EDRF in Human Coronary Arteries

NOBORU TODA, M.D.

Endothelium-derived relaxing factor (EDRF) is widely accepted to be an important physiological vasodilator substance. Depression of its action impairs the ability of blood vessels to relax in response to chemical and physical stimuli, leading it to respond to vasoconstrictor interventions with a strong, persistent contraction. Impairment

HUMAN CORONARY ARTERY

<table>
<thead>
<tr>
<th>Substance P</th>
<th>Histamine</th>
<th>Acetylcholine</th>
<th>Bradykinin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Endothelium (+)

SP 7   PA

H 2-8  7
5-7 2-6

ACh 7
9 8

BK 10 9
8 7

0.5g

10min

Endothelium (–)

SP 7   PA

H 2-8  7
5-7 2-6

ACh 7
9 8

BK 10 9
8 7

0.5g

10min

Fig. 1. Responses to substance P (SP), histamine (H), acetylcholine (ACh) and bradykinin (BK) of coronary artery strips from a 69 year-old male, with and without endothelium. The strips were partially contracted with PGF₂α. Concentrations of substance P, acetylcholine and bradykinin from 10 to 5=10⁻¹⁰, 10⁻⁹, 10⁻⁸, 10⁻⁷, 10⁻⁶ and 10⁻⁵ M, respectively. Concentrations of histamine = 2×10⁻⁸, 10⁻⁷, 5×10⁻⁷ and 2×10⁻⁶ M. 10⁻⁵ M papaverine applied to attain the maximal relaxation.

Key words:
EDRF
Coronary artery
Histamine

Department of Pharmacology, Shiga University of Medical Sciences, Ohtsu, Japan

Japanese Circulation Journal Vol. 56, February 1992 159
of the release and the action of EDRF is therefore regarded as one of factors responsible for coronary vasospasm. This chapter describes the relationship between endothelium and the responsiveness of human coronary arteries to endogenous substances.

1. Response mediated by EDRF in human, monkey and dog coronary arteries

Since the discovery of EDRF by Furchgott and Zawadzki, acetylcholine has been considered the most likely substance to be responsible for the release of the relaxing factor from endothelium. Coronary artery strips obtained from Japanese monkeys and dogs respond to the substance with a concentration-related relaxation, which is abolished by endothelium denudation and treatment with oxyhemoglobin, methylene blue\(^3\) and NO-synthesis inhibitors, such as NG-monomethyl-L-arginine\(^4\) and NG-nitro-L-arginine\(^5\). In endothelium-denuded monkey coronary arteries, acetylcholine produces a slight or moderate contraction that is suppressed by atropine and indomethacin\(^6\). In contrast, human coronary arteries contract dose-dependently in response to acetylcholine; the contraction is not significantly influenced by endothelium denudation\(^6\) but is inhibited by atropine\(^7\). Such a contraction was also obtained in the arteries from a male baby, in which atheromatous changes could not be observed\(^8\). Human coronary artery segments perfused with modified Ringer-Locke solution at a constant flow rate respond to acetylcholine applied intra- and extraluminally\(^8\) with similar magnitudes of pressure increment. In these human arteries responding to acetylcholine with contractions, substance P, bradykinin and Ca\(^{++}\) ionophore A23187 produce moderate or marked relaxations, that are dependent upon the presence of endothelium (Fig. 1). Therefore, human coronary arteries have the ability to release EDRF and to respond well to EDRF; however, the release of EDRF by acetylcholine is if any minimal.

Histamine in low concentrations (up to \(5 \times 10^{-7}\)M) produces a relaxation, and in higher concentrations a contraction in human coronary arteries partially contracted with prostaglandin F\(_{2\alpha}\) (Fig. 1).\(^9\) Removal of endothelium reverses the relaxation to a contraction, and potentiates the contraction induced at high concentrations, as did treatment with methylene blue\(^5,9\). Histamine relaxes monkey and dog coronary arteries dose-dependently. Monkey artery relaxations are abolished by endothelium denudation\(^10\) whereas relaxation of dog arteries is not influenced. Ca\(^{++}\) ionophore A23187 produces a marked relaxation in human, monkey and dog coronary arteries, the magnitudes of the responses being quite similar in the different species. The induced relaxation is abolished or reversed to a contraction by endothelium denudation.

2. Assay of EDRF and cyclic GMP in human coronary arteries

The release of EDRF was detected by a bioassay method using human coronary artery segments with intact endothelium as donor tissue and dog coronary artery strips without endothelium as assay tissue, as described in an earlier report\(^11\). Histamine and substance P applied to the donor tissue produced a moderate relaxation of the assay.

---

*Fig. 2.* Time course of increment in cyclic GMP by histamine of coronary arteries isolated from adults (27 and 43 years old) and seniles (63–78 years old). E(+) and E(−) = with and without endothelium. Cited from Toda and Okamura (1989) with permission.
tissue, which was abolished by treatment of the assay tissue with oxyhemoglobin. Acetylcholine did not relax the assay tissue.

Human coronary arteries with endothelium exposed to bathing media containing histamine increase the content of tissue cyclic GMP measured by radio-immunoassay. The maximal increment is obtained 2 min after the application of the amine (Fig. 2). Removal of endothelium abolishes the stimulatory effect of histamine.

The results so far presented indicate that EDRF is released from human coronary arteries and increases cyclic GMP in smooth muscle cells, possibly by activation of guanylate cyclase, as proved in a variety of blood vessels from many experimental mammals.

3. Endothelium-dependent response of coronary arteries from humans of different ages

Endothelium-dependent relaxations caused by substance P, bradykinin and histamine were compared in arteries from humans of two months, 35-48 years and 63-82 years of age. The responses to substance P (10⁻⁷ M) and bradykinin (10⁻⁹ to 10⁻⁷) did not differ in these arteries. Relaxations and cyclic GMP increments by histamine did not significantly alter with increasing age. The arteries from the senile group had some atheromatous lesions; however, the responses mediated via EDRF do not appear to be attenuated by such a slight histological change. On the other hand, in rabbits and monkeys fed an atherogenic diet, the endothelium-dependent response to chemical stimuli is suppressed. The access of EDRF to smooth muscle is considered to be impaired, because of a barrier to EDRF from reaching the medial layer or a thickened intima.

CONCLUSION

The abilities of endothelium to release EDRF and of smooth muscle to respond to the relaxing factor are quite similar in human, monkey and dog coronary arteries. The quantity and the quality of receptors for endogenous substances appear to be heterogeneous in endothelial cells; therefore, the action and the mechanism of action of these substances vary in the arteries from different species. Responses to EDRF-releasing substances are not impaired in human coronary arteries with slight, localized atherosclerosis, possibly because of some capacity of blood vessels to compensate for the action of EDRF.

REFERENCES

2. FURCHGOTT RF, ZAWADZKI JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980; 288: 373
4. PALMER RMJ, REES DD, ASHTON DS, MONCADA S: L-arginine is the physiological precursor for the formation of nitric oxide in endothelium-dependent relaxation. Biochem Biophys Res Commun. 1988; 153: 1251
8. TODA N, INOUE S, OKUNISHI H, OKAMURA T: Intra- and extraluminal-applied acetylcholine on the vascular tone or the response to transmural stimulation in dog isolated mesenteric arteries. Naunyn-Schmiedeberg's Arch Pharmacol 1990; 341: 30