

## CERAMIDE PRODUCTION VIA NEUTRAL SPHINGOMYELINASE IS A KEY EVENT IN THE NORMOXIC CONTRACTION OF THE DUCTUS ARTERIOSUS

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**Background and aims:** The sphingolipid-derived second messenger ceramide plays an important role in numerous physiological processes. Ceramide generated by neutral sphingomyelinase (nSMase) has been involved in hypoxic pulmonary vasoconstriction (HPV, Cogolludo et al., *Cardiovasc Res* 2009;82:296-302). HPV shares many similarities with oxygen-induced contraction of the ductus arteriosus (DA). Chicken and mammalian DAs present common mechanisms for oxygen sensing/signaling (Cogolludo et al., *Am J Physiol* 2009; 297: L619-L630). We aimed to analyse the putative role of ceramide in the response to oxygen in chicken and human DA.

**Methods:** Contractile tension was recorded in DA rings using conventional organ baths (for human) and wire myographs (for 20-d chicken fetuses). Myocytes from these tissues were isolated by enzymatic digestion.

**Results:** Exposure to oxygen (21%) induced contraction in the pulmonary side but relaxation in the aortic side of chicken DA. Similarly, oxygen increased ceramide content (measured by immunocytochemistry) only in the pulmonary side of 20-d DA. The nSMase inhibitor GW4869 did not affect endothelin-induced contraction but markedly reduced oxygen-induced contraction in chicken DA. Similar results were obtained with an anticeramide antibody. Moreover, the addition of exogenous C6-ceramide and of *Bacillus cereus* sphingomyelinase contracted the pulmonary side of chicken DA but had negligible effects in the aortic side. Finally, the normoxic contraction of human DA rings was markedly reduced by GW4869.

**Conclusions:** Our data indicate that nSMase-derived ceramide is a key event in the signalling cascade of normoxic contraction of chicken and human DA.

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