Renal dopamine receptors: mechanisms of action and developmental aspects

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Abstract

Dopamine is important for renal perfusion, natriuresis, and the control of blood pressure. Modulation of the activities of adenylyl cyclase, phospholipase C and protein kinases is involved in the signal transduction pathway of dopamine. Peripheral dopamine receptors are classified as the DA\textsubscript{1} and DA\textsubscript{2} subtypes on the basis of synaptic localization and their pharmacological profiles. In the kidney, DA\textsubscript{1} receptors are localized in the medial layer of the renal vasculature and along the nephron; DA\textsubscript{2} receptors are found in the glomerulus and the nerves surrounding renal blood vessels. While DA\textsubscript{1} receptor stimulation results in renal vasodilatation and natriuresis, DA\textsubscript{2} receptors may play a synergistic role in the DA\textsubscript{1} modulated natriuresis. There is increasing evidence that these effects of dopamine are attenuated in younger than in older animals. Future studies should be directed to identify the ontogenic differences in vascular and tubular dopamine receptors (density and affinity) and their coupling mechanisms, in order to evaluate the role of dopamine which is frequently used in the management of shock in newborns.

Keywords: Dopamine; Renal vasculature; Renal tubules; Dopaminergic receptors; Signal transduction; Ontogeny

1. Classification of dopamine receptors

Dopamine is an important endogenous catecholamine that has widespread effects both in neural (as a neurotransmitter) and non-neural tissues (as an endocrine and paracrine agent) [1]. As a neurotransmitter dopamine regulates emotion, activity and behavior. Peripherally, dopamine receptors have been described in the kidney [2], adrenergic nerve endings [3], and in numerous blood vessels (renal, pulmonary, mesenteric and coronary arteries) [4–6] outside the central nervous system. Defective intrarenal dopamine metabolism has been suggested as contributing to the pathogenesis of hypertension [7]. This article reviews the mechanism of action of renal dopamine receptor and discusses the developmental aspect and its clinical relevance.

Dopamine receptors are G-protein coupled receptors in the plasma membrane which transduce their signals to the intracellular milieu through a variety of second messengers including adenylyl cyclase (AC), phospholipase C (PLC), and protein kinases [8]. Central dopamine receptors are classified into D\textsubscript{1} and D\textsubscript{2} subtypes based on their pharmacological profiles and signal transduction pathways. D\textsubscript{1} receptors are linked to G\textsubscript{s} proteins which stimulate AC and D\textsubscript{2} receptors are linked to G\textsubscript{i} proteins which have an inhibitory action on AC [9]. Specific antagonist ligands for D\textsubscript{1} and D\textsubscript{2} receptors are SCH 23390 and spiperone, respectively (Table 1). Sibley et al. classified the newly identified receptor subtypes (D\textsubscript{3}, D\textsubscript{4}, D\textsubscript{5} receptors are classified as D\textsubscript{3B}, D\textsubscript{3C}, D\textsubscript{1B} respectively) by comparing their structural and pharmacological properties with the well-defined D\textsubscript{1} and D\textsubscript{2} [9]. The pharmacological properties of DA\textsubscript{1} and DA\textsubscript{2} receptors resemble those of D\textsubscript{1} and D\textsubscript{2} receptors respectively [1,2]. Goldberg et al. classified the peripheral dopamine receptors as DA\textsubscript{1} and DA\textsubscript{2} subtypes, on the basis of synaptic localization [10]. DA\textsubscript{1} receptors are mostly postsynaptic and stimulate AC and/or PLC activity, whereas DA\textsubscript{2} are both presynaptic and
postsynaptic and inhibit AC activity (Table 1). The DA₁ and DA₂ subfamilies also show difference in potency towards various agonists; fenoldopam > dopamine > dipropyl dopamine > apomorphine characterizes the DA₁ receptor while the reverse order (apomorphine > dipropyl dopamine > dopamine > fenoldopam) distinguishes the DA₂ subtype [11].

2. Structure of dopamine receptors

Data on the structure of DA₁ and DA₂ receptors is limited. The central and peripheral dopamine receptors are similar in structure, reconstituted receptor densities and coupling mechanisms [1]. D₁ and D₂ receptor genes are expressed in rat kidneys [12,13]. However, it remains uncertain whether the D₁ and DA₁ receptors are identical as the affinity of the D₁ receptor from striatal membranes to the radioligand ([125I]-SCH 23982) is much greater than the DA₁ receptor from renal proximal tubules [14].

Owing to the cationic nature of both agonist and antagonist ligands, Asp 114 is probably the primary active site for electrostatic interaction. Other interactions, e.g. at Asp 80 and Asp 108 residues, hydrophobic interactions, and hydrogen bonds between Ser residues and catechol hydroxyl groups, may contribute differentially to agonist and antagonist binding [9].

The D₁ receptor is a glycoprotein (MW 72–74 kDa) with a small third cytoplasmic loop and a long C-terminus, which seems to be a characteristic feature of receptors that are coupled to Gₛ and activate AC, such as the β-adrenoceptor. The D₂ receptor is a glycoprotein that shows a wide variation in molecular mass values (94–150 kDa) depending on the tissue and the analytical technique used [15]. The long third intracellular loop with short C-terminal tail may be typical of receptors that are coupled not to Gₛ and AC stimulation, but to other G proteins and effectors such as Gₛ/Gₛ₂ proteins which inhibit AC and open potassium channels.

3. Vasodilatation and natriuresis — localization of receptors and signal transduction

DA₁ receptors have been found in the medial layer of the renal vasculature, juxtaglomerular cells, proximal convoluted tubule (PCT), ascending loop of Henle and cortical collecting duct (CCD); so far there have been no DA₁ receptors demonstrated in distal convoluted tubules [16]. DA₂ receptors are localized to the glomerulus, the renal nerves surrounding renal blood vessels and possibly the renal vascular endothelium (adventitia and intima of intraparenchymal branches) [17–21]. The hemodynamic and direct tubular actions of dopamine, as well as its endocrine effects (renin–angiotensin system), contribute to dopamine-induced natriuresis, which has been postulated to play a significant role in blood pressure regulation [7]. Both vascular [22] and tubular DA₁ [23–26] as well as neuronal DA₂ receptors [27,28] are involved in mediating these effects, while the role of tubular and vascular DA₂ receptors remains to be clarified.

Vascular DA₁ receptor coupled stimulation of AC results in cAMP-mediated activation of protein kinase A. This lowers intracellular calcium levels and results in smooth muscle relaxation. The vasodilatation causes cortical and medullary blood flow to increase which in turn enhances the glomerular filtration rate (GFR). Dopamine also increases GFR by local renin–angiotensin activation resulting in preferential efferent vasoconstriction. Interestingly, there is no significant increase in aldosterone secretion despite activation of the renin–angiotensin system [29].

The mechanism for DA₁ receptor related natriuresis is two-fold. DA₁ receptors on the basolateral membrane have been reported to be coupled to PLC activation leading to diacylglycerol release and protein kinase C activation resulting in the inhibition of Na⁺–K⁺-ATPase activity in PCT, ascending loop of Henle and CCD [30]. The modulation of PLC activity by intrarenal dopamine varies with different salt intake. A tighter coupling between the DA₁ receptor

<table>
<thead>
<tr>
<th>Prototype</th>
<th>Localization</th>
<th>Effect on AC</th>
<th>Effect on PLC</th>
<th>MW (kDa)</th>
<th>Antagonist ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁</td>
<td>caudate, thalamus</td>
<td>Stimulation</td>
<td>?</td>
<td>77–74</td>
<td>SCH 23390</td>
</tr>
<tr>
<td>D₂</td>
<td>caudate, pituitary</td>
<td>Inhibition</td>
<td>?</td>
<td>94–150</td>
<td>spiperone</td>
</tr>
<tr>
<td>Peripheral dopamine receptors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA₁</td>
<td>vascular, juxtaglomerular, tubular</td>
<td>Stimulation</td>
<td>Stimulation</td>
<td>74</td>
<td>SCH 23390</td>
</tr>
<tr>
<td>DA₂</td>
<td>neuronal, vascular, glomerular, tubular (IMCD)</td>
<td>Inhibition</td>
<td>?</td>
<td>?</td>
<td>(S)-sulpiride, domperidone</td>
</tr>
</tbody>
</table>

MW = molecular weight.
AC = adenylyl cyclase.
PLC = phospholipase C.
IMCD = intramedullary collecting ducts.
Table 2
Dissociation constants ($K_d$) and maximum binding densities ($B_{max}$) of different dopamine receptors in rat kidney tubules

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>$K_d$ (nM)</th>
<th>$B_{max}$ (fmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA$_1$-PCT[31]</td>
<td>12.2 ± 1.9</td>
<td>1.03 ± 0.15 x 10$^3$</td>
</tr>
<tr>
<td>DA$_1$-CCD[32]</td>
<td>0.46 ± 0.08</td>
<td>1.41 ± 0.43</td>
</tr>
<tr>
<td>DA$_2$-IMCD[38]</td>
<td>17.2 ± 1.05</td>
<td>935 ± 83</td>
</tr>
</tbody>
</table>

PCT = proximal convoluted tubules.
CCD = cortical collecting ducts.
IMCD = intramedullary collecting ducts.

and AC in the CCD than in PCT has been suggested by Felder et al. despite a greater receptor density in the PCT than in the CCD (Table 2) [31,32]. Natriuresis may also be related to the inhibition of Na$^+$–H$^+$ exchange in the brush border membrane in the PCT, through the accumulation of cAMP [33]. In addition, natriuresis may be enhanced by the reduced medullary hyperosmolality secondary to urea washout with increased medullary blood flow [34].

The role of DA$_2$ receptors in mediating the hemodynamic and natriuretic effects of dopamine is unclear. Some workers have demonstrated DA$_2$ related renal vasodilation resulting in diuresis and natriuresis accompanied by increases in GFR and renal plasma flow [35–37]. Huo et al. found a postsynaptic DA$_2$ like (DA$_{2L}$) receptor that stimulates prostaglandin E$_2$ production from inner medullary collecting duct cells, a significant site where dopamine may influence antidiuretic hormone-related water and electrolyte excretion directly or indirectly [38]. Bertorello and Aperia suggested a synergistic interaction between DA$_1$ and DA$_2$ receptors on the Na$^+$–K$^+$-ATPase activity in PCT despite their opposing effects on AC activity. They postulated a permissive role of DA$_2$ receptors on high affinity dopamine binding to DA$_1$ receptors that may contribute to the synergism [39,40].

4. Ontogeny of the renal dopamine receptor

The renal vasodilation and natriuretic effects of dopamine are less in younger than in older animals [8,41–44]. There is increasing evidence that no vasodilating effect of dopamine occurs in the renal vasculature of newborns [10,45]. We recently demonstrated the absence of renal vasodilation in chronically instrumented newborn piglets (1–3 days old) with low dose dopamine infusions [46]. Low doses of dopamine that induce renal vasodilation in the adult may actually induce renal vasoconstriction in the young because of the propensity for dopamine to stimulate the $\alpha$-adrenoceptor which is well developed by term [47]. No evidence has supported DA$_1$ related vasodilation in the kidney of any mammalian newborns studied in the first 3 days of life. Therefore, DA$_1$ receptors presumably appear gradually after birth.

Natriuresis in response to DA$_1$ agonists is also markedly impaired in the newborn [48]. Kinoshita and Felder suggested a reduced efficiency of DA$_1$ receptor–AC coupling in the PCT of 3-week-old rats compared to that of 20-week-old rats [49]. However, a natriuretic response to dopamine has been reported in human premature neonates which has been considered to suggest a more advanced functional maturation of the receptors in the human compared to animal models [34,50–53]. All except one of these studies are uncontrolled trials. The exception is the study of Cuevas et al. who reported mild to moderate natriuresis with 1 $\mu$g/kg per min but not 2.5 $\mu$g/kg per min of dopamine infusion in a randomized controlled study of 49 premature neonates [51]. There was no significant increase in GFR or urine volume. Therefore, the significance of this isolated observation remains to be validated.

Nevertheless, it has not been determined whether the reduced vasodilatation and natriuretic effects of dopamine in young animals are related to ontogenic differences in DA$_1$ receptor density, affinity, coupling to intracellular second messengers or more distal mechanisms. The ontogeny of the renal DA$_2$ receptor has received less attention. DA$_2$ receptor-specific radioligand (3H-spiroperidol) binding shows higher receptor density in fetal sheep than in newborn or adults [54]. Selective DA$_2$ receptor stimulation increases single nephron GFR in young (24 days) and adult rats and appears to decrease renal vascular resistance in the adult rat. The significance of these effects in the newborn is unknown.

5. Clinical relevance

During critical illness in infants, it is essential to maintain perfusion of the kidney in order to prevent the development of acute renal failure. Dopamine is frequently used for mediating renal vasodilatation and inducing natriuresis and diuresis in adults. However, both clinical and animal data fail to give definitive support to such effects in newborns, although high dose dopamine infusion may have beneficial effects in blood pressure. Future studies should be designed to characterize the ontogeny of vascular and tubular dopamine receptors and their coupling mechanisms. Prospective randomized trials are required to delineate the renal hemodynamic and natriuretic effects of dopamine in premature and term neonates. The information generated will be important to evaluate the role of dopamine which is frequently used in the management of shock in newborns.

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References


