Biochem Pharmacol (Los Angel) 2017, 6.2 (Suppl)
DOI: 10.4172/2167-0501-C1-007

B-type natriuretic peptide prevents postnatal closure of ductus arteriosus by both vasodilation and anti-remodeling in neonatal rats

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Background: The ductus arteriosus (DA) is a unique artery in fetal circulation connecting the pulmonary artery and the aorta and usually closes soon after birth. However, persistent patency of DA is life-saving in patients with some congenital heart diseases such as pulmonary atresia. The physiologic process of postnatal DA closure consists of vasoconstriction and vascular remodeling. We have recently reported that B-type natriuretic peptide (BNP) can exert anti-remodeling effects in pulmonary vasculature. However, its effects on DA are not fully understood. This study was to investigate if BNP can prevent DA closure and its underlying mechanisms.

Methods and Results: *In vivo*, we serially examined effects of BNP (10 mg/kg, ip at birth) on DA closure in neonatal rats at 0 h and 4 h after birth. We found that in control rats, DA spontaneously closed at 4h after birth with luminal occlusion and prominent intimal thickening. Morphologically, BNP prevented DA closure with an increased DA diameter than control rats at 4 h. Histologically, BNP preserved luminal patency and attenuated intimal thickening at 4 h. Ex vivo, BNP attenuated oxygen-induced vasoconstriction of neonatal DA rings. These vaso-dilating effects were blunted by, Rp-8-Br-PET-cGMPS, a cGMP inhibitor. *In vitro*, BNP inhibited Ang II-induced proliferation and migration DA smooth muscle cells. BNP also inhibited Ang II-induced mitochondrial ROS production and calcium overload. Finally, BNP inhibited Ang II-induced ERK1/2 activation. Similarly, all these *in vitro* effects were antagonized by Rp-8-Br-PET-cGMPS.

Conclusion: BNP prevents postnatal DA closure not only by vaso-dilatation but also by anti-remodeling. The mechanisms underlying anti-remodeling effects consist of anti-proliferation and anti-migration, with attenuation of mitochondrial ROS production, intracellular calcium and ERK1/2 signaling, through the cGMP pathway. Therefore, the BNP/cGMP pathway can be a promising therapeutic target for modulation of DA patency.

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