Bradykinin Reduces Long-Lasting TRPV1-Mediated Inward Currents in Afferent Nonfiring Renal Neurons

Kristina Rodionova,1 Christina Forray-Stauss,1 Tilman Ditting,1,12 Karl F. Hilgers,1 Nada Cordasic,2 Peter Linz,1 Christian Ott,12 Roland E. Schmieder,1 Mario Schiffer,1 Kerstin U. Amann,1 Roland Veelken,1
1Universitätsklinikum Erlangen-Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; 2Paracelsus Medizinische Privatuniversität - Nurnberg, Nurnberg, Germany; 3Universitätsklinikum Erlangen, Abteilung für Nephropathologie, Erlangen, Germany.

Background: Bradykinin has been reported to be sympathoexcitatory via renal afferent nerves. Hence we tested the hypothesis that bradykinin directly stimulates cultivated renal nerves with afferent axons.

Methods: Dorsal root ganglion neurons (T11-L2) of rats were investigated in voltage clamp mode to measure inward currents and current clamp mode to assess action potential (AP) generation [neurons classified as tonic (high AP generation upon stimulation), phasic (AP ≤ 5 upon stimulation) or no firing]. Stimulation of TRPV1 receptors by protons (pH 6) with and without the addition of bradykinin (1, 10, 100 µM). 111 DRG renal nerves retrogradely stained with Dil for investigation.

Results: Bradykinin (BK) alone did not induce inward currents nor APs. Proton stimulation (pH 6) of TRPV1 significantly augmented long-term inward currents (baseline -0.360 ± 0.09 nA vs. -1.39 ± 0.34 nA; p < 0.05, mean±SEM) and increased action potential potential in tonic neurons (0 AP/10s vs. 9.57 ± 1.89 AP/10s; p < 0.05, mean±SEM). However, the co-stimulation of renal nerves with protons and BK had any effect only in one specific subgroup of renal neurons: it significantly decreased long-lasting currents in non-firing neurons (AP stimulation with 100µM BK+pH6: -0.02 ± 0.06 nA, 10µM BK+pH6: -0.05 ± 0.06 nA, 1µM BK+pH6: -0.06 ± 0.02 nA vs. pH6: -0.31 ± 0.06 nA; p < 0.05, mean±SEM).

Conclusions: Bradykinin was only able to reduce long-lasting, TRPV1 dependent inward currents in non-firing renal neurons. Alterations of inward currents are likely involved in modulating prostaglandin and proinflammatory peptides (SP, CGRP). Hence, bradykinin might impair the release of neuropeptides from intrarenal axons of a specific subgroup of renal afferent nerves.

The Impact of rs2254524 LSS Polymorphism on Blood Pressure in a New Mouse Model

Sipontina Paolo,1 Messaggio,1 F. E. Cordasic,1 Peter Schiffer,1 Roland Karl,1 Christian Menendez-Castro, Nada Cordasic, Mario Schiffer, Roland Veelken, Kerstin U. Amann, Arif Ekici, Christoph Daniel, Karl F. Hilgers. Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.

Background: Sodium (Na) Transport

Hypertension and CVD: Mechanisms

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Underline represents presenting author.

Research: Poster

Fig. 1: SBP measured by the tail-cuff system in LSS CC and LSS AA mice at 4 weeks of age and in the kidney at 6 months of age. At 3 months, we were able to detect an increase in SBP in LSS AA kidneys and are associated with a faster decline in GFR in hypertensives. These pathways may contribute to the specific kidney injury observed in malignant hypertension.

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RNA Sequencing Reveals Induction of Specific Renal Inflammatory Pathways in a Rat Model of Malignant Hypertension

Andrea Hartner, Carlos Menendez-Castro, Nada Cordasic, Mario Schiffer, Roland Veelken, Kerstin U. Amann, Arif Ekici, Christoph Daniel, Karl F. Hilgers. Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.

Background: In malignant hypertension (MH), far more severe kidney injury occurs than in the “benign” form of the disease. The pathogenesis of this peculiar renal injury of malignant hypertension remains incompletely understood. Using a rat model in which some but not all animals develop MH, we performed an unbiased analysis of gene expression by RNA-sequencing to identify transcriptional changes in the kidney specific for malignant hypertension.

Methods: Renovascular hypertension in rats was induced by placing a 0.2 mm clip on the left renal artery (2K1C). Five weeks later, all 2K1C rats had developed hypertension. Rats were then sacrificed, and renal cortical RNA was extracted from the right kidney exposed to high blood pressure. To distinguish MH from non-malignant hypertension (NMH), we considered two factors: weight loss and typical renovascular lesions. Differential gene expression was assessed in three groups: MH, NMH and normotensive, sham operated controls (N=5 per group for RNA sequencing, N between 8 and 14 for other analyses).

Results: Mean blood pressure measured intraaerically was elevated to a similar degree in MH (207±10 mmHg) and NMH (204±4 mmHg) compared to controls (113±3 mmHg, p<0.05). 886 genes were exclusively regulated in MH only. Principal component analysis revealed a separated clustering of the three groups. The data pointed to an upregulation of many inflammatory mechanisms in MH including pathways which previously attracted little attention in this setting: Transcripts from all three complement activation pathways were upregulated in MH compared to NMH but not in MH compared with controls; immunohistochemistry confirmed complement deposition in MH exclusively. The expression of chemokines attracting neutrophil granulocytes as well as actual granulocyte infiltration were increased only in MH rats (CXC6: 4.1-fold in MH over NMH).

Conclusions: The hypertensive kidney injury in malignant hypertension of 2K1C rats includes a robust expression and deposition of complement components as well as infiltration of neutrophil leukocytes, features which are not observed in the non-malignant course of renovascular hypertension. These pathways may contribute to the specific kidney injury observed in malignant hypertension.

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