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Effects of *Dendroaspis* natriuretic peptide on delayed rectifier potassium currents and its mechanism

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ABSTRACT

Dendroaspis natriuretic peptide (DNP), a newly-described natriuretic peptide, plays an inhibitory role in smooth muscle motility of the gastrointestinal tract. However, the effect of DNP on delayed rectifier potassium currents $I_{K(V)}$ is still unclear. In this study, we sought to investigate the effect of DNP on $I_{K(V)}$ and its mechanism in gastric antral circular smooth muscle cells using the whole-cell patch-clamp technique. DNP significantly inhibited $I_{K(V)}$ in a concentration-dependent manner. LY83583 (1 μmol/l), a guanylate cyclase inhibitor, significantly impaired DNP-induced inhibition of $I_{K(V)}$. Moreover, DNP-induced inhibition in $I_{K(V)}$ was potentiated by the cyclic guanosine monophosphate (cGMP) sensitive phosphoesterase inhibitor zaparinast (0.1 μmol/l). DNP-induced inhibition of $I_{K(V)}$ was completely blocked by KT5823, an inhibitor of cGMP-dependent protein kinase G(PKG), but not affected by KT-5720, a PKA-specific inhibitor. Taken together, our results suggest that DNP inhibits $I_{K(V)}$ via the cGMP/PKG-dependent signaling axis instead of the cAMP/PKA pathway.

1. Introduction

Dendroapis natriuretic peptide (DNP), a 38-amino residue peptide that contains a disulfide ring structure and was originally isolated from the venom of the green mamba, is a new member of the natriuretic peptide family [1]. Up to now, its function of is not so clear. Studies about its physiological functions are limited and mainly focus on the cardiovascular [2], urinary [3] and genital systems [4]. Moreover, little is known about the functional role of DNP in gastrointestinal cells. Kim et al. [5] have for the first time demonstrated that DNP is present in rat colon and can control colonic motility as a local regulator. Our previous study indicated that DNP inhibited gastric motility by increasing the calcium-activated potassium current ($I_{K(Ca)}$) [6]. The effects of DNP may be attributed to the increase in cGMP production and the activation of the inositol triphosphate receptor (IP_3R) [7].

The functions of different types of potassium currents in smooth muscles are variable among different animals as well as among different organs. Yuan et al. [8] identified a current $I_{K(V)}$ and $I_{K(Ca)}$ in pulmonary arterial smooth muscle cells and demonstrated that the delayed rectifier potassium current ($I_{K(V)}$) plays an important role in the regulation of membrane potential, whereas $I_{K(Ca)}$ functions as a critical negative feedback pathway in the regulation of governing membrane potential and vascular contractility. The transient outward potassium currents ($I_{(to)}$) contributed to the maintenance of negative resting membrane potentials in murine antral smooth muscle cells [9]. Koh et al. [10] observed that the basal activation of the ATP-sensitive potassium current (I_{KATP}) contributed to the membrane potential in murine colonic smooth muscles and that I_{KATP} could contribute to dual regulation of membrane conductance and generate either depolarization or hyperpolarization, depending on the open probability of I_{KATP}.

Li et al. [11] demonstrated that there are two kinds of potassium current, $I_{K(Ca)}$ and $I_{K(V)}$ in gastric antral circular myocytes of the guinea-pig. There are some reports to investigate how $I_{K(Ca)}$ participates in regulating gastric motility. Duridanova et al. [12] reported that the oxytocin-related relaxation in guinea-pig antral smooth muscle cells (SMCs) may result from the activation of Ca^{2+}-sensitive K^+ conductivity via activation of IP3-induced release of Ca^{2+} from the submembrane located cisternae of the sarcoplasmic reticulum Ca^{2+} stores and in turn, this evokes a non-inactivating component of $I_{K(Ca)}$, hyperpolarizing the cell membrane. Our previous study [13] also demonstrated that DNP inhibited gastric motility by increasing $I_{K(Ca)}$. However, there are few studies about the relationship between $I_{K(V)}$ and gastric motility. Considering that $I_{K(V)}$ also plays an important role in the regulation of gastric SMC function, in this study we first

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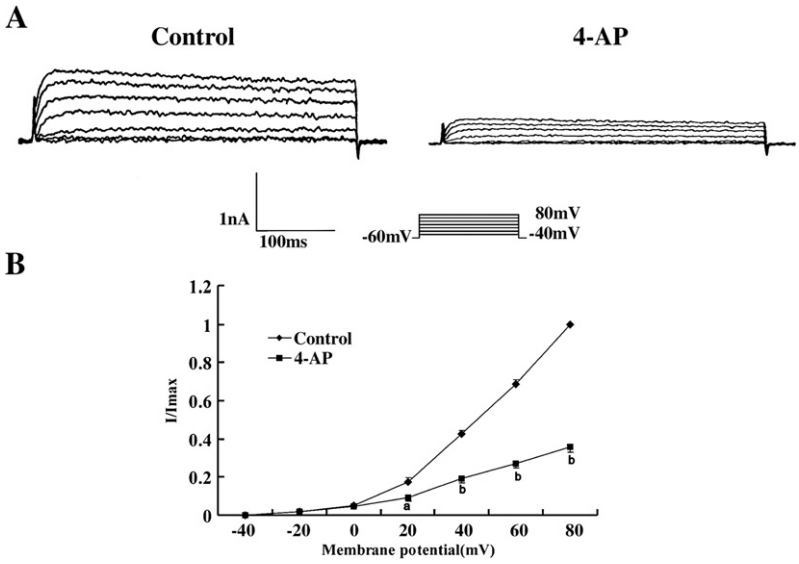

Fig. 1. Effect of 4-aminopyridine on IK(V) in gastric antralcircular myocytes. [a]$P<0.05$; [b]$P<0.01$ vs control group. A shows the raw current traces elicited by depolarizing step pulse. B shows the *I–V* relationships and shows the effect of 4-AP on IK(V).

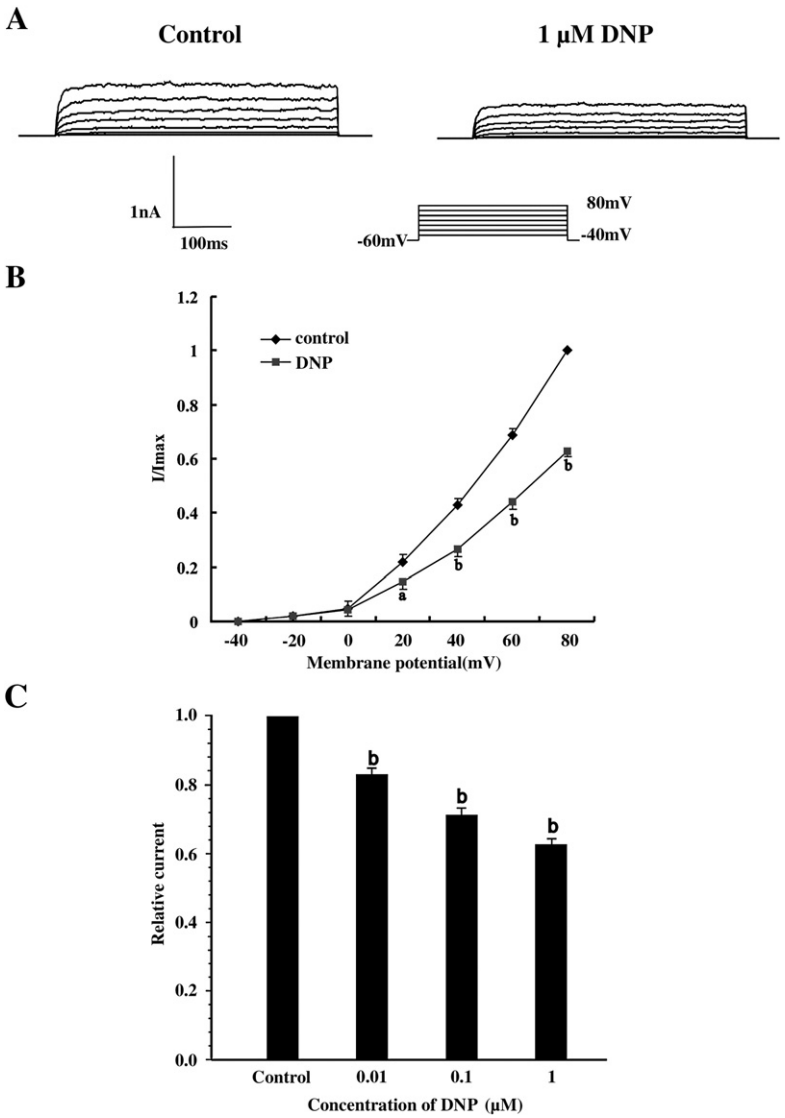

Fig. 2. Effect of different concentrations of DNP on IK(V) in the gastric antral circular myocytes. A shows the raw current traces elicited by depolarizing step pulse. B shows *I–V* relation curve of 1 μM DNP IK(V) C shows the concentration-dependent inhibition of DNP on IK(V) at +60 mV. [a]$P<0.05$; [b]$P<0.01$ vs control group.