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Research Article

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Developmental Changes in the Rat Atriopeptin Hormonal System

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Abstract

We undertook a study of fetal synthesis, storage, and release of atriopeptin (AP). Plasma levels of both atriopeptin immunoreactivity (AP_{ir}) and the NH₂-terminal fragment of the prohormone immunoreactivity (NTF_{ir}) were very high in the fetus (4 and 20 times the maternal plasma, respectively). However, the atrial content of the AP was low, but surprisingly, ventricular content of AP was quite high (relative to the adult) in the fetus and fell postnatally. Atrial AP messenger RNA (mRNA) increased with postnatal age, whereas ventricular mRNA was extremely high in the fetus and fell rapidly after birth. High fetal plasma peptide levels may derive from the mother since infusion of exogenous atriopeptin 24 into the mother resulted in parallel increases in fetal and maternal peptide levels. Fetal plasma AP_{ir} and NTF_{ir} levels partially reflect the markedly reduced total renal metabolic capacity compared with that of the adult. Plasma levels fell progressively after birth; whereas neonatal atrial content rose substantially. Plasma AP and NTF were simultaneously elevated in both the maternal and fetal circulation after vasopressin injection of the mother. The fetus can also respond to exogenous stimuli (vasopressin or indomethacin—presumably via ductal closure) and promptly release substantial amounts of peptide into its circulation. Thus, it appears that the AP hormonal system is functional during fetal life and responds avidly to increases in intracardiac pressure as does the mature animal.

Introduction

Atriopeptins (AP)¹ are spasmolytic, natriuretic, and diuretic peptides found in adult mammalian cardiac atria (1, 2). The peptides have multiple effects, including inhibition of aldosterone, renin and vasopressin release, reduction in systemic blood pressure and enhancement of renal glomerular filtration rate (reviewed in references 3–6). AP release can be stimulated by volume expansion (6) or agents, including 1-desamino-arg⁸-vasopressin (dAVP), that elevate right atrial pressure (7). Plasma levels of AP are elevated in both experimental animals and humans in conditions of systemic hypertension (8, 9), pulmonary hypertension (10), cardiac arrhythmias (11, 12) and the syndrome of inappropriate antidiuretic hormone (13).

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1. Abbreviations used in this paper: AP, atriopeptin, dAVP, 1-desamino-arg⁸-vasopressin; ir, immunoreactivity; NTF, NH₂-terminal fragment of the prohormone.

In the fetus or newborn, total body water is expanded, marked by a shift to a greater extracellular volume (14, 15). During the first few days after birth the neonate generally displays an exaggerated natriuresis and diuresis, resulting in a decrease of total body water and a lowering of extracellular volume toward the adult level (16). Furthermore, patterns of blood flow and vascular resistance alter dramatically with birth (17). To determine the association of AP with blood flow and volume changes associated with birth, we evaluated AP plasma and cardiac levels and determined the capacity for peptide release during late gestational and early neonatal periods in the rat.

Methods

Plasma and cardiac peptide levels. Pregnant Sprague-Dawley rats had pregnancy interrupted at gestational day 20 (E-20) or were allowed to deliver, and their pups were studied on days of life 3, 5, 7, 9, 11, and 21. For evaluation of plasma AP levels and cardiac stores, the fetus or neonate was decapitated. Blood was collected in 0.11 M sodium citrate (1:10, vol/vol) and centrifuged at 10,000 g for 1 min. The cardiac atria and ventricles were separated, homogenized with 1 M acetic acid, boiled for 10 min, and then centrifuged for 5 min at 10,000 g. Both the supernatants and plasma were stored at -70°C until assay.

Maternal to fetal AP transfer. To determine whether AP crosses the placenta, atriopeptin 24 (AP-24) was infused into the mother, and simultaneous blood samples were collected from the mother and fetuses. The 20-d pregnant rats were anesthetized with chloral hydrate (350 mg/kg i.p.). The jugular vein was cannulated for AP-24 infusion (300 ng/kg for 30 min), and the carotid artery was cannulated for blood collection. A midline incision was made in the lower abdomen to expose the uterus. At specific time points one fetus was removed and decapitated and blood was collected.

Maternal and fetal endogenous AP release. dAVP (Peninsula Laboratories, Inc., Belmont, CA) was injected i.v. into anesthetized 20-d pregnant animals (1 µg bolus) or i.p. into the fetus directly through the uterine wall (25 or 50 µg/kg). At time intervals of 2, 5, 15, and 30 min after injection, blood was collected from the mother. One fetus was utilized for each blood sample at the same time points.

Indomethacin is known to precipitate closure of the ductus arteriosus (18, 19). To determine the effect ductal closure on AP release in the E-20 fetus, pregnant animals were given indomethacin (5 mg/kg, Sigma Chemical Co., St. Louis, MO, dissolved in Tris-HCl buffer, pH 8, i.p.) three times daily on gestational days 18 and 19. On day 20 the fetuses were aborted, and plasma and cardiac extracts were prepared and stored for assay. In further studies, aspirin (Sigma Chemical Co.) was suspended in 5% gelatin and administered orally to the pregnant rats (100 mg/kg) three times daily on days 18 and 19. Blood was collected on the following day as in the indomethacin studies. The effect of indomethacin on AP release in the neonate was also studied by injecting indomethacin (5 mg/kg i.p. three times daily) on postnatal day of life 1 and killing on day 2, or neonates were injected on days 3 and 4 after birth and killed on day 5.

Renal AP metabolic rate. In order to determine the catabolism of AP-24 by the kidney, slices from adult kidneys were removed from anesthetized rats and homogenized in phosphate-buffered saline (pH 7.4) with 0.25% bovine plasma albumin to a final dilution of 1:800. For the fetal rats (E-20), four kidneys were combined per study; for neonatal

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rats, (day 3) two kidneys were pooled. For each sample, 990 μ l of diluted kidney in buffer was preincubated at 37°C for 5 min. Then 10 μ l of atriopentin 28 (AP-28) (final concentration 4, 40, 400 nM) was added, and incubated with the homogenate for 10 min. The reaction proceeded at a linear rate for > 10 min, and was stopped by rapid dilution by placing an aliquot of the sample in chilled radioimmunoassay (RIA) buffer and proceeding with RIA. The residual AP-28 was measured and subtracted from the original amount to determine the velocity of the reaction.

AP messenger RNA characterization. Atrial and ventricular RNA were prepared as described previously (Day et al., manuscript submitted for publication) and quantitated by A_{260} . RNA was displayed by electrophoresis through gels of 1.5% agarose in 10 mM NaPO₄, 3.7% formaldehyde (pH 7.5). The accuracy of the relative quantitation was checked by staining the gels with ethidium bromide before blotting the RNA onto nitrocellulose filters. The filters were probed with a purified 760-basepair (bp) AP complementary DNA fragment (Day and Wiegand, unpublished data) labeled to 5×10^7 cpm/ μ g with ³²P by nick translation, washed twice for 15 min in $0.1 \times$ standard saline citrate (SSC) at 20°C and twice for 15 min in $0.01 \times$ SSC at 45°C, and exposed to Kodak XAR film for 16 h as described previously (Day et al., manuscript submitted for publication).

RIA. The specific RIA for AP (20) and for the NH₂-terminal fragment of the prohormone (NTF) (21) have been described previously. Briefly, for the AP RIA, the samples were incubated with 10,000 cpm/tube ¹²⁵I-AP-24 and a 1:300,000 final dilution of guinea pig antiserum generated against synthetic rat AP-24. The cross-reactivity between AP-24 and AP-28 is 100% with this guinea pig antisera. Antibody-bound radioligand was incubated with a 1:10,000 final dilution of anti-guinea pig IgG antiserum (Linco Research Inc., Eureka, MO) at 4°C overnight. After centrifugation at 3,000 g for 30 min, the pellet was washed with 0.25% bovine plasma albumin in 10 mM sodium azide, and radioactivity was counted in a Micromedic Apex gamma counter (Micromedic Systems, Inc., Horsham, PA).

Results

Fetal and neonatal plasma and tissue peptide levels. Baseline fetal and neonatal immunoreactivity (ir) levels of both AP_{ir} and NTF_{ir} were remarkably different from those of the mother. Fig. 1 shows that the AP_{ir} of the fetus was 2.7 ± 0.18 ng/ml and the NTF_{ir} value was 60 ± 12 ng/ml. In contrast, the maternal values were 0.46 ± 0.05 ng/ml for AP_{ir} and 4.3 ± 0.9 ng/ml for NTF_{ir}. By 3 d of postnatal age, both levels had fallen with the NTF_{ir} level falling markedly between 3 and 5 d (Fig. 1).

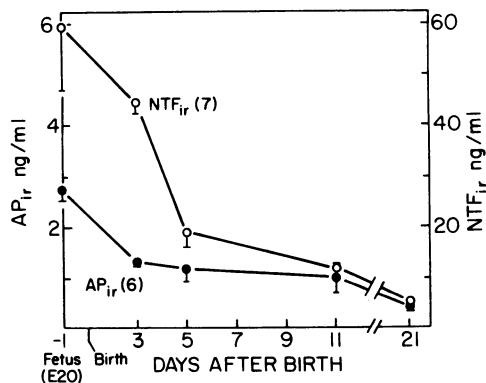


Figure 1. Fetal and neonatal plasma levels of atriopetins. The values are reported as the mean \pm SEM from six animals of each group in AP immunoreactivity (AP_{ir}) and from seven animals of each group in NTF immunoreactivity (NTF_{ir}).

The higher plasma levels of AP in the fetus and their longer circulation time might result from slower removal of the peptide. Comparison of the velocity of AP disappearance when incubated with renal homogenates showed no major differences on a per milligram of tissue basis among adult, fetal, and 3-d-old animals. The removal, therefore, was dependent entirely on the total mass of renal tissue which increased with age. With the highest concentration of AP used (400 nM to approximate maximum rates), removal of AP by the total adult kidney was 205.9 ± 3.8 nmol per 10 min; by 3-d-old kidney, 12.4 ± 1.3 ; and by fetal kidney, 5.5 ± 0.3 ($n = 5$).

Comparison of atrial and ventricular content of AP in the fetal, neonatal, and adult rats was surprising (Fig. 2). The ventricle of the fetus contained 24.8 ± 1.9 ng/mg protein, with this value falling only slightly by 3 d of postnatal age. By 14 d, the level had diminished greatly, and by 21 d was still measurable but very low at 1.2 ± 0.1 ng/mg protein. Atrial content was considerably higher than ventricular levels at all ages but showed the reverse maturational pattern. Levels of AP_{ir} in the fetus were 548 ± 43 ng/mg protein, rising to a peak of 2880 ± 216 ng/mg protein at 3 wk.

AP mRNA levels in neonatal atria and ventricles. The developmental regulation of the AP mRNA was, if anything, more striking than the differences observed in the stored peptide or circulating peptide levels. As shown in Fig. 3 A, AP mRNA levels increase in atria with the same time course and to about the same extent as the observed increase in the stored peptide levels. Ventricular mRNA levels are extremely high in the neonate, approaching the levels seen in atria from adults. These levels fall rapidly over the first 2 wk after birth (Fig. 3 B). The ratio of stored AP_{ir} to mRNA is thus substantially higher in the adult atrium than it is in the neonatal ventricle, suggesting post-transcriptional control of the stored AP_{ir} levels. This control could occur at the level of translation, but is more likely to result from altered processing or secretion of the peptide.

Placental transport of atrial peptide. Maternal infusion of AP-24 resulted in elevated fetal AP levels (Fig. 4). Upon initiation of the infusion, both fetal and maternal levels of AP_{ir} rose rapidly. However, when the infusion was terminated, the maternal level fell to baseline within 5 min while the fetal level plateaued, falling only after 90–120 min. When control studies were done by infusing a comparable volume of saline into the mother, no changes in AP_{ir} were detected in either the mother or the fetus.

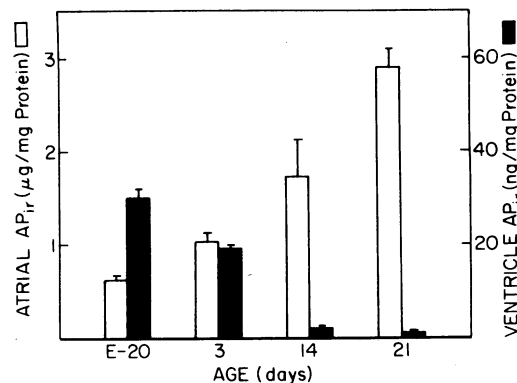


Figure 2. Fetal and neonatal cardiac content of atriopetins. The open bars represent the atrial AP_{ir} ($n = 7$) and the closed bars represent the ventricular AP_{ir} ($n = 10$).

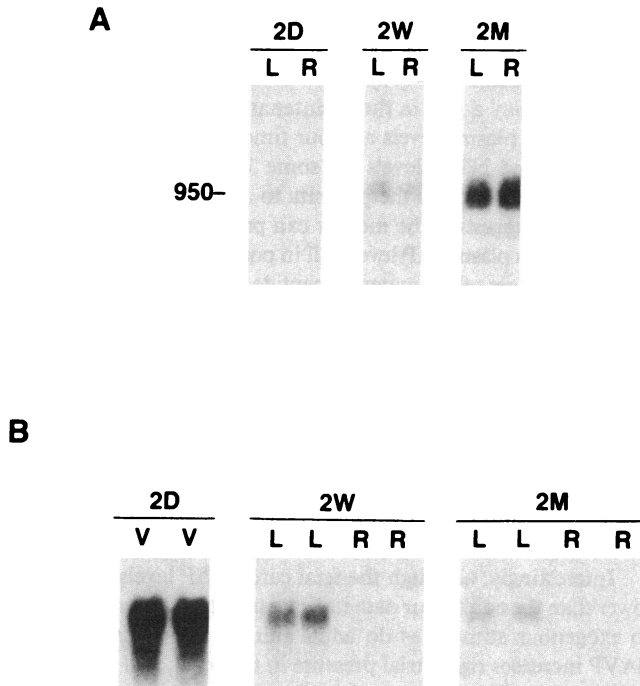


Figure 3. AP and mRNA in atria and ventricles during development. (A) Northern blot of RNA from left and right atria of various age animals. The samples (1 μ g total RNA per lane) were from left (L) and right (R) atria from animals that were 2 d (2D), 2 wk (2W), or 2 mo (2M) old. Samples were prepared, blotted, and probed as described in Methods. (B) Northern blot of RNA from left and right ventricles of various age animals. The samples (10 μ g total RNA per lane) were from the lower half of the whole ventricle (V) or left (L) or right (R) ventricular walls from animals that were 2 d (2D), 2 wk (2W), or 2 mo (2M) old. Samples were prepared, blotted, and probed as described in Methods.

Because it is known that dAVP stimulates the release of both AP-28 and its NTF (but no intact prohormone is released) into the circulation of adult rats (9), experiments were undertaken to discern whether this stimulus would be effective in the already volume-expanded pregnant animal and whether peptide levels in the fetus would be altered. Fig. 5 shows that 1 μ g of dAVP given to the mother prompted a rise in both AP_{ir} and NTF_{ir} in both maternal and fetal animals. The NTF_{ir} level remained high in the mother for at least 30 min after injection, whereas the AP_{ir} level fell to baseline by 30 min. As seen with maternal AP

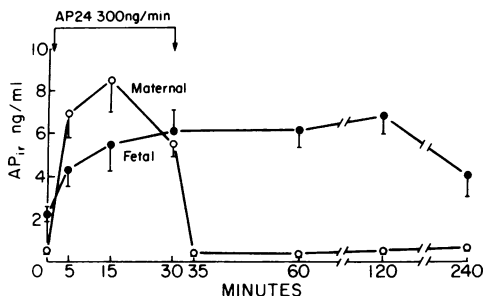


Figure 4. Maternal and fetal atriopeptin levels produced by infusion of exogenous AP-24 into the mother. Values represent the mean \pm SEM for five mothers and 10 fetuses of each group.

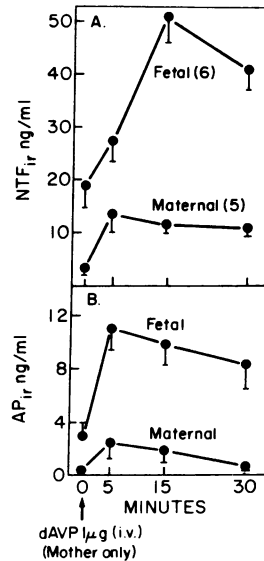


Figure 5. Effect of maternal dAVP stimulation on plasma levels of AP in mother and fetus. Values represent the mean \pm SEM for five mothers and six fetuses of each group.

infusion, however, the fetal levels of both AP_{ir} and NTF_{ir} remained high during that 30 min.

Fetal AP release. The rise in fetal atrial peptide levels after a bolus injection of dAVP probably reflects the placental transfer of both the AP-28 and the remaining high molecular weight NTF. However, some of the fetal response might derive from the effects of any dAVP that crossed the placenta from the mother to the fetus. The uterus was exposed in pregnant rats, and an intraperitoneal injection of dAVP to the fetal animal through the uterine wall produced a striking elevation in AP_{ir} in the fetus (Fig. 6). The lower dose of 25 μ g/kg (i.p.) given to the fetus resulted in no change in maternal levels, but the higher dose of 50 μ g/kg to the 1–2-g fetus doubled the maternal AP_{ir} value. In control fetal animals, a similar volume of saline injected i.p. led to no change in fetal or maternal AP_{ir} levels.

The patent ductus arteriosus allows blood to go from the pulmonary artery where high pulmonary vascular resistance impedes flow to the systemic circulation where vascular resistance is less. Ductal patency is largely maintained by endogenous vascular synthesis of the vasodilator prostaglandins (prostaglandin E₂ and prostacyclin). Agents, such as indomethacin or aspirin,

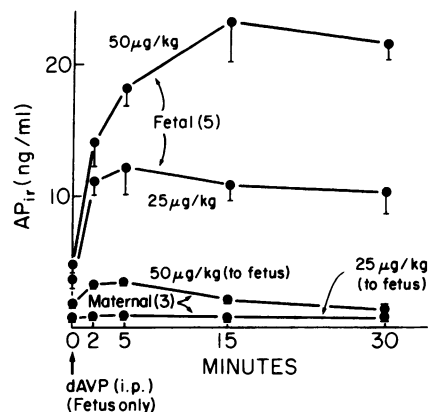


Figure 6. Effect of fetal dAVP stimulation on plasma levels of AP in mother and fetus. Values represent the mean \pm SEM for three mothers and five fetuses of each group.

that inhibit prostaglandin biosynthesis have been demonstrated in many species to close the ductus. Fig. 7 illustrates the changes in AP_{ir} effected by giving the pregnant animal indomethacin and presumably closing the ductus. Administration of indomethacin produced a striking increase in fetal plasma AP_{ir} compared with a control group which received the vehicle. Simultaneously, there was a significant decrement in the AP concentration of the right atrium. No significant differences were demonstrable in the left atrium, the combined ventricles, nor in the maternal plasma AP_{ir} . Furthermore, a 2-d-old neonate (at a time when the ductal closure would have already naturally occurred), which had received indomethacin on day 1 and was killed on day 2, had plasma AP_{ir} levels (indomethacin 4.05 ± 0.53 ng/ml) no different from the control animals (3.17 ± 0.70 ng/ml). Indomethacin treatment of 3- and 4-d-old neonates (sacrificed on day 5) were also not different from controls (indomethacin 1.47 ± 0.32 ng/ml vs. control 0.97 ± 0.18 ng/ml). Treatment of pregnant animals with aspirin (another cyclooxygenase inhibitor) also produced an elevation in fetal plasma AP_{ir} . After 1 d of treatment, the AP_{ir} level was 4.2 ± 0.76 ng/ml ($n = 3$) rising to 10.2 ± 2.3 ng/ml ($n = 6$) with 2 d of treatment and 11.3 ± 1.9 ng/ml ($n = 8$) with 3 d. The AP_{ir} level in the mother did not change during this time.

Discussion

During fetal life, vascular resistances are variable. Blood coming from the placenta goes through the ductus venosus to the heart where a portion goes from the right atrium through the foramen ovale into the left atrium. The remainder of the blood goes into the right ventricle and into the pulmonary artery. However, pulmonary vascular resistances are high during fetal life, and as a result, the blood entering the pulmonary artery passes through the patent ductus arteriosus and enters the systemic circuit via the aorta. The blood that has come across the foramen ovale plus the blood that has come through the ductus arteriosus then is delivered to the systemic circuit. 65% of this blood goes back to the placenta while the other 35% is delivered to the fetal body (17). Because of the large percentage of return to the placenta for oxygenation, the systemic blood pressure in the fetus and vascular resistances are relatively low. After birth, the blood flow pattern changes and the vascular resistances are altered. Once the neonate becomes an air breather and the blood becomes more oxygenated, pulmonary vascular resistances fall and the blood can travel throughout the pulmonary circuit. With increased oxygen tension and decreased prostaglandins, the ductus

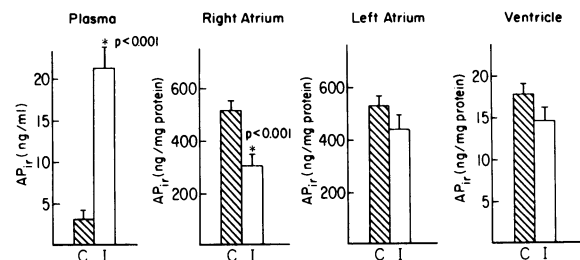


Figure 7. Effect of maternal indomethacin administration on plasma and cardiac levels of AP in fetus. The open bars represent the indomethacin treated group (eight fetuses of each group) and the hatched bars represent the control group (10 fetuses of each group).

arteriosus closes. With the removal of the placenta from the systemic circuit, systemic vascular resistances rise, and blood pressure rises somewhat (17).

AP may play a role in the maintenance of these blood flow patterns. AP_{ir} plasma levels are four times higher than those in the mother and NTF_{ir} levels are some 10 times higher. Atrial peptides appear to cross the placenta to accumulate in the fetal circulation, suggesting the mother can provide a major portion of fetal AP. As plasma AP levels fall in postnatal life, presumably reflecting the loss of the maternal peptide, there is a concomitant rapid elevation in neonatal atrial AP content and synthetic capacity. It is also noteworthy that the fetal ventricles contain considerable AP. Once the fetus is delivered and the pulmonary circuit opens, ventricular peptide and mRNA content progressively falls. Adult ventricular AP synthesis and content are very low, but we recently demonstrated that left ventricular hypertrophy induced by aorta banding rapidly results in the induction of AP mRNA and peptide levels in the left ventricle (Day et al., manuscript submitted for publication).

Interestingly, although the fetal cardiac AP levels are much lower than the adults, our data indicate that the fetus can respond to exogenous stimuli, as do adult animals. Administration of dAVP increases right atrial pressure in the adult, and stimulates AP (7) and NTF release in a dose-dependent manner. This phenomenon is also demonstrated very clearly by the administration of dAVP to the mothers, showing a prompt response in release of AP with an elevation in maternal levels. Similarly, dAVP administered to the fetus causes a prompt rise in fetal AP levels. The experiments observing the effect of indomethacin and aspirin would suggest that the fetal cardiac AP system does respond to changes in intracardiac pressure. If the ductus arteriosus were to close prior to the time of birth, intracardiac pressure (both ventricular and atrial) would rise sharply, and the release of AP would be anticipated. In our studies, indomethacin and aspirin administration to the mother resulted in a pronounced increase in circulating plasma AP levels in the fetus, whereas maternal levels did not change. In contrast, when indomethacin was given after the time when the ductus had closed after birth, there was no such effect.

Whether fetal AP are involved in the regulation of fetal body fluids is unknown. However, after birth when there is a sudden change in blood flow and vascular resistance, the circulating high level of AP may participate in the postnatal diuresis and natriuresis that occurs. Furthermore, the fact that the placenta has been found to be a rich source of AP receptors (22) suggests a possible role in regulation of placental blood flow or fluid exchange. It appears, then, that the AP system develops during fetal life, and that AP can cross the placenta from the mother to the fetus and that release of AP is stimulated by an increase in intracardiac pressures much as is demonstrable in the mature animal. The regulation of AP synthesis and its relation to physiological changes in blood flow and volume regulation in development present challenging problems for resolution.

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