ANP, BNP, and CNP enhance bradycardic responses to cardiopulmonary chemoreceptor activation in conscious sheep

COLLEEN J. THOMAS, CLIVE N. MAY, ATUL D. SHARMA, AND ROBYN L. WOODS
Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Victoria 3010, Australia
Received 6 July 2000; accepted in final form 19 September 2000

The von Bezold-Jarisch reflex is an inhibitory cardiovascular reflex characterized by increased parasympathetic drive to the heart and reduced sympathetic drive to the heart and blood vessels, resulting in bradycardia and hypotension (11, 18). The reflex is evoked by stimulation of cardiopulmonary receptors that are the sensory endings of unmyelinated (C fiber) vagal afferents located predominantly on the ventricular epicardium (11). Most of these cardiac receptors respond to a range of chemical substances including veratrum alkaloids, bradykinin, prostaglandins, capsaicin, serotonin [5-hydroxytryptamine (5-HT)], and phenylbiguanide (PBG) (11). Experimentally, the latter two agents are used most commonly to stimulate the reflex in vivo.

The heart produces its own hormones in myocytes, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), which are released into the circulation in response to physiological stimuli that increase atrial or ventricular stretch, respectively (7), and in association with pathophysiological conditions such as congestive heart failure, hypertension, and myocardial infarction (23). C-type natriuretic peptide (CNP), the other member of the natriuretic peptide family, is found in endothelial cells and the brain and appears to be regulated differently from ANP and BNP. It is considered to be a paracrine regulator of the endothelium and a neuropeptide (21). Plasma CNP levels are increased in septic shock and severe hypovolemic conditions (19), but little changed under the physiological or pathophysiological conditions that are known to be associated with elevated levels of ANP and/or BNP.

In early studies using partially purified cardiac tissue extracts, Ackermann and co-workers (1) demonstrated that atrial, but not ventricular, extracts injected into anesthetized rats had a 5-HT-like action causing bradycardia and hypotension, suggesting that an atrial factor may sensitize cardiac chemically sensitive afferents such as those involved in the von Bezold-Jarisch effect. Subsequently, Thoren et al. (31) and Schultz et al. (24) provided evidence from anesthetized animal studies that, through actions on cardiac vagal afferents, ANP inhibited reflex activation of sympathetic nerve activity normally expected with hypotension. In more recent studies, we reported that in conscious rats, ANP enhanced the sensitivity of von Bezold-Jarisch reflex bradycardia as well as cardiopulmonary baroreflex bradycardia but not arterial baroreflex sensitivity (28, 30, 35). These findings supported our unifying hypothesis (28–30) that ANP has a cardioprotective function via a selective action on cardiac vagal afferents, both chemosensory (1) and mechanosensory (24, 31). Recently, we reported (29) that BNP and CNP administered to conscious rats also...
enhanced cardiac vagal baroreflex sensitivity in response to rapid injections of phenylephrine, a stimulus that preferentially activates cardiac rather than arterial baroreceptors (10), providing the first evidence that all three natriuretic peptides have a similar action on cardiac vagal baroreflexes. From the original study of Ackermann et al. (1), it seemed that BNP may not act like ANP to enhance the von Bezold-Jarisch reflex, because ventricular extracts, which should have contained a high concentration of BNP, did not cause hypotension and bradycardia. Hence, the primary aim of the present study was to determine whether equimolar infusions of all three natriuretic peptides, ANP, BNP, or CNP, could modify the von Bezold-Jarisch reflex. Because all previous evidence of an interaction between ANP and the von Bezold-Jarisch reflex was provided from experiments in rats, much of it in anesthetized animals, in the present study, we established a model to activate this reflex in a conscious animal with resting heart rate (HR) closer to that of humans.

METHODS

Adult Merino ewes (Howard Florey Institute, Melbourne, Australia) were housed in individual cages in an air-conditioned room (constant 21°C) with natural light and dark cycles throughout the study. The sheep were fed daily with 800 g of lucerne-oaten chaff, supplemented once a week with fresh lucerne and every 4 wk with vitamin and mineral supplements (Min-A-Vit; Welcome). Water was provided ad libitum.

Surgical preparation. At least 3 wk before experimentation, all sheep (weight range 38–48 kg) underwent surgery for oophorectomy and bilateral exteriorization of carotid arteries for subsequent ease of arterial cannulation. At least 1 day before experimentation, under local anesthesia (0.5 ml of 2% Xylocaine, Astra, Australia), two polyethylene cannulas (ID 0.58 mm, OD 0.98 mm) were introduced into the jugular veins and advanced toward the heart. One catheter was used to administer drugs close to the right heart to activate the von Bezold-Jarisch reflex. The other catheter was used for natriuretic peptide infusion. A tygon cannula (ID 1.5 mm, OD 2.08 mm) was also inserted into one of the exteriorized carotid arteries to record mean arterial blood pressure (MAP) and heart period (HP). All cannulas were secured and, when not in experimental use, were constantly infused with heparinized saline (25 IU/ml, at 3 ml/h) to maintain patency of the lines for up to 2 wk.

In three sheep, additional coronary arterial catheters (Silastic tubing, ID 0.65 mm, OD 1.19 mm) had previously been implanted for chronic experiments and were used to administer PBG, or other agents to activate the von Bezold-Jarisch reflex, directly into the coronary circulation. Patency of these catheters was maintained with continuous infusions of heparinized saline (same dose as the venous catheters). Of these three sheep, two were unsuitable for inclusion in the present natriuretic peptides study because of a lack of responsiveness to PBG (see below).

Hemodynamic measurements. On each experimental day, the arterial catheter was connected to a Cobe disposable pressure transducer (Lakewood, CO) to measure mean and phasic systemic arterial blood pressure (BP). HP was measured using a tachometer (Baker Medical Research Institute, Melbourne, Australia) triggered by the arterial pressure signal or from the R wave of the electrocardiogram (ECG; ECG 100, Biopac Systems; Goleta, CA). ECG was measured through recording leads across the heart connected to previously implanted subcutaneous stainless steel wires. All hemodynamic variables were recorded continuously on an eight-channel Graphtec chart recorder (Linearorder No. WR3310), and the signals were digitized and recorded at a sampling rate of 50 Hz using the AcqKnowledge data-acquisition system (Biopac Systems) connected to a Pentium computer.

Von Bezold-Jarisch reflex technique. Cardiopulmonary chemoreflex activation (von Bezold-Jarisch reflex) was elicited by bolus injections of the 5-HT₃ agonist PBG (Sigma Chemical) into the jugular vein or coronary artery in the range of 10–90 µg/kg. Doses of PBG were injected in ascending order at 10-min intervals. A minimum of five PBG doses was administered to cover the range of responsiveness from subthreshold to maximum in each animal. From these, three doses were chosen as representative “low”, “medium,” and “high” doses, which we have previously described for the von Bezold-Jarisch reflex in rats (28, 30). Because it is not uncommon for responsiveness to the agonist to vary between animals (17), analysis of the von Bezold-Jarisch reflex was individualized by selecting doses of PBG that elicited threshold, intermediate, and submaximal HR responses in each animal. Although doses of PBG varied according to the sensitivity of each sheep, the same three doses of PBG were always given in the absence and presence of the natriuretic peptides or saline in any given sheep. Maximum changes in HP were determined within 12–14 s after the start of each dose of PBG. Changes in MAP to PBG were recorded at the same time as the maximum bradycardic responses.

Of all sheep examined for von Bezold-Jarisch reflex responsiveness to PBG (total of 10 animals), only ~50% showed the characteristic dose-related bradycardia. The five sheep included in the study demonstrated reproducible, dose-related bradycardic and hypotensive responses to PBG, consistent with a von Bezold-Jarisch reflex effect, with minimal aversive behavior during or after a bolus of PBG. Even at the high doses of PBG, in these sheep, there was no indication that the primary response was tachycardia. On the other hand, the five sheep excluded from the study responded to PBG with only tachycardia and elevated BPs that were accompanied by dose-related aversive behavior, indicative of primary activation of cardiac nociceptors. The tachycardic response was not confined to intravenous administration of PBG, because two of the sheep rejected for the study were instrumented with indwelling intracoronary catheters and PBG given directly into the left coronary artery resulted in the tachycardic and aversive response.

In one of the earliest studied sheep with an indwelling intracoronary arterial catheter, the profiles of bradycardic responses to PBG were similar, whether administered via the intravenous route (jugular venous catheter close to the right atrium) or directly into the coronary artery (Fig. 1). The times for onset of response were different, however, depending on the site of administration: time between start of injection and onset of bradycardia was ~8–9 s with intravenous, and it was ~6–7 s with intracoronary administration. The ~2-s difference is consistent with transit time through the pulmonary circulation before intravenous PBG accessed the ventricular chemosensory afferents. The intravenous route alone was therefore chosen for all other sheep included in the study.

Experimental protocol. In each sheep included in the final study (n = 5), the effect of equimolar doses (10 pmol·kg⁻¹·min⁻¹; infused at 12 ml/h) of α-human-ANP (1–28) (Auspep; Melbourne, Australia), porcine-BNP-32
The order of increased circulating levels of plasma ANP, BNP, and CNP by 10 pmol/kg min−1 into normal sheep should result in increased circulating levels of plasma ANP, BNP, and CNP in the order of ~100 pmol/l above baseline values, which is about 20 times resting levels. Experiments were performed on separate days, in randomized order, at least 3 days apart. In each experiment, baseline hemodynamic measurements were recorded for 20 min, and this was followed by five to seven doses of PBG. The time to complete all doses of PBG, with recovery times in between doses, was 45–60 min. The same doses of PBG were then repeated in the presence of an infusion of one of the natriuretic peptides or vehicle. The infusions lasted 65–80 min, incorporating a 20-min “run-in” period to allow infused natriuretic peptides to reach steady-state levels in the circulation before HR-reflex testing.

Statistical analysis. All HP measurements were converted to HR for statistical analysis. Significant effects of natriuretic peptides or saline infusions on resting BP and HR were determined by paired t-tests. For all other comparisons, data were analyzed by a two-way, repeated-measure ANOVA. To determine effect of treatment with natriuretic peptide or saline on von Bezold-Jarisch reflex, ANOVA of data from each experimental day compared all three doses of PBG before and after each treatment. Where appropriate, Bonferroni adjustment of probability (P) values was made for multiple comparisons. P values of <0.05 were regarded as statistically significant. Values quoted are means ± SE.

RESULTS

Effect of natriuretic peptide infusions on resting hemodynamics. Average resting MAP and HP in the sheep were 75 ± 1 mmHg and 927 ± 31 ms (HR = 68 ± 2 beats/min), respectively. There was a small, significant (P = 0.024) fall in resting BP of 9.5 ± 2.0 mmHg during BNP infusion. However, there was no significant change in resting BP in the presence of ANP (−6.4 ± 1.8 mmHg, P = 0.063), CNP (−3.6 ± 1.1 mmHg, P = 0.125), or saline (+3.0 ± 1.6 mmHg, P = 0.136). Associated with these changes in resting BP, there was a small but significant increase in resting HR with ANP infusion (+10 ± 3 beats/min, P = 0.028) but no change with BNP (+13 ± 10 beats/min, P = 0.246), CNP (+8 ± 3 beats/min, P = 0.062), or saline infusion (−0.2 ± 1.0 beats/min, P = 0.869).

Von Bezold-Jarisch reflex in sheep. Unlike our previous studies in rats (28, 30), 5-HT was not a suitable agent to evoke the von Bezold-Jarisch reflex in sheep due to a lack of reproducibility of bradycardic responses both within and between animals. We also tried nicotine directly into the coronary circulation, and it did not cause bradycardia. In contrast, bolus injections of PBG produced rapid, reproducible, dose-related bradycardia in all the sheep included in the study (for example, see Fig. 2). For the most part, the sheep were undisturbed by PBG injections. However, at the highest doses of PBG, some animals moved during the injection or immediately after [possibly due to the stimulation of pulmonary vagal nociceptor fibers (11)], and some animals experienced syncopal symptoms when the HR fall was prolonged. In most animals, bradycardia began within 6–7 s after the start of each PBG injection, reached a maximum 1–2 s later (~8–9 beats after injection), and was sustained for a further 3–4 s (occasionally longer at the highest doses, particularly in the presence of an infusion of natriuretic peptide, as described later; Fig. 2).

Averaging control periods from all experiments, PBG increased HP by 128 ± 19, 288 ± 48, and 1,152 ± 191 ms in response to low, medium, and high doses, respectively. These changes in HP translated to falls in HR of 7 ± 1, 15 ± 2, and 34 ± 3 beats/min, respectively. The doses of PBG into the jugular vein to achieve these changes in HP were 13 ± 3, 20 ± 3, and 31 ± 4 μg/kg.

BP changes with PBG administration were somewhat variable between sheep, similar to the responses we have previously reported in rats (28, 30). Mean changes in BP recorded at the time of maximum slowing of the heart to low, medium, and high PBG doses were 0.5 ± 1.1, 3.3 ± 2.4, and −3.5 ± 3.5 mmHg, respectively.

Effect of natriuretic peptide infusions on the von Bezold-Jarisch reflex. Equimolar ANP, BNP, and CNP infusions enhanced the magnitude of von Bezold-Jarisch reflex bradycardic responses in sheep (Figs. 2 and 3). Figure 2 illustrates, in one sheep, the greater reflex rise in HP at each of the three doses of PBG during BNP infusion (B compared with A). Figure 3 illustrates, in another sheep, enhanced reflex bradycardia.
to a single (“middle”) dose of PBG during infusion of each of the natriuretic peptides compared with saline control. The grouped data for the effect of three separate doses of PBG on HP are illustrated in Fig. 4A. When responses to all three doses of PBG were contrasted before and after treatment, average falls in HR to PBG were significantly enhanced in the presence of ANP by 94 ± 618% (16 ± 4 beats/min, P = 0.0003), BNP by 142 ± 55% (20 ± 4 beats/min, P = 0.0002), and CNP by 61 ± 16% (12 ± 3 beats/min, P = 0.0013). Saline infusion did not significantly change bradycardic responses to PBG (−25 ± 12% or −4 ± 2 beats/min, P = 0.23; Fig. 4).

In the presence of all three natriuretic peptides, modest hypotension accompanied von Bezold-Jarisch reflex bradycardia (Fig. 4, right). There was a small, significant (P < 0.05) fall in average BP of 6.1 ± 2.7 mmHg to the three doses of PBG with ANP infusion, whereas the falls in BP with BNP (−3.8 ± 1.8 mmHg), CNP (−4.2 ± 2.0 mmHg), or saline (−3.9 ± 2.5 mmHg) infusions were not statistically significant.

**DISCUSSION**

The major finding of the present study was that the three structurally related natriuretic peptides, ANP, BNP, and CNP, markedly enhanced vagal cardiopulmonary chemoreflex control of HR in awake, normal sheep. We established methodology to activate the von Bezold-Jarisch cardiopulmonary reflex in these animals using PBG, a serotonin agonist selective for 5-HT₃ receptors. Sensitivities of the bradycardic re-

---

**Fig. 2.** Sensitizing effect of B-type natriuretic peptide (BNP; 10 pmol·kg⁻¹·min⁻¹) on the von Bezold-Jarisch reflex in a conscious sheep. Dose-related HP and arterial BP responses measured with the same 3 doses of PBG into the jugular vein in the absence (A) and presence (B) of BNP.

**Fig. 3.** A pronounced example in 1 sheep of the natriuretic peptides enhancing the von Bezold-Jarisch reflex. Responses shown are “middle dose” of PBG (750 µg) in the presence of saline infusion (12 ml/h) or equimolar (10 pmol·kg⁻¹·min⁻¹) doses of atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide (CNP).
effective as ANP at sensitizing bradycardic reflexes that BNP, primarily a ventricular product, is just as Bezold-Jarisch-like hemodynamic responses, it is clear atrial but not ventricular extracts activated von Ackermann and co-workers (1) showing that HR close to that of humans. Despite the early study reflex sensitivity in a nonrodent species with resting natriuretic peptides modulates von Bezold-Jarisch-like 30, and present study) or by pressure (29).

The mechanism of action and target site for sensitization of these cardiopulmonary vagal reflexes by the natriuretic peptides have not been elucidated. In rat cardiac cells, mRNA for natriuretic peptide receptors (NP_A, NP_B, and NP_C) has been detected by RT PCR, and cGMP accumulation has been measured in response to treatment with different peptides (15). From these data, it appears that NP_A and NP_C receptors predominate in cardiac ventricular myocytes, whereas all three subtypes are present in cardiac fibroblasts (15). There is no information regarding specific expression of NP_A, NP_B, and NP_C receptors within cardiac sensory afferents, and there is no published information regarding natriuretic peptide binding or receptor mRNA expression in sheep heart. The NP_C receptor may be a possible target, because all three natriuretic peptides recognize it and with not too widely differing affinities (26). Given that the selectivity profile of the NP_A receptor is in the order of ANP \( \geq \) BNP > CNP (26) and for the NP_B receptor is in the order of CNP \( > \) ANP \( > \) BNP (26), it is less likely that enhanced reflex sensitization is through either the NP_A or the NP_B receptor. If the myocytes or other nonneural tissues are the target site for natriuretic peptide action, a secondary agent, such as a prostaglandin, nitric oxide, bradykinin, or serotonin, may then be released to sensitize the vagal afferents. Indeed, Deliva and Ackermann (8) have suggested that ANP acts via the release of a 5-HT_3 agonist, because bolus administration of ANP directly into the pericardium of anesthetized rats did not cause the hypotension and sympathoinhibition evoked by an intravenous bolus of the same dose of ANP. An alternative interpretation is that the lack of effect with intrapericardial administration of ANP (8) implicates a central site of action for the peptide. Whether BNP or CNP is similarly ineffective when applied directly to the epicardial surface of the heart is unknown. Nevertheless, for any of the natriuretic peptides, we cannot exclude the possibility of a site of action in the central nervous system such as one of the circumventricular organs that can be accessed by blood-borne peptides.

In contrast to previous studies using bolus administration of ANP (8) or atrial extract (1) into anesthetized rats, we found no evidence that ANP itself activates von Bezold-Jarisch-like responses. The dose of ANP that we infused into conscious sheep should elevate circulating levels by \( \sim 100 \text{ pmol/l} \) (4), which is within the pathophysiological range achieved by endogenous ANP release (22). It was not accompanied by any significant hypotension or bradycardia. Infused BNP and CNP at the same dose also caused minimal changes in

Fig. 4. A: illustrates averaged dose responses to PBG, measured as maximum changes in HP before (Control, open circles) and during equimolar natriuretic peptide (10 pmol-kg\(^{-1}\)-min\(^{-1}\)) or saline (12 ml/h) infusion (filled circles). B and C: changes in HR and BP, respectively, averaged over all 3 doses of PBG before (Control, open circles) and during (filled circles) natriuretic peptide or saline infusion. *Significant \( (P < 0.05) \) effect of treatment.

responses to PBG were increased by \( \sim 60\% \) with CNP, \( \sim 95\% \) with ANP, and \( \sim 140\% \) with BNP in equimolar doses. We recently reported that each of these peptides enhanced reflex bradycardia from cardiac mechanoreceptor activation (cardiac baroreflex) in rats stimulated by rapid injection of phenylephrine (29) but not on arterial baroreflex pathways (28, 30, 35, and C. J. Thomas and R. L. Woods, unpublished observations). Together, our findings provide support for a general hypothesis that ANP, BNP, and CNP act on cardiac vagal sensory afferent pathways, whether activated chemically (28, 30, and present study) or by pressure (29).

This study provides the first evidence that any of the natriuretic peptides modulates von Bezold-Jarisch-like reflex sensitivity in a nonrodent species with resting HR close to that of humans. Despite the early study from Ackermann and co-workers (1) showing that atrial but not ventricular extracts activated von Bezold-Jarisch-like hemodynamic responses, it is clear that BNP, primarily a ventricular product, is just as effective as ANP at sensitizing bradycardic reflexes activated by PBG. The similar enhancement of von Bezold-Jarisch reflex bradycardic action by the three natriuretic peptides contrasts with the different biological actions of these hormones on other systems. For example, infusions of ANP and BNP are natriuretic and diuretic and increase mesenteric vascular resistance and hematocrit, whereas infused CNP has much weaker effects on renal function or on arterial vascular tone (33, 36).

In the present study, ANP and BNP appeared to be equipotent in enhancing von Bezold-Jarisch responses but not CNP, which has previously been reported to elicit weak (25) or no (28, 36) reflex bradycardia when applied directly to the epicardial surface of the heart. This study also provides the first evidence that any of the natriuretic peptides can enhance Bezold-Jarisch-like responses to a chemical stimulus, because these responses are usually abolished by atrial extracts of the rat (1). As in previous studies using bolus injection of ANP (8) or atrial extract (1), we found no evidence that ANP itself activates Bezold-Jarisch-like responses. The dose of ANP that we infused into conscious sheep should elevate circulating levels by \( \sim 100 \text{ pmol/l} \) (4), which is within the pathophysiological range achieved by endogenous ANP release (22). It was not accompanied by any significant hypotension or bradycardia. Infused BNP and CNP at the same dose also caused minimal changes in
resting hemodynamics, similar to our previous findings in conscious rats (29) or dogs (36). Thus we conclude that ANP, BNP, and CNP in this dose range do not directly activate von Bezold-Jarisch reflexes, but they potentiate the effects of cardiopulmonary reflex activity evoked by other means [PBG in the present study, 5-HT in rats (28, 30)], although the site of this facilitation is yet to be determined.

An unexpected finding from our experiments was that only half the sheep tested displayed a “classical” von Bezold-Jarisch reflex to PBG; that is, dose-related bradycardia. From the 10 sheep tested, 5 were excluded because PBG caused not bradycardia, but tachycardia. This tachycardia appeared to be associated with activation of nociceptors, as evidenced by these (and only these) animals’ aversive responses to PBG administration. We do not believe that those sheep lack the PBG-sensitive vagal afferent fibers that drive the von Bezold-Jarisch reflex, because anesthetized sheep invariably show a bradycardia in response to PBG (n = 10, unpublished observations). It appears, rather, that the excitatory reflex is silenced by anesthesia. Thus it seems that sheep may have a variable population of PBG-sensitive excitatory afferents that, in some conscious animals, can override PBG-induced vagal afferent activation. This is not a species-dependent phenomenon, because in the conscious dog, vagal cooling exposed veratridine-sensitive excitatory cardiac afferent activity (3). Clearly, any further interpretation of our observations in the sheep will require a dedicated study of the excitatory/nociceptive afferents.

A limitation to the interpretation of our study is that for most of the experiments, PBG was administered via the jugular vein, allowing potential activation of both pulmonary and ventricular afferents. We did not observe, however, any obvious change in the pattern of respiration, which is the hallmark of the reflex response to pulmonary afferent stimulation (2). Moreover, the bradycardic response to intracoronary administration of PBG was virtually identical to that after jugular administration, except that it occurred at a shorter latency. The 2- to 3-s time difference is consistent with the transit time of the pulmonary circulation. It was clear many years ago that the major hemodynamic responses to intravenous agents activating the von Bezold-Jarisch reflex were due to left ventricular sensory afferents (6). Any changes in rate or depth of respiration, on the other hand, were due to activation of pulmonary afferents that run in the vagi (2). Nevertheless, we cannot exclude the possibility that all three natriuretic peptides act on afferent pathways deriving from pulmonary vascular as well as left ventricular coronary chemosensitive receptors to enhance bradycardic reflexes.

In summary, in the present experiments, we described the cardiopulmonary chemoreflex (von Bezold-Jarisch reflex) in normal adult sheep for the first time. We also showed that equimolar intravenous infusions of ANP, BNP, and CNP at a dose that caused minimal changes in resting BP or HR markedly enhanced cardiac slowing in response to cardiopulmonary chemo-
genic receptor activation. The shared ability of these hormones to facilitate the activity of parasympathetic reflexes may indicate a common cardioprotective action of the natriuretic peptide family. Further experimentation is required to elucidate the site, mechanism of action, and receptor(s) responsible for this potentially important cardiovascular function.

Perspectives

Clinically, a von Bezold-Jarisch-like reflex may be activated after infarction (27) and may be triggered by factors affecting coronary flow, such as reperfusion after ischemia (25), coronary thrombolysis therapy (18), and during coronary angiography (18). By contrast, there is evidence that cardiac vagal reflex function is impaired in conditions such as myocardial infarction, hypertension (32), or congestive heart failure (16, 20) and that reductions in sensitivity of cardiac sensory receptors may contribute to the pathophysiology of acute or chronic cardiovascular disorders (18). In humans, there is a range of events where activation of the cardiopulmonary chemoreceptors occurs coincident with natriuretic peptide release. ANP and/or BNP release into the circulation is augmented in patients with unstable angina (12, 13), during angioplasty (14), after myocardial infarction (9), and in chronic conditions associated with ventricular dysfunction and cardiac failure (19, 37). On the basis of the results from our present study, we propose that ANP and BNP may be cardioprotective by enhancing parasympathetic activity during times of compromised myocardial blood flow. Although of limited interest as a circulating hormone, CNP may also be of importance in control of coronary blood flow (34), where it may have cardioprotective activity (5) that is different from the other natriuretic peptides. Because CNP is derived from endothelial cells and its receptor has been localized to cardiac tissue (5), our present data showing effective facilitation of parasympathetic reflexes add another dimension to the role of CNP as a local cardiac hormone.

We thank Simon Fitzpatrick and Doug McNestrie for expert technical assistance. We also thank Alan MacDonald and David Iannello for assistance with surgical preparation of the animals.

This study was supported by a block grant from the National Health and Medical Research Council of Australia (No. 983001) and by a grant-in-aid from the National Heart Foundation of Australia (G97M 4900).

REFERENCES

4. Charles CJ, Espiner EA, Richards AM, Nicholls MG, and Yandle TG. Comparative bioactivity of atrial, brain, and C-type...


