BMC Pharmacology

Meeting abstract

Conditional knockout of the secretogranin II gene to reveal biological functions of secretoneurin

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from 14th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Innsbruck, Austria. 21–22 November 2008

Published: 5 November 2008

BMC Pharmacology 2008, **8**(Suppl 1):A32 doi:10.1186/1471-2210-8-S1-A32

This abstract is available from: http://www.biomedcentral.com/1471-2210/8/S1/A32

Secretogranin II (SgII) belongs to the family of chromogranins, which are widely expressed in large dense-core vesicles (LDV) of nerves and neuroendocrine tissues. In LDV SgII is processed to smaller peptides, like secretoneurin (SN). SN was initially described in our lab [1] and has been established as a novel biologically active neuropeptide linking nerves, blood vessels and the immune system. SN releases dopamine and dynorphin from rat striatal slices, potently and specifically attracts monocytes, eosinophils, dendritic and endothelial cells towards a concentration gradient and acts as an angiogenic and vasculogenic cytokine comparable in potency to VEGF. SN contributes to neurogenic inflammation and might play a role in the irritative response in the eye, as it innervates a wide range of ocular tissues. The role of SN in hypoxia-driven induction of neo-vascularization in ischemic diseases like cerebral ischemia or in solid tumours will be subject of studies with a conditional knockout mouse for the secretogranin II gene. For these studies, a targeting vector was generated in our lab. In classical knockout animals the target gene is disrupted by either deleting parts of the gene, or by insertion of foreign DNA sequences into the target gene by site-specific homologous recombination. This genetic rearrangement is present in each cell of the animal right from the start. In conditional knockout animals, the structure and function of the gene of interest is only minimally altered. The gene of interest gets flanked by loxP sites, which serve as cleavage site for the Cre recombinase. In the presence of this enzyme, the gene will be excised precisely while other cells without Cre recombinase remain unaffected. The advantages of the conditional knockout system are: (i) It circumvents problems of simple knockouts such as compensation during development. (ii) Spatial knockout allows the study of gene functions in defined regions or tissues, without complications due to whole-body gene deletion. The generation of a conditional SgII knockout mouse will contribute to a better understanding of the physiological relevance of SN. Alterations of these mice in physiological and pathological conditions central to angiogenesis like wound healing; tissue ischemia following cardiovascular diseases; tumour growth and metastasis will be investigated. Due to the involvement of chromogranins in LDV biogenesis the ablation of SgII might also impair LDV generation.

References

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