Effects of Cardiac Hormones on Arterial Pressure and Sodium Excretion in NPR_A Knockout Mice

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These studies were designed to determine if the atria contains natriuretic substances that act through a non–natriuretic peptide type A (NPR_A) receptor mechanism. C57BL/6 mice, either wild-type NPR_A++ (WT) or NPR_A -- knockout (KO), were anesthetized with pentobarbital. Catheters were placed in the trachea, carotid artery, jugular vein, and bladder. Urine was collected for six 30-min periods. Both groups received an iv injection of 100 ng of rat atrial natriuetic peptide (rANP) in 200 μl of saline after the first period (30 mins) and 200 μl of rat atrial extract after the fourth period (120 mins). ANP injection increased urine flow (UF) to 2.7 ± 0.5 μl/min in the WT versus 1.9 ± 0.2 in KO. Extract increased UF to 7.9 ± 1.5 μl/min in WT versus 2.7 ± 0.4 in KO ($P < 0.01$). ANP increased sodium excretion (ENa) to 0.47 ± 0.10 μmoles/min in WT versus 0.27 ± 0.04 in KO ($P < 0.05$). Extract increased ENa to 1.44 ± 0.47 μmoles/min in WT versus 0.26 ± 0.06 in KO ($P < 0.05$). Extract decreased mean arterial pressure (MAP) to 62 ± 3 mm Hg in the WT versus 81 ± 5 in KO ($P < 0.01$). ENa and MAP responses to extract in KO were not different from responses to 200 μl of saline. A constant 150-min infusion of rat atrial extract increased urine flow by 3-fold and ENa by 5-fold (both $P < 0.05$) in the WT mice but had no significant effect in the KO mice. Thus, acute renal and MAP responses to atrial extracts require the NPR_A receptor. Exp Biol Med 229:813–818, 2004

Key words: ANP; atrial extracts; sodium excretion; furosemide

Introduction

Several peptides produced in the heart have been shown to play important roles in regulating blood volume and blood pressure and to be involved in a number of pathological conditions such as heart failure and hypertension (1). More than 20 years ago, de Bold *et al.* (2) first showed that crude extracts of rat atria produced a striking natriuresis and diuresis when injected into anesthetized assay rats and, in addition, lowered arterial blood pressure. The first substance isolated from these tissue extracts was a 28-amino-acid peptide termed atrial natriuretic factor, which has been more recently referred to as atrial natriuretic peptide (ANP) (3).

There is clear evidence that ANP plays an important role in the regulation of blood pressure and sodium balance. ANP is secreted by the atria in response to mechanical stretch (4) produced by changes in blood volume or arterial pressure (5, 6). Antibodies directed against ANP have been shown to attenuate the renal responses to acute volume expansion (7, 8) and to exacerbate volume dependent forms of hypertension (9). ANP transgenic mice with increased plasma ANP levels show chronic hypotension (10), whereas ANP deficient mice (11, 12) and ANP gene knockout mice (13) exhibit fluid retention and hypertension. Hypertension is also seen in mice with increased ANP clearance receptors and reduced plasma ANP levels (14). More recently, introduction of the ANP gene, to increase the endogenous plasma levels, has been used to treat experimental forms of hypertension (15).

Most, if not all, of the actions of ANP can be attributed to the natriuretic peptide type A receptor (NPR_A), which exists in many tissues including heart, brain, blood vessels, and kidney (16). Several members of the natriuretic peptide family including brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and Dendroaspis natriuretic peptide (DNP) also exert at least part of their actions through this receptor mechanism via activation of cyclic GMP (16). In blood vessels, activation of NPR_A results in vasodilation. In the kidneys, an increase in glomerular filtration rate (GFR) and inhibition of sodium channels in the medullary collecting duct with a resulting marked increase in salt and water excretion are observed (2).

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An important question that remains concerns the possibility of other natriuretic factors in the heart; in other words, substances other than the ANP natriuretic peptide family. Clearly, the natriuretic and diuretic responses to volume expansion or exogenous ANP are attenuated in NPR_A knockout mice (17). Because members of the ANP family appear to act, at least in part, through NPR_A, the ability of NPR_A knockout mice to respond to crude atrial extracts would suggest the existence of such factors. In the current study, we administered crude atrial extracts to both wild-type and NPR_A knockout mice to determine if other natriuretic substances might be present in the heart.

Materials and Methods

The generation of NPR_A knockout mice has previously been described in detail (13). Briefly, a targeting construct was designed to insert a disruptive neomycin resistance gene into exon 4 of the mouse NPR_A gene (*Npr1*) in embryonic stem cells of mouse strain 129/SVJ. Chimeric male mice harboring the mutation were then mated to female mice of strain C57BL/6J. Heterozygotes were intercrossed to generate genotypes (+/+; +/–; –/–). Animals were obtained from our resident colony that was founded with pathogen–free breeding pairs (a generous gift of Dr. David Garbers, University of Texas Southwestern Medical Center). The genotypes are identified by polymerase chain reaction (PCR) assay of genomic DNA from tail snips soon after infants are weaned. The wild–type primers produce a 500–bp product in the (+/+) mouse, the mutant primers produce a 650-bp product in the (–/–) mouse, and both products are present in the (+/–) mouse. All mice were genetically monitored by PCR of tail–snip DNA (13).

Mice of either sex weighing between 22 and 32 g (age approximately 6 weeks) were used for all experiments. Except for an elevated blood pressure and cardiac hypertrophy in the knockout mice, both the wild-type and knockout mice remain healthy for at least 5 months (13). All available evidence suggests that the cardiovascular and renal responses of the heterozygous mice are between the wild-type and knockout mice (13). Therefore, because the use of the heterozygous mice would add very little to the current study, the experiments only employed wild-type and knockout mice to obtain a definitive answer.

The animals were anesthetized with sodium pentobarbital that was diluted 1:5 from a stock solution of 50 mg/ml. The mice were given 90 μl of the diluted solution per 10 g of body weight intraperitoneally (90 mg/kg). Supplemental doses of the diluted pentobarbital of 10–30 μl were given intraperitoneally as needed throughout the experiment. Following a tracheotomy, catheters were placed in the right jugular vein and right carotid artery for infusions and blood pressure measurements and in the bladder for urine collections. For the jugular vein, standard PE10 tubing was used. For the carotid artery, a 5–cm piece of medical grade PTFE Sub-Lite tubing, i.d. 0.006 in., o.d. 0.012 in. (Braintree Scientific, Inc, Braintree, MA), was glued to a 30-cm piece of standard PE50 tubing. For the bladder, a hole was cut in the apex and the catheter inserted up to the neck and secured with 2–0 suture. An 8- to 10-cm piece of PE10 was glued to a 1-cm piece of PE50 and the end of the PE50 flared with heat to create a lip to help hold the catheter in place.

Following these surgical preparations, the mice received 400 μl of 0.9% saline followed by a constant infusion at a rate of 5 μl/min for the remainder of the study. The infusion consisted of 0.9% NaCl for the 60-min equilibration period and the first 30–min urine collection period (control period). Arterial blood pressure and heart rate were monitored continuously via the carotid catheter and recorded on a data acquisition system (DATAQ Instruments, Akron, OH) for later analysis.

The acute injection experiments consisted of six 30-min urine collection periods (180 mins total). All acute ANP injections were made after the first period followed by three 30-min observation periods. Atrial extract was injected at 120 mins, followed by two more observation periods. Isotonic saline was infused throughout these experiments at 5 μl/min.

The infusion experiments also consisted of six 30-min urine collection periods. After the first control period, an infusion of atrial extract replaced the saline infusion and was also given at 5 μl/min. The infusion was maintained for the remainder of the experiment (150 mins). Crude rat atrial extract was prepared by a similar method used in the original study by de Bold et al. (2). Rats were anesthetized with sodium pentobarbital (100 mg/kg) and the hearts removed. The atria were dissected and pooled (approximately 0.5 g of tissue). The atrial tissue was ground for 5 mins in a glass tissue grinder with 3.5 ml of phosphate-buffered saline (pH 7.4) and the suspension spun at 3000 rpm for 10 mins, 4°C. The supernatant was removed and spun again at 4000 rpm for 5 mins, 4°C. The supernatant was diluted 1:5 with Krebs and stored in 500 μl aliquots at –80°C. The same pool was always used for any given set of experiments.

At the end of several experiments, the loop diuretic furosemide was injected to determine if the knockout mice (n = 3) were as capable of increasing the urine flow and sodium excretion as the wild-type (n = 3) in response to a mechanism that does not depend on the NPR_A receptor. For these experiments, the 30-min urine collection period proceeding the furosemide injection was compared to the two 30-min periods immediately after the injection.

Urine was collected in preweighed tubes and the urine volume for each 30-min period determined gravimetrically. Plasma and urine sodium and potassium concentrations were measured by flame photometry (Instrumentation Laboratories 943, Lexington, MA). ANP (rat) and the loop diuretic furosemide were obtained from Sigma Chemical Company (St. Louis, MO).

Statistics. The data are illustrated as mean ± SEM and were evaluated using an analysis of variance with a

repeated measures design for within group comparisons. Student t test was used for all between group comparisons. In all cases, $P < 0.05$ was considered the criterion for statistical significance.

Results

Figure 1 compares the effects of bolus injections of both 100 ng ANP injection and rat atrial extract on mean arterial pressure (MAP), urine flow, and sodium excretion in the wild-type and knockout mice. MAP decreased in the NPR_A wild-type mice with the ANP injection (30 mins, 57 ± 3 mm Hg) but did not appear to change appreciably in the NPR_A knockout mice (30 mins, 71 ± 6 mm Hg) with a statistically significant difference between the groups ($P < 0.05$). The injection of rat atrial extract produced a marked decrease in MAP in the wild-type mice with a maximum decrease at 150 mins to 62 ± 3 mm Hg compared to knockout mice MAP of 81 ± 5 mm Hg ($P < 0.05$). In fact, MAP tended to increase in the knockout mice with the atrial extract injection. Both urine flow and sodium excretion tended to increase more in the wild-type mice compared to the knockout mice, but only sodium excretion was significantly different between the groups for the 30- to 60-min collection period (wild-type, 0.45 ± 0.12 vs. knockout, 0.22 ± 0.03 μmoles/min; $P < 0.05$). Injection of atrial extracts resulted in a dramatic increase in both urine flow and sodium excretion in the wild–type mice but not in the knockout mice (Fig. 1). For the largest change (120–150 mins urine collection), urine flow was 7.9 ± 1.5 μl/min in wild-type mice compared to 2.7 ± 0.4 μl/min in knockout mice ($P < 0.05$), whereas the rate of excretion of sodium was 1.44 ± 0.47 μmoles/min in the wild-type mice compared to 0.26 ± 0.06 μmoles/min in the knockout mice ($P < 0.05$).

Heart weight (Fig. 2, upper panel) was significantly greater in the knockout ($n = 9$) mice compared to the wild-type ($n = 11$) mice (139 ± 13 vs. 103 ± 6 mg, $P < 0.05$). Body weights were not significantly different between the groups (middle panel; knockout, 25 ± 5 vs. wild-type, 25 ± 4 g). Heart weight to body weight ratio, shown in the lower panel, was significantly greater in the knockout mice compared to the wild-type mice (5.4 ± 0.2 vs. 4.1 ± 0.1, respectively, $P < 0.001$).

Furosemide injection (Fig. 3; $n = 3$ for both groups) increased urine flow and sodium excretion 4-fold in both wild–type and knockout mice with no significant differences between the groups.

Rat atrial extract was also infused intravenously at a rate of 5 μl/min for 150 mins in 5 knockout and 6 wild-type mice (Fig. 4). MAP was significantly greater in the knockout mice (75 ± 5 mm Hg) compared to the wild-type mice (61 ± 2 mm Hg) during the first baseline period (15 mins, $P < 0.05$). MAP tended to be higher in the knockout mice than the wild-type during the remainder of the experiment, but the differences were not significant. Both urine flow and sodium excretion rate increased

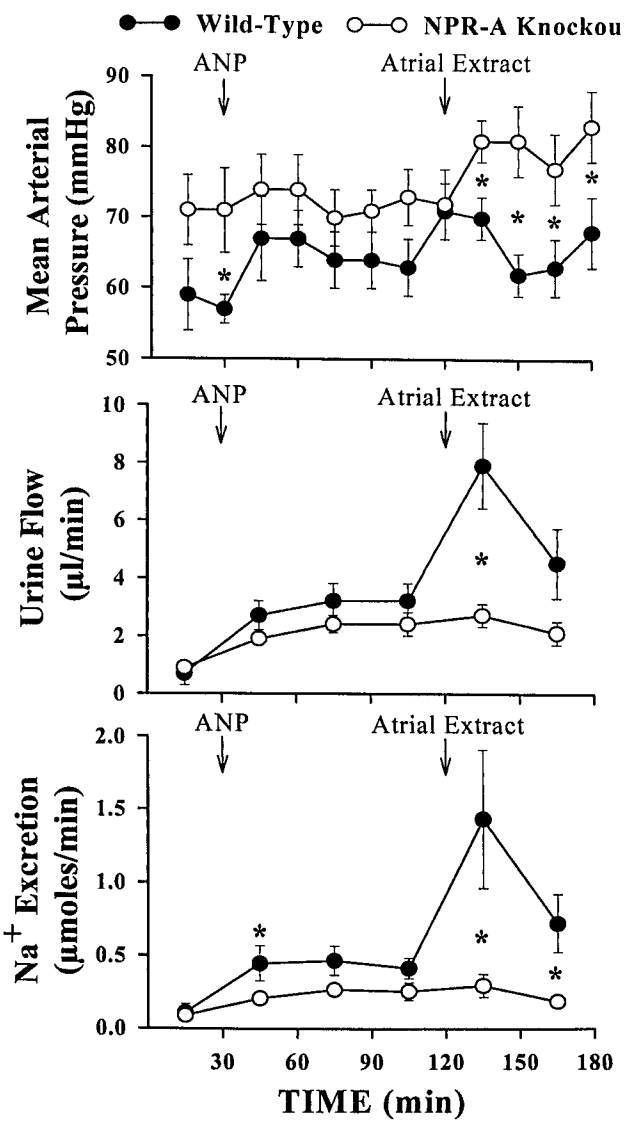

Figure 1. Mean arterial pressure (MAP), urine flow, and sodium excretion rate in wild-type ($n = 6$) and knockout mice ($n = 6$) in response to injections of ANP (100 ng) and rat atrial extracts (200 μl). ANP injections produced a greater natriuresis in the wild–type mice than in the knockout mice and significantly decreased MAP. Atrial extract injections resulted in a striking hypotension, diuresis, and natriuresis in the wild-type mice but not in the knockout mice. Values are means ± SE. In the lower panel, the knockout group standard error bars for some periods were very small and lie within the limits of the symbols used. Asterisk (*) indicates a P value of <0.05 between the wild type and knockout groups (t test).

dramatically (3-fold and 4-fold, respectively, $P < 0.05$ between groups) with the atrial extract infusion in the wild-type mice. Urine flow and sodium excretion tended to increase slightly also in the knockout mice with the extract infusion, but the changes were not significant.

Discussion

The results clearly show that NPR_A is essential for the acute hypotensive, diuretic, and natriuretic responses to rat atrial extracts. In wild-type mice, blood pressure decreased with atrial extract injection, whereas in NPR_A knockout

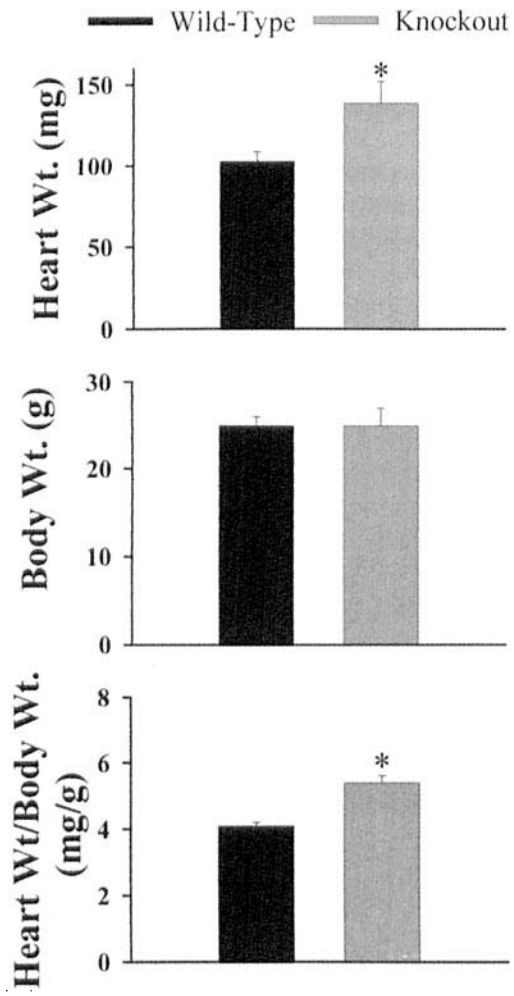

Figure 2. Heart weight (upper panel; $P < 0.02$) and heart weight to body weight ratio (lower panel; $P < 0.001$) were both significantly greater in the knockout mice ($n = 9$) compared to the wild–type mice ($n = 11$). Body weights were not significantly different (middle panel). Values are means ± SE. Asterisk (*) indicates a P value of <0.05 between the wild-type and knockout groups (t test).

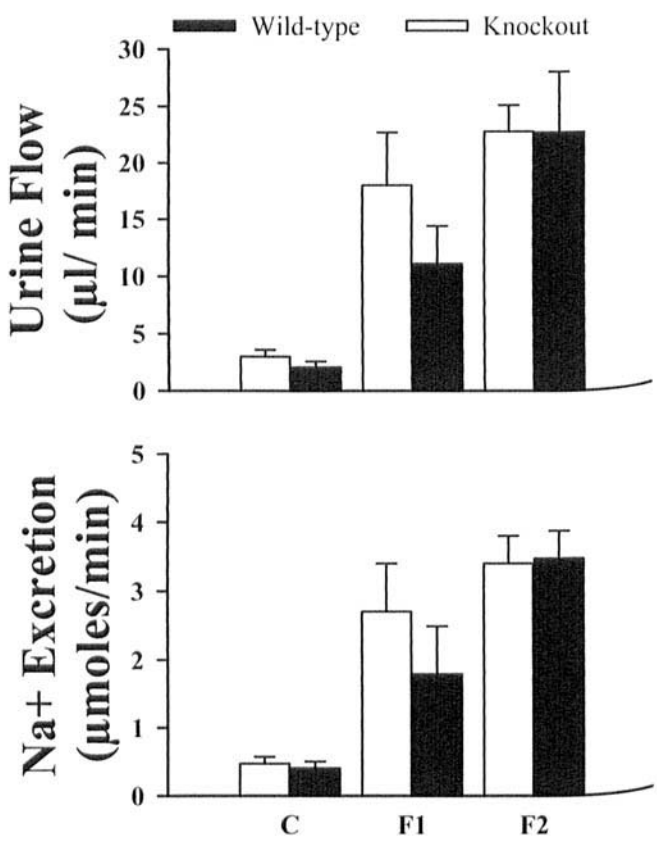

Figure 3. Urine flow and sodium excretion both increased markedly with the furosemide injection, but there were no significant differences between the groups ($n = 3$ for each). The result suggests that the NPR_A knockout mice are capable of increasing urine flow and sodium output with an effective stimulus. "C" represents the control 30-min urine collection period immediately prior to furosemide injection, and "F1" and "F2" represent the two 30-min periods after furosemide injection. Values are means ± SE.

mice, an increase in blood pressure was observed (Fig. 1). The increase in arterial pressure in knockout mice could be attributed to the 200-µl volume of extract given or to unknown factors in the atria that might raise arterial pressure. Both the injection and the 150-min infusion of atrial extracts produced striking increases in urine output and sodium excretion in the wild-type mice (Figs. 1 and 4) but these responses were virtually absent in the NPR_A knockout mice.

The classic studies of de Bold and colleagues (2) demonstrated that rat atrial extracts contain a potent hypotensive, diuretic, and natriuretic substance initially termed the atrial natriuretic factor (ANF). Later, they isolated the 28-amino-acid peptide termed atrial natriuretic peptide (ANP), which appeared to possess all of the properties of atrial extracts (5). Most evidence indicates that ANP exerts its actions through NPR_A. Subsequently, several additional peptides in the ANP natriuretic peptide family were identified. These peptides are structurally similar to ANP and were termed BNP, CNP, and DNP. ANP, BNP, and DNP have natriuretic and hypotensive actions similar to ANP and are believed to exert most of their actions through NPR_A. A large body of evidence supports an essential physiological role for ANP in the regulation of blood volume and blood pressure. Both monoclonal and polyclonal antibodies to ANP have been shown to blunt the diuretic and natriuretic responses to volume expansion (7, 8) and to exacerbate volume-dependent forms of hypertension (9). NPR_A gene knockout mice exhibit decreased renal responses to volume expansion (17) and increased arterial pressure (13).

However, several lines of evidence suggest that important factors other than the ANP natriuretic family may be present in the atria and have significant effects on the kidneys. Previously, Goetz and colleagues (18) performed a very important series of experiments with interesting results that still defy adequate explanation. They produced a natriuresis and diuresis by atrial distension in conscious, cardiac denervated dogs, a response hypothesized to be attributed to secretion of ANP from the atria. However, in subsequent experiments they infused ANP,

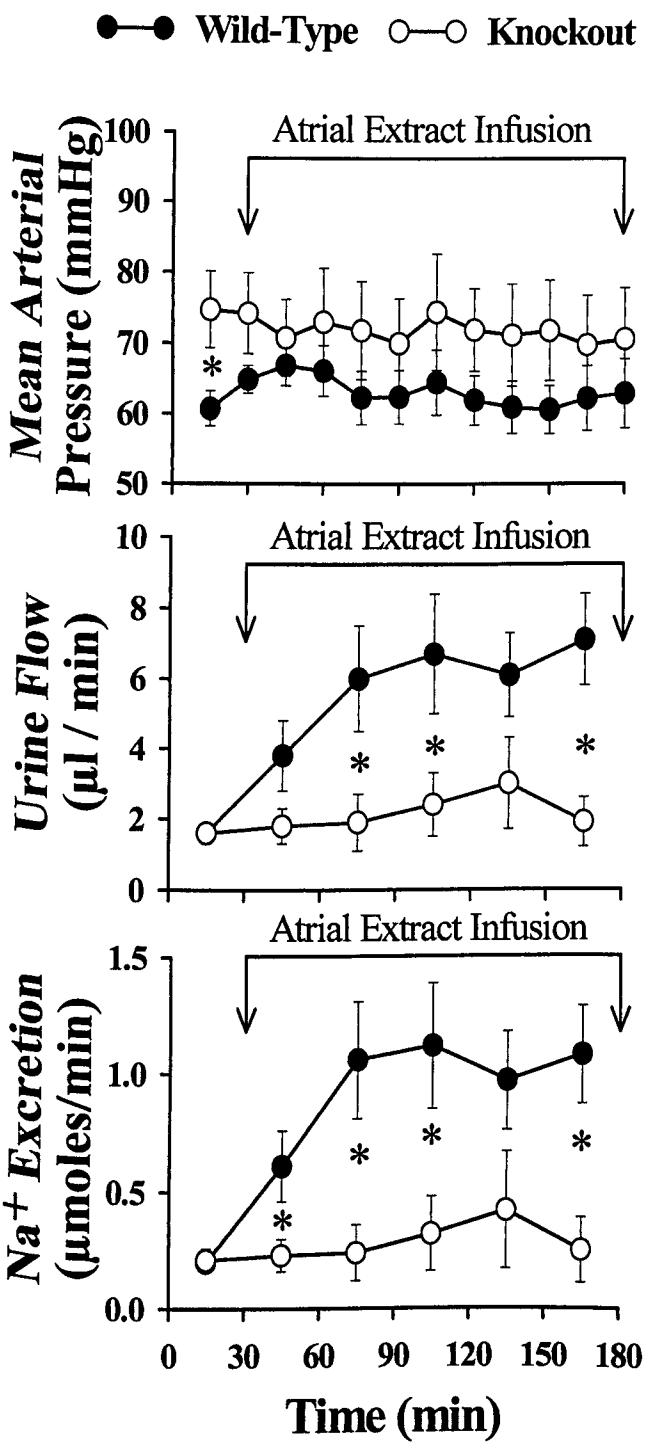

Figure 4. Mean arterial pressure, urine flow, and sodium excretion rate in knockout (n = 5) and wild-type mice (n = 6) with a constant 150-min infusion of rat atrial extract at 5 µl/min. Urine flow and sodium excretion only increased significantly in the wild-type mice. Values are means ± SE. Asterisk (*) indicates a P value of <0.05 between the wild-type and knockout groups (t test).

achieving plasma levels that were many times the normal ANP level, and found that atrial distention produced a similar natriuresis despite the very high ANP levels. In fact, Goetz *et al.* (18) terminated the ANP infusion during the distension period in several experiments so that the distension occurred during a falling plasma level of ANP, and still the natriuresis persisted. Sakata *et al.* (19) observed that acute blood volume expansion in anesthetized rats led to a diuresis and natriuresis with no detectable change in plasma ANP concentration. However, the natriuresis was attenuated in atrial appendectomized rats. Therefore, the natriuretic and diuretic response observed by these investigations is likely due to the release of a humoral agent from the atria, which is clearly not ANP. Reasonable possibilities include BNP, CNP, DNP, or several of the N–terminal proANP peptides, which are known to be released along with ANP by atrial distension (20, 21) and circulate in plasma (22). Both proANP 1-30 and 31-67 have been shown to have diuretic and natriuretic properties (23–26). We have previously shown that atrial extracts contain the entire 126-amino-acid prohormone (21). The prohormone is cleaved to several biologically active peptides during the secretion process (21). Because the N-terminal peptides are not structurally related to ANP, it is hypothesized that they probably exert their actions through receptors other than NPR_A, whereas those structurally related to ANP (BNP, CNP, DNP) should be completely without renal or cardiovascular effects in NPR_A knockout mice. Finally, it is quite possible that the heart contains diuretic or vasoactive substances yet to be identified. The current results clearly show that the primary natriuretic and hypotensive substances present in the rat atria act through NPR_A, at least on an acute basis. It should be pointed out that the plasma levels of ANP in the knockout mice should be elevated due to the volume expansion and negative feedback effects (27). High levels of ANP have been shown to desensitize NPR_B (28). Therefore, the NPR_A knockout mice may not show NPR_B-related effects.

We also considered the possibility that the lack of response to atrial extract in the NPR_A knockout mice could be attributed to a general reduction in the kidney's ability to respond to stimuli and excrete sodium and water, similar to what one sees in heart failure patients. The NPR_A knockout mice are known to develop severe cardiac hypertrophy with increased mortality at 6 months of age (13). Although the current studies were conducted at approximately 6 weeks of age, the NPR_A knockout mice showed significant cardiac hypertrophy (Fig. 2). Kishimoto *et al.* (17) did not find a significant renal response to volume expansion in NPR_A knockout mice. This is somewhat surprising, as the secretion of ANP is only one of several mechanisms involved in the diuretic and natriuretic responses to acute blood volume expansion. Hemodynamics, the nervous system, and several other hormones also contribute. Because this might suggest a generalized impairment of the kidneys in NPR_A knockout mice, we injected wild-type and NPR_A knockout mice with the loop diuretic furosemide. The injection of furosemide produced a striking diuresis and natriuresis that was not different in the two groups. This suggests that the NPR_A knockout mice are capable of increasing salt and water excretion and that the primary

reason for their lack of response to rat atrial extracts is the lack of the specific receptor for ANP. Also, it is apparent that the knockout mice are able to maintain sodium balance despite the lack of NPR_A, which suggests that other renal compensatory mechanisms are functional in mice lacking this receptor.

The diuretic, natriuretic, and hypotensive responses to acute injections and infusions of rat atrial extract were markedly blunted in mice lacking the natriuretic peptide type A receptor. The results strongly suggest that, on an acute basis, physiologically relevant substances in the atria act through this receptor mechanism.

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