Elevating dietary salt exacerbates hyperpnea-induced airway obstruction in guinea pigs

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Mickleborough, Timothy D., Robert W. Gotshall, Jann Rhodes, Alan Tucker, and Loren Cordain. Elevating dietary salt exacerbates hyperpnea-induced airway obstruction in guinea pigs. J Appl Physiol 91: 1061–1066, 2001.—Previous studies have indicated that increased dietary salt consumption worsens postexercise pulmonary function in humans with exercise-induced asthma (EIA). It has been suggested that EIA and hyperpnea-induced airway obstruction (HIAO) in guinea pigs (an animal model of EIA) are mediated by similar mechanisms. Therefore, the purpose of this study was to determine whether altering dietary salt consumption also exacerbated HIAO in guinea pigs. Furthermore, the potential pathway of action of dietary salt was investigated by blocking leukotriene (LT) production during HIAO in guinea pigs. Thirty-two male Hartley strain guinea pigs were split into two groups. One group (n = 16) of animals ingested a normal-salt diet (NSD) for 2 wk; the other group (n = 16) ingested a high-salt diet (HSD) for 2 wk. Thereafter, animals were anesthetized, cannulated, tracheotomized, and mechanically ventilated during a baseline period and during two dry gas hyperpnea challenges. After the first challenge, the animals were administered either saline or nordihydroguaiaretic acid, a LT inhibitor. Bladder urine was analyzed for electrolyte concentrations and urinary LTE4. The HSD elicited higher airway inspiratory pressures (Ptr) than the NSD (P < 0.001) postchallenge. However, after infusion of the LT inhibitor and a second hyperpnea challenge, HIAO was blocked in both diet groups (P > 0.05). Nonetheless, the HSD group continued to demonstrate slightly higher Ptr than the NSD group (P < 0.05). Urinary LTE4 excretion significantly increased in the HSD group compared with the NSD group within treatment groups. This study has demonstrated that dietary salt loading exacerbated the development of HIAO in guinea pigs and that LT release was involved in HIAO and may be moderated by changes in dietary salt loading.

exercise-induced asthma; sodium chloride; eicosanoids

EXERCISE-INDUCED ASTHMA (EIA) has been extensively investigated (7, 14, 28). However, the mechanism(s) unique to exercise that triggers EIA is still unknown. In previous studies, this laboratory has demonstrated that a high-salt diet (HSD) worsens and a low-salt diet (LSD) improves airway function postexercise in human subjects with EIA (18, 29). Although the mechanism(s) by which dietary salt may lead to airway reactivity changes is not yet known, possible mechanisms include a direct effect of sodium and/or chloride on bronchial smooth muscle contractility (32, 38) as well as potential enhancement of the release of mast cell-derived inflammatory mediators, possibly through airway osmolarity changes (11). Bronchial smooth muscle contraction and airway narrowing are the result of either of these events (1).

To address potential mechanisms by which dietary salt may alter the severity of human EIA, an appropriate animal model, likewise responsive to altered dietary salt, is required. Hyperpnea-induced airway obstruction (HIAO) in guinea pigs has been proposed as a potential animal model of EIA in humans (9, 36), by using responses to dry gas isocapnic hyperventilation as a surrogate for exercise challenge. However, whether or not HIAO in guinea pigs is similarly altered as in the human has not been determined. If it is, then this may provide an animal model in which to investigate dietary alterations in salt on HIAO.

One possible avenue for investigation involves bronchoactive eicosanoid mediators that are synthesized by several cell types in the airways and include the cysteinyl-leukotrienes (LTs) (leukotriene C4 and D4), which are excreted in urine as LTE4 (a stable metabolite of C4 and D4) after exercise challenge (22, 37). Leukotrienes have been found to act as mediators of HIAO in guinea pigs. Chapman and Danko (9) found that the LT receptor antagonist FPL 55712 suppressed guinea pig HIAO. In addition, Garland et al. (16) showed that both BW-755c (antagonist for both cyclooxygenase and lipoxygenase) and the LTD4 receptor antagonist ICI-198615 suppressed HIAO. Similarly, Yang et al. (42) found increased LT levels immediately after 5 min of isocapnic hyperpnea. It has been shown that, after dry gas hyperpnea, guinea pig lavage fluid contains increased LT concentrations (19). It appears that LTs can themselves elicit (2, 26) or modulate

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tachykinin release from sensory C-nerve fibers in guinea pig airways (12). It is not known, however, whether LTs are required for any effect of dietary salt loading on airway responsiveness or whether salt acts independently of the LT pathways.

Therefore, in this study, it was hypothesized that a HSD, compared with a normal-salt diet (NSD), would exacerbate HIAO, as exhibited by elevated bronchoconstriction in guinea pigs. Additionally, it was hypothesized that blocking the LT pathway with a LT biosynthesis inhibitor and lipoxygenase (LO) inhibitor, nordihydroguaiaretic acid (NDGA), would block the HIAO bronchoconstrictor response in both NSD and HSD conditions, demonstrating the requirement of an intact LT system for the salt effect to occur.

MATERIALS AND METHODS

Study design and manipulation of salt balance. Forty-two male Hartley strain guinea pigs (428–661 g) were purchased from Harlan (Indianapolis, IN). All animals were maintained in conventional laboratory animal facilities. The Animal Care and Use Committee at Colorado State University approved all procedures in this study, and animals were treated according to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals [DHHS Publication No. (NIH) 85-23, revised 1985, Office of Science and Health Reports, Bethesda, MD 20892]. Animals were housed in individual cages, permitting dietary manipulations on an individual basis.

The animals were divided into two groups. One group (n = 16) of animals ingested a NSD (0.75% salt, which is the normal salt content of guinea pig feed) for 2 wk, whereas the other group of animals (n = 16) ingested a HSD (2% salt) (BIO-SERV, Frenchtown, NJ) diet. Both groups were fed 35% of the requirement of an intact LT system for the salt exacerbation of HIAO, as exhibited by elevated bronchoconstriction in guinea pigs. Additionally, it was hypothesized that blocking the LT pathway with a LT biosynthesis inhibitor and lipoxygenase (LO) inhibitor, nordihydroguaiaretic acid (NDGA), would block the HIAO bronchoconstrictor response in both NSD and HSD conditions, demonstrating the requirement of an intact LT system for the salt effect to occur.

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A nonselective peptido-LT biosynthesis inhibitor and LO inhibitor, NDGA (Cayman Chemicals, Ann Arbor, MI), was used to block LT production and its potential effect on HIAO in guinea pigs. The two diet groups (n = 16) were further subdivided. The HSD group was divided into two groups: one group (n = 8) received NDGA (LT-LO blocked group; HSD-Blo), and the other group (n = 8) received saline (HSD-Con) in a randomized fashion and served as the control group. The NSD group was divided in an identical manner; NSD-Blo (n = 8) and NSD-Con (n = 8).

**Animal preparation.** Animals were initially anesthetized with pentobarbital sodium (Veterinary Laboratories, Lenexa, KS; 65 mg/ml) given at 45 mg/kg ip at 60% of the original dose (from a 13 ml/mg stock solution), followed 10–15 min later with xylazine (Vedco, St. Joseph, MO; 20 mg/ml) given at 7 mg/kg im at 50% of the original dose, and supplemented with local infiltration of the incision site with 0.5 ml of 2% lidocaine (Vedco; 100 mg/ml), before the surgical procedure. The anesthetic plane was maintained by boosting the animals at 5–10% of the original dose of pentobarbital sodium, as required. To assess the depth of anesthesia, heart rate (monitored noninvasively via an electrocardiogram; Space-labs, Richmond, WA; model 90603A), respiratory rate, toe pinch, movement during incision, and corneal reflex were used as a guide. The animals were placed on a heating pad (37°C) for the duration of the experiment. The linguofacial vein or carotid artery was cannulated with PE-50 polyethylene tubing to allow for the administration of drugs. A high cervical tracheostomy was performed, and the trachea was isolated and cannulated with a short piece of polyvinyl tubing (1.67 mm (0.066 in.) ID; 2.42 mm (0.095 in.) OD) attached to a 15-gauge cannula that was connected to a small-animal ventilator (Harvard rodent ventilator, model 683). The inspiratory and expiratory tubes of the ventilator were attached to the tracheal cannula through a Y-type connector with a 3-cm common segment (total dead space 0.3 ml) to minimize conditioning of inspired air. The inspiratory port of the ventilator was connected to a warmed (35–37°C) humidifier through which room air or a 50% O2-50% room air gas mixture passed. The tracheal inspiratory pressure (Ptr) was measured at the tracheal cannula with a pressure transducer (Statham P10 EZ, Gould Instrument Systems, Valley View, OH) and recorded on a chart recorder (Gilion ICT-2H Duograph, Middleton, WI) continuously, for the entire experimental procedure. Amplification of the Ptr signal was assumed to reflect increases in pulmonary system impedance, which were interpreted to indicate airway narrowing, even though other possible contributors to airway narrowing, such as microvascular leakage, were not quantified.

At the end of the protocol, the animals were euthanized with pentobarbital sodium (100 mg/kg iv). After euthanasia, two bladder urine samples (0.5–0.8 ml) were collected by needle aspiration from each animal and stored at −70°C until analysis. Urinary concentrations of electrolytes were measured by an autoanalyzer (Roche Diagnostics, Indianapolis, IN).

**Urinary LTE4 enzyme immunoassay analysis.** Urinary analysis of LTE4 was performed by the ACE competitive enzyme immunoassay (Cayman Chemical). This assay is based on the competition between LTE4 and an LTE4-acetylcholinesterase conjugate (LTE4 tracer) for a limited amount of LTE4 antiserum. A C-18 Sep-Pak light column (Waters) was used to remove proteins and organic contaminants during the preassay preparation. The concentration of each sample was determined from a standard curve ranging from 7.8 to 1,000 pg/ml. The precision of the enzyme immunoassay for LTE4 is 17.6%. Urinary LTE4 excretion is expressed as picograms per milligram urinary creatinine.

**Experimental protocol.** Initial baseline ventilator parameters were set at 60 breaths/min with a tidal volume of 3 ml and an inflation pressure of 10 cmH2O at end inspiration. During this run-in period, the animals breathed warmed and humidified room air. These ventilation conditions are referred to as “quiet breathing.” The animals were allowed 20 min to stabilize during this baseline period. A fixed volume history of each animal (total lung inflation) was obtained twice on each animal by occluding the expiratory port of the ventilator at the beginning of the run-in period.

Immediately thereafter, dry gas hyperpnea (hyperpnea challenge 1) was mechanically imposed for a period of 10 min by using dry 95% O2-5% CO2 delivered at room temperature from a balloon reservoir into the inspiratory port of the mechanical ventilator. Inspiratory inflation pressure was increased to 15 cmH2O, and breathing frequency was increased to 150 breaths/min with a tidal volume of 4 ml for the challenge. After hyperpnea challenge 1, the animals were returned to quiet breathing (posthyperpnea period 1) for 20 min by use of a humidified and warmed inspired gas mixture of 50% O2-50% room air delivered from a balloon. During this period, airway narrowing was quantified as the highest airway PVR recorded during the first 10 min posthyperpnea period. Twenty minutes after the first hyperpnea challenge, a second hyperpnea challenge (hyperpnea challenge 2) was...
Table 1. Electrolyte content of bladder urine, food consumption, and starting and ending weights after 14 days

<table>
<thead>
<tr>
<th>Diet</th>
<th>Food Consumption, g/day</th>
<th>Start of study</th>
<th>End of study</th>
<th>Na⁺, meq/l</th>
<th>Cl⁻, meq/l</th>
<th>K⁺, meq/l</th>
<th>Cr, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal salt (0.75%)</td>
<td>34.4 ± 0.08</td>
<td>393.3 ± 20.6</td>
<td>532.3 ± 16.9</td>
<td>84.9 ± 6.8</td>
<td>49.4 ± 8.0</td>
<td>126.1 ± 14.5</td>
<td>28.7 ± 2.6</td>
</tr>
<tr>
<td>High salt (2%)</td>
<td>32.6 ± 0.43*</td>
<td>373.4 ± 28.8</td>
<td>517.2 ± 20.9</td>
<td>126.8 ± 11.1†</td>
<td>93.6 ± 15.9†</td>
<td>99.5 ± 10.8</td>
<td>25.8 ± 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 16 measurements in each group. Cr, creatinine. *P < 0.001, †P < 0.05, compared with the normal-salt group.

performed in an identical fashion to the first challenge for a 10-min period, followed by 10 min of quiet breathing (posthyperpnea period 2). This second challenge permitted further evaluation of the LT system in HIAO utilizing the fewest number of animals.

To determine the effect of the LT-LO inhibitor in HIAO, 1 ml of the solution (2 mg/kg of the NDGA crystalline solid dissolved in 0.2 ml of methanol and 0.8 ml of 0.9% saline) was administered to the HSD-Blo (n = 8) or NSD-Blo (n = 8) group of guinea pigs through either a linguofacial vein or carotid artery catheter 10 min after the first hyperpnea challenge and was infused at a rate of 0.1 ml/min via a syringe pump (Cole-Parmer Instrument, Vernon Hills, IL; 74900 series multichannel syringe pump). The control groups, HS-Con (n = 8) and NS-Con (n = 8), received either 1 ml of 0.9% saline (n = 4) or 0.8 ml of 0.9% saline with 0.2 ml methanol added (n = 4).

Statistical analysis. Data were analyzed by use of the SYSTAT 8.0 statistical package (SPSS, Chicago, IL). During the initial baseline quiet breathing and posthyperpnea period 1 stage, each minute of the last 5-min time period was averaged to give a single data point for Ptr. Each minute of the 10-min hyperpnea challenges 1 and 2 was averaged to give a single data point for Ptr. In addition, Ptr was statistically analyzed every 2 min during posthyperpnea periods 1 and 2. The effects of diet and time on Ptr were analyzed by a two-way ANOVA with repeated measures across time (pre- and postchallenge) within each diet. The effects of diet, treatment (Con and Blo), and time were analyzed by a three-way ANOVA with repeated measures across time (pre- and posthyperpnea challenge) within each diet. When a significant F ratio was found (P < 0.05), a Bonferroni post hoc multiple pairwise comparison with paired t-tests was used to identify differences in group means (P < 0.05). Because there were no significant differences (P > 0.05) in Ptr noted between the NSD-Con and HSD-Con groups for saline (n = 4) and saline with methanol (n = 4), the two subgroups were pooled and analyzed as one sample population (HSD-Con or NSD-Con group). Unpaired t-tests were conducted between treatments on bladder urine electrolytes, food consumption, and body weight. In addition, differences in the urinary excretion of LTE4 between groups were compared by using paired and unpaired t-tests. Power was calculated at 0.902, using the following data: a minimum detectable difference in means = 0.02, expected standard deviation of residuals = 0.01, number of groups = 4, group size = 8, and P set at 0.05. All statistical tests of significance were set at P < 0.05. Data are expressed as means ± SE.

RESULTS

Body weights, food consumption, and bladder urine electrolyte concentrations are summarized in Table 1. Initial and final body weights among the different treatments did not differ (P > 0.05). Guinea pigs appear to have definite taste preferences, and alterations in the composition of a feed or the introduction of a new feed may result in a decline in food consumption. This may account for the fact that food consumption differed significantly between diets, with the NSD group eating significantly more than the HSD group (P < 0.001). Bladder urinary sodium and chloride concentrations were significantly higher on the HSD compared with the NSD (P < 0.001). No significant differences were noted for bladder urinary concentrations of potassium and creatinine (P > 0.05).

Baseline conditions and airway response to hyperpnea challenge 1. As shown in Fig. 1, the Ptr values for baseline ventilation and during hyperpnea challenge 1 were not significantly different between the two diet groups (P > 0.05). The pattern of the change in posthyperpnea Ptr was consistent with the development of airway obstruction in both groups (Fig. 1). On both diets, the response was similar in that the posthyperpnea Ptr showed an increase as early as 2 min after the...
Dry gas challenge and peaked at 10 min, with a gradual return to baseline values by 20 min. However, the HSD elicited significantly higher posthyperpnea Ptr than the NSD at all time periods ($P \leq 0.05$), suggesting greater airway resistance (Fig. 1).

**Airway response to hyperpnea challenge 2 after infusion of saline (Con groups).** There was no significant difference for Ptr between the HSD and NSD during the hyperpnea challenge 2 ($P > 0.05$) (Figs. 2 and 3). The time course of changes in Ptr for the Con groups is shown in Fig. 2. Both groups demonstrated significant increases ($P < 0.001$) in inspiratory posthyperpnea Ptr values at 6, 8, and 10 min compared with the Ptr value just before the hyperpnea challenge 2 for the respective diet, demonstrating airway obstruction. During this placebo (saline infusion), the HSD-Con group once again exhibited higher posthyperpnea Ptr values than did the NSD-Con group at 8 min ($P < 0.05$) and at 10 min ($P < 0.001$) (Fig. 2).

**Airway response to hyperpnea challenge 2 after infusion of LT inhibitor NDGA (Blo groups).** For the hyperpnea challenge 2, no significant differences ($P > 0.05$) were noted at prehyperpnea, during the hyperpnea challenge, or at 2 min posthyperpnea challenge between NSD-Blo and HSD-Blo (Fig. 3). As shown in Fig. 3, infusion of NDGA, a LT biosynthesis and lipoxygenase inhibitor, blocked the posthyperpnea bronchoconstriction measured in guinea pigs on both diets. Comparing the posthyperpnea Ptr response with and without NDGA infusion in both dietary groups revealed that both NDGA groups demonstrated significant reductions in posthyperpnea inspiratory Ptr values compared with the respective placebo infusion group at 6, 8, and 10 min ($P < 0.001$) (Fig. 3). For comparison, the placebo infusion posthyperpnea Ptr value from Fig. 2 at 10 min is also plotted on Fig. 3. Neither blocked group had posthyperpnea Ptr values rising above the prehyperpnea baseline values. However, the HSD-Blo group still had significantly higher posthyperpnea inspiratory Ptr values than did the NSD-Blo group at 8 and 10 min ($P < 0.05$) (Fig. 3).

**Comparison of airway responses during posthyperpnea periods 1 and 2 for Con groups.** There were no significant differences between posthyperpnea inspiratory Ptr values after hyperpnea challenges 1 and 2 for NSD-Con and HSD-Con, respectively (compare Fig. 1 with Fig. 2) ($P > 0.05$). That is, both challenges resulted in similar posthyperpnea responses for the respective dietary condition.

**Urinary LTE 4 data.** The urinary concentration of LTE4 was significantly greater on the HSD compared with the NSD in the Con group ($P < 0.001$) and in the Blo group ($P < 0.05$) (Table 2). In addition, urinary concentration of LTE4 was significantly greater in the control groups (NSD-Con and HSD-Con) compared with the blocked groups (NSD-Blo and HSD-Blo) within each diet group ($P < 0.001$) (Table 2).

**DISCUSSION**

The results of the present study confirm that a dry gas hyperpnea challenge evokes an airway obstruction...
in guinea pigs and present the novel finding that elevated dietary salt enhances HIAO. The guinea pig model for EIA may therefore be available for investigation of the mechanism of action of dietary salt on airway response to hyperventilation. Furthermore, the nonselective LO and LT biosynthesis inhibitor NDGA prevented the posthyperpnea airway obstruction in guinea pigs on the NSD and those on the salt-enhanced diet, suggesting that an intact LT system is required for HIAO and for the exacerbating action of dietary salt.

Bladder urine samples were analyzed for urinary concentration of electrolytes and demonstrated that, while on the HSD, urinary sodium and chloride concentrations were higher (126 and 93.6 meq/l, respectively) compared with the NSD (84.9 and 49.4 meq/l, respectively). There was no apparent change in glomerular filtration rate (creatinine excretion). Although it is recognized that a bladder urine sample is not representative of a 2-wk dietary protocol, it is at least indicative of the last meal eaten by the guinea pigs. In combination with the dietary data, the urine analyses strongly suggest that dietary goals were met in this study.

In this study, increases in Ptr after each hyperpnea challenge were taken to represent increased airway resistance. Clearly, the airway response to hyperpnea is a complex interaction of both tissue and airway resistance (31) and microvascular leakage (17). However, we have assumed in this study that airway obstruction after hyperpnea is largely a result of bronchial smooth muscle constriction (31), as demonstrated by morphometric studies (31), rather than of microvascular leak.

This study supports data from prior studies (30, 34, 36) that anesthetized, mechanically ventilated guinea pigs develop self-limited bronchoconstriction after dry gas hyperpnea challenge. In addition, in the present study, guinea pigs on high salt intakes had greater airway responses posthyperpnea than did those on their regular-salt diets. This was confirmed with the second hyperpnea challenge in the saline-infused, control animals, in which those on the HSD again had greater airway responses. Thus the salt effect persisted throughout the study and occurred only posthyperpnea. Ptr values during baseline and actual hyperpnea challenges were not different between the two dietary groups. These results support the contention that dietary salt acts on mechanisms unleashed during the hyperpneic challenge.

However, the present study does not provide extensive insight as to the mechanism(s) involved in translating a HSD into the increased airway response to hyperpnea. Salt could potentially interact at the level of stimulus, mediator, or response. The stimulus for HIAO is unknown but may include airway temperature changes (34) and/or injury (10, 15, 19, 33). HIAO is mediated, at least in part, via an inflammatory cascade involving LTs and tachykinins (16, 17, 23, 35, 41, 42). Additionally, these eicosanoids make an important contribution to the development of HIAO in guinea pigs (3, 13, 16, 19, 20, 23, 41). Airway narrowing in HIAO may be due to either enhanced bronchiolar smooth muscle contraction (31, 41), enhanced vascular permeability creating airway edema (17), and/or hyperpermeability resulting in vascular engorgement (27). How dietary salt possibly is involved in any or some of these probable mechanisms remains to be determined. However, the guinea pig model does appear to be appropriate to address these questions.

The present study indicates that a functioning LT system is required for dietary salt to exert its effect. The LT blocker, NDGA, blocked the HIAO response in both NSD and HSD guinea pigs. Although Ptr remained slightly higher during the posthyperpnea period in the HSD group than for the NSD group, this was likely due to the slightly higher baseline Ptr for the HSD group. It is possible that this blocker was nonspecific in its effect on airway reactivity. However, it has been demonstrated that NDGA does not have a nonspecific effect on airway function such as not altering contractile airway responses (39) in isolated guinea pig pulmonary venules or altering pulmonary hemodynamics in neonatal piglets (24, 25). Therefore, it is likely that dietary salt exerts its effect via the same LT pathways as required for HIAO to have its effect normally and does not have an independent pathway.

To attempt to determine any interaction of dietary salt on the inflammatory cascade involving LTs, post-experiment urine concentrations for LT, were determined. Although inconclusive with regard to LT production or when LT concentrations were altered during the time of the experiment, the results imply that LT production was higher in HSD guinea pigs. Furthermore, urinary LT concentrations that were lower after NDGA blockade of LT production provide indirect confirmation of the effectiveness of NDGA on LT production. Clearly, more studies are required to determine whether salt results in elevated LT production during HIAO.

The data from the present study support epidemiological evidence that, in general, the higher the salt intake within a population, the greater the prevalence and the severity of asthma (4–6), and that increased dietary salt worsens bronchiolar smooth muscle reactivity (8, 21, 40). In addition, the data support previous work performed in this laboratory that a HSD worsens and LSD improves postexercise pulmonary function in patients with EIA (18, 29). Hopefully, the guinea pig model can now be utilized to investigate the role of dietary salt in EIA.

In conclusion, although the mechanism of how dietary salt loading augments the development of HIAO in guinea pigs is unknown, this study has clearly demonstrated that increasing salt consumption in guinea pigs results in increased airway obstruction in response to hyperventilation. Furthermore, the results suggest that LT release is important in HIAO and the modification of HIAO by dietary salt. Further studies are needed to elucidate a pathway by which dietary salt loading effects such potential mechanisms, for example, airway osmolarity (initiating stimulus of EIA), inflammatory mediator release, and bronchial...
smooth muscle contraction (EIA response) to cause airway obstruction.

REFERENCES


