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Atrial Natriuretic Peptide during Exercise in Horses

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ABSTRACT Six unfit mares were subjected to maximal and steady state submaximal treadmill exercise to examine exercise-induced changes in the plasma concentration of atrial natriuretic peptide (ANP), a hormone with profound vasodilatory and renal effects, that is released by atrial stretch. In Experiment 1, ANP was measured at each step of an incremental maximal heart rate (HR) test. Exercise was started at 4 m s^{-1}, and speed was increased 1 m s^{-1} each min until HR reached a plateau. In Experiment 2, mares were randomly assigned to either an exercise (EX) or parallel control (CON) trial on day 1 and the alternate trial 1 week later. The horses ran on a treadmill, up a 6° slope, for 1 hour at 55–60% of HR_{max}. Central venous blood was collected at 0, 20, 40, and 60 min during EX or CON. Plasma was stored at −80°C and later thawed, extracted with C18 columns and assayed for ANP by a RIA kit (Peninsula Laboratories, Inc.). Plasma ANP increased 600% ($p<0.05$) from 9 ± 1 pg ml^{-1} (mean ± SE) at rest to 63 ± 14 pg ml^{-1} at HR_{max} in Experiment 1, and from 11 ± 1 pg ml^{-1} at rest to a peak of 40 ± 9 pg ml^{-1} (264%, $p<0.05$) at 40 min of EX in Experiment 2. During CON, ANP did not change ($p>0.05$) from 13 ± 2 pg ml^{-1} at 0 min. There were no significant differences among the three baseline values, observed for the two experiments. Increases in ANP concentration were highly correlated with $\%HR_{max}$ ($r=0.92$). These results suggest a potential role for increasing concentrations of ANP in the cardiovascular/renal responses to maximal and submaximal exercise in horses.

Key words Atrial natriuretic peptide; exertion; horses.

INTRODUCTION

Atrial natriuretic peptide (ANP) is a hormone produced by the heart which may be important in the regulation of blood flow distribution and blood pressure during exercise.[3,5] Granules of ANP are stored within the walls of the atria and are released during atrial stretch.[3] Receptor sites for ANP have been identified in the posterior pituitary, the kidneys, vascular smooth muscle, adrenal cortex, heart, and lung.[2] This hormone causes a rapid and profound vasodilation and a pronounced natriuresis.[1,2,3,8] Atrial natriuretic peptide inhibits vasopressin, renin, and aldosterone secretion and also inhibits the binding of aldosterone at the kidney tubule.[2,8] Specific receptors for ANP have been found in the glomeruli, the thick ascending limb, and the collecting ducts of the kidney, and renal effects of ANP have been attributed to both changes in glomerular filtration rate and changes in tubular sodium reabsorption.[1,2,3,8] Cardiovascular effects of ANP are rapid (seconds) and include vasodilation, bradycardia, and hypotension.[3,8] The action of ANP on the posterior pituitary and the kidney takes minutes,[3,8] and the circulating half-life of ANP is 1–15 min.[3,8]

At the onset of exercise, there is a significant shift of blood volume from the venous vessels to the arterial side of the circulatory system.[14,15] This increase in venous return is accompanied by simultaneous increases in blood flow to the working muscles and to cutaneous vascular beds associated with thermoregulation.[14,15]

The redistribution of blood volume and flow during exercise is facilitated by venoconstriction and arterial vasodilation.[14,15] Exercise-induced changes in vascular tone are rapid and are mediated, in part, through increases in sympathetic neural outflow to the peripheral vasculature and through local chemoreceptor mechanisms.[15] Modulation of the response involves input from both the high and low pressure baroreceptors.[14,15]

The low pressure (cardiopulmonary) baroreceptors are volume receptors located primarily within the atria and the pulmonary circulation.[15] During the onset of exercise, increased venous return results in an increase in atrial pressure and atrial stretch. Atrial stretch in turn causes a neuroendocrine response or cardiopulmonary baroreflex. Nerves within the atria serve as stretch receptors, sensing volume overload or underload. The output from these nerves is conducted centrally via vagal afferents and integrated into the central control of peripheral vascular tone.

The endocrine component of this cardiopulmonary baroreflex involves the release of ANP. Circulating ANP increases during exercise in humans;[5,7,8,11] however, there are no published data on concentrations of ANP in blood at rest or during exercise in horses.

The spleen of the horse contracts at the onset of exercise, increasing circulating blood volume by 4 to 12 l.[12,13] This volume load increases right atrial pressure from 5–10 torr at rest, to over 20 torr during the onset of exercise (McKeever, unpublished observation). Presumably this volume load also affects atrial volume and stretch as well as atrial pressure, and consequently stimulates the release of ANP.

It is well documented that plasma ANP concentration increases during maximal and submaximal exercise in humans;[4,5,7,11] thus, we hypothesized that exercise should also cause an increase in plasma ANP concentration in horses. Therefore, the primary objective of the present study was to measure ANP-like substances during graded maximal exercise in the horse.

MATERIALS AND METHODS

Six clinically normal mares ranging in age from 4 to 12 years and body weight from 427 to 560 kg were used in this study. The left carotid artery had been surgically relocated to a subcutaneous position at least 6 months prior to the experiment. The horses were accustomed to running on the treadmill, but were otherwise untrained. This experiment was performed in accordance with the Guiding Principles in the Care and Use of Animals of the American Physiological Society and regulations of the Institutional Laboratory Animal Care and Use Committee of The Ohio State University.

In Experiment 1, blood samples were collected from a jugular vein at rest and at the end of each step of an incremental maximal exercise test. During the test, heart rate (HR) was monitored using an equine HR meter (Polar Electro, Finland) and data were recorded during the last 10 seconds of each 1 min stage of the treadmill test. The horses ran on a treadmill (Sato Treadmill, Sweden) at a fixed incline of 6°. The HR_{max} test was started at a treadmill velocity of 4 m s^{-1} and speed was increased 1 m s^{-1} each min until HR reached a plateau.

The effects of submaximal steady state exercise were examined in Experiment 2. Each mare participated in two randomly ordered trials separated by no less than 7 days. An exertion trial, during which the mares ran on the treadmill for 1 hour, and a control trial, during which the mares stood on the treadmill for the same period, were conducted. The treadmill was inclined at 6° for both trials. During the exertion trial, the mares ran at a speed (previously determined during an incremental speed test) that produced HR of 55–60% of each mare's maximum HR. All trials were conducted between 0800 and 1300 hours with ambient temperatures between 5–10°C.

A catheter (Angiocath, Deseret Co, Sandy, UT) was placed in the right jugular vein for obtaining blood samples (Experiment 1). Central venous samples were obtained from a polyethylene catheter (PE 240, Becton

Table 1. *Serial dilution of extracted plasma (3 ml) collected from a horse exercised for 5 min at 80% of HR_{max}*

Column 1 represents the dilutions: 8 parts in 8 (undiluted), 4 parts in 8, etc. Data indicate the assay is linear for horse plasma

Dilution	Observed (pg ml^{-1})	Expected (pg ml^{-1})	% O/E
8 in 8	75	–	–
4 in 8	37	38	99
2 in 8	21	19	112
1 in 8	10	9	107

Dickenson & Co, Parssippany, NJ) inserted into the right atrium via the right jugular vein in Experiment 2. Blood samples (10 ml) were obtained just prior to the start of exercise and the end of each step of the incremental HR_{max} test. Blood samples were drawn at 0, 20, 40 and 60 min of exercise or parallel control in Experiment 2. The blood was placed into pre-chilled tubes and centrifuged for 20 min at 4°C. Plasma samples were stored at −80°C for later analysis.

Before thawing, 50 µl of aprotinin (0.8 mg ml^{-1}, Sigma Chemical Company, St. Louis, MO) was added to each tube of plasma (Note—a better alternative is to place 100 µl of this solution into the blood collection tubes prior to collecting the samples). Plasma for the measurement of ANP was acidified (1.0 N HCl equivalent to 10% of sample volume) and extracted onto C18 columns (Prepsep, Fisher Scientific, Pittsburgh, PA). After adsorption the sample was eluted using methanol and trifluoroacetic acid (90.0% methanol, 9.5% distilled water, 0.5% trifluoroacetic acid). The eluate was dried in a Speed Vac evaporator/concentrator (Savant Instruments, Inc., Farmingdale, NY) and then was assayed using a commercially available radioimmunoassay kit (Peninsula Laboratories, Belmont, CA) and standard RIA procedures.[5] The primary antibody for the measurement of ANP was specific for a fragment of the ANP molecule that is highly conserved in mammalian species. The standards used in the kit contain human alpha-hANP; thus, the values measured in the present study represent ANP-like or ANP immunoreactive substances. Standards and each horse plasma sample were run in duplicate. Additionally, plasma from one of the horses was spiked with 64 pg of human control ANP. These samples were extracted, assayed, and used to calculate a percentage recovery rate for the extraction procedure. The extraction recovery of known quantities of ANP was 90% and the coefficient of variability within the assay was 8%. In addition, a parallelism study was performed using 3 ml of plasma collected from an exercising horse (80% HR_{max} for 5 min). A serial dilution of the extracted plasma was made with the kit's buffer. Results contained in Table 1 indicate good linearity under dilution.

The data from Experiment 1 were analyzed with an analysis of variance for repeated measures, and post-hoc comparisons of means were made with Dunnett's test. The null hypothesis was rejected when $p<0.05$. Data from Experiment 2 were analyzed as a cross-over design by analysis of variance for repeated measures to detect significant main effects of group (exertion or control), time, and interactions between the main effects. When significant main effects or interactions were detected, a one-way analysis of variance for repeated measures was used to test each treatment group (EX or CON) over time, and Dunnett's test was used to compare exercise means to baseline control. The relationship between mean ANP concentration and mean $\%HR_{max}$ was examined by fitting data to both linear and monoexponential functions using nonlinear least squares regression. The null hypothesis was rejected at $p<0.05$. Values in the figures represent means ± standard errors of the means.

RESULTS

Heart rate data from Experiment 1 can be found in Fig. 1. Heart rate increased from

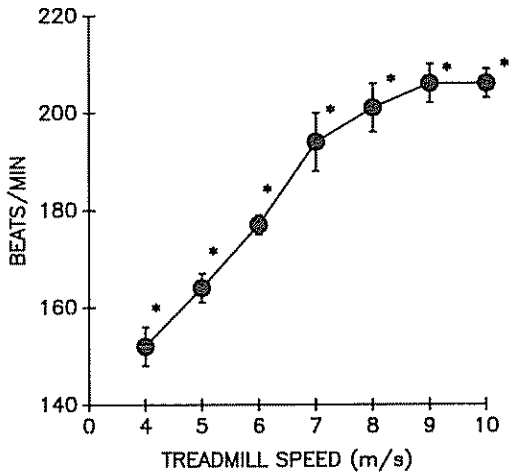

Fig. 1 Mean ± SE for heart rate response to incremental exercise. $*p<0.05$: Means within a curve significantly different from resting control. Values reported correspond to treadmill speeds from 4 to 10 m s^{-1}. Resting mean was 39 ± 2 beats min^{-1}.

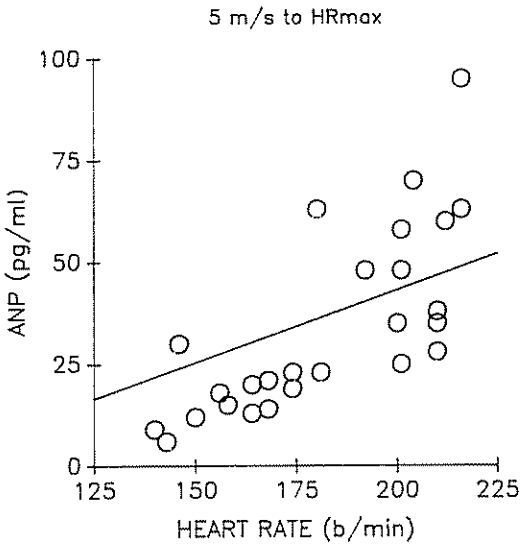

Fig. 3. Scatter plot and regression line for atrial natriuretic peptide vs. heart rate during the incremental exercise test. Values reported correspond to treadmill speeds from 4 m s^{-1} to 10 m s^{-1} (HR_{max}).

40 ± 2 beats min^{-1} at rest to a mean of 206 ± 4 beats min^{-1} (HR_{max}) at 9 m s^{-1} (Fig. 1). Plasma ANP increased 600% ($p<0.05$) in a linear fashion with increasing work intensity, from 9 ± 1 pg ml^{-1} at rest to 63 ± 14 pg ml^{-1} at 9 m s^{-1} (Fig. 2). Atrial natriuretic peptide increased during steady state submaximal exercise, from 11 ± 1 pg ml^{-1} at rest to a peak of 40 ± 9 pg ml^{-1} (264%, $p<0.05$) at 40 min and remained elevated through 60 min of exertion. During parallel control, ANP did not change ($p>0.05$) from 13 ± 2 pg ml^{-1} at 0 min. There were no significant differences among the three baseline values observed for the two experiments. Mean ANP concentration was strongly correlated with mean HR (Fig. 3; $r=0.91$) and mean $\%HR_{max}$ (Fig. 4; $r=0.92$). The relationship between ANP concentration and $\%HR_{max}$ was not better described by an exponential function ($p>0.10$, $r=0.97$).

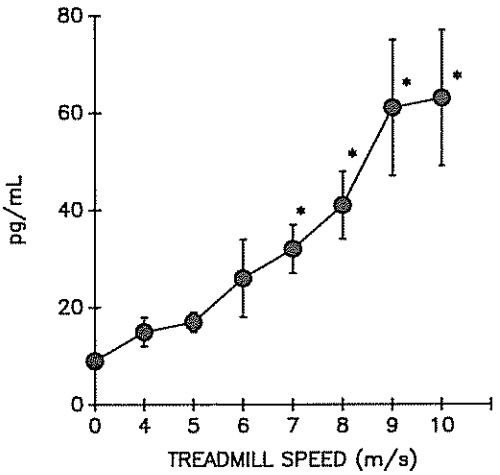

Fig. 2 Mean ± SE for plasma atrial natriuretic peptide response to incremental exercise. $*p<0.05$: Means within a curve significantly different from resting control.

DISCUSSION

The present study is the first to quantify plasma immunoreactive-ANP in resting and exercising horses. Resting concentrations of circulating immunoreactive ANP of 9 to 11 pg ml^{-1} in the horse are similar to the 9 to 20 pg ml^{-1} reported for humans.[5,6,11] The observation of a linear increase in plasma ANP

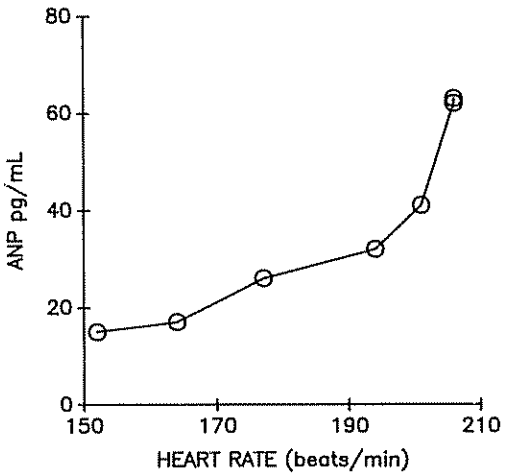

Fig. 4 Mean plasma atrial natiuretic peptide vs. mean hart rate during the incremental exercise test. Values reported correspond to treadmill speeds from 4 to 10 m s^{-1}.

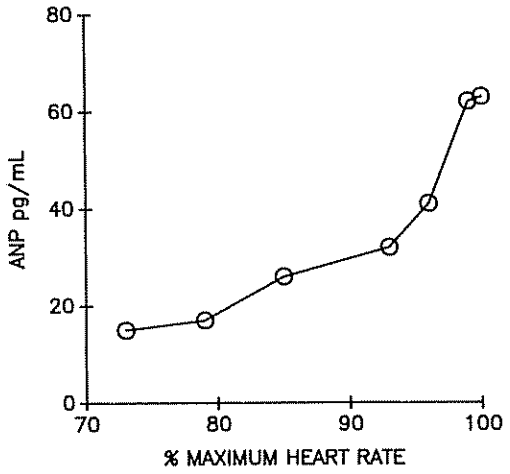

Fig. 5 Mean plasma atrial natriuretic peptide vs. mean percent of maximum heart rate during the incremental exercise test. Values reported correspond to treadmill speeds from 4 to 10 m s^{-1}.

during most of an incremental maximum heart rate exercise test suggests a relationship between plasma ANP concentration and work intensity. Such a relationship has not, to our knowledge, been reported in horses. The plasma concentration of immunoreactive ANP in the horses of the present study was 63 pg ml^{-1} during the final step of HR_{max} test. This is similar to the 75 to 82 pg ml^{-1} and 70 pg ml^{-1} reported for maximally exercised humans.[5,11] Interestingly, ANP rose in a linear fashion with increasing treadmill speed (i.e. work intensity). Plasma ANP also appears to increase linearly with HR (Fig. 3) and percentage of HR_{max} (Fig. 4). However, at approximately 90–95% of HR_{max} the relationship between HR and ANP becomes curvilinear up to HR_{max}, where both HR and ANP reached plateaus. The relationship between HR and ANP concentration may only be relevant over the linear range identified in Fig. 4. This relationship is being examined to determine relevance to aerobic performance in the horse.

In humans, ANP increases during dynamic submaximal cycle exercise[7] and steady state (75% $\dot{V}O_{max}$) submaximal exercise,[4] but not during isometric exercise.[7] The hemodynamic responses to submaximal exercise have been investigated extensively in the horse; however, no work has been published on the effects of submaximal exercise on ANP in the horse. During the steady state exercise performed in Experiment 2 (55–60% HR_{max}), plasma ANP increased to a plateau at approximately 63% of the maximum level observed during Experiment 1. Mean ANP is highly correlated with both mean HR (Fig. 3, $r=0.91$) and mean $\%HR_{max}$ (Fig. 4, $r=0.92$). The relationship between ANP and HR appears to be linear over most of the incremental HR_{max} test. In humans, ANP concentration has been correlated ($r=0.96$) with increased HR during dynamic cycling exercise.[7] Similarly, the concentration of ANP attained during steady state exercise in horses appears to be dependent upon the percentage of HR_{max}.

As this is the first study to document plasma concentrations of ANP in the horse, we decided that it would be prudent to collect parallel control data on horses standing on the treadmill. Resting plasma ANP concentrations appeared to be similar in both experiments. The plasma ANP concentrations did not change during parallel control, indi-

cating that the increase seen during exercise was not caused by upward drift in response to some perturbation not associated with exertion. Studies involving humans have not had parallel control trials; thus, interspecies comparisons regarding drift cannot be made.

On a practical level, ANP may be involved in accommodating the exercise related shifts of blood volume in the horse. This fluid shift may play a role in the onset of exercise-induced pulmonary hemorrhage (EIPH),[9] a pathological problem which affects many horses in competition.[10]

A fragment of the ANP molecule has been tested in humans for the treatment of hypertension, ascites associated with heart failure, and renal disorders. Atrial natriuretic peptide lowers vascular fluid volume and decreases vascular resistance—actions similar to those caused by furosemide, a drug currently used to treat humans with the aforementioned conditions and horses with EIPH. Atrial natriuretic peptide is a naturally occurring agent which may be useful for the treatment of epistaxis in racehorses. Future research should correlate hemodynamic changes and ANP during exercise.

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Effects of Exercise on Plasma Concentrations of Prostaglandins and Thromboxane B_2

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ABSTRACT. Plasma concentrations of prostaglandins (6-keto-PGF_{1a}, PGF_{2a}, PGE) and thromboxane (TXB_2) were measured in 5 Thoroughbred horses running on a level treadmill. The exercise protocol was a 3 min warm up (4 m s^{-1}), a 3 min rest, 2 min at 4 m s^{-1}, 2 min at 7 m s^{-1}, and 3 min at a speed eliciting a maximum rate of O_2 consumption ($\dot{V}_{O_2}$max) (14–16 m s^{-1}). Horses walked (1.5 m s^{-1}) for 30 min at the end of the exercise period. Blood samples were drawn from the pulmonary artery prior to the warm up, at the ends of the 7 m s^{-1} and $\dot{V}_{O_2}$max runs, and 15 min into the post-exercise period. Prostanoid concentrations in these blood samples were measured by radioimmunoassay. Concentrations of 6-keto-PGF_{1a} were elevated above resting values in all samples. The concentration of TXB_2 was significantly greater at the end of the post-exercise period than at all other sample times, while PGE and PGF_{2a} concentrations were unchanged throughout the experiment. The effects that these changes in the concentrations of prostanoids during exercise may have on cardiovascular function remains to be elucidated.

Key words: Horses; prostaglandins; thromboxane; exercise.

INTRODUCTION

Arachidonic acid (AA) derivatives exert a number of important biological effects. Leukotrienes, products of the action of lipoxygenase on AA, affect primarily the immune system,[24] particularly by acting as chemotactic agents for leukocytes and causing increased vascular permeability.[3] The latter action may be important in inflammation by enhancing the potential for movement of compounds into and out of capillaries. The present study concentrated solely upon the prostanoids, AA products resulting from the action of cyclo-oxygenase.

In addition to well documented effects on the reproductive system[16] and platelet aggregation,[2] prostanoid actions on various portions of the cardiovascular system have received much attention.[1,15] It has been demonstrated that prostaglandins (PG) of the E series, especially PGE_2, and PGI_2 (prostacyclin) can act as vasodilators.[9] These actions have been observed on arterioles, as well as post-capillary venules. Conversely, PGF compounds have been shown to cause constriction of venules and veins.[24] Thromboxane compounds act in platelet aggregation, and can also cause vasoconstriction.[6,9] Studies using specific inhibitors of cyclo-oxygenase have demonstrated only slight changes in the resting blood pressures of normotensive or hypertensive humans.[24] In hypotensive states, however, these inhibitors tend to improve circulation and survival.[8] While these observations lead to much speculation, the exact role that these effects have upon the regulation of blood pressure and regional blood flow has yet to be elucidated.

The potential for direct relationships existing between prostanoid concentrations and alterations in various cardiovascular parameters raises a question as to the role of these interactions during exercise, when changes in the cardiovascular parameters