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Review Article

Intrarenal Dopamine Metabolism

Isaac D. Hodapp, He Liu

Biology Department, Morosky College of Health Professions and Sciences, Gannon University, Erie, PA, USA.

In the past 40 years, dopamine has been shown to have a greater influence on the body than previously thought. Not only is it produced in the central nervous system as a neurotransmitter, but also by the renal system regulating sodium homeostasis and influencing vasodilation. The metabolism of dopamine in the renal system starts with L-DOPA uptake, which is thought to be the rate limiting step of dopamine synthesis, performed by Na^+-dependent cotransporters (B^0 and ASCT2) and Na^+-independent transporters (LAT1 and LAT2). Variations as to which transporter is dominant can be observed in hypertensive vs. normal animals. L-DOPA uptake is affected by Na^+ concentrations, gastrin concentration, and activation of α(2C)-adrenoceptor. The synthesis of dopamine is through the decarboxylation of L-DOPA catalyzed by aromatic L-amino acid decarboxylase and is influenced by Na^+ concentration (where greater Na+ molarity increases activity). The degradation of dopamine is completed by monoamine oxidase and catechol-O-methyltransferase before it is excreted into the urine as homovanillic acid. While this process shows the complete metabolism of dopamine, there are other findings that suggest alternative pathways of dopamine production. This review will provide greater details regarding the metabolism steps of dopamine in the renal system.

Keywords: dopamine, kidney, L-DOPA, sodium, blood pressure

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Introduction

Within the past 40 years dopamine, a catecholamine which is a precursor for epinephrine and norepinephrine, an important neurotransmitter in the brain, has been seen to hold an even greater array of influence on the body than the many actions previously thought: efficient movement, pleasure driven behavior, delicate equilibrium for optimal memory, directing attention, problem solving, prolactin secretion, pain control, and nausea control [1-3]. It wasn't until dopamine infusions were found to improve kidney function in acute renal failure patients and urinary concentration of dopamine were noted as being up to 20 times greater than the concentration of noradrenaline that the possibility of dopamine having an even wider spectrum of influences on the body arose [4]. Dopamine receptors have been apparent in various peripheral tissues such as the kidneys, lungs, blood vessels and pancreas [5]. The only place noted for dopamine production outside of the central nervous system has been the renal system. Dopamine is shown to have a rather large influence on sodium homeostasis by controlling excretion as well as holding vasodilator properties, both of which help to maintain a normal blood pressure [6]. The physiological effects of dopamine may attribute to both the metabolism to maintain the dopamine level and the variation in dopamine receptors. This review, based on related research articles in PubMed, will provide greater details regarding the dopamine metabolism in the renal system (Fig. 1), including the processes of L-DOPA uptake and what influences it, decarboxylation of L-DOPA into dopamine, degradation of

* Correspondence:He Liu, Email: liu017@gannon.edu

dopamine until excretion, and lastly evidence that suggests alternative pathways.

L-DOPA Uptake

The uptake of L-DOPA is regarded as being the rate-limiting step of dopamine synthesis [7]. The substrate of dopamine, L-dihydroxyphenylalanine (L-DOPA), is transported into the proximal renal tubule epithelial cells through several carrier proteins, including both Na^+-dependent cotransporters and Na^+-independent transporters. L- type amino acid transporter 1 (LAT1) and L- type amino acid transporter 2 (LAT2) are responsible for L-DOPA uptake in a Na^+ independent manner [7-10]. In wild-type rats, LAT2 was found almost exclusively responsible for L-DOPA uptake [7, 11]. However, in Na^+-free medium, human kidney slides only accumulated nearly half of the amount of dopamine found at 160 mM Na^+ as shown in an earlier study [12], presumably via LAT2. In pig renal epithelial cells, gene silencing of LAT2 with siRNA reduced L-DOPA accumulation by 85% [13, 14]. Some studies showed that the accumulation of L-DOPA in the epithelial cells was dependent on extracellular Na^+ [15, 16]. Inhibition of the enzyme Na^+/K^+ ATPase by ouabain in high Na^+ medium reduced the concentration gradient across the cell membrane and levels of dopamine and its metabolites in the cell [12, 15]. Na^+-dependent amino acid transport systems, in particular, B^0 and ASCT2, seemed involved in the L-DOPA uptake [7-10, 17]. In the spontaneously hypertensive rat model, L-DOPA uptake was mediated by multiple carriers (50% through LAT1, 25% through LAT2, and 25% through Na^+-dependent amino acid transport system B^0 [7]). The involvement of Na^+-dependent transporters makes the L-DOPA uptake responsive to extracellular Na^+ concentration. In cultured opossum kidney cells, low sodium solution (137 mM K^+ plus 5 mM Na^+) reduced L-DOPA uptake by 25% compared to the control condition (137 mM Na^+ plus 5 mM K^+) [18]. In animal experiments, the responses appeared to be age-dependent and with a variation in the regulation pattern of transporter gene expressions. Table 1 lists the results of these studies.

The uptake of L-DOPA is under the effect of other hormones. Gastrin concentration increase from 25 nM to 50 nM stimulated the renal tubular uptake of L-DOPA by almost two-fold via LAT1 in cultured human and mouse cells [22]. In contrast, the activation of α(2C)-adrenoceptor inhibited L-DOPA uptake [23].

Decarboxylation of L-DOPA

After uptake into the cytoplasm, L-DOPA is converted into dopamine through a decarboxylation reaction catalyzed by aromatic L-amino acid decarboxylase (L-AADC or AADC), which was found at a high level in mouse kidney (both cortex and medulla) [24] and in human kidney homogenate [25]. In particular, L-AADC was found only in the proximal convoluted tubule and proximal straight tubules of the rat nephron [26]. High-salt intake increased L-AADC activity in rats, while there was no significant change in dopamine degradation [27-29]. Carbidopa, a peripheral DOPA-decarboxylase inhibitor significantly decreased urinary dopamine output and sodium excretion in humans [30-32].

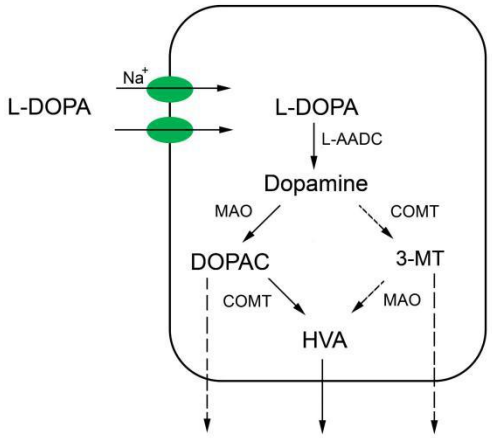

Fig 1. Cellular pathway of dopamine metabolism in proximal renal tubule epithelial cells. L-DOPA: L-dihydroxyphenylalanine; DOPAC: dihydroxyphenylacetic acid; 3-MT: 3-methoxytyramine; HVA: homovanillic acid; L-AADC: L-amino acid decarboxylase; MAO: monoamine oxidase; COMT: catechol-O-methyltransferase. Solid lines denote main pathways while dashed lines denote alternative pathways.

Degradation

As shown in Figure 1, dopamine is catabolized by the enzyme monoamine oxidase (MAO) into dihydroxyphenylacetic acid (DOPAC), then further methylated by another enzyme catechol-O-methyltransferase (COMT) to its final metabolite homovanillic acid (HVA) before being excreted in the urine [33]. The combination of the two enzymes in the reverse order degrades dopamine in an alternative pathway to the same product [33]. Administration of COMT inhibitors entacapone [34, 35], nitecapone [36], or 3,5-dinitrocatechol [37] elevated renal dopamine activity and increased sodium excretion in a more effective manner than L-DOPA [35] as well as the kidney-specific pro-drug to dopamine, glu-dopa [36]. In mice with one or both copies of the COMT gene deleted, the natriuretic effects of acute sodium loading were reduced by 60-70% [9]. Administration of the MAO inhibitor phenelzine also showed similar effects [36].

Table 1. Age-dependent and strain-dependent variations in the regulation of L-DOPA transporter gene expressions under high-salt intake

Strain	Age Comparison		Effects	Gene Expression	Reference
	Young	Old			
Fischer 344 rats	6-month	24-month	**Age effect:** 2-fold increase in urinary dopamine and DOPAC, but not seen in old rats. **High-salt effect:** 2.6-fold increase in natriuretic response seen in young rats but only 2.3-fold in old rats.	N/A	[19]
Wistar-Kyoto rats	4-week	12-week	**High-salt effects:** higher urinary dopamine and DOPAC in young rats, but no change in old rats.	**High-salt effects:** higher LAT1, lower LAT2, lower $B^0$and lower ASCT2 in young and rats; lower LAT1, lower LAT2, lower B^0 and lower ASCT2 in old rats. **Age effects:** higher LAT1, LAT2, lower ASCT2, and lower lower B^0 in old rats.	[17, 20]
Spontaneously hypertensive rats (SHR)	4-week	12-week	**High-salt effects:** higher dopamine and DOPAC in both young and old rats. Higher tubular update of L-DOPA.	**High-salt effects:** lower LAT1, lower LAT2, and lower B^0 in **young rats;** lower LAT2, higher ASCT2, and higher B^0 in old rats.	[17, 20]

Wistar-Kyoto rats	13-week	91-week	**Age effects:** no significant difference in urinary L-DOPA, dopamine, and DOPAC between young and old rats.	**Age effects:** lower LAT1, higher LAT2, higher ASCT2 expression in old rats.	[21]
Spontaneously hypertensive rats (SHR)	13-week	91-week	**Age effects:** higher urinary L-DOPA in young rats but higher urinary DOPAC in old rats.	**Age effects:** lower LAT1, higher LAT2, and higher ASCT2 expression in old rats.	[21]

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Alternative pathways

In addition to the pathways described above, it is possible that other unknown pathways are present. An earlier study showed that homogenized kidney tissue increased dopamine production under elevated NaCl, KCl, and NH_4Cl [38]. A higher intake of phosphate was observed to increase dopamine excretion [39]. Lastly, 3-O-methyldopa (OM-dopa) has been found to be a substrate for intrarenal dopamine production through demethylation [40].

Conclusion

Dopamine plays a key role in sodium homeostasis and vasodilation, both of which contribute to blood pressure regulation. Understanding the metabolism of dopamine in the renal system can lead us toward better treatment options for disorders such as kidney failure and hypertension. The rate of dopamine synthesis is dependent on L-DOPA uptake by Na^+-dependent cotransporters (B^0 and ASCT2) and Na^+-independent transporters (LAT1 and LAT2). Observations in hypertensive vs. normal animals showed variations in the dominant roles of different transporters. The rate of uptake is influenced by a few factors including Na+ concentration, gastrin concentration, and activation of α(2C)-adrenoceptor. Na^+ concentration also holds influence on the decarboxylation of L-DOPA which is catalyzed by L-AADC. Dopamine may be degraded then excreted in the urine as HVA after being broken down by MAO and COMT. Dopamine synthesis may also have other pathways indicated by another possible substrate 3-O-methyldopa and the influence of NaCl, KCl, NH_4Cl, and phosphate on renal dopamine production.

Conflict of interest

None.

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