Eur J Appl Physiol (2001) 85: 450–456
DOI 10.1007/s004210100478

ORIGINAL ARTICLE

T.D. Mickleborough · R.W. Gotshall · E.M. Kluka
C.W. Miller · L Cordain

Dietary chloride as a possible determinant of the severity of exercise-induced asthma

Accepted: 1 May 2001 / Published online: 8 August 2001

Abstract Dietary sodium chloride (NaCl) has been shown to alter the severity of exercise-induced asthma, but it is not known if the sodium and chloride ions have independent effects in this regard. The hypothesis tested in the present study was that both a low sodium, low chloride diet and a high sodium, low chloride diet would improve post-exercise pulmonary function in subjects with exercise-induced asthma (EIA) compared to a normal NaCl diet (NSD); but that neither of these diets would have an effect on post-exercise pulmonary function in control (non-EIA) subjects. Eight subjects who suffered from EIA and eight subjects who did not (control) took part in a double-blind crossover study. Pre- and post-exercise pulmonary function was assessed after 2 weeks on a NSD, a low NaCl diet (LSD, low sodium, low chloride) or a sodium bicarbonate diet ($NaHCO_3$ diet, high sodium, low chloride). A 1 week washout period occurred between diets. Altering dietary sodium or chloride had no effect on pre-exercise (baseline) pulmonary function in either group or on post-exercise pulmonary function in control subjects. However, both the LSD and the $NaHCO_3$ diet lessened the deterioration in post-exercise pulmonary function in EIA subjects. Comparing results from pre- to post-exercise, forced expiratory volume in 1 s (FEV_1) at 15 min post-exercise differed significantly ($P < 0.05$) between diets [mean (SEM) 7 (4)% on the LSD, 14 (4)% on the $NaHCO_3$ diet, and 19 (2)% on the NSD]. Similar patterns were observed for forced vital capacity (FVC), forced expiratory flow rate at 25%–75% FVC and peak expiratory flow rate. The $NaHCO_3$ diet lessened the deterioration of post-exercise pulmonary function, but not to the extent of LSD. These data suggest that both sodium and chloride contribute to the worsening of EIA symptoms seen after consuming a normal or high NaCl diet.

Keywords Exercise induced bronchoconstriction · Dietary salt · Asthma · Metabolic acidosis · Eicosanoids

T.D. Mickleborough (✉)
School of Sport Science, Physical Education and Recreation, University of Wales Institute, Cardiff, CF23 6XD, UK
E-mail: Tmickleborough@uwic.ac.uk
Tel.: +44-2920-417077
Fax: +44-2920-416589

R.W. Gotshall · E.M. Kluka · L. Cordain
Department of Health and Exercise Science, Colorado State University, Fort Collins, CO 80523-1582, USA

C.W. Miller
Department of Physiology, Colorado State University, Fort Collins, CO 80523-1582, USA

Introduction

We have recently reported that a high NaCl diet (HSD) worsened and a low NaCl diet (LSD) improved post-exercise pulmonary function in subjects with exercise-induced asthma (EIA) (Gotshall et al. 2000; Mickleborough et al. 2000). Numerous studies have implicated dietary NaCl in the severity of asthma (Burney 1987; Burney et al. 1986, 1987; Carey et al. 1993; Javaid et al. 1988; Medici et al. 1993; Tribe et al. 1994). A few studies have been directed towards elucidating a possible mechanism whereby the sodium ion in dietary NaCl could influence airway reactivity in asthmatics (Pavord et al. 1990; Tribe et al. 1994).

Only one study (Medici et al. 1993) has attempted to evaluate an independent contribution of the chloride ion to the severity of the symptoms of asthma. 14 asthmatics were placed on HSD or high sodium citrate diets. Salt loading, regardless of type, worsened the symptoms of asthma and increased the use of inhaled steroids. They suggested that sodium is the sole mediator of the effect of NaCl on asthmatics. Any potential independent effect of chloride, separate from sodium, on EIA has not been investigated.

Chloride may exert an independent physiological effect in some pathophysiological states. In hypertension

research, there have been many studies implicating the chloride ion as the main contributor to elevated blood pressure during dietary NaCl loading. For example, sodium loading with anions other than chloride has failed to produce elevated blood pressures in models of salt-sensitive hypertension (Kurtz and Morris 1984; Shore et al. 1988). In addition, several studies of NaCl-induced hypertension have suggested that the anion in NaCl may be responsible for changes in renal acid-base balance (Batlle et al. 1994; Sharma and Distler 1994). It has been shown that a relative metabolic acidosis is present in NaCl-sensitive subjects during dietary NaCl loading, resulting in a decrease in intracellular pH ($[pH]_i$; Batlle et al. 1994; Sharma and Distler 1994; Sharma et al. 1990). This association between metabolic acidosis and hypertension may occur at the level of cells other than kidney cells (Batlle et al. 1994), such as smooth muscle cells and mast cells, which are important in the pathogenesis of EIA. It is possible that manipulation of dietary sodium salts, with or without chloride, may have differing effects on other known or possible determinants of EIA, such as the ion transport exchange systems in the plasma membrane (Pavord et al. 1990; Tribe et al. 1994) and eicosanoid (e.g. cyteinyl leukotrienes, prostaglandins and thromboxane) synthesis from mediator releasing cells in the airways (Finnerty and Holgate 1990; Finnerty et al. 1992; Freed et al. 1987).

Therefore, the present study was undertaken both to confirm the previous observations (Gotshall et al. 2000; Mickleborough et al. 2000) that altering dietary NaCl influences the severity of EIA, and to extend these data to evaluate the influence of high and low chloride diets on post-exercise bronchoconstriction in subjects with EIA. The hypothesis tested in the present study was that both a low sodium, low chloride diet and a high sodium, low chloride diet would improve post-exercise pulmonary function in EIA subjects compared to a normal NaCl diet (NSD), but that neither of these diets would have an effect on post-exercise pulmonary function in control (non-EIA) subjects.

Methods

Subjects

Eight subjects suffering from clinically diagnosed EIA, and eight subjects with no history or signs of asthma (control) volunteered for this study. The subjects were recruited from a population of university students, and each subject completed a health questionnaire and gave written informed consent to participate prior to enrolment in the study. The study was approved by the Human Subjects Committee at Colorado State University and complied with the laws of the United States of America. All EIA subjects had EIA and were free of atopic asthma as previously diagnosed by their physician. The EIA subjects had a history of post-exercise shortness of breath, and intermittent wheezing, which could be relieved by bronchodilator therapy after exercise. All EIA subjects tested positive for EIA, as indicated by a drop of greater than 10% in post-exercise forced expiratory volume in 1 s (FEV_1) compared to pre-exercise values at an initial screening test (American Thoracic Society 2000). Control subjects were free of EIA using the same criteria. Table 1 indicates that the two groups were well matched according to age and physical characteristics.

Study design

This study was conducted as a double-blind randomized crossover trial. All subjects entered the study on their NSD, which varied according to each subjects' normal dietary NaCl intake; after which they were randomly assigned to either a LSD (low sodium, low chloride) or $NaHCO_3$ diet (high sodium, low chloride) for 2 weeks. Thereafter, they followed a 1 week washout period (NSD) and then switched to the alternative diet. Throughout the study, all subjects were placed on a menu-driven diet designed to provide 1,500 mg · day^{-1} of sodium and 2,315 mg·day^{-1} of chloride, whether on the LSD or $NaHCO_3$ diet. During the $NaHCO_3$ diet, the base diet was supplemented each day with 14×1 g capsules, containing 4,000 mg of sodium and 14,370 mg of bicarbonate. However, with the LSD, subjects consumed the base diet plus placebo (sucrose) capsules. The 24 h excretion of urinary electrolytes was measured at the beginning of the study and at the end of each treatment period to monitor dietary compliance.

Protocol and measurements

Subjects were instructed to avoid any strenuous physical exertion during the 24 h prior to the exercise challenge test and to refrain from medications; the time from last dose being dependent upon the type of EIA medication in use by the EIA subject. At an initial screening and at the end of each treatment period, the subjects underwent an exercise challenge test, used regularly for the diagnosis of EIA (American Thoracic Society 2000), and were given pre- and post-exercise pulmonary function tests. All subjects were required to achieve pre-exercise FEV_1 values that were at least 80% of baseline values, achieved during screening, in order to ensure that the subjects' values were not depressed prior to exercise. Post-exercise pulmonary function tests were conducted at 1, 5, 10 and 15 min post-exercise. Pulmonary function tests were conducted on all subjects using a Sensormedics Vmax Autobox DL (Sensormedics Corporation, Yorba Linda, Calif.) and required subjects to record a total of three acceptable spirograms according to the spirometry standards of the American Thoracic Society (1995).

The exercise challenge test required each subject to run on a Quinton Treadmill (model 640, series 90, Quinton Instrument Company, Seattle, Wash.) using a standard graded protocol of incrementally increasing intensities up to 85%–90% of predicted maximum heart rate (American Thoracic Society 2000). Once the target heart rate was achieved a constant intensity protocol was applied, which required subjects to exercise at a steady state for a further 6 min at the target heart rate. At the end of the 6 min of steady-state exercise, the treadmill gradient was elevated by 1% per minute until the subject was fatigued in order to achieve an estimate of peak exercise intensity. The exercise protocol used to achieve the target heart rate differed in treadmill speed and gradient for each subject. Heart rate was determined from the electrocar-

Table 1 Subject characteristics (mean and SEM). For definitions see Table 3

Group	Gender (men, women)	Age (years)	Body mass (kg)	Height (cm)	Peak O_2 uptake ($ml \cdot min^{-1} \cdot kg^{-1}$) NSD
EIA	4,4	22.0 (1.5)	67.0 (4.0)	171.0 (2.0)	42.8 (1.4)
Control	4,4	23.0 (0.9)	68.0 (2.0)	171.0 (3.0)	54.1 (1.4)*

*$P < 0.05$, significant difference in peak oxygen uptake between EIA and control group

Table 2 Mean (SEM) 24 h urinary excretion of sodium, potassium, chloride and creatinine (milligrams per day). For definitions see Table 3

Group	LSD	NSD	$NaHCO_3$
EIA			
Sodium	1,761 (202)[a]	3,447 (220)[b]	6,266 (713)[c]
Chloride	3,043 (453)[a]	4699 (476)[b]	2722 (241)[a]
Potassium	1,833 (252)	2,183 (222)	2,141 (182)
Creatinine	1,415 (109)	1,722 (272)	1,426 (70)
24 h volume (ml)	893 (37)[a]	1146 (84)[b]	1543 (115)[c]
Control			
Sodium	1,466 (1460[a]	3,466 (222)[b]	6,260 (339)[c]
Chloride	2,805 (154)[a]	4,442 (303)[b]	2,794 (192)[a]
Potassium	1,629 (190)	1,456 (202)	1,548 (188)
Creatinine	1,470 (193)	1,543 (200)	1,656 (216)
24 h volume (ml)	1139 (139)[a]	1601 (167)[b]	2112 (204)[c]

[a,b,c]Significance, $P < 0.05$. Values with the same letter are not statistically different; differing letters show significance among values, across diets

diogram. Environmental conditions were 23°C and 50% relative humidity.

Urine analysis

The 24 h excretions of electrolytes in the urine were analysed for sodium, chloride and potassium (Beckman Astra analyser, Beckman Instruments, Inc., LaBrea, Calif.). Urinary excretion of creatinine was determined by a modified Jaffe rate reaction, using the same instrument, in order to verify the completeness of the 24 h urine samples.

Statistical analysis

Data were analysed using the SYSTAT 8.0 statistical package (SPSS Inc., Chicago, Ill.). Pre-exercise and post-exercise pulmonary function values were examined for the effect of diet (LSD, NSD, $NaHCO_3$) and for the effect of the presence of EIA by a 2-factor, repeated measures ANOVA, with both treatment and time as *within-subject* effects. A Tukey's post-hoc multiple pairwise comparison was used to isolate the differences ($P < 0.05$). The data were analysed for the presence of carry-over effects between treatments, by employing a 2×2 ANOVA crossover design. Power was calculated at 0.925, using a sample size of $n = 8$ (per group). All statistical tests of significance were set at $P < 0.05$.

Results

The control group demonstrated a significantly higher level of fitness (peak oxygen uptake, $P < 0.05$) compared to the EIA group (Table 1). Five EIA subjects were using Albuterol and three subjects Terbutaline, both of which are short-acting β_2 agonists. No EIA subjects reported any medications, such as steroids, being used for maintenance therapy. Subjects demonstrated dietary compliance with sodium enhancement on the $NaHCO_3$ diet and sodium restriction on the LSD as indicated by the 24 h urinary excretion of sodium (Table 2). Thus, a graded dose of dietary sodium was achieved in this study from 1,466–1,761 mg·day^{-1} for the LSD to 6,260–6,266 mg·day^{-1} for the $NaHCO_3$ diet. In addition, dietary chloride compliance was also successful in the current study, as there was no significant difference between the LSD (2,805–3,043 mg·day^{-1}) and $NaHCO_3$ (2,722–2,794 mg·day^{-1}); both being significantly lower than the NSD (4,442–4,699 mg·day^{-1}). There was no change in potassium excretion or glomerular filtration rate, as indicated by creatinine excretion.

No significant differences were observed in pre-exercise (baseline) pulmonary function among diets in either group (Table 3). All baseline pulmonary function values for the three diets fell within the normal parameters established for men and women at rest (Crapo et al. 1981), indicating that no airflow limitations were present.

Table 4 shows the post-exercise pulmonary function values in the control and EIA subjects. There were no significant differences in post-exercise pulmonary values by time or diet for the control subjects (Table 4). However, in the EIA subjects, the post-exercise values (Table 4) for forced vital capacity (FVC) and FEV_1 were highest for LSD and lowest for the NSD, the $NaHCO_3$ diet being intermediate. There was a significant difference between the LSD and NSD ($P < 0.05$), but not between the $NaHCO_3$ diet and the LSD ($P > 0.05$), or NSD ($P > 0.05$) in post-exercise pulmonary function in EIA subjects. The FEV_1:FVC ratio decreased on all diets post-exercise compared to pre-exercise values. However, the FEV_1:FVC ratio was not altered among diets post-exercise.

The differential effect of the percentage change in FEV_1 pre- to post-exercise in control and EIA subjects, respectively, is shown in Figs. 1 and 2. No significant differences in the percentage change in FEV_1 pre- to post-exercise were observed for the control subjects on any diet (Fig. 1). The EIA subjects (Fig. 2) demonstrated a significant reduction ($P < 0.05$) in the mean (SEM) percentage change in FEV_1 pre- to post-exercise,

Table 3 Mean (SEM) baseline pre-exercise pulmonary function in control and exercise-induced asthma (*EIA*) subjects. There were no significant differences for any variables among diets or groups. *FVC* Forced vital capacity, *FEV_1* forced expiratory volume in 1 s, *LSD* low salt diet, *NSD* normal salt diet, *$NaHCO_3$* sodium bicarbonate diet

Diet	Control			EIA		
	FVC (l)	FEV_1 (l)	FEV_1/FVC (%)	FVC (l)	FEV_1 (l)	FEV_1/FVC (%)
LSD	5.51 (0.29)	4.26 (0.21)	77.0 (2.0)	5.10 (0.25)	4.10 (0.24)	80.4 (3.0)
NSD	5.55 (0.32)	4.42 (0.39)	80.0 (3.0)	5.00 (0.29)	4.02 (0.21)	80.4 (2.0)
$NaHCO_3$	5.56 (0.28)	4.39 (0.33)	80.0 (3.0)	4.92 (0.27)	4.14 (0.23)	84.1 (3.0)

in a graded fashion from LSD [7.0 (4)%] to $NaHCO_3$ diet [14.0 (4)%] to NSD [19.0 (2)%] at 15 min post-exercise.

A 2×2 ANOVA crossover design was used to test for the presence of carry-over effects and indicated that none were present ($P > 0.05$) for all measures of lung function. In addition, there were no significant period effects or group-by-period interactions.

Discussion

This study has confirmed in a new set of subjects the previous observations (Gotshall et al. 2000; Mickleborough et al. 2000) that a LSD ameliorated the decline in post-exercise pulmonary function in EIA subjects, without any affect in non-EIA subjects. Additionally, the data indicate that a reduction in dietary chloride in the face of sodium elevation also attenuated the decrement in post-exercise pulmonary function in subjects with EIA. The current study represents the first report that dietary loading with high sodium and low chloride ($NaHCO_3$) attenuated the decrement in pulmonary function in EIA subjects, but not to the extent of a LSD (low sodium, low chloride).

These results suggest that the chloride ion is probably involved in the effect of dietary NaCl on the severity of EIA. However, it appears that the sodium ion also plays a role, as high sodium in the diet ($NaHCO_3$) prevented the attainment of the level of improvement in pulmonary function seen with a LSD. In a previous study (Gotshall et al. 2000), a HSD depressed post-exercise FEV_1 to values below that of the NSD. These data, along with the current data, imply that both elevated sodium and chloride worsen pulmonary function in EIA.

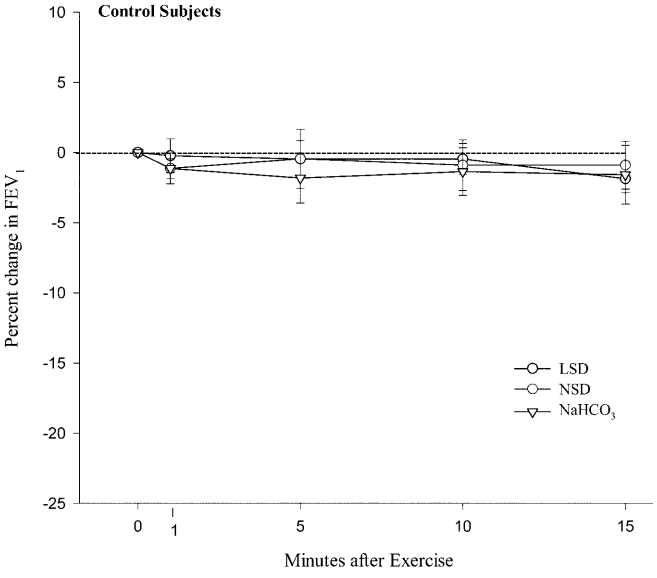

Fig. 1 The mean (SEM) percentage change in $FEV_1$from pre- to post-exercise in control subjects across the three diets. For definitions see Table 3

The biological mechanisms that might explain the role of dietary NaCl intake in airway responsiveness remain uncertain but it could be due to intrinsic alterations of cellular ion transport. It has been shown that high dietary sodium loads inhibit Na^+/K^+ adenosine triphophatase (ATPase) activity in erythrocytes of normotensive men (Weissberg et al. 1985). The mechanism of this inhibition is unclear. However, with increased sodium influx and an inhibited Na^+/K^+ ATPase, Na^+-Ca^{2+} exchange could become the predominant mechanism for restoring intracellular sodium concentrations ($[Na^+]_i$) towards normal. This in turn could lead to a

Table 4 Post-exercise pulmonary function in control and EIA subjects (mean and SEM). There were no significant differences in control subjects for post-exercise values by time or diet. For definitions see Table 3

	Control			EIA		
	FVC (l)	FEV_1 $(l)_1$	FEV_1/FVC (%)	FVC (l)	FEV_1 (l)	FEV_1/FVC (%)
LSD						
1 min	5.40 (0.26)	4.25 (0.33)	78.7 (3.0)	5.11 (0.26)*[a]	4.17 (0.25)*[a]	81.2 (3.0)*[a]
5 min	5.41 (0.28)	4.24 (0.33)	78.3 (3.0)	5.14 (0.30)*[a]	4.00 (0.25)*[a]	77.8 (4.0)*[a]
10 min	5.39 (0.32)	4.24 (0.34)	78.7 (2.0)	4.83 (0.31)*[a]	3.84 (0.23)*[a]	79.5 (3.0)*[a]
15 min	5.42 (0.32)	4.18 (0.35)	77.1 (3.0)	4.69 (0.31)*[a]	3.78 (0.23)*[a]	80.6 (3.0)*[a]
NSD						
1 min	5.42 (0.29)	4.37 (0.35)	80.6 (3.0)	4.80 (0.30)*[a]	3.78 (0.26)*[a]	78.7 (2.0)*[a]
5 min	5.44 (0.32)	4.40 (0.35)	80.9 (2.0)	4.63 (0.31)*[b]	3.47 (0.25)*[b]	74.9 (3.0)*[a]
10 min	5.42 (0.34)	4.38 (0.37)	80.8 (3.0)	4.40 (0.31*[b]	3.40 (0.24)*[b]	77.3 (3.0)*[a]
15 min	5.45 (0.31)	4.38 (0.35)	80.4 (3.0)	4.19 (0.31)*[b]	3.23 (0.22)*[b]	77.0 (2.0)*[a]
$NaHCO_3$						
1 min	5.45 (0.25)	4.34 (0.32)	79.6 (3.0)	4.96 (0.28)*[a]	4.10 (0.25)*[a]	82.7 (3.0)*[a]
5 min	5.40 (0.32)	4.31 (0.34)	79.8 (3.0)	4.87 (0.31)*[a,b]	3.90 (0.25)*[a,b]	80.0 (3.0)*[a]
10 min	5.52 (0.30)	4.33 (0.34)	78.4 (2.0)	4.57 (0.31)*[a,b]	3.62 (0.28)*[a,b]	79.2 (3.0)*[a]
15 min	5.44 (0.32)	4.32 (0.27)	79.4 (3.0)	4.56 (0.31)*[a]	3.57 (0.27)*[a,b]	78.3 (2.0)*[a]

*$P < 0.05$ Compared to respective pre-exercise value, for EIA subjects
[a,b,c]Comparisons by diet for the post-exercise time period within specific variable; different letters designate significant difference

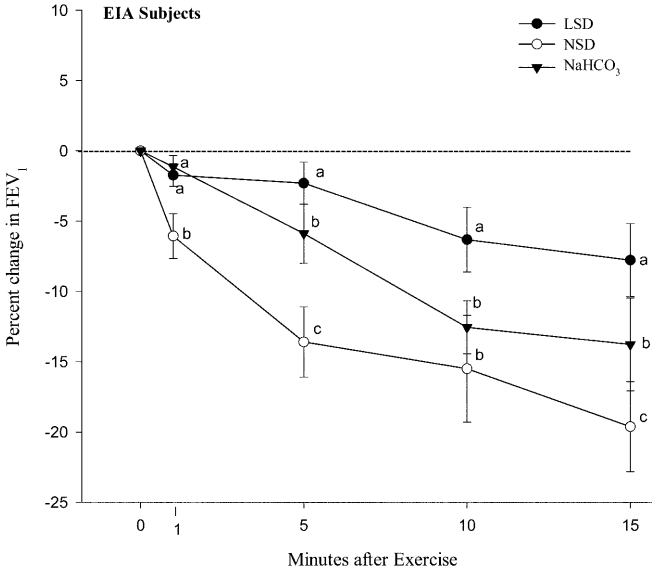

Fig. 2 The mean (SEM) percentage change in FEV_1 from pre- to post-exercise in subjects with EIA across the three diets. For definitions see Tables 1 and 3. [a,b,c]Significance, $P < 0.05$. Values with the same letter are not significantly different; differing letters show significance among values, across diets

rise in free intracellular calcium concentrations ($[Ca^{2+}]_i$), and an increase in bronchial smooth muscle contraction (Carey et al. 1993).

It is possible that the chloride ion may also play a significant role in influencing the severity of EIA. As stated above, Medici et al. (1993) substituted NaCl with sodium citrate in an equimolar concentration in 14 asthmatics. They demonstrated that while bronchial reactivity was sensitive to dietary changes in NaCl, the sodium ion, and not the chloride ion most probably mediated this effect. However, increasing evidence in several animal models has suggested that the anionic component of NaCl may contribute to hypertension (Kotchen et al. 1983; Kurtz and Morris 1984; Passmore et al. 1985; Wyss et al. 1987). Kurtz and Morris (1984) confirmed earlier studies (Passmore et al. 1985) using rats given desoxycorticosterone (DOC) that NaCl induced hypertension, while an equimolar amount of sodium in dietary $NaHCO_3$ did not. They found that replacing dietary chloride with bicarbonate without changing dietary sodium reversed hypertension induced by DOC and NaCl. These findings suggest that, in rats given DOC and a fixed amount of dietary sodium, the anionic component of the sodium salt can determine the occurrence, progression, and reversal of hypertension. Kurtz et al. (1987) and others (Luft et al. 1990; Shore et al. 1988) extended these observations to humans by substituting non-chloride salts for NaCl in the diets of salt-sensitive hypertensive men. It was shown that NaCl elevated blood pressure while the non-chloride salts did not.

Numerous studies of NaCl-induced hypertension have shown that the anion may be responsible for changes in renal-acid base homeostasis (Batlle et al. 1994; Sharma and Distler 1994; Sharma et al. 1990). These studies have shown that sodium salts such as $NaHCO_3$ and sodium citrate induce a metabolic alkalosis and do not raise blood pressure as effectively as NaCl in hypertensive individuals. This may indicate a role for the anion in the pressor effect of NaCl. It has been demonstrated (Batlle et al. 1994; Sharma and Distler 1994; Sharma et al. 1990) that a relative metabolic acidosis is present in NaCl-sensitive subjects during dietary NaCl loading with an attendant decrease in $[pH]_i$. This link between metabolic acidosis and hypertension can be envisioned at the level of cells other than kidney cells, such as smooth muscle cells and mast cells (Batlle et al. 1994), which are important in the pathogenesis of an acute bronchospasm in EIA. Manipulation of dietary sodium salts, with or without chloride, may have different effects on other known or possible determinants of EIA such as eicosanoid synthesis, and the plasma membrane Na^+/H^+ antiporter mechanism.

In lymphocytes obtained from a rat model of genetic hypertension, it has been demonstrated that increased metabolic acid production is compatible with intracellular acidosis, where reduced $[pH]_i$ stimulates the Na^+-H^+ exchange mechanism, thereby promoting cellular influx of Na^+ and increasing $[Na^+]_i$ (Batlle et al. 1994). This rise in $[Na^+]_i$ may contribute to an increase in $[Ca^{2+}]_i$ via the Na^+-Ca^{2+} exchange mechanism (Batlle et al. 1994). In addition, $[Ca^{2+}]_i$ may also be increased via Ca^{2+}-H^+ exchange (Batlle et al. 1994). It has been shown that provision of sodium as $NaHCO_3$ or sodium citrate can suppress the activity of the Na^+/H^+ antiporter by neutralizing acid overproduction generated during NaCl loading (Batlle et al. 1993, 1994). In response to a metabolic acidosis the activity of the Na^+/H^+ antiporter has been shown to increase in renal proximal cells (Preisig and Alpern 1988), platelets (Livne et al. 1987), erythrocytes (Resnick et al. 1987), and leukocytes (Batlle et al. 1990; Redon and Batlle 1994), of individuals with essential hypertension and in the NaCl-sensitive Dahl/Rapp rat.

It is conceivable that a high NaCl diet may enhance the release of eicosanoids from cells in the airways, such as mast cells, eosinophils, and alveolar macrophages. Although, extrapolation of data from cells other than inflammatory mediator cells to the pathogenesis of EIA is speculative, it is possible that a reduced $[pH]_i$, resulting in increased $[Ca^{2+}]_i$, also occurs in cells in the airways, resulting in the release of inflammatory mediators, such as histamine and cysteinyl leukotrienes. Mast cells are important in the pathogenesis of acute bronchospasm following exercise due to activation of pro-inflammatory mediators. It has been shown that mast cells contain a Na^+/H^+ antiporter (Friis and Johansen 1996; Praetorius et al. 1998), Na^+/K^+ ATPase (Cabado et al. 1998; Knudsen 1995), and that in rat peritoneal mast cells a high $[Na^+]_i$ increases $[Ca^{2+}]_i$, via inhibition of the Na^+-Ca^{2+} exchanger, resulting in histamine release (Praetorius et al. 1998). It remains to be determined the effects of dietary NaCl loading on the release of eicosanoids and histamine from mast cells in subjects with EIA.

Clearly, if $[pH]_i$ or the Na^+/H^+ antiporter is to be implicated in the pathogenesis of EIA, then HCO_3^--dependent mechanisms cannot be ignored. The tendency toward intracellular acidosis should enhance not only Na^+-H^+ exchange, but Na^+-dependent Cl^--HCO_3^- exchange as well, which defends against cell acidification by acting as a pathway for HCO_3^- entry into the cell in exchange for intracellular Cl^-. Batlle and coworkers (Batlle et al. 1990, 1993) studied the kinetic properties of both the Na^+-dependent and Na^+-independent Cl^--HCO_3^- exchangers in freshly isolated lymphocytes from rats with genetic hypertension. They demonstrated that a change in $[pH]_i$ was clearly dependent on extracellular Cl^- concentrations, such that when Cl^- was removed from the external media there was a rapid increase in $[pH]_i$, (alkalosis) due to HCO_3^- entry into the cell via the Na^+-dependent Cl^--HCO_3^- exchanger. It is conceivable that a diet high in Cl^- works in the opposite manner and reduces $[pH]_i$, thereby resulting in metabolic acidosis.

The current study did not distinguish between the potential effects of reducing the Cl^- and increasing the HCO_3^-. Clearly, in the high sodium, low chloride diet, bicarbonate intake was increased. Further studies using various anions as substitutes for chloride need to be accomplished in order to determine more fully any role of chloride per se in modifying EIA. Based on the hypertension model described above, there is at least a significant rationale for investigating the possibility.

In conclusion, while the mechanism is imprecise as to how changes in dietary NaCl affect post-exercise pulmonary function in EIA, it is apparent that in the current study the $NaHCO_3$ diet attenuated the decrement in post-exercise pulmonary function, but not to the extent of the LSD. The lowering of dietary NaCl did ameliorate the decrement in pulmonary function of EIA, but did not normalize pulmonary function in this small sample of EIA subjects. Additionally, the anion component of sodium chloride apparently was a contributor to this response. The data suggest that there must be a physiological defect present in EIA, and not in control subjects, which is modified by the ions to affect the observed changes in pulmonary function in EIA.

Acknowledgements This study was supported by a grant from the College Research Council, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.

References

American Thoracic Society (1995) Standardization of spirometry – 1994 update. Statement of the American Thoracic Society. Am J Respir Crit Care Med 152:1107–1136

American Thoracic Society (2000) Guidelines for Methacholine and Exercise Challenge Testing – 1999. Am J Respir Crit Care Med 161:309–329

Batlle DC, Saleh A, Rombola G (1990) Reduced intracellular pH in lymphocytes from the spontaneously hypetensive rat. Hypertension 15:97–103

Batlle DC, Sharma AM, Alsheikha MW, Sobrero M, Saleh A, Gutterman C (1993) Renal acid excretion and intracellular pH in salt-sensitive genetic hypertension. J Clin Invest 91:2178–2184

Batlle D, Redon J, Gutterman C, LaPointe M, Saleh A, Sharma A, Rombola G, Ye M, Alsheikha W, Gomez L, et al (1994) Acid-base status and intracellular pH regulation in lymphocytes from rats with genetic hypertension. J Am Soc Nephrol 5:S12–S22

Burney P (1987) A diet rich in sodium may potentiate asthma. Epidemiologic evidence for a new hypothesis. Chest 91:143S–148S

Burney PGJ, Britton JR, Chinn S, Tattersfield AE, Platt HS, Papcosta AO, Kelson MC (1986) Response to inhaled histamine and 24 hour sodium excretion. BMJ 292:1483–1486

Burney PG, Britton JR, Chinn S, Tattersfield AE, Papacosta AO, Kelson MC, Anderson F, Corfield DR (1987) Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. Thorax 42:38–44

Cabado AG, Vieytes MR, Botana LM (1998) Inhibition of Na+/K+ ATPase under hypertonic conditions in rat mast cells. Life Sci 63:1227–37

Carey OJ, Locke C, Cookson JB (1993) Effect of alterations of dietary sodium on the severity of asthma in men. Thorax 48:714–718

Crapo RO, Morris AH, Gardner RM (1981) Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis 123:659–664

Finnerty JP, Holgate ST (1990) Evidence for the roles of histamine and prostaglandins as mediators in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. Eur Respir J 3:540–547

Finnerty JP, Wood-Baker R, Thomson H, Holgate ST (1992) Role of leukotrienes in exercise-induced asthma. Inhibitory effect of ICI 204219, a potent leukotriene D4 receptor antagonist. Am Rev Respir Dis 145:746–749

Freed AN, Peters SP, Menkes HA (1987) Airflow-induced bronchoconstriction: role of epithelium and eicosanoid mediators. J Appl Physiol 62:574–581

Friis UG, Johansen T (1996) Dual regulation of the Na+/H+ – exchange in rat peritoneal mast cells: role of protein kinase C calcium on pHi regulation and histamine release. Br J Pharmacol 118:1327–1334

Gotshall RW, Mickleborough TD, Cordain L (2000) Dietary salt restriction improves pulmonary function in exercise-induced asthma. Med Sci Sports Exerc 32:1815–1819

Javaid A, Cushley MJ, Bone MF (1988) Effect of dietary salt on bronchial reactivity to histamine in asthma. BMJ 297:454

Knudsen T (1995) The Na+/K(+)-pump in rat peritoneal mast cells: some aspects of regulation of activity and cellular function. Dan Med Bull 42:441–454

Kotchen TA, Luke RG, Ott CE, Galla JH, Whitescarver S (1983) Effect of chloride on renin and blood pressure responses to sodium chloride. Ann Intern Med 98:817–822

Kurtz TW, Morris RC (1984) Dietary chloride and bicarbonate as determinants of desoxycortocosterone hypertension. J Hypertens 2:371–373

Kurtz TW, Al-Bander HA, Morris RC Jr (1987) "Salt-sensitive" essential hypertension in men. Is the sodium ion alone important? N Engl J Med 317:1043–1048

Livne A, Balfe JW, Veitch R, Marquez-Julio A, Grinstein S, Rothstein A (1987) Increased platelet Na+-H+ exchange rates in essential hypertension: application of a novel test. Lancet I:533–536

Luft FC, Zemel MB, Sowers JA, Fineberg NS, Weinberger MH (1990) Sodium bicarbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive man. J Hypertens 8:663–670

Medici TC, Schmid AZ, Hacki M, Vetter W (1993) Are asthmatics salt-sensitive? A preliminary controlled study. Chest 104:1138–1143

Mickleborough TD, Cordain L, Gotshall RW, Tucker A (2000) A low sodium diet improves indices of pulmonary function in exercise-induced asthma. J Exerc Physiol 3:46–54

Passmore JC, Whitescarver SA, Ott CE, Kotchen TA (1985) Importance of chloride for deoxycorticosterone acetate-salt hypertension in the rat. Hypertension 7:I115–120

Pavord ID, Dutt S, Carey OJ, Spence D, Brand S, Bing RF (1990) Red blood cell sodium transport in asthma. Thorax 45:799

Praetorius HA, Friis UG, Praetorius J, Johansen T (1998) Evidence for a Na+/Ca2+ exchange mechanism in rat peritoneal mast cells. Pflügers Arch 437:86–93

Preisig PA, Alpern RJ (1988) Chronic metabolic acidosis causes an adaptation in the apical membrane Na/H antiporter and basolateral membrane Na(HCO3)3 symporter in the rat proximal convoluted tubule. J Clin Invest 82:1445–1453

Redon J, Batlle D (1994) Regulation of intracellular pH in the spontaneously hypertensive rat. Role of bicarbonate-dependent transporters. Hypertension 23:503–512

Resnick LM, Gupta RK, Sosa RE, Corbett ML, Laragh JH (1987) Intracellular pH in human and experimental hypertension [published erratum appears in Proc Acad Sci USA (1988) Apr 85(7):2367]. Proc Natl Acad Sci USA 84:7663–7667

Sharma AM, Distler A (1994) Acid-base abnormalities in hypertension. Am J Med Sci 307 [Suppl 1]:S112–S115

Sharma AM, Kribben A, Schattenfroh S, Cetto C, Distler A (1990) Salt sensitivity in humans is associated with abnormal acid-base regulation. Hypertension 16:407–413

Shore AC, Markandu ND, MacGregor GA (1988) A randomized crossover study to compare the blood pressure response to sodium loading with and without chloride in patients with essential hypertension [published erratum appears in J Hypertens (1988) Nov 6(11):i]. J Hypertens 6:613–617

Tribe RM, Barton JR, Poston L, Burney PG (1994) Dietary sodium intake, airway responsiveness, and cellular sodium transport. Am J Respir Crit Care Med 149:1426–1433

Weissberg PL, West MJ, Kendall MJ, Ingram M, Woods KL (1985) Effect of changes in dietary sodium and potassium on blood pressure and cellular electrolyte handling in young normotensive subjects. J Hypertens 3:475–480

Wyss JM, Liumsiricharoen M, Sripairojthikoon W, Brown D, Gist R, Oparil S (1987) Exacerbation of hypertension by high chloride, moderate sodium diet in the salt-sensitive spontaneously hypertensive rat. Hypertension 9:III171–175