Mechanisms contributing to angiotensin II induced increases in nerve-evoked contractions of mouse tail artery

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Angiotensin II (Ang II) contributes to the regulation of blood pressure, with elevated levels linked to hypertension. In the skin, Ang II is a factor that regulates normal blood flow and disruption of Ang II signalling may modify skin blood flow in diseases such as diabetes and scleroderma. This study investigated the effects of Ang II (0.1 - 1 nM) on nerve-evoked contractions (NECs) of mouse tail artery. The mouse tail artery supplies blood to the skin of the tail and plays a role in thermoregulation similar to that of digital arteries in humans. The tissues used in this study were removed from mice that had been deeply anaesthetized with isoflurane and decapitated. Distal segments of the mouse ventral tail artery were mounted isometrically in wire myographs and stimulated either by electrical stimulation of the perivascular sympathetic axons with 50 stimuli at 2 Hz or by contractile agents. In addition, electrically evoked noradrenaline (NA) release was studied using amperometry. The artery segments were pinned in a recording chamber and NA was detected using a carbon fibre electrode placed on the artery surface (Brock & Tan, 2004). All measurements were made relative to pre-treatment responses and comparisons were made with responses in time-matched tissues from the same animal that did not receive the test agent.

Ang II (0.3 - 1 nM) increased NEC, while producing only a small increase in resting force. All the following experiments used 1 nM Ang II. The Ang II type 1 receptor antagonist losartan (0.1 μM, n = 4) abolished the facilitation of NECs produced by Ang II (losartan + Ang II, 130 ± 20%; Ang II, 547 ± 88%; P < 0.05), while the Ang II type 2 receptor antagonist PD 123319 (1 μM, n = 3) did not change the facilitation of NECs produced by Ang II (PD 123319 + Ang II, 400 ± 59%; Ang II, 472 ± 65%). The non-selective cation channel blocker SKF-96365 (10 μM, n = 10) on its own reduced NECs (SKF, 75 ± 8%; time control, 97 ± 5%; P < 0.05) and in its presence the facilitation of NECs produced by Ang II was attenuated (SKF + Ang II, 414 ± 82%; Ang II, 720 ± 129%; P < 0.05). The L-type Ca^{2+} channel blocker nifedipine (1 μM, n = 4) had no effect on NECs on its own (NIF, 96 ± 6%; time control, 92 ± 8%), or on the facilitatory effect of Ang II on NECs (NIF + Ang II, 770 ± 375%; Ang II, 863 ± 203%). The potential role of previously reported mediators of Ang II type 1 receptor-mediated contractions were assessed using drugs to block the effects of rho kinase, protein kinase C, cyclooxygenase, inositol 1,4,5-trisphosphate, 20-HETE, superoxide, hydrogen peroxide and α_2-adrenoceptors but none of these agents reduced the facilitatory effect of Ang II on NECs (data not shown). Amperometry revealed that Ang II did not change NA release compared to a time matched control (Ang II, 100 ± 5%; time control, 93 ± 4%; n = 6 for both). Ang II produced a leftward shift in the concentration response curve for the α_1-adrenoceptor agonist phenylephrine (0.1 - 10 μM, n = 7) without changing the maximal response to this agent. While in the absence of Ang II the artery did not respond to the α_2-adrenoceptor agonist UK-14304 (0.001 - 1 μM n = 8), it did in its presence. In the presence of both α_1 and α_2-adrenoceptor blockade (prazosin, 0.1 μM; idazoxan, 1 μM), Ang II produced a leftward shift in the concentration response curves for K^+ (20 - 50 mM) without changing the maximum response to this stimulus.

In summary, these data suggest that Ang II increases NECs by activating post-junctional Ang II type 1 receptors, in part by increasing Ca^{2+} entry through SKF-96365 sensitive channels.

Brock JA, Tan JH. (2004) Selective modulation of noradrenaline release by α_2-adrenoceptor blockade in the rat-tail artery in vitro. *British Journal of Pharmacology* **142:** 267-274.