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ROLE OF ENDOTHELINE-1 IN ARTERIAL HYPERTENSION

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Arterial hypertension is the most common cardiovascular disease which is usually caused by combination of several multifactorial abnormalities, including autonomic nervous system function, renin-angiotensin-aldosterone system (RAAS), baroreceptor reflexes, genetic factors, psychological stress, environmental and dietary factors (1). Along with abovementioned reasons some vasoactive peptides, especially endothelin-1 (E1), a substance with vasoconstrictor properties, is an important regulator of the vascular tone acting in physiological antagonism with atrial natriuretic hormone, prostacyclin and other vasodilator agents (2). The role of E- 1 in hypertension has attracted increasing interest over the past few years. It has been established that the presence of an intact endothelium is crucial for the action of several vasoactive agents (3), however less is known about endothelial function in healthy subjects, borderline hypertension or hypertensive patients (4). Studies of E-1 in established mild to severe hypertension have shown conflicting results, because the E1 levels reported in the different studies cannot be compared directly because of differences in antibody characteristics and comparatively small number of participant groups (5, 6). However, the multiple regression analyses further strengthen the link between blood pressure and endothelin levels, consistently showing that diastolic blood pressure (DBP) had the highest impact of the variables studied (4). These findings suggest that a disturbed endothelial function could be present before changes in basal sympathetic / parasympathetic tone occur (4). Among endothelins, E1 is the only endothelin synthesized in endothelial cells (7) producing a marked vasoconstriction and long-lasting hypertensive effect (8). Both normal (5) and elevated (9) concentration of E1 have been reported in established hypertension. In experimental studies it was shown ET1 overexpression in the vascular wall in certain models of experimental hypertension: Deoxycorticosterone acetate (DOCA) – salt treated rats, stroke-prone spontaneously hypertensive rats (SHR), angiotensin – II (Ag-II) infused rats, and 1-kidney 1-clip Goldblatt rats, while it has not been overexpressed in SHR, 2-kidney 1-clip hypertensive rats, or L-nitroarginine methylester (L-NAME) –treated rats (10). The endothelin system does not appear to play an important role in SHR (11), however, some reports have suggested that increased vasoconstrictor responses to ET1 and a role for endothelins exist in SHR (12). By authors opinion these results may reflect differences in strains of hypertensive rats and experimental approaches. It was established that activation of vascular endothelin production is associated with hypertrophic remodelling of resistance arteries which can be regressed by endothelin antagonists leading to decrease in arterial pressure (13).

In DOCA-salt hypertensive animals E1 expression is increased in the vasculature and glomeruli of the kidney and enhanced renal E1 production may result in renal vasoconstriction and water and sodium retention, contributing to the progression of renal failure. DOCA salt-treated SHR develop malignant hypertension and vascular and glomerular fibrinoid necrosis, reducing by endothelin antagonists (10, 14). At the same time vasopressin, which stimulates endothelin expression in vitro, could be responsible for the activation of prepro-E1 gene expression in the vasculature of DOCA – salt hypertensive rats, because treatment with V1-vasopressin antagonist resulted in the abolition of enhanced vascular prepro- E1 gene expression in the treated rats (15).

In Ag-II-infused rats endothelin antagonists reduced cardiac and small-artery hypertrophic remodelling (10), that is in contrast with the each effect of these drugs in renin dependent 2-kidney 1 clip Goldblatt hypertensive rats, which do not exhibit generalized vascular overexpression of E1 (16) or respond to endothelin antagonists with blood-pressure lowering (17). Other models of hypertension, such as SHR and long-term L-NAME treated rats, that respond to angiotensin antagonism, do not seem to have a significant endothelin contribution (10). Thus, the endothelin system is activated in low-renin, salt-sensitive and moderate to severe forms of hypertension. The relationship between Ag-II and the endothelin system is complex, and its participation in pathophysiology of hypertension remains to be clarified (10).

An increasing number of studies suggest that E1 plasma levels are usually normal in human hypertension, while in severe form of hypertension, particularly in black patients E1 plasma concentration may be increased (18, 19). Normotensive offspring of hypertensive parents have enhanced plasma endothelin responses to mental stress, suggesting a genetically determined endothelial dysfunction revealed at an early stage preceding the development of hypertension (20).

In clinical investigations it was shown, that patients with chronic kidney disease (CKD) lack the diurnal variation in arterial stiffness seen in matched subjects without CKD. With regard to the endothelial system 24-hour variation in plasma E1 has revealed á night-time rise in patients with CKD compared with fall in healthy volunteers and medium-term dosing with a selective ETA receptor antagonist produces a greater fall in nocturnal blood pressure compared with an alternative blood pressure lowering method with a similar overall 24-hour antihypertensive profile (21). In other study it has been shown that nocturnal dip in plasma E1 in healthy volunteers is reversed in patients with CKD. The explanation for this diurnal variation in endothelin system activation is unclear, but assumingly it may be based on the regu37 lation of ET1 mRNA and protein in the kidney by circadian protein period 1, which contributes to the regulation of renal sodium transport and so blood pressure (21, 22).

Nighttime dosing of antihypertensive medication is well recognized treatment strategy (21). In clinical trials were assessed the efficacy of a combined inhibitor of the endothelin-converting enzyme and neutral endopeptidase the effect of inhibitor on blood pressure was significantly higher at night suggesting that E1-may be a key mediator in the 24- hour control of blood pressure (21, 23).

A group of authors (24,25,26) have considered the several possible mechanisms involving in improving blood pressure dipping by ETA receptor antagonist sitaxentan, suggesting nocturnal upregulation of the endothelin system in CKD. Given a suitable pharmacokinetic profile regarding sitaxentan which has a plasma half-life of H" 10 hours allows once a day dosing of this drug. Aside from this, the effects of an sitaxentan relate to the degree of renin-angiotensin system blockade, because ACE inhibitor or Ag-II receptors antagonist potentiate the effects of ETA antagonist at night. Finally, treatment with a selective ETA receptor antagonist may allow an unblocked ETB receptor to promote natriuresis and diuresis (27) allowing recovery of a dipping blood pressure phenotype.

A recent report (28) showed that clock gene period-1 (PER-1) knockout mice have a similar blood pressure phenotype as the circadian clock knockout mices. PER-1 knockout mices exhibited a 24-h mean blood pressure that was 18mm Hg less than in wild-type mices. PER-1 knockout mices also had elevated levels of inner medullary E1 compared with wild-type mices. Given the known role of E1 in mediating the inhibition of ENaC and regulation of blood pressure, the observation of increased E1- in PER-1 knockout mices provided one possible mechanism which contributes to the blood pressure phenotype in these mices (29, 30).

In other investigations it was shown that E1 contributes to endothelial progenitor cells (EPCs) reduction and dysfunction via an ETA/NADPH oxidase pathway-induced oxidative stress in salt-sensitive hypertension (31). In this study both ETA and ETB receptors were expressed in EPCs, but only ETA receptors were significantly increased in EPCs of DOCA-salt rats. EPC number and function were reduced un DOCA-salt rats compared with sham controls and both were reversed by in vivo blockade of ETA receptors or NADPH oxidase. ROS level was elevated in EPCs from DOCA-salt rats, accompanied by increased EPC telomerase inactivation and apoptosis, which were reduced by ETA or NADPH oxidase blockade.

The different findings suggest that disturbances in the endothelial function may be involved in the early development of hypertension and disturbed endothelial function could be present before changes in basal sympathetic/parasympathetic tone occur, which is supported by the study showing that the release of prostacyclin, another endothelium derived vasoactive substance during physiological stress is markedly elevated in untreated, early hypertension (4, 32). It is also believed the possible causal relationship between endothelin and neuropeptide "Y", which might reflect elevated basal sympathetic tone better than norepinephrine (32) in the development of sustained hypertension.

In conclusion it may be suggest that E1 may participate in vascular damage in cardiovascular disease and blood pressure elevation in experimental models and human hypertension and its antagonists could become effective disease modifying agents in different forms of cardiovascular disease.

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ენდოთელინი-1-ის როლი არტერიული ჰიპერტენზიის დროს

თსსუ, სამედიცინო ფარმაკოლოგიისა და თერაპიის [13] დეპარტამენტები

მრავალი კვლევით ნაჩვენებია ენდოთელინი-1-ის (E-1) მონაწილეობა სისხლძარღვთა ტონუსის რეგულაციაში. გამოვლენილია, რომ ენდოთელიუმის ფუნქციის დარღვევას შეიძლება ადგილი ჰქონდეს ბაზალური სიმპათიკური/პარასიმპათიკური ტონუსის ცვლილებამდე. ექსპერიმენტული კვლევებით რეგისტრირებულ იქნა სისხლძარღვთა კედელში E-1 ჭარბი ექსპრესია ვირთაგვების არტერიული ჰიპერტენზიის ისეთ მოდელებში, როგორიცაა: დეოქსიკორტიკოსტერონ/ აცეტატით (DOCA) ინდუცირებული ჰიპერტენზია, ინსულტისადმი მიდრეკილების მქონე სპონტანურ-ჰიპერტენზირებული ვირთაგვების (SHR), ანგიოტენზინი II-ის (Ag-II) ინფუზიით გამოწვეული და ცალი თირკმელი 1 კლიპით (1K-1C) მოდელირებული გოლდბლატის ჰიპერტენზიის მქონე ცხოველები, მაშინ როდესაც SHR-ში, 2-თირკმელი- 1-კლიპი და L-ნიტრო-არგინ-მეთილსტერინი (L-NAME) გამოწვეული ჰიპერტენზიის დროს E-1-ის ჭარბი ექსპრესია არ იყო გამოხატული. დადგენილ იქნა, რომ ვასკულური E-1-ის პროდუქციის აქტივაცია ასოცირდება რეზისტიული არტერიების ჰიპერტროფული რემოდელირებასთან და ვაზოპრესინის (V) გამოთავისუფლებასთან, ვინაიდან EA და V1 რეცეპტორების ანტაგონისტები DOCA-მარილოვანი ჰიპერტენზიის დროს ამცირებდნენ სისხლძარღვებში პრეპრო E-1-ის გენის გაძლიერებულ ექსპრესიას და აქვეითებდნენ სისხლის არტერიულ წნევას. რაც შეეხება 2K-1C, SHR და L-NAME-თი ჰიპერტენზიის მქონე ცხოველებს, დადასტურებულ იქნა E-1-ის უმნიშვნელო როლი ამ ტიპის ჰიპერტენზიის ფორმირებაში. არტერიული ჰიპერტენზიის მქონე მშობლების შთამომავლებში მენტალური სტრესის საპასუხოდ ადგილი ჰქონდა E-1-ის პლაზმური დონის მომატებას, რაც მიუთითებს გენეტიკურად დეტერმინირებული ენდოთელიუმის დისფუნქციის შესახებ, რომელიც შეიძლება გამოვლინდეს ადრეულ ეტაპზე და წინ უსწრებდეს არტერიული ჰიპერტენზიის განვითარებას. ამასთან ერთად, კლინიკური კვლევებით თირკმლის ქრონიკული დაავადების მქონე პაციენტებში, ჯანმრთელი სუბიექტებისაგან განსხვავებით, დადგენილ იქნა E-1-ის პლაზმური დონის 24 საათიანი ვარიაბელობა მისი პლაზმური კონცენტრაციის მომატებით ღამის საათებში. სავარაუდოდ, E-1-ის მსგავს ფლუქტუაციას საფუძვლად უდევს E-1-ის mRNA-ას და თირკმლის პროტეინის ცირკადული პროტეინის პერიოდი-1-ით რეგულაცია, რომელიც გავლენას ახდენს ნატრიუმის ტრანსპორტზე და სისხლის არტერიულ წნევაზე. ასევე ნაჩვენებია, რომ EA-რეცეპტორების ბლოკადა ამცირებდა ოქსიდაციური სტრესის მოვლენებს.

დასკვნის სახით პოსტულირებულია, რომ E-1 არტერიული ჰიპერტენზიის დროს მონაწილეობს სისხლძარღვთა დაზიანებაში, რის გამოც მისი ანტაგონისტები

შესაძლოა ეფექტურ მამოდიფიცირებულ საშუალებებად მოგვევლინოს სხვადასხვა კარდიოვასკულური დაავადებების დროს.