Published in final edited form as:
Curr Opin Nephrol Hypertens. 2009 January ; 18(1): 28–32. doi:10.1097/MNH.0b013e32831a9e0b.

Dopamine and Angiotensin as Renal Counter Regulatory Systems Controlling Sodium Balance

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Abstract

Purpose of the review—To review the recent evidence demonstrating how the renal dopaminergic and angiotensin systems control renal electrolyte balance through various receptor mediated pathways with counter regulatory interactions.

Recent Finding—Stimulation of the renal renin angiotensin system (RAS) results in increased sodium reabsorption, while the opposite is true for stimulation of the renal dopaminergic system. An underactive renal dopaminergic system has been associated with increased sodium reabsorption and hypertension. Recent findings indicate novel cell surface receptor mediated mechanisms by which these two renal endocrine systems directly counter-regulate each other. Each of the dopamine receptors (D_1R through D_5R) have been implicated in dopamine mediated natriuresis, in addition to counter-regulating the angiotensin type 1 R (AT_1R). Dopamine D_1-like (D_1R and D_5R) stimulation has also been found to induce an AT_2 receptor (AT_2R) dependent natriuresis. Recently, it has also been discovered that reactive oxygen species (ROS) can play a role in inactivating the D_1 receptor and activating the AT_1R.

Summary—Current therapeutic interventions for hypertension predominantly involve correction of an overactive renin angiotensin aldosterone system. Recent evidence suggests that stimulation of the renal dopaminergic system and possibly activation of AT_2 receptors, as well as decreasing ROS, may provide additional therapeutic approaches.

Keywords

Dopamine Receptors; Angiotensin Receptors; Counter-regulation; ROS; hypertension

Introduction

The counter-regulation of the renal dopaminergic and RAS will be examined in this review from the perspective of receptor-receptor interactions. The first part of the review will highlight the recent studies examining how the dopaminergic system impacts the regulation of the AT_1R. The next part of the review will summarize recent evidence that the dopaminergic system up regulates and activates the angiotensin type 2 receptor (AT_2R). The third section will review the evidence that the dopaminergic system in part counter-regulates the RAS by decreasing the production of ROS.

Dopamine inhibition of the angiotensin type 1 receptor (AT_1R)

The kidney, which regulates sodium and water balance, is a central organ in the regulation of electrolyte levels and blood volume in the body. Guyton described the relationship between blood pressure and sodium excretion as the pressure natriuresis curve. Increases in blood pressure cause increased natriuresis in order to return the blood pressure to normal. However, impairments in the pressure natriuresis relationship cause a rightward shift in the curve necessitating increased blood pressure in order to restore blood volume to normal. The

biochemical mechanisms governing the pressure natriuresis are just beginning to be understood with the RAS and dopaminergic systems acting as counter regulatory pathways involved in this process. There are two principal pathways which are responsible for the regulation of blood pressure, namely the natriuretic intrarenal dopamine system and the anti-natriuretic RAS (1). In order to conserve sodium during times of low sodium intake, the RAS is up-regulated in order to produce angiotensin II (Ang II). Stimulation of the principal membrane bound cell surface receptor for Ang II, the AT_1R, leads to sodium reabsorption. In order to eliminate sodium during times of high sodium intake the local renal production of dopamine is increased leading to inhibition of sodium reabsorption. Hypertension, or an inappropriately high blood pressure, can result when the kidney is unable to eliminate sodium and thus retains excess water leading to increased blood volume.

The renal renin-angiotensin system is a hormone cascade with the peptide hormone Ang II acting as its major product. Ang II exerts its effects primarily through the stimulation of the angiotensin type 1 receptor (AT_1R) leading to sodium reabsorption by the proximal tubule of the kidney. The first paper clearly showing the inhibitory activity of dopamine on the Ang II dependent increase in renal brush border sodium uptake *in-vitro* was shown by Sheikh-Hammad et al.(2), who measured radioactive Na^{22} uptake in isolated renal proximal tubule brush border vesicles. Both the D_1-like and D_2-like receptor activities were necessary for full inactivation of an Ang II dependant increase in sodium uptake. Cheng et al. then determined that the dopaminergic effect was accompanied by a downregulation of the AT_1R both *in-vivo* as well as in cultured cells suggesting that the effect was not dependent on an intact kidney (3). Zeng et al. further demonstrated that Ang II stimulation caused a decrease in the D_5R in proximal tubule cells from WKY and SHR (4). Ang II stimulation caused a decrease in expression of AT_1R in WKY cells yet caused an increase in AT_1R expression in SHR. The AT_1R and D_5R were also found to co-localize in cells with the SHR rats having a lower basal expression of D_5R. The AT_1R and D_5R are thought to be counter-regulatory since AT_1R knock-out animals have increased expression of D_5R, and D_5R knock-out mice have an increased expression of AT_1R.

Gildea et al. recently showed which D1-like receptor was responsible for the downregulation of the AT_1R in human renal proximal tubule cells (5). Using antisense oligos specific to the D_1R or the D_5R in primary cultured human renal proximal tubule cells, they presented evidence that it was the D_5R that was mediating the D1-like effect on AT_1R. These studies utilized renal proximal tubular cells in which the D_1R was uncoupled from adenylyl cyclase stimulation. The D_5R downregulation of the AT_1R was intact in adenylyl cyclase uncoupled cells further suggesting that this was a D_1R and possibly a cAMP independent effect. This paper also showed for the first time that c-src is activated by stimulation of D1-like receptors and that the downregulation of the AT_1R is mediated by a c-src and a proteasome dependent protein degradation mechanism. Similarly, Li et al. showed that the D_5R that caused the ubiquitination and proteasomal degradation of the AT_1R, using both in-vitro and in-vivo techniques (6). He suggested that that the elevated blood pressure (relative to controls) in D_5R knock-out mice was due to the over-expression of the AT_1R. Another important finding was that the elevated blood pressure in the D_5R knock-out mice could be returned to baseline using an AT_1R inhibitor, losartan. They further showed that the D_5R and AT_1R physically interact at the cell surface by co-immunoprecipitation and that the AT_1R that is ubiquitinated and degraded by the proteasome is the n-glycosylated form of the AT_1R. How c-src is activated by the D_5R and what role it plays in the ubiquitination and degradation of the AT_1R is yet to be determined. The dopamine D4 receptor (D_4R) knockout mice also have over-expression of renal AT_1R and a differential response to an AT_1R inhibitor, losartan, with the D4 knockout mice displaying an extended decrease in blood pressure reduction with bolus infusion of the AT_1R antagonist (6). There may be direct antagonism between the dopamine and the renin angiotensin system since either the D_1R, D_3R, or D_5R can physically interact with the AT_1R (7–10).

Dopamine dependant up-regulation of the angiotensin type 2 receptor (AT_2R)

The stimulation of the AT_2R antagonizes many of the effects of the AT_1R (11). The AT_1R and the AT_2R can physically interact producing the antagonism between the two signaling pathways (12). The fact that the stimulation of the AT_1R increases Na/KATPase activity has been demonstrated numerous times, while the AT_2R was shown to inhibit Na/KATPase in isolated rabbit renal proximal tubule cells (13,14). AT_2R stimulation was also shown to induce natriuresis in obese Zucker and steptozocin induced diabetic rats via a nitric oxide, soluble guanylyl cyclase and cGMP mechanism (15,16). In human renal proximal tubule cells, it was also shown that this same downstream pathway leads to cGMP export from the cell and inhibited sodium absorption (17). Gildea et al. found that in immortalized human renal proximal tubule cells, D1-like stimulation caused the AT_2R to translocate to the cell surface and opposed the ability of AT_1R to decrease the expression of caveolin 1, and this only occurred in cells isolated from normotensive patients (18). Salomone et al. showed that D_1-like stimulation caused AT_2R to translocate to the brush border of the rat renal proximal tubule *in-vivo*. This paper also showed that pharmacologically blocking the AT_2R blocked the dopamine D1-like dependent natriuresis (19). Interstitial infusion of fenoldopam, a D_1-like specific agonist, caused a proximal tubule dependent natriuresis in salt loaded adult rats, and co-infusion of an AT_2R specific blocking compound, PD-123319 (20), blocked the effect, suggesting that the AT_2R is necessary for D1-like effects on natriuresis.

The production of Ang II is down-regulated in high salt conditions and intrarenal dopamine production is increased (1,21). The elimination of the Ang II peptide is by a proteolytic cascade with the conversion of Ang II to Ang III by aminopeptidase A (APA) and the conversion of Ang III to Ang IV by aminopeptidase N (APN), both of which are highly expressed in the brush border of the renal proximal tubule (11). Natriuresis in salt loaded rats was induced by renal interstitial infusion of an AT_1R inhibitor, losartan, and the natriuresis is fully blocked by the AT_2R inhibitor PD-123319 (20). Ang III appears to be the preferred substrate for AT_2R dependent natriuresis because the Ang III induced natriuresis is blocked by the AT_2R inhibitor PD-123319, and is enhanced by blocking the conversion of Ang III to Ang IV by an APN inhibitor (22). In addition, natriuresis caused by infusion of renal interstitial Ang II is blocked if you inhibit the conversion of Ang II to Ang III with an APA inhibitor (23). Perhaps the D1-like receptor or some other effect of increased sodium load may increase the conversion of Ang II to Ang III mediated by APA, or may decrease the activity of APN, which would produce an increase in the level of Ang III. A recent study showed that increasing sodium intake in rats caused an upregulation of total kidney expression of AT_2R (24). In cell fractionation experiments AT_2R and APN shifted to higher density cell fractions interpreted as being inhibited by internalization. The underlying mechanisms behind how dopaminergic stimulation coupled with AT_1R inhibition and AT_2R stimulation results in natriuresis remains to be determined.

The dopaminergic system as an antioxidant

Excess Ang II production can lead to renal pathology mediated through the AT_1R, causing excess growth, inflammation, and fibrosis resulting in chronic hypoxia (25) and increased generation of reactive oxygen species (ROS) (26). Dopamine stimulates antioxidant activity (27) and can counter-regulate Ang II signaling. Both the dopamine D_2 receptor (D_2R) and the D_5R knock-out mice have increased ROS production (28,29). Interestingly, stimulation of D_5R transfected HEK cells decreased ROS generation and was found to be independent of cAMP and PKA (28). In the case of D_5R knock-out mice, there is over expression of the AT_1R (8). Even though losartan was shown to bring the elevated blood pressure in D_5R knock-out mice back to normal and apocynin was also shown to return the blood pressure back to

baseline, it has not been shown that adding losartan blocks ROS production in these mice. In D_2R knock-out mice, there is no report of over expression of AT_1R, but it was documented that there was an increase in aldosterone secretion, a known downstream target of Ang II (29). Consistent with the increase in aldosterone being AT_1R mediated, increased sodium intake reduced the increase in aldosterone secretion. The addition of spironolactone, an aldosterone antagonist, normalized blood pressure but did not reduce urinary 8-isoprostane secretion, a measure of renal ROS generation. The dopamine D3 receptor (D_3R) knock-out mice are also hypertensive, and have over-expression of the AT_1R (9). Interestingly, addition of the dopamine D_3R specific agonist, PD128907, decreased expression of AT_1R in renal proximal tubule cells from WKY but increased expression of AT_1R in SHR. The addition of PD128907 also increased D_3R expression in proximal tubule cells isolated from WKY rats but not in proximal tubule cells isolated from SHR, implying not just lack of signaling but differential signaling of the D_3R in SHR. The D_3R and AT_1R were also found for the first time to co-localize and co-immunoprecipitate from rat renal proximal tubule cells.

Some aspects of the dopaminergic system are not associated with an increase in ROS. G-protein coupled receptor kinase 4 (GRK4) is a kinase shown to phosphorylate and inactivate the D_1R (1). Over-expression of a genetic variant of GRK4- (A142V) in mice was shown not to increase ROS (30). The polymorphic version of the construct causes hypertension, presumably the result of hyperphosphorylation and inactivation of the D_1R, while the wild type version of the construct did not (31). The inactivation of the D_1R, at least in this instance, is not linked to the increased generation of ROS. While direct evidence that the D_1R specifically controls the antioxidant status of renal cells does not yet exist, it is known that an increase in ROS may inhibit D_1R (32,33). Addition of high salt diet alone did not cause a significant increase in blood pressure in Sprague-Dawley rats whereas the addition of an oxidant induced salt sensitivity (a sodium chloride mediated increase in blood pressure). The salt sensitive rats were further shown to have a defect in the D_1-like receptor dependent increase in fractional sodium excretion, cAMP production, and Na/KATPase activity, but showed no defect in dopamine production as measured by dopamine secreted into the urine.

In the obese Zucker rat model of ROS dependent hypertension, it was found that the D_1R was hyperphosphorylated by GRK_2 and was unable to inhibit Na/KATPase (34). It was further shown that this defect is due to an inability to activate phospholipase C (PLC). In this particular model of hypertension, the D1-like receptor dependent inhibition of Na/KATPase is insensitive to inhibition of PKA but is sensitive to PKC inhibitors. Interestingly, they showed that the defect in D_1R coupling to adenylyl cyclase in obese rats is reversed by dephosphorylating the D_1R in isolated membranes, yet does not restore PLC activation. There is an increase in the incidence of hypertension as well as an increase in the generation of ROS and inflammation with age. In a recent paper, it was shown that age related hypertension in rats may be reversed through the use of exercise which reduces several measures of ROS and inflammation in the kidneys from old rats, while at the same time increasing the abundance of D_1R (35). A paper by Banday et al. showed that increased oxidative activity (stimulated by L-buthionine sulfoximine) caused an increased AT_1R abundance in the renal proximal tubule and subsequent hypertension (36). The use of tempol (a novel cell permeable superoxide dismutase mimetic), reversed the oxidative stress induced increase in blood pressure. They further showed a heightened sensitivity to Ang II dependent increases in inositol triphosphate accumulation, PLC activation, MAP Kinase activation, Na/KATPase activity and NHE_3 activity.

Summary

The natriuretic renal dopaminergic system collectively opposes the anti-natriuretic activity of the RAS by both down-regulating the AT_1R, up-regulating the AT_2R and inhibiting ROS generation. Each of the individual dopamine receptors has been shown to oppose the activity

of the AT_1R, with the D_1R, D_3R, and D_5R physically interacting with the AT_1R. The cell signaling pathways used by the individual members of the dopamine receptor family are complex and interconnected, yet work together to maintain normal blood pressure at least in part by inhibiting RAS activity and ROS production.

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