Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol18Issue1abst158P.pdf

Alpha Calcitonin gene-related peptide protects the vasculature in L-NAME-induced hypertension

F. Argunhan[1], X. Kodji[1], A. A. Aubdool[1], M. Nandi[2], J. E. Clark[3], S. D. Brain[1]. [1]Vascular Biology Group, King's College London, London, United Kingdom, [2]Institute of Pharmaceutical Science, King's College London, London, United Kingdom, [3]The Rayne Institute, King's College London, London, United Kingdom.

Introduction: Alpha Calcitonin Gene-Related Peptide (αCGRP) is a potent vasodilator neuropeptide that has recently been shown to be protective in AngII-induced hypertension (1,2). The current study aimed to characterize L-NAME-induced experimental model of hypertension and elucidate whether αCGRP's protective mechanism involves nitric oxide (NO) and ATP-sensitive K^+ channels.

Method: All *in vivo* procedures were carried out in accordance to the UK Home Office Animals (Scientific Procedures) Act 1986. L-NAME (1mg/ml) was administered in drinking water of age matched (8-10 weeks) male C57BL/6J wild type (WT) and αCGRP knock-out (KO) mice. After 14 days, the left carotid artery was cannulated under terminal anaesthesia (Isoflurane; 5% induction, 2% maintenance) for measurement of mean arterial blood pressure (MAP) (2). A subcohort of L-NAME treated WT mice were cannulated and received intravenous (i.v.) injection of the CGRP receptor antagonist BIBN 4096 BS (0.3mg/kg). Additionally, a selective ATP-sensitive potassium channel (K_{ATP}) inhibitor PNU 37883 (2mg/kg, *i.v.*) was used to investigate the role K_{ATP} channels play in blood pressure regulation. Data is expressed as mean ± SEM (n=5-7) and analysis was performed using 2-way ANOVA followed by Bonferroni *post hoc* test.

Results: Figure 1 shows that control WT and αCGRP KO mice had similar MAP whereas the L-NAME treated WT mice developed significantly higher MAP, as expected. MAP was further exacerbated in αCGRP KO mice and in WT mice injected with the antagonist BIBN 4096 BS. The K_{ATP} inhibitor, PNU 37883, did not show a significant difference in mean arterial blood pressure across groups.

Conclusion: Chronic treatment with L-NAME induced hypertension in αCGRP WT mice, as expected, which was further exacerbated in αCGRP KO mice or with CGRP antagonist treatment. In conclusion, a model of hypertension has been established and novel data suggests that the protective role of αCGRP is independent of endogenous NO formation. The protective mechanism does not appear to be mediated by ATP- sensitive potassium channels. Thus, the actual protective mechanism of αCGRP is presently unclear.

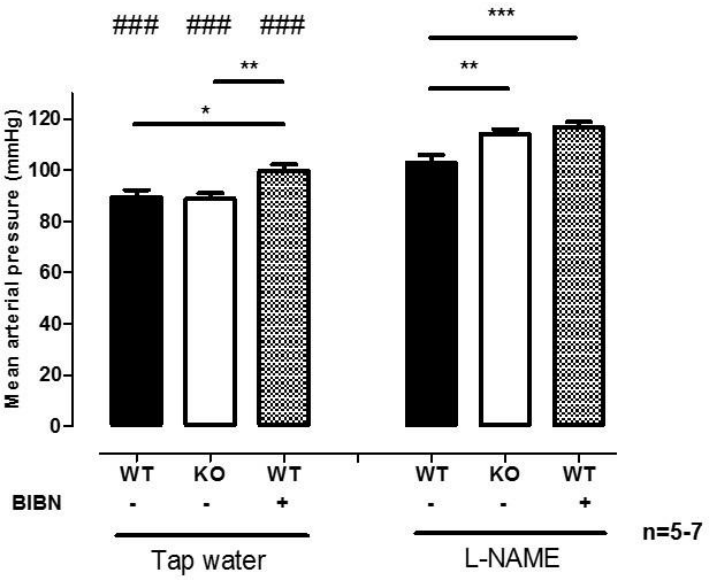

Figure 1 Investigating nitric oxide depletion on mean arterial blood pressure of WT and αCGRP KO mice receiving normal tap-water or 1mg/ml L-NAME, and of WT mice receiving intravenous injection of CGRP receptor antagonist BIBN4096BS (BIBN). Values represent mean ± SEM, * P<0.05, ** P<0.01, *** P<0.001 between indicated groups and ### P<0.001 tap water vs L-NAME.

References:

1. Smillie SJ *et al.* (2014). *Hypertension* **63**(5): 1056-1062.
2. Aubdool AA *et al.* (2017). *Circulation* **136**(4):367-383.

Acknowledgements and Funding Sources ***FA is supported by an MRC studentship.***