194

ANTI-CONTRACTILE VASCULAR RESPONSES TO 5' AMP-ACTIVATED PROTEIN KINASE ACTIVATION; THE ROLE OF PERIVASCULAR ADIPOSE TISSUE AND THE INFLUENCE OF AGING

H Melrose, A Heagerty, G Edwards, C Austin *University of Manchester*

doi:10.1136/heartjnl-2013-304019.194

Introduction 5' AMP-activated protein kinase (AMPK) is a serine/threonine kinase with a plethora of vital physiological roles, including regulation of energy metabolism. AMPK is present in the three major components of the vasculature: smooth muscle (VSM), the endothelium and perivascular adipose tissue (PVAT) and is known to augment bioavailability of the endogenous vasodilator nitric oxide (NO) via activation of endothelial nitric-oxide synthase (eNOS). Although it is known that AMPK can modulate VSM and endothelial function, it is unknown whether AMPK can modulate the anti-contractile effects of PVAT, despite the expression of both AMPK and eNOS by perivascular adipocytes. Aging is an independent risk factor for cardiovascular disease and is associated with altered arterial contractility. It is known that AMPK activity in skeletal muscle is reduced with advanced aging, however it is unknown whether the effects of AMPK on arterial contractility are modulated by age. Therefore we investigated the effects of activation of AMPK on arterial contractility in the presence and absence of PVAT and whether these effects are modulated by aging.

Methods and Results Third order mesenteric endothelium-intact arteries were harvested from male Wistar rats aged 3 months old (m.o.) and 24 m.o. and contractility to increasing concentrations of the thromboxane A2 receptor agonist U46619 (10 nM-3 μM) was assessed via wire-myography in the presence and absence of PVAT and the AMPK activator A769662 (10 μM). Results (expressed as mean±SE) were analysed using two-way ANOVA (Bonferroni post-hoc). In 3 m.o. rat arteries, A769662 caused a reduction in subsequent contractions to increasing concentrations of U44619, in both the presence of PVAT (max increase in tension (1–3 μM U46619, mN/mm) : control 0.55 ±0.07 (n=3); +A769662 0.37±0.04 (n=4); p=0.0018) and absence of PVAT (control 1.20±0.52 (n=6); +A769662 0.60±0.22 (n=3)). However in 24 m.o. rat arteries, A769662 only caused a reduction in the presence of PVAT (control 0.88±0.15 (n=8); +A769662 0.55±0.17 (n=8); p=0.0054), and had no effect in PVAT-denuded vessels (control 0.85±0.11 (n=8); +A769662 0.83±0.11 (n=8)).

Summary young animals. In older animals, however, AMPK activation can only elicit this effect in the presence of PVAT. These findings are consistent with differential changes in the expression and/or signalling of AMPK in the VSM and endothelium compared to PVAT with age. Further studies are currently being undertaken to investigate the mechanisms behind these differences.