Presence and interaction in tissues of atrial natriuretic peptide, oxytocin and vasopressin: new insights

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Summary

Atrial natriuretic peptide, oxytocin and vasopressin are three well known and widely studied molecules since many years. They have been fully characterised from a genetic and biomolecular point of view and a number of receptor-dependent functions have been recognised for them. Nevertheless, in the last years our group has conducted morphologic studies, using an immunohistochemical approach complemented by molecular biology techniques, and could show non-canonical localization and co-localization of these peptides in normal and pathologic tissues, that permitted us to postulate that they may be involved in a wider range of functions than usually assumed and not yet fully understood. In this minireview we summarise some of the main results that open new scenarios in the comprehension of the biologic activities of these peptides and allow to postulate a role for them as diagnostic tools.

Key words

Hypothalamic magnocellular nuclei, Breast, Prostate

Introduction

The atrial natriuretic peptide or atriopeptin (ANP) was found by de Bold (1985) first in the atrial myocardiocytes. ANP is secreted as a pro-hormone, the so called atriopeptinogen, with 126 amino acids that is reduced by selective enzymatic scission to a circulating peptide of 28 amino acids with a disulfuric bridge that is critical for its biological activity.

To date, two other peptides of the same natriuretic family (NPs), specifically the brain natriuretic peptide (BNP) and the C-type natriuretic peptide (CNP), have been described. ANP is mainly expressed by atrial myocardiocytes, while ventricular myocardiocytes secrete above all BNP. Both ANP and BNP regulate blood pressure and volume, also through the involvement of the renin-angiotensin-aldosterone system; by contrast, CNP is expressed mostly in brain and endothelial cells.

Specific membrane-receptors for NPs have been identified; these receptors are coupled with a guanylate cyclase and are indicated as NPR-A and NPR-B. The selectivity of NPR-A for the three NPs members is, respectively, ANP>BNP>CNP, while the selectivity of NPR-B is, respectively, CNP>ANP>BNP.

Oxytocin (OT) is a nonapeptide hormone with a disulfuric bridge between two cysteine aminoacids. The OT is synthesized by hypothalamic magnocellular supraop-

tic (SON) and paraventricular (PVN) nuclei, but OT has also been detected in several extra-hypothalamic areas of the brain. The OT plays its traditional roles on the uterus and mammary gland and moreover, similar to vasopressin (VP), OT is able to reduce sodium excretion from kidney, to induce vasorelaxation in canine arteries by activating V1-vasopressinergic receptors (Katusic et al.,1986) and to produce vasodilatation in pulmonary vasculature (Russ et al.,1992). The infusion of OT in the canine vertebral artery induced dilation of the vertebral, anterior spinal and basilar arteries (Suzuki et al.,1992), while the infusion of a high concentration of OT induced vasoconstriction of the renal artery in the rat (Loichot et al., 2001).

It is well-known that oxytocin and vasopressin are synthesized by hypothalamic paraventricular and supraoptic nuclei, but immunohistochemical study showed that also the "accessory nuclei", a cluster of magnocellular neurons situated between the paraventricular and supraoptic nuclei (SON and PVN, respectively), synthesized both vasopressin (Fig 1a) (Farina Lipari and Valentino, 1993) and oxytocin (Fig 1b) (Farina Lipari and Valentino, 1995).

Interestingly, a functional relationship between OT and ANP secretion has been described. Indeed it has been shown that cardiac ANP-release in bloodstream occurs after stimulation by hypothalamic OT (Gutkowska et al., 1997). Moreover, other investigations on the hypothalamic SON, PVN and periventricular nuclei showed co-existence of ANP and OT in the adult rat (Jirikowski et al., 1986; Chriguer et al., 2001). Further investigations demonstrated that ANP, OT and VP are present also in a number of non-canonical sites where they probably participate in a wide variety of species specific activities of the body, some of which have been object of our investigations in the past.

OT, VP and ANP during hypothalamic development

We carried out several studies by immunohistochemistry and PCR analysis to provide a possible morpho-functional relationship between the appearance of OT and VP in the SON and PVN during development. Therefore we analysed developing rats from the 15th day of prenatal life to postnatal life (Farina Lipari et al, 2001). The research evidenced that VP-peptide appears in the SON at the 16th day (Fig. 2a) and in the PVN at the 18th day (Fig. 2b) of prenatal life; by contrast, OT-peptide becomes detectable in SON and PVN only at the 2nd day of postnatal life (Figs. 2c and 2d). Furthermore, PCR-analysis showed that VP-mRNA appears, as the VP-peptide, on the 16th day of intrauterine life; surprisingly, OT-mRNA appears on the 18th day of prenatal life, while OT-peptide appeared only at the 2 nd day after birth.

In an analogous study about ANP secretion we found that in the SON both ANP-peptide (Fig. 3a) and ANP-mRNA appear at the 18th day of prenatal life (Farina Lipari et al, 2005). Since the suprachiasmatic nucleus is involved in neurosecretion as well as the SON and PVN, we extended the investigations for ANP to the suprachiasmatic nucleus, where ANP-peptide appeared at the 16th day of prenatal life (Fig. 3b) (Farina Lipari et al., 2007).

All together these results indicate that in the SON both VP and ANP appear approximately at the same time of foetal life, which is possibly due to the fact that they play antagonist roles in the regulation of body fluid; by contrast, OT-peptide,

differently from VP and ANP, appears in postnatal life, so during the intrauterine life the release of cardiac ANP is totally independent by the hypothalamic OT-peptide.

OT and ANP in exocrine glands

Other researches by our group further investigated in which non canonical organs OT and ANP are present and possibly involved in modulation of biological activity. Since both ANP and OT have a role in regulation of body fluids, we carried out investigations on a modified sweat gland, the mammary one, both normal (from rabbit) and tumoral (from human) (Farina Lipari et al., 2003; Valentino et al., 2005, 2008). Analysing rabbit non-lactanting breasts we showed that ANP is present in the cellular apical or perinuclear area of the lobular ducts and, interestingly, it often co-localized with OT. In human breast cancer the results by immunohistochemistry and RT-PCR evidenced a reduction of ANP, but not OT, during cancer progression so that we hypothesized that this molecule could be addressed as a novel marker to predict breast cancer progression.

Analogous studies were also been carried out on human normal and hyperplastic prostate. In normal prostate ANP was localized in glands as well as in stromal cells; we postulated that in glands ANP could have a role in regulating the electrolyte composition of prostatic fluid, while in stromal cells adjacent to the periglandular vessels ANP could regulate the muscular tissue tonicity and the fluidity of prostatic fluid. In hyperplastic prostate, ANP-immunopositivity modestly increased in the glandular cells, while it strongly increased in the stromal cells; moreover, OT-positivity increased in glandular, but not in stromal, cells of hyperplastic prostate (Fig. 4). At last, we postulated that in the prostate OT may induce ANP expression, via a paracrine mechanism, similar to what has already been shown for the heart (Gutkowska et al.,1997).

Finally, we recently performed an immunohistochemical research on ANP and insulin in the human foetal pancreas from non diabetic and diabetic mothers, evidencing that ANP and insulin colocalise in beta-cells of pancreatic insulae of foeti from diabetic mothers but not in those from non-diabetic ones, suggesting that in the former a paracrine feed-back between these hormones could be present (Fig. 5) (Valentino et al., 2009).

Conclusion

In the last years our investigations, performed mainly using morphologic techniques, added new information about ANP, OT and VP cell and tissue distribution, in normal and pathologic tissues, both from humans and other mammals. These studies permit us to postulate that these molecules may be involved in the homeostasis of a wider number of organs than supposed before. In our opinion, although our studies are not conclusive, this field of biology is still open and morphologic data, complemented with biomolecular ones, may permit in the future to perform new investigations which could offer results useful for biologists, physicians and evolutionary scientists.

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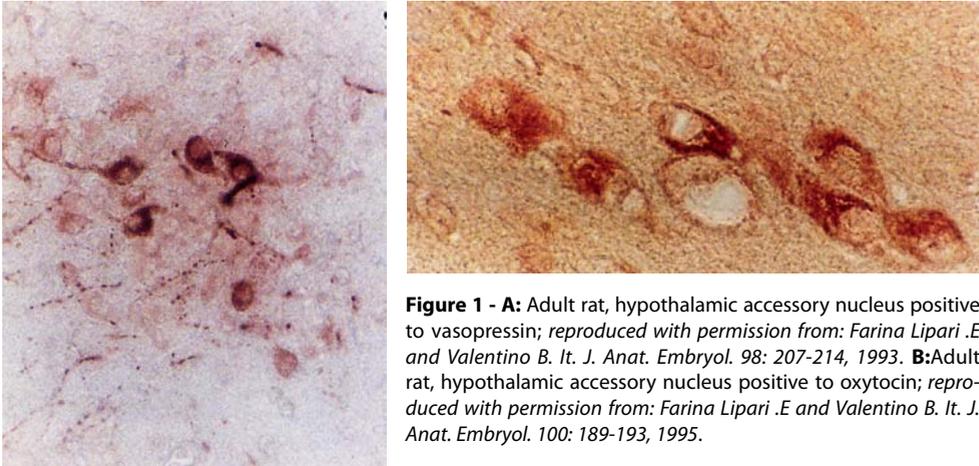
Figures

Figure 1 - A: Adult rat, hypothalamic accessory nucleus positive to vasopressin; *reproduced with permission from: Farina Lipari .E and Valentino B. It. J. Anat. Embryol. 98: 207-214, 1993*. **B:**Adult rat, hypothalamic accessory nucleus positive to oxytocin; *reproduced with permission from: Farina Lipari .E and Valentino B. It. J. Anat. Embryol. 100: 189-193, 1995*.
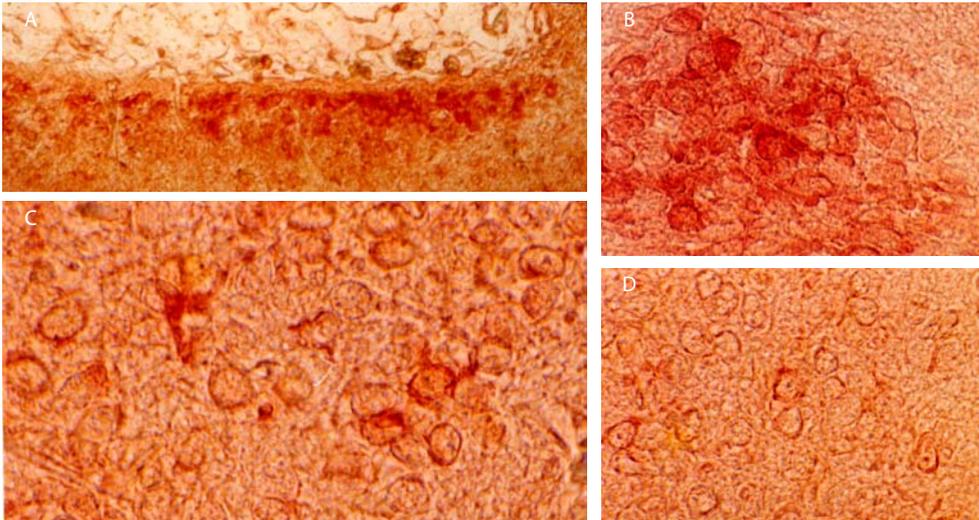

Figure 2 - A: Rat embryo, 16th prenatal day, supraoptic nucleus positive to vasopressin. **B:** Rat embryo 18th prenatal day, paraventricular nucleus positive to vasopressin. **C:** Rat newborn, 2nd postnatal day, supraoptic nucleus positive to oxytocin. **D:** Rat newborn, 2th postnatal day, paraventricular nucleus positive to oxytocin. *Reproduced with permission from: Farina Lipari E. et al., Eur. J. Histochem. 45: 163-168, 2001.*
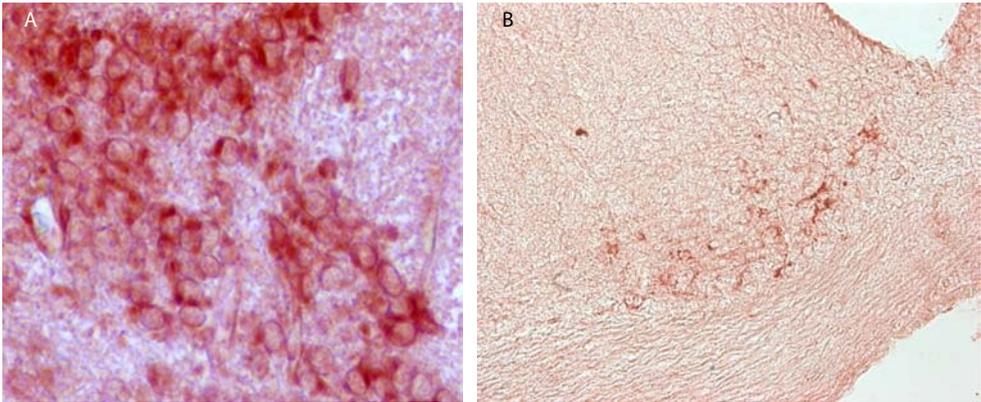
Figure 3 - A: Rat embryo, 18th prenatal day, supraoptic nucleus positive to ANP; *reproduced with permission from Farina Lipari E. et al., Eur. J. Histochem .49: 379-384, 2005*. **B:** Rat embryo, 16th prenatal day, suprachiasmatic nucleus positive to ANP; *reproduced with permission from Farina Lipari E. et al., It. J. Anat. Embryol. 112: 19-25, 2007*.
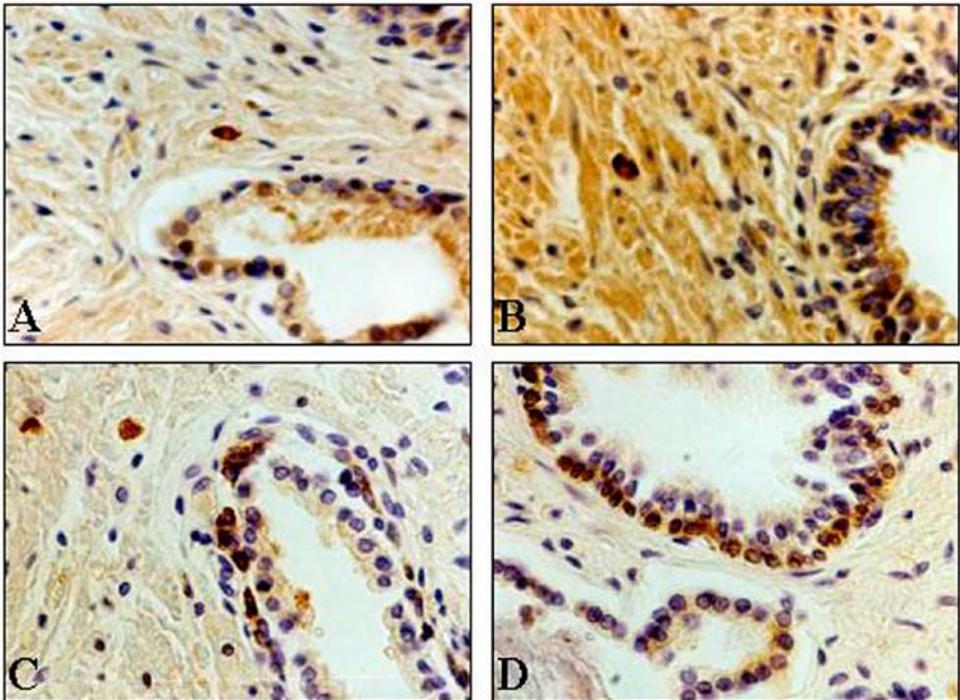

Figure 4 - Normal (**A** and **C**) and hyperplastic (**B** and **D**) human prostate: positivity for ANP (**A** and **B**) and oxytocin (**C** and **D**). *Reproduced with permission from: Farina Lipari E. et al., Eur. J. Histochem. 47: 133-138, 2003.*
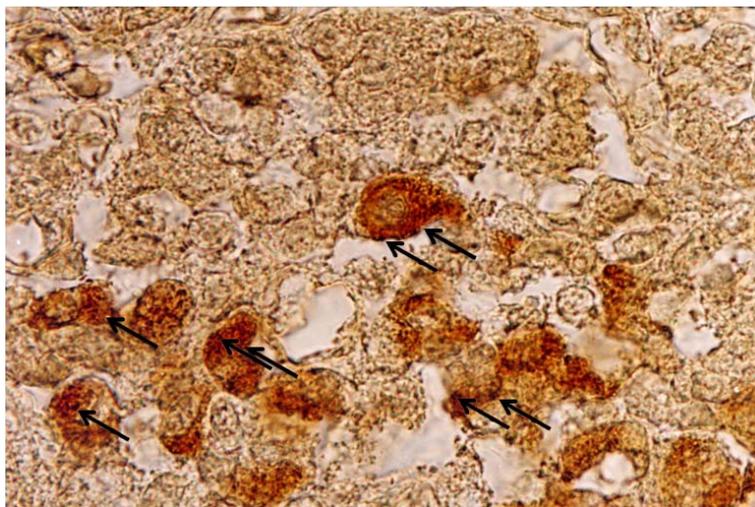
Figure 5 - Foetal pancreas from diabetic mother. Double immunostaining for ANP (small black dots: arrows) and insulin (orange-brown). *Reproduced with permission from: Valentino B. et al., It. J. Anat. Embryol. 114: 21-114, 2009.*