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Cocaine increases circulating levels of atrial natriuretic peptide and pro atrial natriuretic peptide N-terminal fragment in conscious rats

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Abstract

We examined the effects of intravenously administered cocaine (1 and 3 mg/kg) on haemodynamics (mean arterial pressure, heart rate and right atrial pressure), plasma immunoreactive atrial natriuretic peptide (immunoreactive ANP) and immunoreactive N-terminal peptide of proANP (immunoreactive N-terminal ANP) in conscious, chronically cannulated Sprague-Dawley rats. The direct effect of cocaine (10^{-6}–10^{-4} M) was also studied in primary cultures of neonatal rat cardiac ventricular myocytes. Intravenous injection of 1 mg/kg or 3 mg/kg of cocaine caused an immediate peak rise in mean arterial pressure (1 mg/kg: 44 ± 3 mm Hg, $n = 8$; 3 mg/kg 49 ± 2 mm Hg, $n = 12$), which was followed by a dose-dependent sustained pressor response. The right atrial pressure rose simultaneously and 10–20 s later heart rate decreased. Plasma immunoreactive ANP levels increased significantly (1 mg/kg: 56 ± 10 pmol/l; $n = 8$; 3 mg/kg: 130 ± 54; $n = 12$) and also immunoreactive N-terminal ANP levels rose significantly 2 min after the injection of the higher cocaine dose (230 ± 27 pmol/l, $n = 12$). Significant correlations between plasma immunoreactive ANP levels and all haemodynamic variables were found, especially between mean arterial pressure and plasma immunoreactive ANP levels ($r = 0.86$, $P < 0.001$). In neonatal rat ventricular myocyte cultures, the highest concentration of cocaine (10^{-4} M) reduced ANP release into the incubation medium ($-41 \pm 14\%$, $n = 5$) but the reduction was not statistically significant. Our results show that cocaine dose dependently increases ANP and N-terminal ANP secretion into the circulation in conscious rats and that this increase is mediated by haemodynamic changes. Thus, plasma ANP and N-terminal ANP levels could be used as markers for acute cocaine-induced cardiac toxicity.

Keywords: Cocaine; ANP (atrial natriuretic peptide); ANP, N-terminal; Mean arterial pressure; Heart rate; Right atrial pressure

1. Introduction

Cocaine, an alkaloid extracted from *Erythroxylon coca*, has several harmful effects on the cardiovascular system (Rezkalla et al., 1990; Isner and Chokshi, 1991; Kloner et al., 1992), and its cardiovascular side effects have been reported to cause considerable medical problems in emergency room patients (Brody et al., 1990). In animal experiments, acute cocaine doses have been reported to decrease coronary calibre and coronary blood flow in dogs, thus diminishing myocardial oxygen supply (Hale et al., 1989a). Cocaine also induces electrical abnormalities in rats (Hale et al., 1989b) and dogs (Schwartz et al., 1988) and increases the cardiac work load by elevating blood pressure, which may lead to myocardial ischaemia or infarction (Cregler and Mark, 1985; Wang et al., 1988). Cocaine increases arrhythmias and the risk of sudden death, and its depressive effect on the heart may cause transient cardiomyopathy. Accelerated atherosclerosis, increased thrombus formation and hypertension have also been reported (Kloner et al., 1992).

Atrial natriuretic peptide (ANP) is a cardiac hormone that is stored as a 126-amino acid prohormone (proANP) in atrial granules. In response to atrial stretch, proANP is cleaved and released into the circulation as a 98-amino acid N-terminal peptide (N-terminal ANP) and a 28-amino acid C-terminal peptide (ANP), the major biologically active hormone (Needleman et al., 1989; Brenner et al.,

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1990; Ruskoaho, 1992). Other stimuli for ANP release include tachycardia and various endothelial and neurohumoral factors (adrenoceptor agonists, vasopressin, angiotensin and endothelin) (for review see Ruskoaho, 1992). Plasma ANP levels are increased in various diseases such as hypertension and severe cardiac and renal insufficiency. Measurement of plasma ANP levels may also be used in the diagnosis of these diseases (Perrella et al., 1991; Ruskoaho, 1992). ANP functions as a compensation mechanism in these pathological conditions by decreasing blood pressure, renin, aldosterone and vasopressin secretion and by stimulating natriuresis and diuresis (Brenner et al., 1990).

In this study we examined the effects of cocaine on haemodynamic variables, plasma ANP and N-terminal ANP levels in conscious, chronically cannulated rats. We also studied the correlations between the changes in haemodynamic variables and circulating peptide levels. In addition, the possible direct effect of cocaine on ventricular myocyte ANP secretion was studied by using neonatal rat cell cultures.

2. Materials and methods

2.1. Animals and experimental preparation

Male Sprague-Dawley rats (260–360 g) were obtained from the Research Animal Centre of the University of Oulu, Finland. Under chloral hydrate anaesthesia (300 mg/kg i.p.) rats were surgically prepared with polyethylene cannulas, as described previously (Ruskoaho et al., 1989a, b). The left femoral artery was cannulated for recording arterial pressure and heart rate, the left femoral vein for vehicle or cocaine injections and the right atrium was cannulated via the jugular vein for recording the right atrial pressure. The distal ends of the cannulas were passed s.c. to the back of the neck and sutured in place. After the operation cannulas were filled with heparinized saline, animals were allowed to recover for 1 day. During that period they were housed individually and had free access to food and water.

2.2. Experimental procedure

Rats were placed in a test cage and the arterial and right atrial cannulas were connected to pressure transducers (MP-15, Micron Instruments, Los Angeles, CA, USA) for recording mean arterial pressure, heart rate and right atrial pressure, as described previously (Ruskoaho et al., 1989b). The venous cannula was connected to a syringe for cocaine injections. After an equilibration period of 30 min rats were given either 0.9% saline or cocaine hydrochloride (1 mg/kg or 3 mg/kg) in a volume of 1 ml/kg followed by 0.5 ml of 0.9% saline, the total injection time being about 30 s. Arterial blood samples of 1.0 ml for measurements of plasma immunoreactive ANP and immunoreactive N-terminal ANP were taken 5 min prior to and 2, 6 and 30 min after the beginning of cocaine or vehicle administration. Blood samples taken were replaced by an equal volume of blood from a donor rat. To examine the correlations between cardiovascular parameters and ANP release, heart rate, mean arterial pressure and right atrial pressure were recorded continuously throughout the experiments. The experimental protocols were approved by the Committee for Animal Experimentation of the University of Oulu.

2.3. Cell preparation

Cells were prepared as described by Tokola et al. (1994). Briefly, 2- to 3-day-old Sprague-Dawley rats were decapitated, the thorax was opened and the heart was perfused with disaggregation medium (collagenase and $CaCl_2$ in PBS, Dulbecco's phosphate-buffered saline). The tissues were dispersed by sequential incubations in the disaggregation medium. The cells were filtered, washed twice in Dulbecco's modified Eagles medium (DMEM/F-12) supplemented with foetal calf serum and antibiotics, and placed into cell culture bottles for 50–60 min. Cells not attached to the bottles were plated into collagen-coated plastic culture wells in 2 ml of serum-containing medium for 24 h. Thereafter the medium was replaced with a complete serum-free medium (CSFM). After 48 h incubation in CSFM, the wells were allocated to test groups and the medium was replaced with CSFM containing vehicle or vehicle supplemented with cocaine hydrochloride. The final concentrations of cocaine in the culture medium were 10^{-6}, 10^{-5} and 10^{-4} M. The media were replaced every 24 h and the experiment lasted for 48 h.

2.4. Plasma and incubation medium levels of immunoreactive ANP and immunoreactive N-terminal ANP

Blood samples from rats were taken into pre-cooled EDTA tubes on ice, centrifuged immediately (2000 × g, 10 min, at +4°C) and the plasma was stored at −20°C until assayed by radioimmunoassay (RIA). ANP was extracted by Sep-Pak C18 cartridges as described previously (Ruskoaho et al., 1989a). For the ANP RIA the plasma extracts and the cell culture medium samples (100 μl) were incubated in duplicate with 100 μl of specific rabbit antiserum in a final dilution of 1/25 000 (Vuolteenaho et al., 1985; Ruskoaho et al., 1989a). After incubation for 48 h at +8°C the immunocomplexes were precipitated with sheep antirabbit antiserum in the presence of 500 μl of 1.2 M ammonium sulphate, pH 7, followed by centrifugation for 40 min at 3000 × *g*. The sensitivity of the assay was 0.8 pmol/tube. The turning point (ED_{50}) of the standard curve was 20 pmol/tube. The intra-assay and interassay variations were 5% and 14%, respectively.

N-terminal ANP was determined directly in 25 μl aliquots of EDTA-treated plasma (Vuolteenaho et al., 1992). The plasma samples were incubated with specific rabbit antiserum (200 μl, 1/40000 final dilution) and ^{125}I-labelled human Tyr-(*O*)-proANP-(79–98) (200 μl, 10000 cpm) overnight at +4°C. The bound and free fractions were separated with double antibody in the presence of polyethylene glycol. Synthetic human proANP-(79–98) was used as the standard. This compound and purified human and rat proANP-(1–126) were recognized with similar avidity, whereas the antiserum did not recognize human or rat ANP at all (cross-reactivity < 0.01%). The sensitivity of the assay was 40 pmol/l plasma and the within and between assay coefficients of variation were < 10% and < 15%, respectively.

2.5. Materials

Cocaine hydrochloride was from the University Pharmacy (Helsinki, Finland) and heparin was from Leiras (Helsinki, Finland). Foetal calf serum, DMEM/F-12 and PBS were from Gibco Europe (Paisley, Scotland, UK); CSFM components other than DMEM/F-12 were from Sigma Chemicals (St. Louis, Missouri, MO, USA), collagenase was from Millipore Corp. (Bedford, MA, USA) and cell culture dishes were from Falcon (Plymouth, England, UK).

2.6. Data analysis

The results are expressed as means ± S.E.M. The statistical significance of differences between the treatment groups was analysed with two-way ANOVA which used repeated measures. Haemodynamic values, and plasma and incubation medium levels of immunoreactive ANP and plasma immunoreactive N-terminal ANP at 2, 6 and 30 min were compared to the levels before treatment by an analysis of variance (ANOVA) followed by Duncan's test. Values of $P < 0.05$ were considered statistically significant. In addition, linear regression analysis was used to study the correlations between plasma ANP level and haemodynamics.

3. Results

3.1. Effect of cocaine on haemodynamic variables in conscious rats

Conscious, chronically cannulated rats ($n = 28$) had a mean arterial pressure of 118 ± 2 mm Hg, heart rate of 410 ± 4 beats/min and right atrial pressure of 0.2 ± 0.1 mm Hg before administration of vehicle or cocaine. Injection of vehicle did not alter mean arterial pressure, heart rate or right atrial pressure (Fig. 1). Intravenous cocaine at doses of 1 and 3 mg/kg caused an immediate decrease in heart rate (1 mg/kg: −63 ± 6 beats/min, $F = 9.1$, $P < 0.05$, $n = 8$; 3 mg/kg: −96 ± 8 beats/min, $F = 18.4$, $P < 0.05$, $n = 12$) which gradually returned to normal levels in 20–30 min (Fig. 1). Cocaine also caused a significant rise in mean arterial pressure (1 mg/kg: +44 ± 3 mm Hg, $F = 22.3$, $P < 0.05$, $n = 8$; 3 mg/kg: +49 ± 2 mm Hg, $F = 28.5$, $P < 0.05$, $n = 12$) and right atrial pressure (1 mg/kg: +1.8 ± 0.3 mm Hg, $F = 16.6$, $P < 0.05$, $n = 6$; 3 mg/kg: +2.9 ± 0.2 mm Hg, $F = 7.8$, $P < 0.05$, $n = 11$). The rapid increase in mean arterial pressure was followed by a more modest pressor response, the duration of which was greatly dependent on the dose (Fig. 1). The 3 mg/kg dose caused stronger acute responses for all the variables measured than the 1 mg/kg dose did, but the clearest difference between the two doses was on the level and duration of the sustained mean arterial pressure response ($F = 5.4$; $P < 0.001$). With 1 mg/kg of cocaine mean arterial pressure was still significantly elevated 2 min and with 3 mg/kg 10 min after

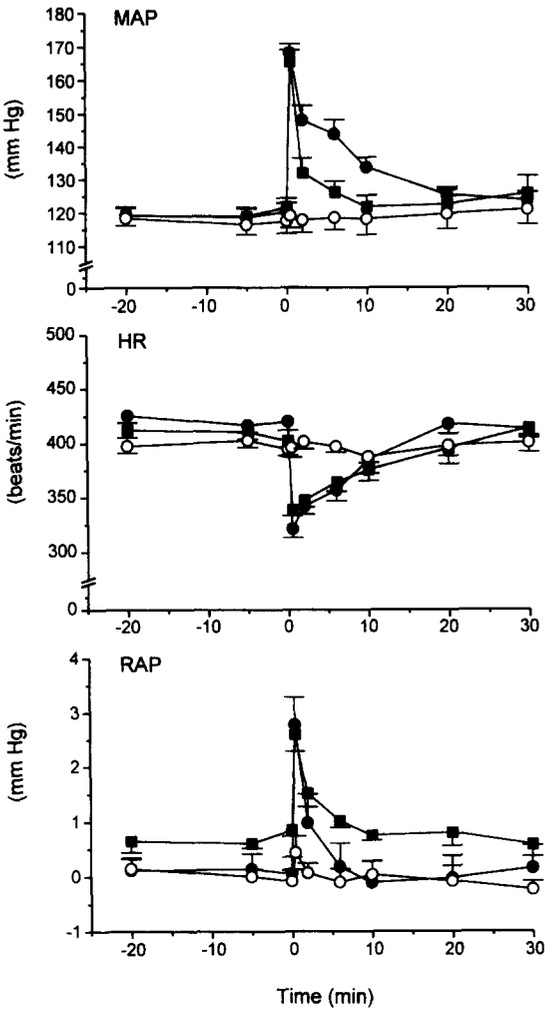

Fig. 1. The effect of intravenously administered cocaine on mean arterial pressure (MAP), heart rate (HR) and right atrial pressure (RAP) in conscious rats. *Open circle*, vehicle; *black square*, cocaine 1 mg/kg; *black circle*, cocaine 3 mg/kg. Results are expressed as means ± S.E.M.

cocaine administration. The difference in heart rate responses between the two cocaine doses was smaller ($F = 2.2$ and $P = 0.032$) and for the right atrial pressure the difference was not significant. Compared to the control group the changes were highly significant for all the variables in both treatment groups ($P < 0.001$).

3.2. Effect of cocaine on plasma ANP and N-terminal ANP levels in conscious rats

The basal plasma immunoreactive ANP level in cannulated rats was 52 ± 4 pmol/l. Cocaine injection caused a rapid increase in plasma ANP levels, the changes being $+56 \pm 10$ pmol/l with the lower dose and $+97 \pm 17$ pmol/l with the higher dose when measured 2 min after injection (Fig. 2). Six minutes after injection, the ANP level in the lower treatment group had already begun to fall but remained increased in the higher dose group (even higher than at 2 min), being $+130 \pm 54$ pmol/l above the pretreatment level (Fig. 2). The peak changes were highly significant in both treatment groups (1 mg/kg: $F = 5.9$, $P < 0.05$; 3 mg/kg: $F = 8.8$, $P < 0.05$) compared to basal values. There was also a statistically significant difference between the two treatment groups ($F = 2.91$, $P < 0.05$). The basal immunoreactive N-terminal ANP level in cannulated rats was 761 ± 41 pmol/l ($n = 28$). Injection of cocaine at a dose of 1 mg/kg caused a rise of $+148 \pm 63$ pmol/l ($F = 0.04$, not significant) and 3 mg/kg a rise of $+230 \pm 27$ pmol/l ($F = 3.2$, $P < 0.05$) in immunoreactive N-terminal ANP level (Fig. 2). The changes in the higher dose group were statistically significant compared to the control group ($P < 0.05$). The difference between the lower dose and control group was not significant. Changes in haemodynamic variables were highly significantly correlated to changes in plasma immunoreactive ANP levels, the mean arterial pressure correlating the best of these variables (Fig. 3). The increase in immunoreactive N-terminal ANP in response to cocaine infusions also showed a positive linear correlation with the increase in mean arterial and right atrial pressures (Fig. 4).

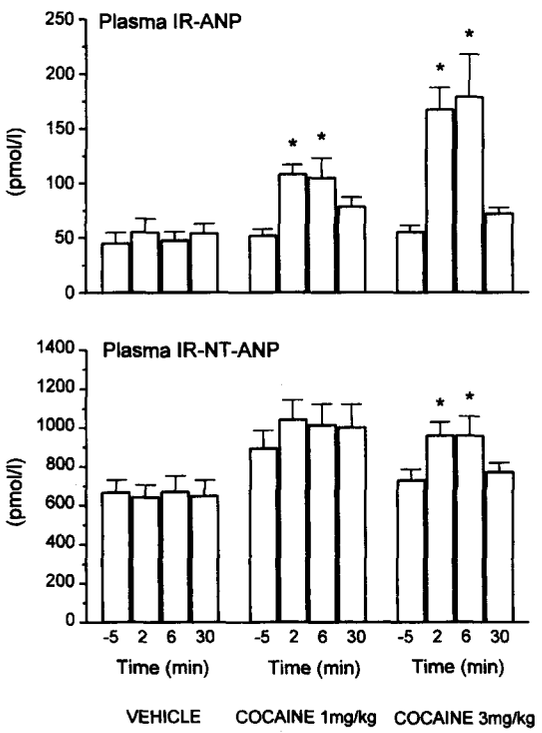

Fig. 2. The effect of intravenously administered cocaine on plasma immunoreactive atrial natriuretic peptide (IR-ANP) and N-terminal fragment of pro-ANP (IR-NT-ANP) levels in conscious rats. The blood samples were taken 5 min prior to and 2, 6 and 30 min after treatment. Results are expressed as means ± S.E.M. * $P < 0.05$ vs. before treatment values (ANOVA followed by Duncan test).

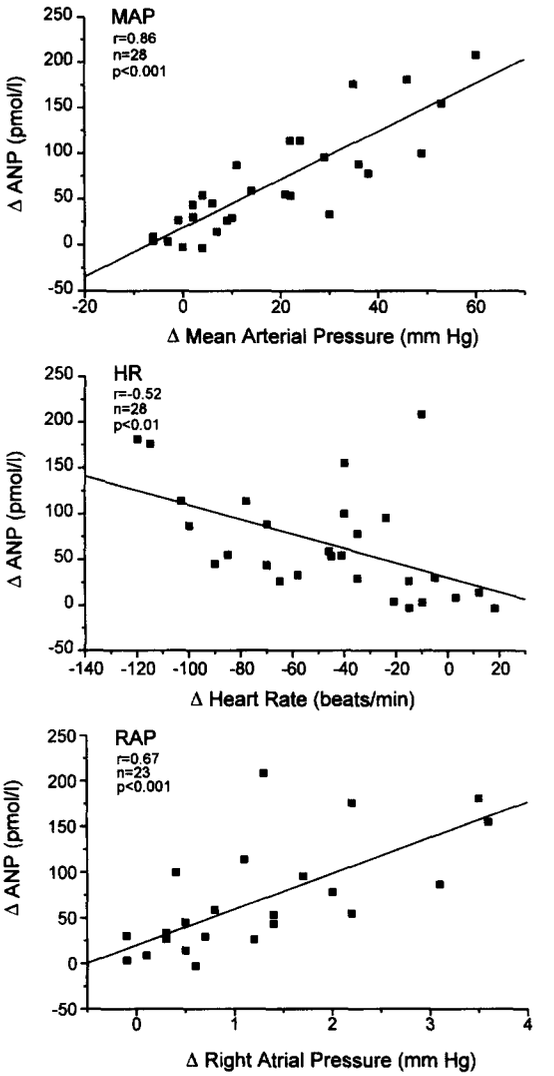

Fig. 3. The correlation between plasma immunoreactive atrial natriuretic peptide (ANP) level and haemodynamic changes in response to intravenously administered cocaine in conscious rats. MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure. Linear regression analysis was used.

3.3. Effect of cocaine on ANP release from neonatal rat cardiac myocytes in cell cultures

A complete serum-free medium was prepared using the components known to support the maintanance of primary neonatal cardiac myocytes (Shields and Glembotski, 1988). This CSFM formulation resulted in cultures that could be maintained for relatively long periods of time, and spontaneously contracting cells were seen from the second day in culture. In neonatal rat ventricular myocyte cultures, the basal secretion of ANP was 5.36 ± 0.35 nmol/ml/24 h ($n = 24$). As shown in Fig. 5, administration of cocaine did not stimulate ANP release from ventricular cultures. In fact, the highest dose (10^{-4} M) seemed to inhibit immunoreactive ANP release into the incubation medium ($-41 \pm 14\%$, $n = 5$) but the reduction was not statistically significant (Fig. 5). In contrast, acidic fibroblastic growth factor (acidic FGF), used as a positive control substance, stimulated ANP release from ventricular cells (Fig. 5); after 48 h of incubation, immunoreactive ANP levels of acidic FGF-treated ventricular myocytes were 4-fold higher than those of control cells, as reported previously (Tokola et al., 1994).

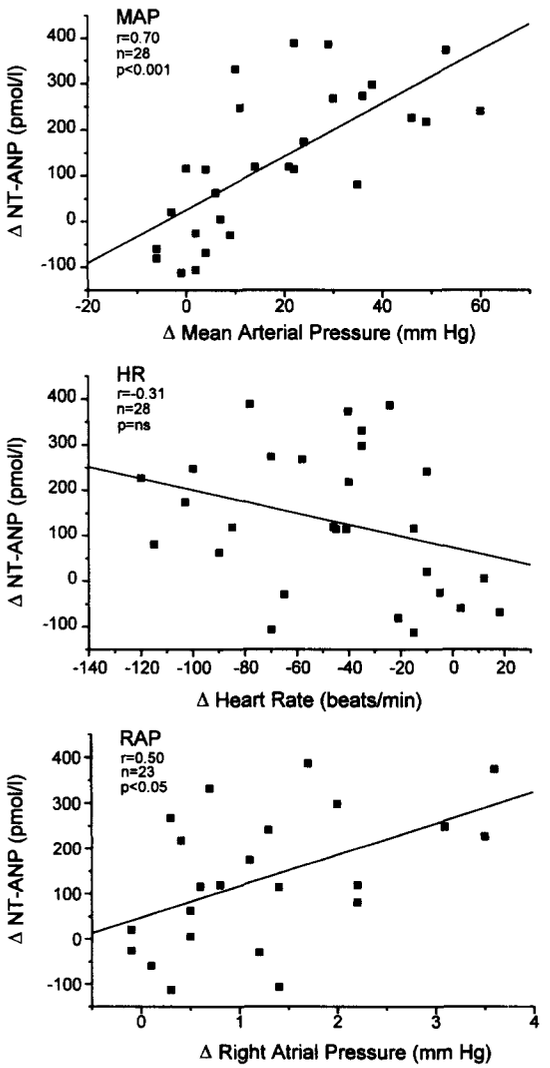

Fig. 4. The correlation between plasma immunoreactive N-terminal fragment of proANP (NT-ANP) level and haemodynamic changes in response to intravenously administered cocaine in conscious rats. MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure. Linear regression analysis was used.

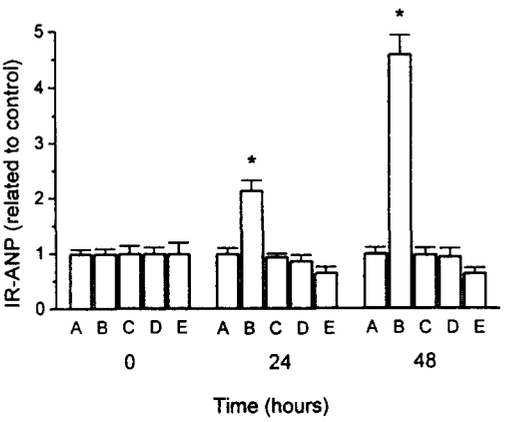

Fig. 5. The effect of cocaine on release of immunoreactive atrial natriuretic peptide (ANP) in ventricular myocytes. (A) Vehicle; (B) acidic fibroblast growth factor (acidic FGF) 50 ng/ml of culture medium; (C) cocaine 10^{-6} M; (D) cocaine 10^{-5} M; and (E) cocaine 10^{-4} M. Rat ventricular myocytes were incubated for 24 or 48 h in serum-free medium containing acidic FGF or cocaine hydrochloride at the concentrations indicated. The values represent 24-h accumulation of immunoreactive ANP (IR-ANP) in the culture medium expressed as means ± S.E.M. relative to control. * $P < 0.05$ (ANOVA followed by Duncan's test).

4. Discussion

We examined the effects of cocaine on haemodynamics and plasma ANP and N-terminal ANP levels in conscious rats, and studied the relationships between ANP levels and haemodynamic changes. In addition, we studied whether cocaine has direct effects on myocyte ANP release in vitro. Our findings on the effect of cocaine on mean arterial pressure were similar to those reported by other groups (Pitts et al., 1987; Knuepfer and Branch, 1992; Smith et al., 1993; Tella et al., 1993). Cocaine was found to increase mean arterial pressure in conscious rats. The pressor response was biphasic, with an acute rise followed by a more modest sustained pressor response. In addition, we observed that cocaine induced an acute rise in the right atrial pressure, but the pressor response was shorter, since the right atrial pressure returned to basal value much more rapidly than did mean arterial pressure, in about 10 min. Heart rate was found to slow abruptly about 10–20 s after the increase in mean arterial and right atrial pressure.

Other studies of the mechanism of cocaine-induced pressor responses have shown that the initial pressor response is mediated by the central nervous system in con-

scious rats (Wilkerson, 1988; Kiritsy-Roy et al., 1990: Knuepfer and Branch, 1992; Tella et al., 1993). The sustained pressor response seems to depend on the peripheral actions of cocaine, actions including inhibition of presynaptic reuptake of catecholamines, which leads to potentiation of the sympathetic nervous system and release of epinephrine from the adrenal medulla (Chiueh and Kopin, 1978; Kiritsy-Roy et al., 1990). The rise in arterial pressure in this phase is caused primarily by α_1-adrenoceptor-mediated vasoconstriction (Knuepfer and Branch, 1992; Tella et al., 1993).

The elevated pressure also starts a compensatory baroreflex which slows heart rate and modifies pressure levels during the sustained response (Pitts et al., 1987; Kloner et al., 1992; Knuepfer and Branch, 1992). Slowing of the heart rate could thus be considered as a physiological mechanism which helps the organism to maintain circulatory homeostasis. Cocaine affects the heart in several ways, however. First, cocaine is known to block the fast sodium channels of animal myocytes, which depresses depolarization, slows the conduction velocity and may lead to arrhythmias (Hale et al., 1989b; Przywara and Dambach, 1989; Billman, 1990). This could also explain the finding that cocaine has direct negative ionotropic effects on the myocardium and may cause dilated cardiomyopathy in humans (Weiner et al., 1986; Morcos et al., 1993; Perreault et al., 1993). Increased calcium flux into myocytes may contribute to contraction band necrosis and coronary artery spasm (Kalsner, 1992; Kloner et al., 1992). Finally, the increased sympathetic output also plays a major role in the heart by causing coronary artery spasm through its alpha-stimulator effects, possibly leading to ischaemia or infarction (Rezkalla et al., 1990).

ANP is a cardiac hormone that is secreted primarily by atrial myocytes in response to local wall stretch (Lang et al., 1985). Early data showed that a variety of neurohumoral and endothelial factors such adrenaline, angiotensin, endothelin or vasopressin can also induce the release of ANP (Ruskoaho, 1992). In the present study, the plasma ANP level increased dose dependently in conscious rats when cocaine was administered. All the haemodynamic changes had a statistically significant correlation with plasma ANP changes, suggesting that cocaine-stimulated ANP release may be explained by a change in atrial wall stretch. This agrees with previous studies showing that ANP secretion may be facilitated by an increase in sympathetic tone (for review see Ruskoaho, 1992) and that the increase in plasma ANP level in vivo after the administration of norepinephrine, phenylephrine, and other α_1-adrenoceptor agonists closely parallels the elevation of left ventricular afterload and atrial pressure (Katsube et al., 1985, Stewart et al., 1990). The α_1-adrenoceptor agonists are also reported to have a pressure-independent stimulator effect on ANP secretion (Ruskoaho et al., 1989b) and even β-adrenoceptor stimulaton may play some role (Rankin et al., 1987; King et al., 1991). Thus, the cocaine-induced ANP release from the heart could be mediated directly by norepineprine of sympathetic neural origin and epinephrine of adrenal medullary origin. However, as we also found that cocaine has no stimulatory effect on cardiocytes, we can conclude that cocaine increases plasma ANP levels mainly through its α_1-adrenoceptor-mediated haemodynamic effects, particularly by increasing the left atrial pressure, since the change in mean arterial pressure correlated better with the plasma ANP and N-terminal ANP changes than did the change in the right atrial pressure. In fact, in our study cocaine slightly decreased ANP secretion into the incubation medium in ventricular myocytes. This agrees with a recent study showing that cocaine acts directly on cardiac myocytes to produce a negative inotropic effect and decreases peak intracellular Ca^{2+} concentration (Qiu and Morgan, 1993), since several experimental manipulations or drugs that affect the concentration of intracellular Ca^{2+} influence ANP release (Ruskoaho, 1992).

The major storage form of ANP in myocytes is the 126-amino acid proANP-(1–126), which is cleaved into the N-terminal fragment of proANP-(1–98) and the C-terminal peptide ANP-(99–126) during or shortly after release (Needleman et al., 1989; Ruskoaho, 1992). N-terminal ANP is secreted by the heart in equimolar amounts with ANP and is cosecreted with ANP in response to atrial stretch both in vitro (Dietz et al., 1991) and in vivo (Itoh et al., 1988; Sundsfjord et al., 1988). Since N-terminal ANP has a reduced clearance compared with the C-terminal ANP (Katsube et al., 1986), N-terminal ANP circulates at a concentration 10–20-fold higher than that of ANP, as also shown in this study. Under our experimental conditions, acute cocaine administration resulted in simultaneous increases in both N-terminal ANP and ANP levels, indicating that cocaine acts mainly by altering the secretion of ANP and not its peripheral clearance from the circulation.

Natriuretic peptides could be of value clinically in two different ways. Firstly, they could be used as therapeutic agents (Ruskoaho, 1992). Secondly, the concentration of natriuretic peptides in plasma could give valuable diagnostic information about cardiac function (Struthers, 1994). N-terminal ANP concentration may especially be helpful since it can rapidly be measured in unextracted samples of blood. Both plasma ANP and N-terminal ANP concentrations have been reported to be raised in patients with heart failure and to increase further as the disease progresses (Perrella et al., 1991). Numerous studies have shown statistically significant positive correlations between circulating peptide levels and cardiac filling pressures (Perrella et al., 1991; Struthers, 1994). ANP measurements may provide valuable prognostic information in patients with chronic heart failure (Gottlieb et al., 1989) and after acute myocardial infarction (Svanegaard et al., 1992) and can be used to identify patients at risk of congestive heart failure (Davis et al., 1992). Studies by Lerman et al. (1993)

suggest that N-terminal ANP assays might be useful for the detection of patients with mild, even symptomless heart failure. A decrease in plasma ANP level may also be used as a marker of the effect of treatment in these conditions (Katoh et al., 1986; Perrella et al., 1991). The raised circulating levels of ANP reflect heightened cardiac secretion of the peptide in response to increased atrial stretch, but there is also a contribution from the ventricular myocardium when the ventricular function is chronically impaired (Yasue et al., 1989).

In the present study, plasma ANP and N-terminal ANP levels correlated significantly with the acute cardiotoxic effects of cocaine, e.g. the higher the plasma peptide levels were, the greater were the haemodynamic changes induced by acute intravenous administration of cocaine. Thus, our observations suggest a role for these peptides as a relatively simple, non-invasive marker of acute cocaine-induced cardiac toxicity. There are, however, some pitfalls. Although circulating levels of ANP are elevated in cardiac failure, the secretion of peptide is also responsive to a number of physiological stimuli including exercise, tachycardia, posture, water immersion and sodium intake (Ruskoaho, 1992). Concentrations of natriuretic peptides are also raised in chronic renal insufficiency, cardiac insufficiency and in severe hypertension. The first two of these should be readily detected during routine clinical assessment. Further, the acute response to cocaine unrelated to any clear underlying pathological condition can be distinguished from chronic conditions which lead to elevations of ANP and NT-ANP levels by repeated measurements of peptide levels in plasma. Thus, a trough plasma natriuretic peptide concentration may provide useful information about the acute harmful effects of cocaine on cardiac function. The possibility that the plasma ANP concentration might also reflect the long-term effects of cocaine on cardiac function remains to be studied.

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