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Review article

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CYTOCHROME P-450 METABOLITES IN RENAL CIRCULATION AND EXCRETION – INTERACTION WITH THE NITRIC OXIDE (NO) SYSTEM

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The role of CYP-450 dependent arachidonic acid (AA) metabolites (vasoconstrictor 20-HETE and vasodilator EETs) and NO in control of blood pressure (MABP) and kidney function remains unclear. NO affects the activity of heme-containing enzymes, like CYP-450 related monooxygenases, moreover, their activity depends on Na^+ intake. The focus of this review and underlying studies is on the role of high sodium intake (pro-hypertensive factor) in interrelation between CYP-450 and NOS. The acute vs. chronic non-selective inhibition of CYP-450 AA metabolites (ABT), and selective inhibition of 20-HETE (HET 0016) has also been tested. The renal artery flow (RBF, Transonic probe), medullary blood flow (MBF, laser-Doppler flux), renal excretion, and medullary tissue NO (selective electrode) were measured in male anaesthetized Wistar rats. We conclude that on standard Na^+ intake, opposed effects of 20-HETE and EETs are almost in equilibrium; however, in the renal circulation the vasodilator EETs influence slightly prevails. High sodium intake stimulates NOS, which limits CYP-450 impact on MABP and kidney function. However, this protection disappears after prolonged sodium intake. Long-lasting high sodium intake lowers NO bioavailability and promotes systemic and intrarenal vasoconstrictor activity of 20-HETE. Opposed effects of NO and AA metabolites of CYP-450 on water and solute excretion are also described.

Key words: *CYP-450 metabolites, NOS, sodium intake, intrarenal circulation, renal excretion*

Metabolites of both prostaglandin cyclooxygenase (COX) and cytochrome P-450 pathways of arachidonic acid (AA) metabolism are engaged in the control of intrarenal circulation, and this review will focus on the latter. A particular attention will be given to the role of P450 dependent agents and their interaction with nitric oxide system (NOS), and the dependence of the interrelation of the two systems on sodium intake.

Arachidonic acid is converted by cytochrome P-450 (CYP-450) dependent epoxygenases to epoxyeicosatrienoic acids (EETs, epoxides) and by ω-oxidases to hydroxyeicosatetraenoic acids (HETEs) (*Fig. 1*). Both groups of metabolites are now recognized as major regulators of renal and cardiovascular function and may show pro- or antihypertensive properties.

The epoxygenases synthetising EETs, primarily members of the CYP2C and CYP2J family, form four EET regioisomers: 5,6-; 8,9-; 11,12- and 14,15-EET. However, the main products having vasorelaxant and natriuretic activity in the kidney are 11,12- and 14,15-EET. They exert very important antihypertensive action, however, EETs are further hydrolysed by soluble epoxide hydrolases (sEH) to the corresponding dihydroxyeicosatrienoic acids (DHETs), which attenuates or eliminates vasorelaxant activity (1).

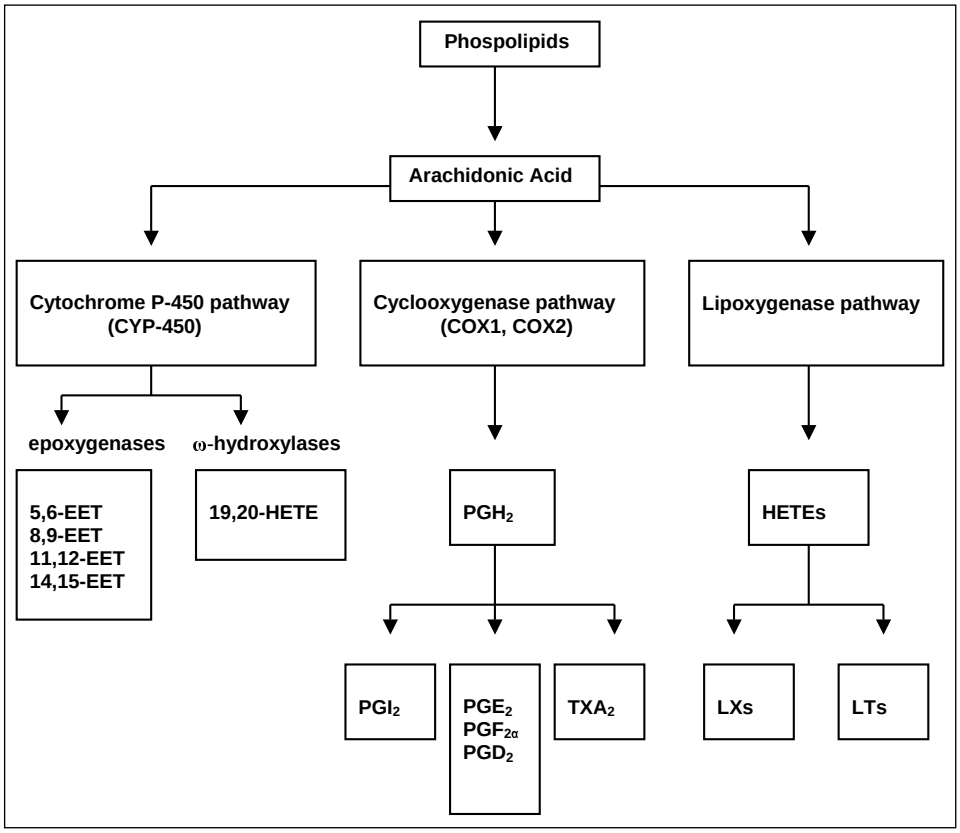

Fig. 1. Major pathways of arachidonic acid metabolism. EETs – epoxyeicosatrienoic acids, products of CYP-450 epoxygenases. 19- , 20-HETE (hydroxyeicosatetraenoic acid), product of ω-hydroxylase. PGX – prostaglandins H_2, I_2 (prostacyclin), E_2, $F_{2\alpha}$, D_2 . TXA_2 - thromboxan A_2. LXs – lipoxins; LTs – leucotrienes.

Epoxides, identified with the endothelium-derived hyperpolarizing factor (EDHF) are released from endothelial cells. They stimulate large-conductance calcium activated K^+ channels (BK_{Ca}) (2), which results in K^+ efflux from the smooth muscle cells and subsequent membrane hyperpolarization. EETs can oppose the actions of different vasoconstrictors, *e.g.* endothelin-1 or angiotensin II (Ang II). Interestingly, the renal microvascular dilatation induced by the latter agent seems to be mediated by AT_2 receptor activation and epoxide production (1). In addition, EETs have anti-inflammatory effects in the endothelium, stimulate angiogenesis, and prevent migration of arterial smooth muscle cells (3). In the proximal tubules and collecting ducts of the kidney, EETs inhibit sodium and water reabsorption, and upregulation of their activity seems to play an important role in adaptation to high sodium intake (4).

CYP4A family is mainly responsible for synthesis of 20-HETE – functionally the most important metabolite of ω-hydroxylation in many tissues (4). 20-HETE is a potent constrictor of small arterioles in the cerebrum, skeletal muscles and in the kidney. In the latter organ it also augments the response of the tubuloglomerular feedback (TGF), which enhances 20-HETE's prohypertensive action. Moreover, many vasoconstrictors, *e.g.* Ang II, arginine vasopressin (AVP) or endothelins, enhance the synthesis and release of 20-HETE in the kidney and vascular smooth muscle cells (VSMC) (4). On the other hand, 20-HETE inhibits Na^+-K^+-ATPase activity in the proximal tubule and Na^+-K^+-$2Cl^-$ co-transport in the thick ascending limb of the loop of Henle, which forms the background of its antihypertensive properties. It should be pointed out that an association of vasoconstrictor action leading to a decrease in medullary perfusion, and of inhibitory effect on tubular reabsorption is a unique feature of 20-HETE. Most of local or systemic mediators work in concert to regulate medullary perfusion and tubular work: they simultaneously enhance medullary blood flow (MBF) and inhibit salt reabsorption (which promotes fluid excretion) or reduce MBF and enhance reabsorption (promoting fluid retention) (5, 6).

Nitric oxide (NO), the third player in the game beside EETs and 20-HETE, has a crucial role in regulation of blood pressure, showing strong antihypertensive properties dependent on dilatation of arterial blood vessels and a decrease of peripheral vascular resistance. In the kidney NO helps maintain sufficient blood perfusion in different zones by dilating the intrarenal arterioles. A recent study suggests that aquaporin 1 (AQP-1) transports NO out of endothelial cells into vascular smooth muscle cells, which is essential for full expression of endothelium dependent relaxation (7).

NO also plays an important role in mediating pressure natriuresis, attenuating TGF responses and inhibiting tubular transport (8, 9). Locally synthetized NO stimulates natriuresis by reducing Na^+ reabsorption in the proximal tubule, medullary thick ascending limb of Henle's loop (mTAL) and in the cortical collecting duct. However, some studies reported antidiuretic and antinatriuretic

action of NO derived from neuronal isoform (nNOS). It was suggested that nNOS-generated NO mimics vasopressin (AVP) activity in the tubules (10, 11).

There is sufficient evidence indicating that the vasodilator NO produced by medullary thick ascending limb cells counterbalances circulating as well as paracrine and autocrine vasoconstrictors. One of the substances antagonised functionally and directly by NO (enzymatic competition) is 20-HETE. The mechanism is related to the chemical nature of NO which combines with heme-containing enzymes, including CYP-450 related monooxygenases (4). The counter-regulatory interaction between NO and 20-HETE is especially interesting because they have opposed direct actions on renal vascular function, and because they reduce each other's bioavailability. An important factor limiting the synthesis of 20-HETE is local tissue oxygen concentration; reduced formation of 20-HETE in response to lowered tissue oxygenation increases medullary blood flow (12, 13). This mechanism plays an important role in the protection of the renal medulla from anoxia and tissue injury. The functional equilibrium of factors mentioned above is critical for maintenance of optimal renal perfusion and seems to be important for blood pressure regulation. Considerable amount of evidence indicates that the rate of medullary perfusion plays a crucial role in long term control of arterial blood pressure, probably *via* influencing urinary concentration and pressure natriuresis mechanisms (14, 15). In the present paper new information is added to the current knowledge of the subject, based on our simultaneous measurements of the perfusion and NO bioavailability in the renal medulla of anaesthetized rats.

It should be pointed out that the activity of NOS and CYP-450 enzymes and generation of the active products is modified by sodium intake. The nature of this influence seems very complex and includes both up- and downregulation of a number of enzymes in different regions of the kidney. A relevant clinical observation is that in patients who developed NaCl dependent mild hypertension, an increase in renal vascular resistance is related to impaired NO production (16). It is well known that high sodium diet enhances expression of all the three isoforms of NOS in the renal medulla and, remarkably, of nNOS activity in macula densa cells located in the renal cortex (17). On the other hand, in young rats low sodium diet was reported to significantly enhance eNOS activity in the renal glomeruli, macula densa and renal vasculature, and nNOS activity in the tubules (18).

As mentioned above, high salt intake increases the activity of CYP2C isoform and production of EETs in the kidney (19) and lowers renal production of 20-HETE (4, 20). On the other hand, high sodium intake upregulates CYP-450 hydroxylases localized outside the kidney; the production of 20-HETE increases in the mesenteric arteries (21) and the vessels of the skeletal muscles (22). Moreover, in different animal models of hypertension both up- and down-regulation of CYP-450 enzyme activity is observed (reviewed in (23).

A marked increase in the renal metabolism of EET is observed in hypertension and during salt loading. During the development of hypertension in SHR rats, enhanced transformation of EETs to DHET has been reported (24). With respect to 20-HETE, its increased generation may be associated either with the development of hypertension or with blood pressure reduction, as observed in studies with Sprague-Dawley rats (4, 25). The actual response seems to depend on the specific site of 20-HETE generation. It was reported that in salt-sensitive Dahl rats a decrease in generation of 20-HETE by enzymes predominantly localized in the thick ascending limb may result in an increase in blood pressure. On the other hand, the same response may be associated with an increase in 20-HETE generation by enzymes located in the vicinity of preglomerular vessels (24).

The uncertainty about the exact role of metabolites of the CYP-450 pathway in the development of hypertension, the apparent dependence of this role on sodium intake, together with the evidence on the competitive molecular antagonism of CYP-450 and NO synthesis prompted us to design functional studies aimed at elucidation some of the problems involved. To this purpose, effects of experimental interventions changing the activity of CYP-450 and NOS on blood pressure and renal circulation and excretion were examined in normal rats maintained on diets with different Na^+ content. In part of the studies medullary tissue NO signal (reflecting local NO bioavailability) was continuously measured using a selective electrode (polarographic method).

It should be emphasized that a part of the difficulty with defining the role of active substances generated by CYP-450 enzymes in the control of blood pressure has been the lack of inhibitors that would be highly selective for each of the two sub-pathways of monooxygenation. In some of our studies we used N-hydroxy-N'- (4-butyl-2 methylphenyl) formamidine (HET0016), a selective inhibitor of ω-hydroxylase which is responsible for generation of 20-HETE (26). However, the inhibitor requires a specific solvent (β-cyclodextrin), which *per se* seems to have some biological activity; this complicates interpretation of the results.

In our experiments with anaesthetized male Wistar rats, during renal artery infusion of HET0016, a selective inhibitor of 20-HETE generation, an increase (16%, $p<0.05$), in medullary blood flow (MBF) was observed, with total and cortical blood flow remaining unchanged (*Fig. 2*) (26). Increased medullary perfusion was accompanied by a significant increase in medullary tissue NO signal (NO selective electrode). This was not a trivial change (+330 pA); it was comparable with the increase (+550 pA) observed after renal artery infusion of S-Nitroso-N-acetyl-D,L-penicillamine (SNAP), an NO donor (27). The observed increase in NO signal after 20-HETE inhibition represents about 60% of the maximum response to a large hypotensive dose of SNAP. These data accord well with the results of a study in which inhibition of 20-HETE synthesis contributed up to 50-75% of the vasodilator response to NO donors (28). Interestingly, after nonselective inhibition of CYP-450 enzymes with 1-

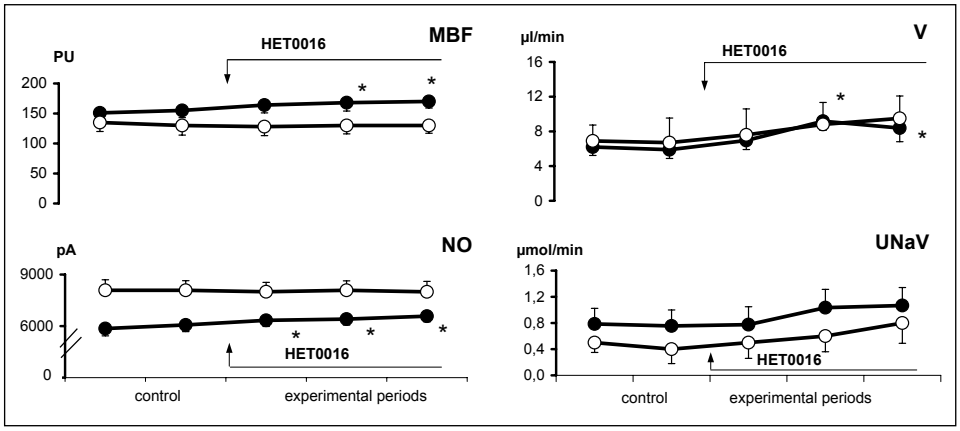

Fig. 2. Effects of infusion of a selective inhibitor of 20-HETE synthesis (HET0016: 0.3 mg/kg/h, solid circles) or solvent (β-cyclodextrin: 1.42 mg/kg/h; open circles) on renal medullary blood flow (MBF) and medullary tissue NO (left panel: ref. (15) and renal water (V) and sodium ($U_{Na}V$) excretion (right panel).
PU – laser-Doppler perfusion units. NO signal – picoamperes (pA). * significantly different from control periods ($P<0.05$).

aminobenzotriazole (ABT), a modest selective decrease in MBF (8.3%, $p<0.05$), accompanied by a slight, transient increase in medullary tissue NO signal (~ 200 pA), was observed in rats maintained on standard diet (*Fig. 3*). Taken together, our results suggest that under basic conditions (standard Na^+ intake), the opposed influences on medullary blood flow of vasodilator EETs and vasoconstrictor 20-HETE are almost in equilibrium, with a minor prevalence of vasorelaxant effect of EETs. Selective elimination of 20-HETE uncovers the role of EETs in the control of medullary circulation. The mechanism of the increase in medullary perfusion is probably complex: a direct effect of elimination of vasoconstrictor 20-HETE may be enhanced by increased NO bioavailability in the medulla dependent on elimination of NO - CYP-450 competition, and possibly also the generation of vasodilator EETs is further increased because of the transfer of substrate (AA) from the ω-hydroxylation to epoxygenation pathway.

To explore the role of enhanced sodium intake, in Wistar rats we applied high sodium diet (4% Na^+) for 10 or 21 days. High sodium intake for ten days had no effect on mean arterial blood pressure (MABP), renal haemodynamics, or on the pattern of the response to ABT; however, it was associated with a significantly higher NO signal measured in the medullary tissue (*Fig. 3*). Augmentation of NO production in response to high sodium intake probably occurs not only in the kidney but also in many other organs and vascular beds (29). Most likely, this response is responsible for the maintenance of systemic blood pressure and renal haemodynamics at the level observed under control conditions (standard diet).

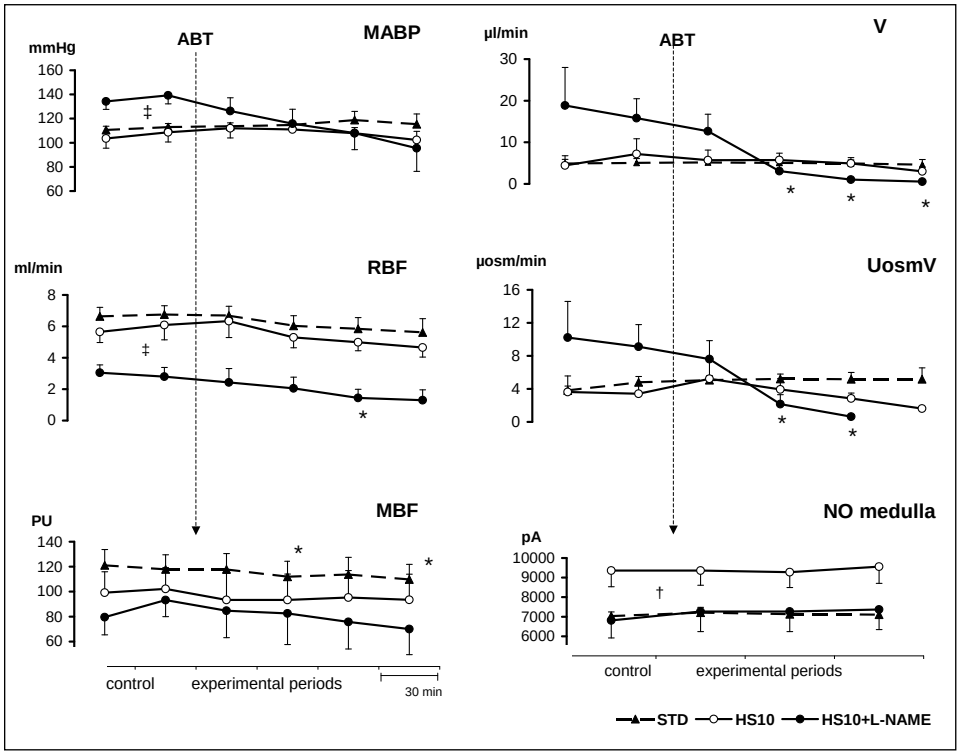

Fig. 3. Effects of non-selective inhibition of CYP-450 monooxygenases (ABT) on mean arterial blood pressure (MABP), total renal and medullary blood flow, renal excretion and tissue NO in rats maintained on standard (STD) or high sodium (HS) diet for 10 days.
Rat groups – untreated (HS10) or pre-treated with NO inhibitor L-NAME (50 mg/L in drinking water) (HS10+L-NAME). RBF, MBF, V, UosmV – total renal blood flow, medullary blood flow, diuresis, solute excretion. * significantly different from control periods ($P<0.05$); † control values significantly different from control group (STD) ($P<0.05$ by unpaired Student t test); ‡ control values significantly different from L-NAME pre-treated group (HS10+L-NAME) ($P<0.02$).

Prolongation of high sodium intake to three weeks induced a different response pattern. MABP was modestly elevated (126±2 mmHg, n=37) (31) or even substantially ($p<0.05$) higher (140±4 mmHg) (30) than the level of 107±2 mmHg (n=49) observed on standard diet. RBF and CBF were also significantly higher (by 48% and 40%, respectively; $p<0.05$), however, perfusion of the inner medulla was not increased. Interestingly, our earlier studies (30) using separate measurement of outer- and inner medullary blood flow (laser-Doppler technique) showed that perfusion of outer medulla was significantly lower after 3 weeks of high sodium intake (4% Na^+) than in rats maintained on low sodium diet (102±13 vs. 168±15, respectively) and much lower than the level normally observed in rats on standard diet.

Since NO signal in inner medullary tissue of rats maintained on HS diet for 3 weeks was substantially higher (by more than 700 pA) than in rats on standard diet, we can argue that higher bioavailability of NO in this region is responsible for the maintenance of blood flow at the baseline level. On the other hand, one can reason that in the outer medulla, a decrease in bioavailable NO was likely related to high consumption of NO utilized for neutralization of the oxidative stress which follows high sodium transport in the thick ascending limb of Henle's loop, located in this zone. Such a decrease in local NO could be responsible for the low blood flow observed in the outer medulla (30). However, this hypothesis should be supported by studies of the dynamics of nitrate excretion during exposure to high sodium intake and, if feasible, separate determination of NO signal in the outer an inner medulla.

It should be emphasized that AA metabolites of CYP-450 enzymes seem to play more important role in control of blood pressure and renal haemodynamics in prolonged (3 weeks) as compared to short term high sodium intake. Vasoconstrictor 20-HETE may be partly responsible for higher blood pressure in the former rats, since both acute and chronic inhibition of CYP-450 activity with ABT caused a decrease in MABP (8%, $p<0.03$ and 7%, NS; respectively). It will be noticed that the decrease in MABP after acute inhibition of CYP-450 is not simply related to elimination of NO - CYP-450 competition and higher systemic NO bioavailability, since the response to ABT was even slightly deeper in rats pretreated with L-NAME (50 mg/L dissolved in drinking water was given during 4 days before an acute experiment) (31) than in untreated rats maintained on high sodium diet for three weeks. On the other hand, short term (10 days) exposure to high sodium diet probably stimulates NO synthesis, which compromises CYP-450 related vasoconstrictor effect of 20-HETE and limits the possible effect on MABP. As was shown in *Fig. 3*, elimination of NO (L-NAME treatment) in rats maintained on HS diet for 10 days significantly elevated their blood pressure but subsequent application of the CYP-450 inhibitor decreased MABP to the baseline values.

After acute and chronic ABT treatment the remarkable change observed in the kidney was a decrease in inner medullary blood flow (by16%, $p<0.03$ and 34%, NS; respectively) (30, 31). These results suggest that under prolonged high sodium intake (3 weeks), vasorelaxant EETs together with NO help maintain inner medullary blood flow at the level comparable with that observed in rats on standard diet. With long duration of high sodium intake, the role of NO seems to be more important, since in the experiments in which NO synthesis was eliminated by chronic administration of L-NAME, both total renal and medullary blood flow were very substantially reduced (by 75%, $p<0.001$ and 47%, $p<0.001$, respectively). In rats maintained on HS diet for 10 days, the decrease in RBF in response to L-NAME was comparable to that observed in rats maintained on HS diet for 21 days, however their medullary perfusion was unaffected. Simultaneous elimination of NO and CYP-450 derived metabolites brought the total renal blood flow to an extremely low level (*Fig. 3*). Probably, during high sodium intake the

dependence of whole kidney perfusion on adequate production of both - NO and EETs is enhanced. The same is true for medullary circulation but here the role of NO and EETs seems to depend also on the time of exposure to high sodium intake.

In general, these findings are consistent with the results of others (reviewed above), showing that in the kidney high sodium intake stimulates production of vasodilator EETs, whereas in other organs and tissues it augments the synthesis of 20-HETE, a major vasoconstrictor which increases systemic blood pressure in normal Wistar rats.

Considering the important functional role in blood pressure control of NOS and CYP-450 enzymes, *via* generation of metabolites acting directly on blood vessel diameter or, indirectly, on renal tubular transport, we present also the results of inhibition of these enzymes on renal sodium and water excretion. Selective inhibition of 20-HETE modestly but significantly increased diuresis and tended to increase sodium excretion in rats maintained on standard diet (*Fig. 2*). These results were unexpected since elimination of 20-HETE, an inhibitor of reabsorption in the proximal tubule and thick ascending limb of Henle's loop, should have an opposite effect. However, the modest diuresis and natriuresis could have been secondary to the observed increase in both MBF and tissue NO (*Fig. 2*). An increase in MBF and peritubular hydrostatic pressure, followed by increased back-leak of solute and water in the tubules could have been responsible for the increase in V and $U_{Na}V$ (31, 32). Moreover, there is good evidence indicating that 20-HETE augments sensitivity of tubuloglomerular feedback response of the afferent arterioles (4) and its elimination with HET0016 could enhance excretion secondary to an increase in glomerular filtration rate (GFR). In addition, one could suspect that elimination of one pathway of arachidonic acid metabolism (ω-hydroxylation) can cause a transfer of AA substrate to other active pathways (33, 34); this could result in enhanced synthesis of natriuretic prostaglandin E_2 (PGE_2). All these indirect effects could have prevailed over the direct action of 20-HETE on tubular transport. It will be noticed that in earlier studies, nonselective inhibition of cytochrome P-450 with 17-octadecynoic acid (17-ODYA), eliminating both 20-HETE and natriuretic EETs, also resulted in an increase in V and $U_{Na}V$, associated with an increase in renal papillary blood flow and renal interstitial hydrostatic pressure but no change in RBF and GFR (35). On the other hand, in our own studies, nonselective inhibition of CYP-450 enzyme activity with ABT had no effect on sodium and water excretion in rats maintained on both standard and high sodium diet for 10 days (*Fig. 2*). It should be stressed, however, that the inhibition was not associated with any increase in medullary blood flow.

Evidently, prolongation of high sodium intake to three weeks uncovered the importance of CYP-450 related AA metabolites in tubular transport regulation. In an earlier study from our laboratory (30), after chronic inhibition of CYP-450 activity with ABT, the values for diuresis, natriuresis and urine osmolality were significantly lower than in non-treated HS controls. (V: 6.0±1.1 vs. 11.2±1.4

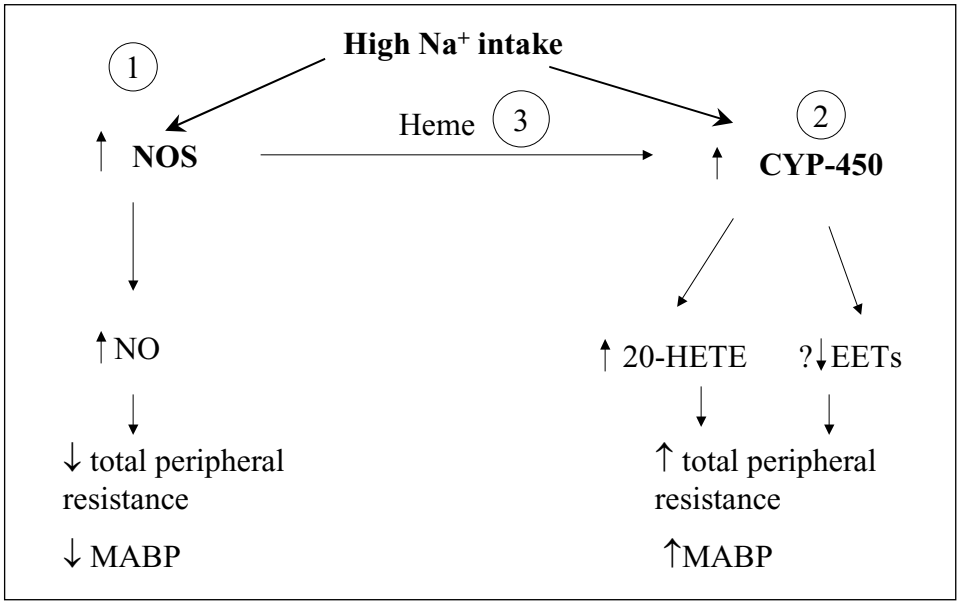

Fig. 4. Suggested changes in NOS and CYP-450 activity during high sodium intake. Role in control of MABP.
(1) High sodium intake seems to be responsible for increased NOS activity and higher production of vasodilator NO. (2) High sodium intake seems also responsible for increased activity of CYP-450 enzymes. Probably, enhanced synthesis of 20-HETE in the arteries of skeletal muscles leads to an increase in total peripheral resistance and MABP. (3) NO may modulate the formation of CYP-450 products by binding to heme moiety and inhibiting the cytochrome P-450 activity.

µl/min/g; $U_{Na}V$: 0.6±0.2 vs. 2.4±0.5 µmol/min/g; Uosm: 675±49 vs. 880±40 mosmol/kg H_2O). Acute inhibition of CYP-450 in rats maintained on HS diet for 3 weeks also caused a significant decrease in water excretion (46%, $p<0.05$) and tended to decrease sodium excretion. These results suggest that, under sufficiently long exposure to high sodium intake, 20-HETE and EETs play an important role in volume and electrolyte homeostasis. The role is even more essential in situation in which NOS system is impaired, since in L-NAME pre-treated rats inhibition of CYP-450 activity (with ABT) caused a marked decrease in water and total solute excretion whereas no response to ABT was seen in 10-days' HS rats (*Fig. 3*). It is likely that in the kidney the role of natriuretic and vasodilator EETs is very pronounced, especially under high sodium diet (23), and their elimination by ABT could account for both an increase in sodium reabsorption and in reduction of kidney perfusion (*Fig. 3*).

In summary, we conclude that on normal sodium intake opposed systemic vascular effects of 20-HETE and EETs are in equilibrium, however, the latter seems to prevail as a controller of intrarenal circulation. High sodium diet

stimulates NO synthesis, which limits the influence of CYP-450 dependent active substances on blood pressure and kidney function (*Fig. 4*). However this protective action disappears after prolonged high sodium intake, which probably lowers NO bioavailability and promotes systemic and intrarenal vasoconstrictor action of 20-HETE.

Apart from essential hypertension, increased arterial pressure is a complicating factor in numerous clinical conditions, *e.g* in diabetes or polycystic kidney disease, and in pregnancy. Broadly speaking, end organ damage associated with renal and cardiovascular disorders is a major cause of morbidity and mortality in highly developed populations. In this context, attempts to appropriately modulate the activity and interaction of the two major AA pathways involved in acute and long term regulation of blood pressure (epoxygenation and hydroxylation) may bring benefits to patients with any form of hypertension and the related end organ damage.

This study was approved by Ethical Research Committee of Medical Research Center of Warsaw, Poland.

Conflict of interest statement: None declared.

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All of these metabolites are ACTIVE. P450 oxidize many lipophilic compounds to make them. More water soluble for excretion. Xenobiotic. Mechanism to remove foreign life from the body. it also removes drugs.Â C.Taken at the same time, alcohol and acetaminophen compete for CYP2E1 so less toxic metabolite. D.With the longer time gap, only alcohol reacts with CYP2E1. E.None of the above. Taken at the sametime, aclhol and acetaminophen compete for CYP2E1 so less toxic metabolite is ofrmed. Statins could be considered xenobiotics(exogenous substances metabolized by the body). Many xenobiotics are oxidized by cytochromes P450 in order to. A.Make them carcinogenic. B,Increase their solubility in an aqueous environment. Introduction The cytochrome P450 (CYP) superfamily is one group of important Phase I metabolizing enzymes that oxidize a number of endogenous compounds and xenobiotics, including more than 90% of clinically used drugs [1]. Endo-genous compounds metabolized by CYPs include fatty acids, steroids, fat-soluble vita-mins, bile acids, and many other lipophilic com-pounds.Â the vasculature and regulation of renal sodium. excretion by modulating the expression and. activity of ion channels such as BK channels, inwardly rectifying K channels, or epithelial.Â Role of cytochrome P450-mediated arachidon-ic acid metabolites in the pathogenesis of car-diac hypertrophy. Drug Metab Rev 2013; 45: 173-195. The Cytochrome P450 Enzymes page the CYP enzyme families and focuses on the biological activities associated with several family members.Â Critical to the function of CYP enzymes are the interactions of amidic groups of specific amino acids in the enzyme with the sulfur atom of the cysteine in the active site. Table of Human CYP Enzyme Family Members. CYP Family.Â These three mechanisms include renal excretion, CYP-mediated metabolism, and conjugation reactions that are predominantly glucuronidation reactions.Â Of these metabolites, the most significant with respect to vascular functions and inflammation are 12-HETE, 19-HETE, and 20-HETE. The primary enzymes generating 20-HETE are CYP4A11 and CYP4F2. The increase in renal vascular resistance shifts the pressure-natriuretic relationship to higher pressures and opposes the development of renal injury.Â : Renal cytochrome P-450-arachidonic acid metabolism: Localization and hormonal regulation in SHR.Am J Physiol262: F591â€“F599, 1992pmid:1566872. OpenUrl PubMed Google Scholar. â†µ.Â : Transforming growth factor-beta, 20-HETE interaction, and glomerular injury in Dahl salt-sensitive rats.Hypertension45: 643â€“648, 2005pmid:15723968. OpenUrl Abstract/FREE Full Text Google Scholar. â†µ. Structures of Cytochrome P450 Enzymes. Thomas L. Poulos and Eric R Johnson. 3. 1. Introduction.Â This arrangement is not only found in all P450s but in two closely related proteins, nitric oxide synthase (NOS) and chloroperoxidase (CPO). Both NOS and CPO are heme-thiolate enzymes and like P450s catalyze monooxygenation reactions.Â Membrane interactions with the catalytic domain of microsomal P450s could promote the transfer of hydrophobic substrates from the membrane to the P450 and could also orient the protein to facilitate interactions with P450 reductase as the two proteins diffuse along the sur-face of the endoplasmic reticulum.Â Thus, the structure of all compo-nents of the P450cam monooxygenase system now are known. The Pdx and Pdr structures are.