Aging and endothelin-1 induced vascular contractions

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Summary. Contractions produced by endothelin-1 (0.3–30 nM) have been investigated in aorta, renal arteries and mesenteric arteries from 2- and 24-month-old Sprague-Dawley rats. In senescent rats the EC_{50} values of endothelin-1 for aorta and renal artery were significantly increased (aorta: from 6.2 to 12 nM; renal artery: from 5.2 to 7.8 nM). For mesenteric artery the EC_{50} value (4.3 nM) was unchanged by aging, whereas the maximal contractile response to endothelin-1 was enhanced (from 8.3 to 11.7 mN). In contrast, there was no significant age-related difference in the maximal endothelin-1 response of aorta and renal artery.
The present data demonstrate a reduced sensitivity for aorta and renal artery and an enhanced maximal response to endothelin-1 in the mesenteric artery in senescent rats.
Key words. Endothelin-1; aging; vascular effects.

Sufficient documentation exists for morphological and functional changes in vascular smooth muscle as a consequence of the aging process[1]. The increased peripheral resistance observed in older animals may reflect augmented vasoconstriction and reduced vasodilation[2]. Endothelin-1 has recently been isolated from porcine aortic endothelial cells[3]. This 21-amino acid peptide is one of the most potent vasoconstrictors known, producing increases in blood pressure presumably by activating the phosphoinositide system. Endothelin-1 may, therefore, act as an endogenous modulator of vascular smooth muscle tone[3]. The presence of endothelin has been demonstrated in humans by an immunological method[4], moreover, relatively low endothelin levels have been found in elderly subjects. At present it is unknown whether age-related alterations occur in the vascular responsiveness to endothelin.

In the present study, we investigated endothelin-1 induced contractions in three different vascular beds of young (2 months old) and senescent rats (24 months old). Male rats (SIV 50, Sprague-Dawley) were killed by decapitation; aorta and renal and mesenteric arteries were carefully isolated, freed from adhering fat and connective tissues, and cut into rings of 3–4 mm length. The rings were mounted in an organ bath filled with carbogen saturated Krebs-Henseleit solution (pH 7.4; 35 °C) by means of two L-shaped wires and placed under an initial load of 10 mN. Responses were recorded isometrically. After a 60-min equilibration period, the preparations were contracted with 3 μM noradrenaline. The integrity of the endothelium was assessed by the ability of the preparations to relax in response to 1 μm acetylcholine. After washout of acetylcholine and noradrenaline, the rings were again contracted with either 3 μm noradrenaline or 30 nM porcine endothelin (Peninsula Labs). The values given in the table are means ± SEM. Statistical analysis was done with Student's t-test.

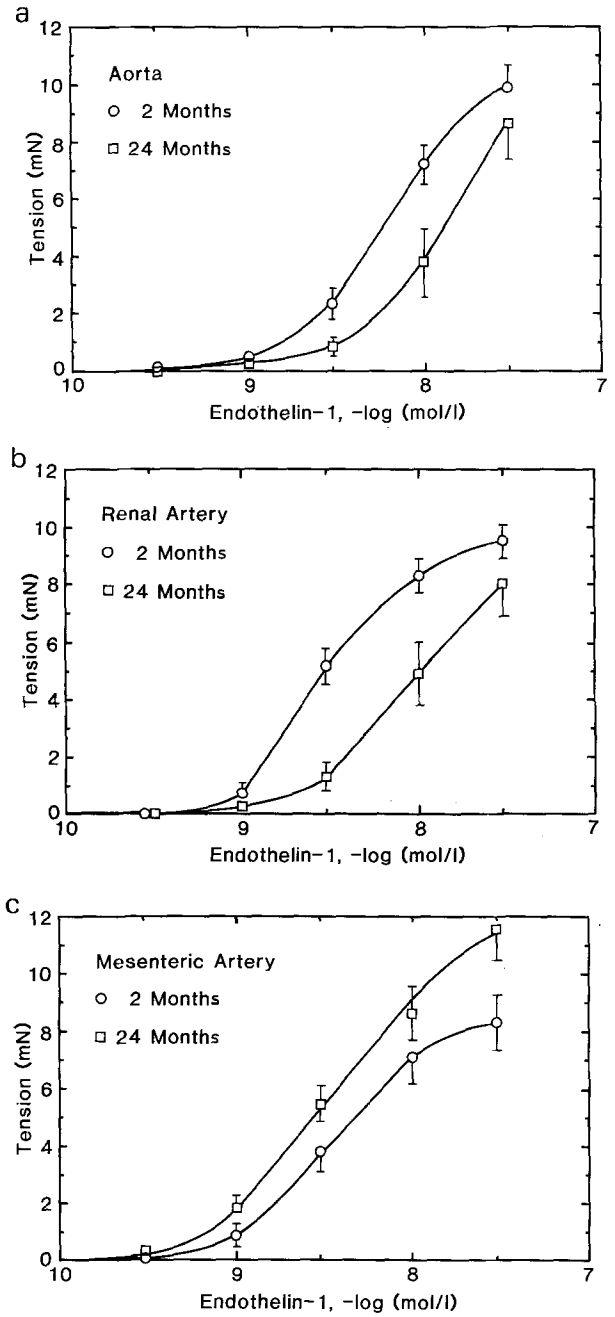
Endothelin-1 produced concentration-related contractile responses in all the preparations (fig.). Tension induced by 30 nM endothelin was unaltered in the aorta and the renal artery of the older group relative to the younger one ($p < 0.05$), although a tendency to decreased tension development was apparent in the 24-month-old animals (table). The EC_{50} values of endothelin-1 for aorta and renal artery were significantly increased in senescent rats. For mesenteric artery, the EC_{50} value was unchanged by aging; the maximal response, however, was significantly greater in the senescent animals. The maximal responses to noradrenaline paralleled those to endothelin-1; that is, in the aging process there were unchanged responses in aorta and renal artery, and a significantly increased response in mesenteric artery (table).

The present study indicated that endothelin-1 is a very potent constrictor of aortic, renal, and mesenteric artery vascular smooth muscle of both young and senescent rats. The data demonstrate that age-related alterations occur either in vascular smooth muscle sensitivity, or in maximal response. These alterations varied between

Characterization of endothelin-1 and noradrenaline-induced contractions of three vascular preparations of 2- and 24-month-old rats.

Vascular bed	Endothelin-1 EC_{50} (nM)		Maximum contraction (mN)		Noradrenaline Maximum contraction (mN)	
	2 months	24 months	2 months	24 months	2 months	24 months
Aorta	6.2 ± 0.9	12 ± 2.0*	10.2 ± 0. 5	8.7 ± 1.4	7.9 ± 0.8	8.9 ± 0.9
Renal artery	5.2 ± 1.1	7.8 ± 0.7*	9.5 ± 0.4	8.0 ± 3.8	8.5 ± 0.5	8.2 ± 1.7
Mesenteric artery	4.3 ± 0.7	4.0 ± 1.0	8.3 ± 0.8	11.7 ± 1.2*	5.2 ± 0.6	8.9 ± 1.4*

Values given are x ± SEM, n = 4–5. An asterisk (*) indicates a significant difference ($p < 0.05$) from the 2-months group.



Concentration-response curves of endothelin-1 on aorta (*a*), renal artery (*b*) and mesenteric artery (*c*) of 2-month-(o) and (□) 24-month-old Sprague-Dawley rats. Each point represents the mean ± SEM of 5–8 experiments.

blood vessel types, because a sensitivity change (indicated by statistically different EC_{50} values) only occurred in the aorta and renal artery, and maximal response changes were found only in the mesenteric artery.

Although these findings substantiate age-dependent alterations of vascular smooth muscle responsiveness to endothelin-1, the steps which are modified by the aging process between the endothelin-1 receptor and the final response (i.e. contraction) remain unknown. Of importance here, however, is that any age-related changes in the maximal response to endothelin paralleled those to noradrenaline [5]. This may possibly indicate that convergent post-receptor processes are effected; for example, the α_1-adrenoceptor and endothelin-1 receptor coupling to a common G-protein, or this coupling to phospholipase C. Additionally, O'Donnel and Wanstall [5] have postulated that the reduced sensitivity of the aorta from aged rats to noradrenaline may reflect alterations in the membrane potential or in voltage-sensitive calcium channels; such factors could account for the lower sensitivity of aorta and renal artery. The present results demonstrate a reduced sensitivity of the aorta and the renal artery, and an enhanced maximal contractile response to endothelin-1 in the mesenteric artery in senescent rats. In vivo experiments are required, however, to clarify the implication of these findings and their relevance to cardiovascular function in the elderly population.

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