Soluble vasoactive factors derived from vascular endothelium modulate the tone of underlying smooth muscle cells. Stimulation of intact, ie, endothelialized, vessels with acetylcholine causes vasodilatation by release of endothelium-derived relaxing factors (EDRFs), mostly NO and hyperpolarizing factor(s) (EDHF). The endothelium also produces contractile factors (EDCF) of different origin. Thus, any reduced endothelium-dependent relaxation or even vasoconstriction could result from either loss of EDRFs, (enhanced) generation of EDCFs, or a combination of both. EDCF-mediated vasoconstriction might prevail with increasing age, as well as disturbed endothelial function, for example, in hypertension or type 2 diabetes. In addition to reduced generation of vasodilator prostaglandins (PGs), such as PGI$_2$, enhanced production of vasoconstrictor prostanooids has been described. Oxygen-derived free radicals and isoprostanes, generated by exaggerated oxidative stress, are further members of the EDCF family. Thus, EDCFs represent an inhomogeneous group of compounds with different chemical identity.

In the few last years, vasocontractile prostanoids, generated by endothelial cyclooxygenase(s) (COX[s]), have come into focus as significant EDCFs. One reason for this is the upregulation of endothelial COXs and enzymes of PG-endoperoxide catabolism during the aging process and hypertension with enhanced generation of these compounds; another reason is the low selectivity of prostanooids for their membrane receptors. Vasoconstrictor prostanooids act on vascular smooth muscle cells via the thromboxane–prostanoid (TP) receptor. However, reactive oxygen species and other primary PGs, including PGI$_2$, at higher concentrations, may also activate this receptor and cause vasoconstriction.

In this issue of *Circulation Research*, Wong and colleagues demonstrate generation of a prostanooid-type EDCF in the hamster aorta in vitro. Treatment of the vessels with nonselective inhibitors of COX-1/2 or selective COX-2 inhibitors prevented these contractions, whereas selective COX-1 inhibitors were ineffective. This suggests a constitutively expressed COX-2 as source of EDCF formation. Although earlier studies had already considered COX-2–derived prostanooids as EDCFs, the present study identifies a less well-known product, PGF$_2\alpha$, as the only EDCF in this particular model. The acetylcholine-induced generation of PGF$_2\alpha$ (and PGI$_2$) in intact hamster aortae disappeared after endothelial denudation. Any vasomotor action of other prostanooids and PGI$_2$ could be excluded, as well as the involvement of the prostacyclin receptor for signal transduction.

Endothelial COXs, rather than those of vascular smooth muscle cells, are the main source of PG-endoperoxide generation in the vessel wall, the immediate precursors of terminal PGs. In SHR rats, enhanced COX-1 expression was found to be associated with generation of EDCFs, possibly PG endoperoxides and PGI$_2$. However, in other species including humans, PGI$_2$ is generated by both endothelial COX-1 and COX-2, and it is the COX-2, rather than COX-1 (ie, the regulated form of the enzyme) that synthesizes the majority of vascular PGs. Thus, the demonstration of an entirely COX-2–dependent EDCF formation could have some impact.

All prostanooids signal via G protein–coupled membrane receptors. Stimulation of TP receptors increases Ca$^{2+}$ entry by opening of both voltage- and receptor-operated channels, with subsequent increase in cytosolic Ca$^{2+}$ and smooth muscle contraction. TP receptors are not selective for thromboxane but may also bind other prostanooids. In the study of Wong et al., acetylcholine-induced aortic contractions were attenuated or abolished by 3 structurally different thromboxane receptor antagonists but not by an antagonist to the F-series–prostanoid (FP) receptor, ie, the specific binding site for PGF$_2\alpha$. Other potential candidates for TP-mediated contractions of smooth muscle cells, such as 8-isoprostanes, PGI$_2$, PGE$_2$, and oxygen-derived free radicals, could be excluded. Thus, the EDCF, stimulated by acetylcholine and acting via the TP receptor, was most likely PGF$_2\alpha$.

Endothelium-dependent contractions are augmented with aging, involve both COX-1 and COX-2, and are potentiated by oxidative stress. In the study of Wong et al., there were larger contractions in aortae from aged compared to young hamsters. This was explained by an age-related reduced generation of EDRF. The expression of TP receptors remained unchanged, similar to another study from the same group in aged rats. In this study on normotensive and...
hypertensive rats, genomic expression of endothelial COX-1 was increased, suggesting a greater potency to generate and release EDCFs in aging and hypertension.7 A significant contribution of COX-1–derived EDCFs in the study of Wong et al10 in hamsters is unlikely. Thus, there might be species differences not only regarding the chemical identity of EDCF(s) but also the biosynthetic pathways and site(s) of action. Hirao et al11 have shown that the EDCF, generated by reendothelialized femoral artery of rats 4 weeks after photochemical endothelial injury, was mainly PGF₂α and PGH₂ but not thromboxane A₂. This would confirm PGF₂α as EDCF, contributing to the reduced vasodilation of reendothelialized femoral arteries.

What is the significance of these data for humans? First, it should be noted that COX-2 was the main enzyme involved in EDCF, i.e., PGF₂α release in the hamster aorta. In humans, COX-2 rather than COX-1 produces the majority of vascular PGs in healthy14 and atherosclerotic areas.18 However, PGF₂α is certainly not a major product, but rather PGI₂ and PGE₂ are both potent vasodilators in most vascular beds of humans. In contrast to this, COX-1 is the main regulated enzyme in the rat aorta,19 in which many studies on the identity of EDCF were performed.1 Thus, the prostandyn synthetic pathways in humans appear to be closer to the hamster than the rat, as also suggested by the authors.

Regarding TP receptors, the authors present some preliminary data suggesting an EDCF/PGF₂α–mediated contraction of renal arteries in hypertensive diabetics. These contractions were mimicked by exogenous PGF₂α and antagonized by antagonists of TP but not FP receptors. Thus, PGF₂α might also act as EDCF via the TP receptor in humans. Further studies have to establish this. The VIGOR study demonstrated an increase rather than decrease of blood pressure with the selective COX-2 inhibitor rofecoxib in patients with elevated cardiovascular risk.20 This raises the question for a (patho)physiological role of COX-2–derived PGF₂α acting as EDCF via TP receptors in humans. Because of its relatively low endothelial production rate as opposed to PGI₂ and/or PGE₂, both being vasodilators, and the short half-life of circulating PGF₂α (<1 minute), this appears to be less likely. In a recent review by the same group, the contribution of PGF₂α to endothelium-dependent contraction has been considered marginal.1 On the other hand, there might be situations, such as senescence, in which metabolic enzymes may become insufficient to degrade efficiently released PGs in conditions of elevated biosynthesis, including PGH₂, thromboxane A₂, and PGF₂α.21 Because of the rapid hydrolysis of thromboxane A₂ into the inactive thromboxane B₂ and the (spontaneous) conversion of PGH₂ into PGF₂α, PGF₂α may locally accumulate and cause vasoconstriction. For example, high levels of PGF₂α were found in the cerebrospinal fluid of patients with cerebral transient ischemic attacks or stroke, even in the absence of subarachnoid hemorrhage.22

Overall, Wong et al10 have demonstrated convincing evidence for COX-2–derived PGF₂α as an EDCF acting via TP receptor in the hamster aorta. This provides pharmacological evidence for TP receptor antagonists as useful tools to correct imbalances between EDRF/EDCF. This could be an argument for the revival of the concept of thromboxane receptor blockade to prevent regional ischemia. This concept must not necessarily be realized by thromboxane receptor antagonists, the development of which, unfortunately, has been stopped after the first larger clinical trials with these compounds failed. Natural vasodilator epoxygenesatrienoic acids offer an alternative and were recently reported to cause vasodilation via competitive, direct inhibition of TP receptors.23

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References


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