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Impact of ageing and hypertension on vasorelaxation to positive modulators of calcium-sensing receptors

V. Ho,.St George's. University of London, London, UNITED KINGDOM.

Introduction: Positive modulators of the calcium-sensing receptor (calcimimetics) have been shown to induce relaxation in different vascular regions and reduce blood pressure in some models of hypertension and chronic kidney diseases[1,2]. Inhibition of voltage-gated calcium channels (VGCC), a commonly used anti-hypertensive strategy, has also been implicated in the vascular action of calcimimetics. However, the potential effect of ageing which is a major risk factor for hypertension remains unknown.

Method: Male Wistar rats and Spontaneously Hypertensive rats (SHR) (younger: 10-12 weeks; older: 29-34 weeks) were killed by cervical dislocation, and small mesenteric and femoral arteries were isolated for isometric tension recording. Relaxant responses in methoxamine-precontracted vessels are shown as mean±sem (n=4-6) and analysed by two-way analysis of variance of the whole data set.

Results: Relaxation to calindol was attenuated in mesenteric arteries from older Wistar rats (younger Wistar: pEC_{50}=5.9±0.1, E_{max}=100±3%; older Wistar: pEC_{50}=5.6±0.1, E_{max}=100±4%; P<0.05) or younger SHR (pEC_{50}=5.7±0.1, E_{max}=94±4%, P<0.01), and further reduction was seen in older SHR (pEC_{50}=5.1±0.1, E_{max}=106±9%; P<0.01 vs younger SHR or older Wistar). Similar results were observed for cinacalcet (data not shown). In femoral arteries, calindol and cinacalcet induced smaller relaxation than in mesenteric arteries (calindol: pEC_{50}=5.3±0.1, relaxation at 30µM =73±8%; cinacalcet: pEC_{50}=5.4±0.3, relaxation at 30µM=36±11%; P<0.01). Femoral relaxation to calindol was reduced in older Wistar (pEC_{50}=5.0±0.1, relaxation at 30µM =41±17%, P<0.01), or younger SHR (pEC_{50}=4.8±0.1, relaxation at 30µM=53±14%, P<0.01), but was restored in older SHR (pEC_{50}=5.5±0.2, relaxation at 30µM=83±8%; P<0.01 vs younger SHR or older Wistar). Again, similar results were obtained for cinacalcet (data not shown). On the other hand, ageing had no significant effect on relaxation induced by the VGCC activator verapamil in mesenteric arteries, whereas slightly larger relaxations were seen in SHR (younger Wistar: pEC_{50}=7.3±0.1, E_{max}=96±5%; older Wistar: pEC_{50}=7.2±0.1, E_{max}=98±5%; younger SHR: pEC_{50}=7.6±0.2, E_{max}=99±11%; older SHR: pEC_{50}=7.5±0.3, E_{max}=109±16%, P<0.05 vs Wistar). No differences were found in femoral arteries (younger Wistar: pEC_{50}=7.0±0.3, E_{max}=102±13%; older Wistar: pEC_{50}=7.0±0.2, E_{max}=104±10%; younger SHR: pEC_{50}=6.9±0.1, E_{max}=97±5%; older SHR: pEC_{50}=6.8±0.2, E_{max}=102±12%).

Conclusion: Ageing or hypertension alone reduces relaxation to calcimimetics in rat mesenteric arteries and femoral arteries, but their combined effects differ depending on the vascular region. The underlying mechanism is yet to be identified, but appears independent of voltage-gated calcium channels.

References:

(1) Thakore P and Ho WSV (2011). *Br J Phamracol* **162**: 749-762

(2) Smajilovic S *et al.* (2011). *Br J Phamracol* **164**: 884-893