Natriuretic Peptides as Antigrowth Factors

Ellis R. Levin

CONTENTS

Natriuretic Peptides as Antigrowth Factors
Natriuretic Peptides and Development
Astrocyte Proliferation: Which Natriuretic Peptide and Which Receptor?
Natriuretic Peptides as Antigrowth Factors: Signaling to the Nucleus
Natriuretic Peptides as Antigrowth Factors: Nuclear Targets
Natriuretic Peptides as Antigrowth Factors: Cell Cycle
Summary
Acknowledgment
References

NATRIURETIC PEPTIDES AS ANTIGROWTH FACTORS

The natriuretic peptides act as antigrowth factors for a variety of cells (1), including mesangial (2), vascular endothelial (3) and smooth muscle cells (4), and astrocytes (5). All three members of this family of peptides (ANP, BNP, and CNP) have been shown to inhibit cell proliferation, at least in vitro. This is particularly evident when cells are stimulated to divide by growth factors, such as platelet-derived growth factor (PDGF) or basic fibroblast growth factor (bFGF). CNP has been shown to also inhibit arterial intimal thickening in vivo, probably through inhibiting vascular smooth muscle proliferation induced by vascular injury (6). Therefore, understanding the mechanisms whereby the natriuretic peptides inhibit cell growth may lead to therapeutic applications to prevent the development of disease resulting from deregulated cell proliferation. This chapter explores the mechanisms of antiproliferation and the specific actions of the natriuretic peptides to limit cell growth.

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223
NATRIURETIC PEPTIDES AND DEVELOPMENT

The natriuretic peptides and their receptors can often be detected temporally at the time of organ development. Regarding the central nervous system (CNS), we have found that atrial natriuretic peptide can be secreted from fetal rat diencephalic neurons in primary culture. These cells, comprised 85% by hypothalamic cells, express ANP mRNA as early as embryonic d 14, a time when the hypothalamus is just being formed (7). We have also been able to detect the binding of ANP and the expression of natriuretic peptide clearance receptors (NPRC) and guanylyl cyclase receptors (undetermined subclass) (8), as early as embryonic d 15. These data strongly suggest that the natriuretic peptide system plays a developmental role, perhaps to regulate proliferation or to modulate the actions of other neurotransmitters on astroglia or other cells within the CNS. There may be an important interaction with other neuropeptide systems at this time. For instance, we found that the expression of the endothelin system in the brain coincides with the hypothalamic expression of the natriuretic peptides, and that endothelin can limit the actions of ANP to generate cGMP in astrocytes (9). In turn, the natriuretic peptides can inhibit endothelin signaling and action on astroglia (see Natriuretic Peptides as Antigrowth Factors: Signaling to the Nucleus). It has already been reviewed in Chapter 11 that ANP can interact with the angiotensin system and other CNS neurotransmitter systems. Thus, the temporal and anatomical expression and interaction with other important neurotransmitter systems strongly suggests important roles for the natriuretic peptides in the CNS.

A very analogous situation to the brain is the postnatal vasculature in which the natriuretic peptides limit the actions of other important vasoactive proteins. Therefore, it is likely that the details of growth and developmental regulation by the natriuretic peptides in the CNS will be similar in other organ systems. Although an in-depth examination of the steps by which the natriuretic peptides limit growth will be given only for the astrocyte in culture, many of the details have been confirmed in other systems, most notably cultured vascular smooth muscle cells, and can therefore be used as a general guide to the role and actions of the natriuretic peptides in other organ systems.

ASTROCYTE PROLIFERATION: WHICH NATRIURETIC PEPTIDE AND WHICH RECEPTOR?

It is well recognized that all three natriuretic peptides (NPs) and their receptors are expressed in the CNS. There are some differences in the anatomical location of the peptides and certainly of the receptors (10,11), as determined from immunocytochemical and ligand-binding localization in brain slices. This diversity may indicate unique functions of the peptides within the CNS. The neurophysiology of the NP has already been reviewed in depth earlier in this text. Regarding astrocyte proliferation, we showed that both ANP and BNP have a roughly equipotent capacity to inhibit the nuclear incorporation of thymidine into cultured diencephalic astrocytes, an index of DNA synthesis and cell proliferation (5). The receptors expressed on the cell membrane probably dictate the specificity of NP effects, since all three family members appear to have the potential to inhibit growth.

In various models of cell proliferation, the NPs have been reported to work through the production of cGMP (Fig. 1). In cultured mesangial cells, it has been shown that the NPs stimulate cGMP and inhibit cell proliferation, and that exogenous cGMP mimics the effects of the NP (2). Supporting a guanylyl cyclase mechanism, several vasoactive