Editorial Comments

Vascular cytochrome P450 in the regulation of renal function and vascular tone: EDHF, superoxide anions and blood pressure

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Introduction

Renal cytochrome P450 (CYP)-dependent arachidonic acid metabolites have a wide and contrasting spectrum of biological effects. The profile and relative rates of eicosanoid production not only influence renal haemodynamics and tubular ion and water transport but may also play a determinant role in mechanisms associated with the development of hypertension. The eicosanoids generally thought to play major roles in regulating these functions are the epoxideicosatrienoic acids (EETs) and their derivatives which activate Ca^{2+}-dependent K⁺ (K_{Ca}) channels in endothelial and smooth-muscle cells, as well as 20-hydroxyecosatetraenoic acid (20-HETE) which exerts an antagonistic effect on K_{Ca} channel activity. There are also reactive oxygen species (e.g. superoxide anions) generated during the enzymatic conversion of arachidonic acid by CYP within the vascular wall, which have both acute and chronic effects on vascular homeostasis.

NO, EDHF and the control of vascular tone

Nitric oxide (NO) and prostacyclin (PGI₂) are the best-characterized vasodilatory endothelium-derived autacoids; however, a third type of agonist-induced, endothelium-dependent relaxation can be evidenced in the presence of a combination of nitric oxide synthase and cyclo-oxygenase inhibitors. Since this NO/PGI₂-independent relaxation was not observed in the presence of depolarizing concentrations of K⁺ and was co-incident with vascular smooth-muscle hyperpolarization, the relaxation was assumed to be mediated by an endothelium-derived hyperpolarizing factor (EDHF). The relative importance of NO and EDHF in mediating endothelium-dependent vasodilatation alter on descending the vascular tree, such that EDHF becomes the predominant endothelium-derived modulator of arteriolar dilatation. Most resistance-sized arteries are thought to be hybrids which express both the NO and the EDHF synthases. It is in these vessels that the loss of one vasodilator system can be compensated for by an increase in the output of the other (for review see [1]).

Although various EDHF’s have been described in different vascular beds, there is compelling new evidence suggesting that the hyperpolarizing factor produced by coronary and renal arteries is a CYP epoxygenase-derived metabolite of arachidonic acid. Indeed, inducing the expression of the CYP 2C epoxygenase in porcine coronary arteries increases the endothelial generation of 11,12-EET and enhances both the bradykinin-induced hyperpolarization and relaxation of vascular smooth-muscle cells [2]. Using an antisense approach to attenuate either the activity or the expression of the endothelial CYP 2C, on the other hand, attenuates all of the EDHF-mediated responses [2]. EDHF/EET-mediated relaxation is generally attributed to the activation of K_{Ca} channels, although a role for EETs in the modulation of Cl⁻ conductance cannot be ruled out.

Other actions of EETs

The role of EET/EDHF in the vasculature may well extend beyond its function as a vasodilator to the regulation of a number of genes in the vascular wall. Indeed, in endothelial and smooth-muscle cells, EETs can be incorporated into phospholipids and thus remain in the vascular wall long enough to produce chronic effects [3]. The exogenous application of EET to cultured or native endothelial cells decreases the activity of NF-κB and attenuates the TNF-α-induced
expression of vascular cellular adhesion molecules (VCAM)-1 [4]. In renal epithelial cells, EETs also stimulate tyrosine phosphorylation and induce mitogenesis, while the transfection of renal epithelial cells with an active CYP epoxidegenase indicates that 14,15-EET functions as an intracellular messenger in response to epidermal growth factor. EETs may also play a role in angiogenesis as EETs derived from glial cells have been reported to elicit tube formation in co-cultured cerebral microvascular endothelial cells [5].

Other CYP-derived products

The putative EDHF synthase (a CYP enzyme homologous to 2C9) is also a physiologically relevant source of reactive oxygen species, and its overexpression of CYP 2C9 in coronary artery endothelial cells markedly increases reactive oxygen species generation in addition to that of the EETs [6]. The consequences of superoxide anion and/or hydrogen peroxide production by CYP 2C9 range from the impairment of NO-mediated relaxation to a chronic elevation in the activity of the redox-sensitive transcription factor NF-κB and the expression of VCAM-1 [6], i.e. the opposite of the effects observed following exogenous EET application. Thus, while the anti-inflammatory CYP product EDHF/EET may be the dominant endothelium-derived vasoactive autacoid in states associated with a manifest ‘endothelial dysfunction’, the enhanced activation of the CYP-like EDHF synthase may be detrimental to vascular homeostasis, as a consequence of the simultaneous generation of EETs and reactive oxygen species. It is also possible that lipid peroxides generated during the CYP reaction are able to scavenge NO in much the same way as described for 15-lipoxygenase and prostaglandin H synthase [7].

20-HETE and its interaction with NO

Of the CYP isoforms identified to date in the kidney, most generate 20-HETE when incubated with arachidonic acid. A few EET-generating enzymes (from the 2A, 2E, 2C, and 2J families) have been detected but it is likely that different CYP isoforms generate different EET profiles in different parts of the kidney. 20-HETE which is endogenously produced by smooth-muscle cells from small renal and cerebral vessels, is thought to be involved in the development of myogenic tone, since it increases smooth-muscle tone by inhibiting large conductance K_{Ca} channels, inducing depolarization, and increasing [Ca^{2+}], probably by activating L-type Ca^{2+} channels [8]. NO may also modulate the formation of 20-HETE by binding and inactivating the CYP haem moiety in much the same way that it inhibits EDHF synthase.

20-HETE is also involved in the regulation of sodium transport. The mechanism underlying this effect is thought to be a 20-HETE-induced activation of protein kinase C, which phosphorylates the z-subunit of the Na-K-ATPase, thus inhibiting its activity. Intrarenal infusion of an inhibitor of 20-HETE and EET production in rats induced diuresis and natriuresis, which are associated with an increase in renal papillary blood flow.

Soluble epoxide hydrolase and hypertension

While EETs are potent vasodilators and exert anti-inflammatory properties [4], there is evidence suggesting that CYP expression, EETs, dihydroxyeicosatrienoic acid (DHET), and 20 HETE generation are increased in hypertension [9]. Notably, there is a marked increase in the renal metabolism of EET to DHET, suggesting that either the activity or the expression of the soluble epoxide hydrolase (sEH) increases during the development of hypertension [9]. Indeed, the sEH has recently been suggested to play a key role in hypertension, based on the findings that:

(i) deletion of the soluble epoxide hydrolase gene lowered systolic blood pressure and altered arachidonic acid metabolism in male mice [10];
(ii) an sEH inhibitor decreased DHET formation and markedly reduced blood pressure in adult spontaneously hypertensive rats (SHR) [11]; and
(iii) the expression of sEH was markedly higher in renal microsomes from genetically hypertensive animals than from Wistar rats [11].

However, the expression of sEH, unlike the generation of EET, was elevated in SHR from birth and was not a phenomenon that could be directly correlated to the age of the animals or, more importantly, to the development of overt hypertension. The ‘DHET-induced hypertension’ hypothesis moreover assumes that elevated concentrations of EETs are beneficial, while elevations in DHET are detrimental. Currently no experimental evidence exists to support this, and although the vascular response of DHET varies markedly with the vessel studied, DHET is a potent vasodilator in the coronary circulation [12]. One possibility, yet to be addressed is that there may be a gradual switch-over of the substrate metabolized by the CYP enzymes in the kidney. For example, renal CYPs of the 2C and 2J families also metabolize linoleic acid to epoxyeicosatrienoic acid and its derivatives [13] and several studies have suggested an sEH-dependent pathway for the nephrotoxicity induced by 9,10- and 12,13-epoxyeicosatrienoic acid [14–16]. Although a direct relationship between enhanced linoleic acid metabolism by CYPs and the development of hypertension is speculative, a diet high in linoleic acid potentiates hypertension in the Dahl salt-sensitive rat [17], suggesting that CYP derivatives other than the EETs might be important in the genesis of some forms of hypertension.
References

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