Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue3abst055P.pdf

Complex effects on rat aorta tone of acute methylglyoxal treatment

Shamsaldeen YA, Benham CD, Lione Lisa. University of Hertfordshire, Hatfield, Hertfordshire, UK

The cardiovascular dysfunction caused by diabetes is classically considered as a consequence of hyperglycaemia. However, there is increasing interest in other carbohydrate metabolites such as methylglyoxal (MGO) which is elevated in plasma concentration up to 100 fold in some diabetic patients. (1,3&4). Serum MGO elevation is correlated with diabetic complications such as diabetic neuropathy and vascular dysfunction (5) and has acute effects on TRPA1 channels. The vanilloid channel TRPV4 enhances sustained endothelium Ca^{+2} entry that induces vasodilators; nitric oxide (NO), endothelium derived hyperpolarization factor (EDHF) and PGs activation and release (1). The aim of this study was to investigate the acute effects of MGO on vascular function in rat aorta.

Aortic rings from male Wistar rats (N>4) that had been euthanized by a schedule 1 procedure, were isolated and suspended in organ baths attached to a transducer allowing quantitative isometric tension measurement. Aortic rings were pre-contracted with noradrenaline (300nM) followed by carbachol induced relaxation. Methylglyoxal (100uM) was applied for 15, 40, 120 minutes prior to noradrenaline to examine maximal carbachol induced relaxation (0.3mM & 1mM). For antagonist studies; L-NAME (100uM) was applied 15 minutes prior to MGO and the TRPV4 antagonist, HC-067047 was applied 40 minutes prior to MGO. Mixed model 2-way ANOVAs and one way ANOVAs followed by post hoc Bonferroni tests were performed to compare mean responses across treatment groups.

Carbachol (CC) and the TRPV4 agonist RN1747 relaxed noradrenaline induced contractions and the latter showed concentration dependent block by HC-067047. Control noradrenaline induced contractions were sustained but became transient following 120 minutes MGO pre-incubation. This MGO induced relaxation was reduced following L-NAME or HC-067047 pre-incubation (MGO alone: 97.1±2.2% max. relaxation ***p▪ 0.001, L-NAME+MGO: 37.1±18.3% relaxation p▪ 0.05, HC-067047+MGO: 13.2±16.6% max. relaxation p▪ 0.05, Vs control; 12.7±11.1% max. relaxation).

Shorter MGO incubation (40 minutes) did not induce relaxation of noradrenaline contractions but did as previously reported reduce carbachol induced relaxation: (CC 0.3mM: 23.1±10.3% relaxation **p▪ 0.01 and CC 1mM: 26.5±11.5% relaxation **p▪ 0.01, versus control: CC 0.3mM: 60±7.5% relaxation p▪ 0.05 and CC 1mM: 72.3±12% relaxation) (2).

These results show that the effects of MGO are complex, including both stimulation and inhibition of vasorelaxant mechanisms. The molecular mechanisms are unclear but might involve changes in TRPV4 and or eNOS signalling (2).

1) Baylie R L & Brayden JE, Acta Physiol 203:99, 2011

2) Dhar A et al, BJP 161:1843, 2010

3) Eberhardt M et al, JBC 287:28291, 2012

4) Jia X et al, FASEB, 20:E871, 2006

5) Sheader EA et al, Biochemical Pharmacology 61:1381, 2001