determined by a number of factors besides dietary sodium and water intake, which was strictly controlled in our study, with one of the main factors being renal perfusion pressure. An increase in renal perfusion pressure can be followed by a decrease in PRA through the renal baroreceptor mechanism, especially when the baseline blood pressures during normoxia range below the threshold pressure for the pressure-dependent renin release, which had been determined to be ~89 mmHg in conscious dogs (6). In our dogs, the average baseline MAP was 5–10 mmHg above this threshold pressure for renin release. Furthermore, the increase in MAP, when switching from normoxia to hypoxia, was almost identical in both experimental protocols (Fig. 2). Overall, the decrease in PRA during hypoxia does not seem to be tied to the increase in MAP, and thereby renal perfusion pressure, in the control dogs.

PRA may also be influenced by the activity of the sympathetic nervous system (5). The increase in HR, MAP, and cardiac output during acute hypoxia in our experiments most likely reflected hypoxic sympathetic activation (Fig. 2; Table 2). The insignificantly higher HR in theophylline experiments was possibly because of the positive chronotropic effect of theophylline through inhibition of cardiac $A_1$ receptors (20). The increase in minute ventilation during hypoxia (although less than in our laboratory’s previous study (11) because of the smaller tube size used in the former study) demonstrates chemoreceptor activation and stimulation of respiratory drive (Table 1). All of these parameters were not different between the protocols. In addition, it is generally agreed that the same degree of sympathetic stimulation must not be present in all parts of the organism, and even if there were a slight increase in renal sympathetic nerve activity, this may not necessarily be reflected in increased PRA levels (14).

Nonphysiological or otherwise extreme experimental conditions may increase “stress” and sympathetic activity and consecutively PRA and aldosterone levels tremendously. For instance, development of hypocapnic hypoxia, as observed in our study, is the normal physiological response toward hypoxia. If individuals cannot lower their arterial CO$_2$ tension (normocapnic or hypercapnic hypoxia), e.g., because of mechanical hypoventilation during anesthesia or caused by CO$_2$ admixture to the inspiratory gas (14), or if hypoxia is very severe, e.g., 7% or less inspiratory O$_2$ concentrations, renin and consecutive aldosterone concentrations may increase, e.g., via a higher degree of stress combined with extremely increased sympathetic stimulation and an increase in ACTH concentrations (18). ACTH may increase aldosterone independently from the renin-angiotensin system and was found to be increased in conscious rats, especially during normocapnic or hypercapnic hypoxia, whereas it remained in the range of control levels during hypoxia (10% O$_2$) alone (18).

Aldosterone. PAC decreased during hypoxia in both experimental protocols. The decrease may be partially mediated by the decrease in plasma potassium concentration (Table 1). Interestingly, in the theophylline experiments, plasma aldosterone decreased in the presence of unchanged PRA and ANG II concentrations. Usually, it is expected that aldosterone concentrations do not decrease when PRA levels remain constant, according to the renin-ANG II-aldosterone pathway (Fig. 1). Possibly, hypoxia inhibited the secretion of aldosterone from the suprarenal gland directly, as it has been shown that hypoxia is able to reduce 18-hydroxylase activity and the conversion from cortisol to aldosterone in zona glomerulosa cells (2). Reduced activity of the ACE during hypoxia can be ruled out as a cause for the fall in aldosterone (15). Plasma ACE concentrations in the present study remained stable. Moreover, if the conversion from ANG I to ANG II was debilitated by hypoxia, plasma ANG II concentrations should have decreased in theophylline experiments too, but they did not (Fig. 1).

An increase in ANP and AVP concentrations may also be combined with a decrease in PRA and/or PAC (9, 13). However, in our experiments, ANP and AVP did not increase.

The coupling between renin and aldosterone during hypoxia was also found altered by Vonmoos et al. (24). Different from our study, they described no change in PRA and ANG I, but a decrease in ANG II and a blunted increase in aldosterone concentrations during hypoxia in healthy human volunteers treated with a competitive dopamine antagonist. The reason for not finding a decrease in PRA and ANG I during hypoxia was most likely the very-low-PRA baseline value in their individuals, probably as a result of an unrestricted sodium intake. Our study adds to their findings in that it shows that the decrease in aldosterone
may occur independently from a decrease in the PRA and ANG II concentrations (theophylline protocol), i.e., the lower aldosterone concentration during hypoxia must not be coupled to lower ANG II concentrations.

Renal excretions. In both protocols, urine volume and potassium excretion increased by ~50% during hypoxia, whereas the sodium excretion remained in the range of the normoxia period (Table 3).

The lack of an increase in sodium excretion during hypoxia is possibly mediated by no significant effect on the pulmonary vasculature. In both protocols, changes in GFR were not responsible because GFR remained constant during hypoxia in the experiments (ketone bodies?).

Within the 2 h of hypoxia, the compensation for respiratory alkalosis by means of bicarbonate excretion, occurring as a result of the physiological attempt to compensate for the respiratory alkalosis that develops during hypoxia (Table 1). Because of the low-sodium intake, potassium cations probably had to substitute sodium cations to go with the increasingly excreted bicarbonate anions to maintain electroneutrality.


