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Physiological and pathological effects of complete sGC deletion

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By catalyzing the production of the intracellular signaling molecule cGMP NO-sensitive guanylyl cyclase (NO-GC), as the major receptor for NO, has a key function within the NO/cGMP cascade. The pharmacological importance of the enzyme is reflected by NO donors used for the therapy of coronary heart disease. NO-GC is made up of one β subunit and one α subunit. As there are two α subunits (α_1 and α_2), two different GC isoforms are known to exist ($\alpha_1\beta_1$ and $\alpha_2\beta_1$). In the cardiovascular system, vasorelaxation and inhibition of platelet aggregation are mediated by the $\alpha_1\beta_1$ GC. As the α_2 subunit is mainly found in nerve cells of the CNS, the $\alpha_2\beta_1$ heterodimer is believed to participate in synaptic plasticity. The role of NO-GC in the gastrointestinal tract is still unclear. NO is contributing to non-adrenergic non-cholinergic (NANC) relaxation of gastrointestinal smooth muscle.

Using mice deficient in the β_1 subunit we investigated the role of NO-GC in vascular and intestinal tissues. These mice do not express any of the α subunits and reveal no detectable cGMP synthesis upon NO stimulation. Thus mice lacking the β subunit are in fact total NO-GC knock out mice. Whereas mice heterozygous for the β_1 subunit of NO-GC were phenotypically undistinguishable from WT, homozygous GC-KO mice died prematurely. 3-week-old homozygous GC-KO mice exhibit considerable growth retardation shown by a 40% reduced body weight. KO mice surviving until day 18+ are hypertensive and die from gastrointestinal dysmotility leading to ileus and perforation. By substituting normal rodent chow with fiber-free diet we were able to rescue GC-KO mice.

In order to find out the relative contribution of smooth muscle cells to the GC-KO phenotype we are currently investigating smooth muscle specific GC-KO mice (SMKO). Tamoxifen was used for induction of the tissue-specific KO. SMKO mice do not reveal the reduced life expectancy of total GC-KO mice. However, tamoxifen-injected SMKO animals develop hypertension within several weeks. This model of a slowly developing hypertension further underlines the importance of constitutively released endothelial NO as major regulator of blood pressure.