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Oral presentation

Lessons from soluble guanylate cyclase alpha1 knockouts

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SGC is a heme containing heterodimer having two known active isoforms, α1β1 and α2β1. Particularly the former is suspected to be important in smooth muscle relaxation while the latter would be involved in neurologic systems. Since no isoform specific inhibitors exist, we generated knockout mice for the α1 isoform in order to investigate its function in the systems involving the NO/sGC pathway. The deletion of exon 6 resulted in mice expressing a non-frameshifted inactive protein. Hence the mice could be considered as cyclase death knockins, avoiding phenotypes due to enzyme function independent structural functions of the protein. We observed that these knockout mice retained full viability and fertility. The male mice developed hypertension around 12 to 14 weeks of age while the female mice did not. Ovariectomy did not influence the blood pressure in a different way than in wild type littermate controls. Both in the male and female knockout mice the NOS-inhibitor L-NAME raised the blood pressure to a similar extent as in wild type mice. NO-donors lowered blood pressure in male but not female mice. These observations show that the importance of the NO/sGC system in blood pressure regulation is gender-specific and that in female mice other mechanisms, probably EDHF, play the major role. It furthermore demonstrates that NO has sGCα1β1 independent activities in blood pressure regulation, either acting through the sGCα2β1 isoform or through sGC independent mechanisms such as direct influence on K+ channels. Phenotyping in a NOS-1 dependent system showed that α1β1 is also involved in NOS-1 derived NO signalling.

In parallel experiments in supposedly NOS dependent shock models that could be inhibited by methylene blue we observed that the shock was retained even in the absence of NO, and based upon ion channel inhibition, probably is due to (an) EDHF.

Taken together, these data show that our current concepts on both normal blood pressure regulation and vasodilatory shock are too simple, and that also in these phenomena sGC independent effects of NO and NO independent inflammatory shock mechanisms should be taken into account. Also the specific role of the sGC isoforms is only at the beginning of its elucidation.