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Renal dopamine system in chronic renal insufficiency

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ABSTRACT

In the periphery, physiological dopamine increases renal blood flow, decreases renal resistance and acts on the kidney tubule to enhance natriuresis and diuresis. Dopamine receptors can be divided into D_1-like (D_1 and D_5) receptors that stimulate adenylyl cyclase and D_2-like (D_2, D_3 and D_4) receptors that inhibit adenylyl cyclase. Both the D_1-like and D_2-like receptors are expressed in the kidney. Dopamine is synthesized in the epithelial cells of the proximal tubules which are endowed with a high aromatic *L*-amino acid decarboxylase (*L*-AADC) activity. Dopamine of renal origin behaves as an endogenous natriuretic hormone interacting with tubular D_1-like receptors to inhibit the Na^+-K^+ ATPase and Na^+-H^+ exchanger, as a paracrine/autocrine substance. Dopamine newly synthesized in tubular epithelial cells undergoes extensive deamination and methylation by monoamine oxidase and catechol-*O*-methyltransferase, respectively. During moderate sodium surfeit, dopamine of renal origin accounts for ~50% of sodium excretion. In experimental and human hypertension a reduced renal production of dopamine and a D_1 receptor-G protein coupling defect have been reported. Patients suffering from chronic parenchymal diseases with a compromised renal function present a reduced renal dopamine output which correlates well with the degree of

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deterioration of renal function. However, in contrast to what has been found in sodium-sensitive primary hypertension, renal dopamine may behave appropriately in experimental and human renal insufficiency, as a compensatory natriuretic hormone.

INTRODUCTION

Dopamine is a catecholamine playing two important roles in neurobiology:1) as an intermediate in the biochemical pathway from the amino acid tyrosine to norepinephrine and epinephrine and 2) as a direct neurotransmitter in its own right. In neurons, dopamine is synthesized by the initial hydroxylation of tyrosine by tyrosine hydroxylase to *L*-3,4-dihydroxyphenylalanine (*L*-Dopa) followed by the decarboxylation by aromatic *L*-amino acid decarboxylase (*L*-AADC) to dopamine. The role of dopamine as a neurotransmitter in the regulation of motor function and behaviour in the central nervous system is well established. However, it is only during the past two decades that peripheral dopamine has been characterized as an important modulator of renal sodium excretion and blood pressure by direct actions on renal epithelial ion transport and by modulation of the secretion of hormonal/humoral agents such as aldosterone, catecholamines, renin, 5-hydroxytryptamine and vasopressin. The actions of endogenous renal dopamine on water and electrolyte transport are modest in euvolemic conditions but become magnified during moderate sodium excess. Thus, following a moderate acute or chronic sodium load, up to 50% of sodium excretion is mediated by dopamine produced by the renal proximal tubules. In this paper there will be a brief discussion of the renal dopamine synthesis and metabolism and the potential role of intrarenal dopamine as a paracrine regulator of sodium homeostasis. The potential role of the renal dopamine system in the regulation of sodium balance during early chronic renal insufficiency will be also examined.

RENAL DOPAMINE RECEPTORS

When dopamine is released peripherally, it acts on receptors distinguishable from classical α and β-adrenoceptors and it is now well accepted that there are specific dopamine receptors in many peripheral tissues, including certain vascular beds, and, particularly, in the kidney[1]. Peripheral dopamine receptors have been subdivided into two major families as D_1–like (includes D_1 and D_5, the rat homologues of which are D_{1A} and D_{1B}) and D_2-like (includes D2, D3 and D4) dopamine receptors based on the stimulation and inhibition of adenylyl cyclase, respectively[2]. This has been achieved with the help of specific agonists for D_1 (fenoldopam) and D_2 (quinpirole) receptors and antagonists (SCH 23390 for D_1 and domperidone for D_2). These receptors belong to the rhodopsin-like family and are called G protein-coupled receptors because of their interaction with heterotrimeric G proteins, composed of α, β and γ subunits[3]. The D_1–like receptors cause direct vasodilatation, diuresis and natriuresis. On the other hand, D_2–like receptors cause indirect vasodilatation by inhibition of norepinephrine release and also inhibit aldosterone production within the adrenal gland[1].

The role of dopamine as a regulator of renal function was first recognized in the early 1970s, when it was found that dopamine increased the glomerular filtration rate and sodium excretion[4]. These observations led to extensive clinical use of dopamine to improve renal function in critically ill patients. It soon became apparent that dopamine had a natriuretic effect, independent of the increase in glomerular filtration rate. The

renal localization of D_1-like and D_2-like dopamine receptors has been studied with radioligand binding and autoradiographic studies[5]. The D_1-like receptors are present in the smooth muscle of renal arteries and juxtaglomerular apparatus and in the renal tubules whereas the D_2–like receptors are expressed in the intimal layer of the renal vasculature, glomeruli, sympathetic nerve terminals and renal tubules. The tubular D_1-like dopamine receptor density is higher in humans than in rats. In addition, the density of D_1-like receptors is higher in the proximal tubule than in the distal part of the nephron. Either the D_1-like and D_2-like receptors have been found in both the apical and basolateral membranes of the proximal tubule. Although there are two classes of dopamine receptors, the natriuretic effect of dopamine is primarily mediated by D_1-like receptors[1].

DOPAMINE, AN INTRARENAL HORMONE

Studies on renal dopamine content and on the relationship between the amount of dopamine filtered and the amount of dopamine and dopamine metabolites excreted in urine first suggested that dopamine was formed in the kidney[4]. This was confirmed by studies into the rate of dopamine formation from *L*-DOPA in slices and isolated proximal tubules[6,7]. The kidney is endowed with one of the highest decarboxilating activities in the body and most of the *L*-AADC is located in the proximal convoluted tubules[7]. This was confirmed for the cytosolic fraction of rat renal cortical cells and rat medullary cells. At most, the rat renal medulla forms about 6-8% of dopamine[8] whereas *L*-AADC in the renal medulla of the human kidney accounts for 26% of that determined in the renal cortex[9]. The first evidence suggesting that the renal synthesis of dopamine is submitted to some sort of regulation was obtained under *in vivo* experiments and showed that sodium loading is accompanied by an increased urinary excretion of dopamine[1]. This has been found to occur both in humans and laboratory animals and a low sodium diet results in a decrease in the urinary excretion of dopamine. The increased urinary excretion of sodium during high sodium (HS) intake is also dependent on an increased production of dopamine, since blockade of dopamine receptors attenuates the natriuresis that accompanies a high renal delivery of sodium[10]. The tubular transport of *L*-DOPA has been characterized as an active process with great structural specificity[11]. We have reported in both human and rat kidney preparations that the production of dopamine is not only closely dependent on the extracellular sodium, but also appears to be related to the transtubular reabsorption of sodium[9,12]. These results suggested that the tubular uptake of *L*-DOPA is coupled to that of sodium, its rate being determined by the rate of transcellular movement of sodium (figure 1). Until now the most powerful stimulus known to increase the renal production of dopamine is sodium loading, though chloride and protein intake may also be of importance[1]. It is, therefore, understandable why HS intake has been used by several groups of researchers as an experimental tool for the study of the renal dopaminergic system. The mechanism responsible for such an increased urinary excretion of dopamine during HS intake appears to involve mainly an enhancement of *L*-AADC activity[13].

Dopamine of renal origin has autocrine and paracrine natriuretic effects in the kidney. The natriuretic effect of intrarenal dopamine was first observed after administration of the dopamine prodrug gludopa[2]. Gludopa is devoid of pharmacological activity per se but is converted to *L*-DOPA and then to dopamine by sequential actions of the brush border enzyme γ-glutamyl

transpeptidase (γ-GT) and cytosolic *L*-AADC in proximal tubules, where both enzymes exist in abundance[14]. Administration of physiological quantities of gludopa was accompanied by a significant natriuresis with no detectable change in intrarenal blood flow, indicating a predominantly tubule effect[10,15]. During conditions of normal sodium balance, intrarenal dopamine is a major physiological regulator of urine sodium excretion. Studies employing a specific D_1-like receptor antagonist (SCH-23390) have demonstrated that ~50% of basal sodium excretion is controlled by endogenous renal dopamine[10,16]. Administration of SCH-23390 at low infusion rates directly into the renal artery engendered a dose-dependent antinatriuresis that was reversible on cessation of infusion[10]. No changes in renal blood flow and glomerular filtration rate were observed. These studies were the first to show that dopamine acts as a paracrine substance, locally modulating renal sodium excretion. A recent study further provided direct evidence for a natriuretic effect of endogenous renal dopamine[17]. Infusing uninephrectomized rats with antisense oligodeoxynucleotides directly into the renal interstitial space reduced the expression of D_{1A} receptor protein by ~ 40% without influencing D_{1B} (D_5) receptors. This was accompanied with a decrease in the urinary excretion of sodium in conditions of both normal and high sodium intake. Very little is known about the role of the D_2-like receptor family in the control of renal function and sodium handling compared with the large amount of information available for D_1-like receptors.

Dopamine of renal origin has been found to undergo extensive deamination to 3,4-dihydroxyphenylacetic acid (DOPAC), *O*-methylation to 3-metoxytyramine (3-MT) and deamination plus *O*-methylation to homovanillic acid (HVA)[18,19] (figure 1) and the high levels of metabolic enzymes such as types A and B monoamine oxidase (MAO-A and MAO-B) and catechol-*O*-methyltransferase (COMT) have been considered important determinants in the overall availability of renal dopamine. MAO-A is more important than MAO-B for deamination of renal dopamine[19]. In rat renal cortical slices incubated with *L*-DOPA, deamination by MAO was found to be the major metabolic pathway for renal dopamine[20] whereas in the intact kidney COMT was suggested to play a major physiological role in the regulation of the renal dopamine tonus[4]. Taken together, these findings raised the question of whether the intracellular localization of COMT is such that it plays the most important physiological role for the regulation of the renal dopamine system whereas MAO may be more

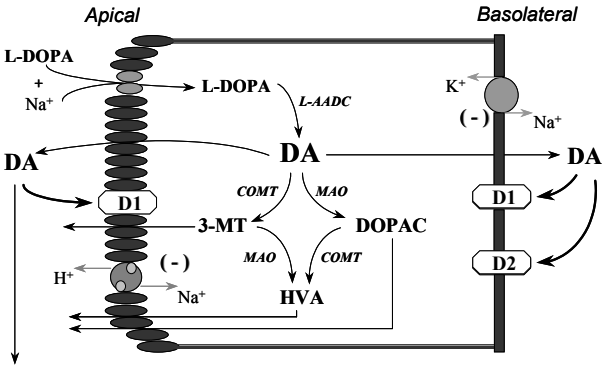

Figure 1: Schematic representation of the mechanisms involved in the synthesis, outward transfer and metabolism of dopamine in an epithelial cell of proximal tubules. Tubular uptake of *L*-Dopa is a saturable and sodium-dependent mechanism. Once inside the cell, *L*-Dopa is decarboxylated by aromatic *L*-amino acid decarboxylase (*L*-AADC) to dopamine (DA), which is then transported to the extracellular medium. Dopamine can activate specific receptors (D_1 and D_2) located at basolateral and apical cell borders leading to inhibition of Na^+-K^+ ATPase and Na^+-H^+ exchanger. Once inside the cell, dopamine is extensively deaminated by monoamine oxidase (MAO) to 3,4-dihydroxyphenylacetic acid (DOPAC), *O*-methylated by catechol-*O*-methyltransferase (COMT) to 3-metoxytyramine (3-MT) and deaminated plus *O*-methylated to homovanillic acid (HVA). Dopamine and dopamine metabolites leaving the cell through the apical cell border are excreted in urine.

of a housekeeping enzyme. Dopamine excreted in urine is mainly derived from intrarenally produced dopamine. Because the daily urinary excretion of both DOPAC and HVA is several fold that of the parent amine[21], these two amine metabolites are used as useful parameters for the assessment of the renal dopaminergic system activity as well as of the activity of the corresponding metabolizing enzymes.

Na^+-K^+ ATPase activity constitutes the driving force for tubular sodium reabsorption and much work has gone into the effect that dopamine has on regulating Na^+-K^+ ATPase activity. Dopamine inhibits Na^+-K^+ ATPase activity in the entire nephron including the proximal tubule, the thick ascending limb of Henle (mTAL), the distal tubule, and the cortical collecting duct [22,23]. The major cell signaling pathways whereby dopamine mediates inhibition of Na^+-K^+ ATPase are depicted in figure 2. In the proximal tubule, both protein kinase A (PKA) and protein kinase C (PKC) are involved in the phosphorylation of the α-subunit of the Na^+-K^+ ATPase, whereas in the mTAL and the cortical collecting duct only PKA is required[22,23]. PKC may inhibit Na^+-K^+ ATPase also by stimulation of PLA_2 activity and the generation of 20-HETE by cytochrome P-450 (figure 2). Dopamine also inhibits the Na^+-H^+ exchanger (NHE) and the Na^+-Pi cotransporter in the apical membrane of the proximal tubules[2]. The inhibitory action of dopamine on NHE is predominantly due to D_1-like receptors leading to activation of cAMP and PKA. In addition, renal proximal tubule apical NHE activity can also be inhibited via G proteins directly, independently of cAMP and phosphorylation mechanisms or by stimulation of P-450 eicosanoids, such as 20-HETE. As a result of these actions of dopamine, intracellular Na^+ is too low to stimulate Na^+-K^+ ATPase activity.

Intrarenal dopamine can act in connection with other natriuretic hormones and can oppose

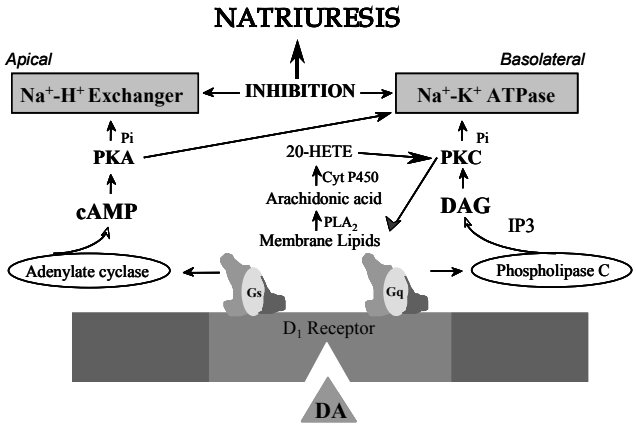

Figure 2: Schematic representation of D_1-like dopamine receptor and associated cellular signaling mechanisms in the nephron that mediate the inhibition of sodium-transporting proteins and increase renal sodium excretion. Protein kinase C (PKC), directly or via PLA_2, may phosphorylate Na^+-K^+ ATPase. Protein kinase A (PKA) directly phosphorylate Na^+-H^+ exchanger. IP3, inositol triphosphate; DAG, diacylglycerol; Cyt P450, cytrochrome P450; Pi, phosphorylation.

the effects of anti-natriuretic hormones by short-term and long-term effects. Evidence has been gathered that the natriuretic effect of atrial natriuretic peptide (ANP) requires the presence of dopamine receptors[24,25]. In addition, the inhibitory effect of dopamine on Na^+-H^+ exchanger in the proximal tubule is potentiated by ANP[26]. The interaction between circulating ANP and intrarenal dopamine should contribute to a well-balanced sodium homeostasis by allowing for adjustment between extrarenal volume sensors and local renal sensors. The recent findings that ANP can recruit intracellularly located D_1 receptors to the plasma membrane[4] offers an explanation for how ANP interacts synergistically with renal dopamine. By a way of contrast, dopamine opposes the effects of antinatriuretic factors, such as angiotensin II (AII), 5-hydroxytryptamine (5-HT) and α-adrenoceptor stimulants. Dopamine and α-adrenergic agonists conteract each other's effect on the basolateral

Na^+-K^+ ATPase[27]. Acting through D_1-like receptors dopamine inhibits the stimulatory effect of AII on Na^+-K^+ ATPase in part by reducing angiotensin I receptor (AT_1) expression in proximal tubules[2]. This supports the view of a cross-talk between the dopamine and renin-angiotensin system in the renal proximal tubule. In renal proximal tubules, 5-hydroxytriptophan is decarboxylated by *L*-AADC to 5-HT in the same cellular compartment where the renal synthesis of dopamine takes place[28]. The nature of the antagonistic effects of natriuretic dopamine and antinatriuretic 5-HT in renal tissues appears not only to depend on the reciprocal effects of the two amines on renal sodium excretion, but has also to do with the intracellular availability of their amino acid precursors, competition for decarboxylation by *L*-AADC and the ability of the newly-formed amines to leave the cellular compartment[29]. Acting through D_1-like receptors dopamine inhibits vasopressin-dependent water permeability and sodium transport in the rat cortical collecting duct[30]. Finally, dopamine acting through a D_2-like receptor significantly enhances the production of prostaglandin E_2 in the collecting duct. This effect appears to be mediated via PLA_2 [31].

RENAL DOPAMINE SYSTEM IN CHRONIC RENAL INSUFFICIENCY

Patients suffering from chronic renal insufficiency have a reduction in the urinary excretion of dopamine and metabolites, the extent of which is related to the degree of renal failure[32]. However, the residual tubular units in patients with compromised renal function maintain an intact ability to take up and decarboxylate *L*-DOPA to dopamine and deaminate the newly-formed amine to DOPAC[32]. The reduced renal dopamine output in chronic renal insufficiency may essentially result from the reduced number of functional tubular units endowed with the ability to produce dopamine. Several studies addressed the question of whether the decreased synthesis of renal dopamine in chronic renal failure may compromise sodium excretion and contribute to the increase of blood pressure. Casson[33] studied eight patients with chronic glomerulonephritis who were in stable chronic renal failure, comparing them with five age-matched normal subjects. The studies were carried out under metabolic balance conditions, first on a low sodium diet and then with added sodium chloride. The urinary excretion of dopamine was much lower in the patients than in the control subjects and did not rise in the patients on salt loading when compared with the normal response observed in the control subjects. This suggested that the abnormal retention of sodium in chronic renal failure is accompanied by failure to mobilize dopamine in kidney. However, most of the patients in this study were previously treated with several anti-hypertensive drugs and received a low sodium diet during a reduced number of days, which may have been insufficient to decrease the possible cumulative sodium balance in those patients with chronic renal insufficiency. We examined the 24h ambulatory blood pressure responses to changes in sodium intake in seventeen pre-hypertensive untreated IgA-N patients with near normal renal function to determine whether a reduced renal dopaminergic activity in the early stage is related to salt sensitivity of blood pressure[34]. In these 17 IgA-N patients with near normal renal function, a reduced production of dopamine in renal proximal tubules was related to a rightward shift in the “pressure-natriuresis” curve. In addition, the salt-sensitive IgA-N patients presented a reduced GFR in comparison to the salt resistant ones. This suggests that the decreased production of renal dopamine in the salt-sensitive

group was related to a reduced number of tubular units endowed with the ability to produce dopamine. Interestingly, the increase in renal dopamine synthesis during salt loading in salt-sensitive IgA-N patients was more pronounced than in the salt resistant ones. To our knowledge, this was the first study to suggest that salt sensitivity of blood pressure in humans suffering from chronic renal parenchymal diseases is accompanied with a compensatory response of the renal dopaminergic system during salt loading. This behavior of the renal dopaminergic system in IgA-N patients with salt-sensitive blood pressure contrasts with the findings in a subset of patients with salt-sensitive primary hypertension and young healthy normotensive subjects with a family history of hypertension[35,36]. In these conditions, there seemed to be a normal delivery of *L*-DOPA to the renal tubular cells, but a defective uptake or conversion of dopamine in this cellular compartment.

The physiological role of the renal dopamine system in renal insufficiency was addressed further in studies performed with animal models of reduced renal mass. Issac et al.[37] provided evidence for an increased dopamine output per residual nephron in the remnant kidney from rats submitted to ¾ nephrectomy. This was associated with the enhanced fractional excretion of phosphate by the remnant kidney. In the uninephrectomized rat model we have also found an enhanced renal dopaminergic activity per residual nephron that responded to HS intake with further increase in dopamine synthesis[38]. This indicates that renal dopamine may play an important role in keeping uninephrectomized rats within sodium balance. Conclusive evidence was recently provided for the effect of endogenous renal dopamine as a paracrine substance, locally modulating renal sodium excretion in conditions of reduced renal mass[39]. Uninephrectomized, ¾ nephrectomized and Sham control rats were evaluated before, during and after volume expansion with saline (5% bw) which resulted in similar natriuretic responses in the three groups. When the rats were infused with the D_1 antagonist SCH-23390 ($30\mu g.h^{-1}.kg^{-1}$) a decrease in the urinary excretion of sodium was observed in the three groups during both normal and high sodium intake. However, the decrease in sodium excretion induced by the selective D_1 antagonist was more pronounced throughout the study in the ¾ nephrectomized rats indicating that renal dopamine plays an important role in renal sodium handling during early chronic renal insufficiency[39].

CONCLUSION

In light of the present evidence it is likely that in chronic renal parenchymal diseases the sodium sensitivity of blood pressure is accompanied with an absolute decrease in renal dopamine synthesis which is related to a reduced number of tubular units endowed with the ability to synthesize the amine. However, this is accompanied with an enhanced dopamine output per residual nephron in tandem with dopamine-sensitive enhanced natriuresis indicating that renal dopamine may play an important role in tubular sodium handling during early chronic renal insufficiency.

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