Published in final edited form as:

Clin Exp Nephrol. 2012 February ; 16(1): 17–24. doi:10.1007/s10157-011-0494-1.

Convergence of major physiological stimuli for renin release on the Gs-alpha/cyclic adenosine monophosphate signaling pathway

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Abstract

Control of the renin system by physiological mechanisms such as the baroreceptor or the macula densa (MD) is characterized by asymmetry in that the capacity for renin secretion and expression to increase is much larger than the magnitude of the inhibitory response. The large stimulatory reserve of the renin–angiotensin system may be one of the causes for the remarkable salt-conserving power of the mammalian kidney. Physiological stimulation of renin secretion and expression relies on the activation of regulatory pathways that converge on the cyclic adenosine monophosphate/protein kinase A (cAMP/ PKA) pathway. Mice with selective Gs-alpha ($G_s\alpha$) deficiency in juxtaglomerular granular cells show a marked reduction of basal renin secretion, and an almost complete unresponsiveness of renin release to furosemide, hydralazine, or isoproterenol. Cyclooxygenase-2 generating prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) in MD and thick ascending limb cells is one of the main effector systems utilizing $G_s\alpha$ -coupled receptors to stimulate the renin–angiotensin system. In addition, β -adrenergic receptors are critical for the expression of high basal levels of renin and for its release response to lowering blood pressure or MD sodium chloride concentration. Nitric oxide generated by nitric oxide synthases in the MD and in endothelial cells enhances cAMP-dependent signaling by stabilizing cAMP through cyclic guanosine monophosphate-dependent inhibition of phosphodiesterase 3. The stimulation of renin secretion by drugs that inhibit angiotensin II formation or action results from the convergent activation of cAMP probably through indirect augmentation of the activity of PGE_2 and PGI_2 receptors, β -adrenergic receptors, and nitric oxide.

Keywords

Cyclooxygenase; Nitric oxide synthase; Phosphodiesterase; Macula densa; Baroreceptor; ACE inhibition

Introduction

A characteristic of the physiological regulation of renin secretion is its striking asymmetry in the response reserve to inhibitory and stimulatory challenges, with the amplitude of stimulatory responses being markedly greater than the amplitude of inhibitory responses. When the baroreceptor mechanism is activated by an elevation of blood pressure, there is a significant decrease in renin release. However, this inhibitory change of renin release is much smaller than the stimulation of renin release caused by a reduction of blood pressure. For example, early experiments by Kirchheim et al. [1] in conscious dogs showed that a reduction of blood pressure from 100 to 60 mmHg caused a 7-fold increase of plasma renin while an increase from 100 to 140 mmHg reduced plasma renin by only about 10% indicating that >90% of the total response bandwidth occurs in the subnormal stimulatory pressure range. Similarly, in the isolated perfused juxtaglomerular (JG) apparatus preparation used to assess macula densa (MD) control of renin secretion, i.e., the regulation of renin release by changes of luminal sodium chloride (NaCl) concentration, about 80% of the total response was seen to occur in response to lowering luminal NaCl concentration below the normal level of 35 mM [2]. Since the renin–angiotensin system, both by its direct renal effects and by its effect on aldosterone production, is perhaps the most important physiological mediator of renal salt handling, one could argue that the regulatory asymmetry of the renin–angiotensin system is the underlying cause for the apparently asymmetrical regulation of salt balance. A summary of this asymmetry may be that salt conservation is in general much more powerful than salt excretion with the result that even extreme reductions in salt intake are, in general, better tolerated and more quickly corrected than salt excess.

There is substantial evidence in support of the notion that the Gs- α /cyclic adenosine monophosphate/protein kinase A (Gs α /cAMP/PKA) pathway is the most important intracellular signaling cascade for stimulation of renin secretion and renin expression. The magnitude of the stimulatory reserve of renin release in response to physiological interventions results from the multiple pathways that converge on this, the most effective cellular mechanism causing renin stimulation. In this review we will summarize evidence that this signaling route dominates both acute and chronic stimulatory responses through control of release of renin and transcriptional activation and recruitment.

JG cell-specific Gs α deletion

The absolutely critical role of the Gs α /cAMP/PKA signaling cascade in the physiological regulation of renin secretion has recently been highlighted by studies in mice with deletion of Gs α in JG granular cells [3, 4]. Gs α deletion was achieved by crossbreeding mice in which Cre recombinase was expressed under control of the endogenous renin promoter by recombinant knock-in into the Ren-1d locus of two renin gene mice, with animals in which exon 1 of the *GNAS* gene was enclosed between loxP sites [5, 6]. At the DNA level, native Gs α was found to be significantly reduced in the whole kidney and almost completely abolished in single JG cells of mice with one copy of the modified renin locus and two copies of loxP-flanked *GNAS* [3]. This was associated with a marked reduction of Gs α mRNA and protein in the renal cortex and in JG cells. Renin expression and renin secretion were markedly reduced in the Gs α -deficient mice. Because of the severe reduction of Gs α in JG cells, it is likely that reduced signaling through this G protein is directly responsible for the depression of the renin system; these results suggest that Gs α -dependent signal processing is needed in a non-redundant fashion for the maintenance of high basal levels of renin expression and renin release. Furthermore, the stimulation of renin secretion caused acutely by furosemide, hydralazine, or isoproterenol was virtually abolished. To the extent that furosemide stimulates renin secretion through the MD and hydralazine through the baroreceptor, these data suggest that Gs α is required for the major regulatory inputs that

increase renin secretion in vivo. Therefore, G-protein-coupled receptors causing activation of adenylyl cyclase (AC) are in the center of the physiological regulation of renin release. We will discuss the evidence that activation of E-prostanoid (EP) receptors EP₂ and/or EP₄ by PGE₂ and of I-prostanoid (IP) receptor by PGI₂, of β -adrenergic receptors by sympathetic transmitters, and nitric oxide (NO) synthase are the main routes for cAMP-dependent renin regulation.

Prostaglandins in renin release

Starting with the early observations by Larsson et al. [7] that arachidonic acid increases and indomethacin reduces plasma renin activity, various metabolites of arachidonic acid have been suggested as potent regulators of renin secretion [8]. The relevance of prostaglandins to renin secretion, particularly for regulation through the MD mechanism, became strikingly apparent when it was demonstrated that the inducible cyclooxygenase isoform COX-2, was constitutively expressed in MD cells [9]. Expression of COX-2 in the tubular contact region also includes cells of the thick ascending limb (TAL) where it is typically patchy and irregular [10–13]. Conversion of prostaglandin H₂ (PGH₂) into the bioactive PGE₂ is catalyzed by prostaglandin E₂ synthases, and immunocyto-chemical evidence has demonstrated the presence of a membrane-associated PGE₂ synthase in MD cells of both rats and rabbits [14, 15].

Studies in the isolated rabbit JG apparatus have shown that acute, non-specific COX inhibition with flufenamic acid or flurbiprofen virtually completely abolished the increase in renin secretion caused by a decrease in MD NaCl concentration [16]. Direct evidence for a role of COX-2 has been obtained in an extension of these studies in which the specific COX-2 inhibitor NS-398 was also found to prevent the stimulation of renin secretion by low NaCl while the putative COX-1 blocker valeryl salicylate did not have this effect [17]. The application of a biosensor technique has provided direct evidence linking MD NaCl delivery to local PGE₂ release [18]. In this approach, human embryonic kidney (HEK) 293 cells were stably transfected with the mouse PGE₂ receptor EP₁, a receptor subtype that is coupled to the IP₃ pathway and whose activation therefore causes an increase in cytosolic calcium. Transfected HEK cells responded to PGE₂ with a dose-dependent increase in intracellular calcium ([Ca]_i) and this effect was blocked by the EP₁ inhibitor SC51322. In dissected and perfused TAL/MD preparations from the rabbit, [Ca]_i in a transfected and fura-2-loaded sensor cell positioned at the basolateral aspect of MD cells was seen to increase in response to removal of luminal NaCl or the presence of furosemide. Somewhat surprisingly in view of studies on TAL cells in culture (see below), positioning of the sensor cell close to a TAL cell had no effect on [Ca]_i. Of major importance is the observation (Fig. 1) that most of the change in [Ca]_i occurred in the NaCl concentration range between 20 and 40 mM, exactly the concentration range in which NaCl concentration affects renin secretion in a similar preparation [2].

The role of PGE₂ in the physiological regulation of renin release has also been examined using in vivo methods. The stimulation of renin release or renin expression produced by furosemide or a low Na diet was blunted by the administration of indomethacin or the COX-2 specific inhibitor rofecoxib [19–22]. Rofecoxib also normalized the elevated levels of urinary prostaglandin excretion and plasma renin activity in patients with genetically verified Bartter's syndrome due to mutations of the Na–K–2Cl transporter (NKCC2) or renal outer medullary potassium channels (ROMK) [23]. An acute reduction of perfusion pressure by renal arterial constriction caused an increase in the renal venous plasma concentration of the PGI₂ metabolite 6-keto-PGF_{1 α} , and this was paralleled by an increase in renin secretion [24]. Furthermore, the stimulation of renin secretion induced in a non-filtering kidney model by a reduction of blood pressure was virtually abolished by indomethacin [25]. A role of the G α -coupled IP receptors in baroreceptor-dependent renin release is also suggested by

studies in which the rise of plasma renin during chronic renal artery constriction was found to be blunted in IP-deficient mice, an effect that was mimicked by a COX-2 specific inhibitor [26].

The mechanisms by which reductions in luminal NaCl cause stimulation of PGE₂ release and COX-2 expression have been studied in cell lines derived from the MD and from TAL cells [27, 28]. In both lines of cells a reduction in medium NaCl caused a prompt and dose-dependent increase in PGE₂ release that was essentially completely inhibited by NS-398 and was therefore largely mediated by COX-2. The onset of this response preceded any increase in COX-2 expression, suggesting that it was the result of an increase in COX-2 activity and/or of an activation of phospholipase A₂ (PLA₂) followed by increased availability of arachidonic acid. Presence of PLA₂ in MD cells and regulation of PLA₂ in parallel to that of COX-2 has recently been demonstrated [12]. In both TAL and MD cells in culture, a reduction in medium NaCl also augmented the expression of the mRNA and protein expression of COX-2 [27, 28]. Ion substitution studies indicate that the extracellular signal for COX-2 stimulation appears to be a reduction in Cl rather than in Na concentration, a finding that is remarkably concordant with the Cl-dependency of renin secretion shown earlier in an entirely different preparation. The intracellular signaling events leading to the stimulation of COX-2 activity and expression are initiated by rapid phosphorylation of p38 and Erk1/2 kinases [27]. Participation of MAP kinases in COX-2 expression is supported by the inhibitory effects of SB 203580 and PD 98059, inhibitors of p38- and Erk1/2-mediated signaling events [27, 28]. The increased expression of COX-2 through the MAP kinase pathway appears to reflect both a transcriptional activation and an increased stability of the mRNA [29]. These observations are in agreement with findings in other cell types in which MAP kinases are critically involved in regulating COX-2 expression in response to cytokines, growth factors, and hypertonicity [30–32].

To investigate the long term role of COX-2 in the regulation of renin secretion, experiments were performed in mice with targeted deletion of COX-2. Basal levels of plasma renin concentration (PRC) were significantly reduced in conscious COX-2 knockout mice, and this effect was independent of genetic background variations since it was seen in three different strains of knockout mice [33]. Low PRCs in this state of chronic COX-2 deficiency are the consequence of the absence of the stimulatory effect of prostaglandins on renin expression and the resulting reduction of the expression of renin mRNA and of the renin content in the renin-producing JG cells [33–35]. The markedly reduced renin expression and plasma renin in COX-2 knockout mice indicates that COX-2 plays a critical role in maintaining normal renin levels. Based on the evidence reviewed above, it seems likely that PGE₂ generated by COX-2 causes an activation of the cAMP/PKA pathway that results in increased renin transcription and enhanced stability of renin mRNA. Chronic treatment with the COX-2 inhibitor rofecoxib does not consistently mimic the renin-suppressing effect of COX-2 deletion [36, 37], a difference that may be related to the marked upregulation of COX-2 in the rofecoxib-treated animals [36].

COX-2 deletion and the resulting reduction of EP₂/EP₄ receptor activation has the predictable consequence that physiological stimuli signaling through the COX-2 dependent MD pathway are less effective in acutely enhancing renin secretion. Thus, the stimulatory effect of furosemide administration on plasma renin has been found to be markedly reduced in COX-2-deficient mice [33]. Interestingly, however, the same reduction of release efficiency has also been observed following administration of hydralazine and isoproterenol [33], although the stimulation of renin release by adrenergic receptor activation should be independent of prostaglandin synthesis [38]. Furthermore, there was a marked reduction in the renin release response to inhibition of angiotensin-converting enzyme (ACE) or angiotensin II (ATII) receptor blockers [33]. The marked reduction of the response of renin

release in the COX-2-deficient mice to acute administration of furosemide, hydralazine, isoproterenol, quinaprilate, and candesartan suggests that the level of renin expression is a non-specific determinant of the magnitude of the acute release response. Therefore, a basic rule for the control of renin secretion seems to be that persistent activation or deactivation of feedforward signaling leads to an adaptation in renin expression and the size of the releasable renin pool in the same direction. This chronically induced adaptation affects the response to any superimposed acute stimulation.

Nitric oxide in renin release

NO is generated from L-arginine in a complex reaction catalyzed by NO synthases (NOS) and requiring the co-substrates nicotinamide adenine dinucleotide phosphate and oxygen and the co-factors tetrahydro-biopterin, flavin adenine dinucleotide and heme. The family of NOS consists of at least three members, the constitutive neuronal and endothelial isoforms (nNOS and eNOS) and the inducible isoform (iNOS). A potential role of NO in the control of renin secretion has been suspected because of the proximity of NOS-containing and renin-producing granular cells. The conspicuous presence of nNOS in MD cells has been of particular interest [39, 40], but endothelial cells, the classical site of eNOS expression, are also potential sources of NO with access to JG cells.

There is convincing evidence that NO is an important constituent of the signaling pathway controlling renin release through both the MD and baroreceptor mechanism. Perhaps the most direct evidence for an involvement of NO comes from experiments in the isolated perfused JG apparatus preparation in which NOS inhibition prevented the increase in renin secretion caused by a reduction in luminal NaCl concentration while the addition of L-arginine during perfusion with low NaCl further enhanced renin release [41]. Studies examining the MD mechanism by the indirect approach of testing whether loop diuretic-induced stimulation of renin secretion is sensitive to NOS inhibitors have shown that the administration of NOS inhibitors abolished the increase in renin release caused by furosemide pretreatment in dissected rat renal microvessels and in intact animals [21, 42–44]. Plasma renin activity in nNOS knockout mice and basal renin secretion in isolated perfused kidneys from nNOS^{-/-} or eNOS^{-/-} mice were found to be consistently lower than in wild-type animals, suggesting that tonic release of NO enhances renin release in mice [45]. The relative increase of renin secretion produced by furosemide was essentially normal in nNOS^{-/-} or eNOS^{-/-} mice, but was markedly reduced in nNOS/ eNOS double-knockout mice. This recent evidence would suggest that NO affecting renin release is derived from both nNOS and eNOS isoforms. A role for NO in the stimulation of renin through the baroreceptor is suggested by the observations in intact dogs and isolated rat kidneys that NOS inhibitors markedly reduce the stimulation of renin release by a reduction of perfusion pressure [46, 47].

Several investigators have accumulated evidence to suggest that NO stimulates renin secretion through activation of the cAMP/PKA pathway. This activation is likely to result from inhibition of phosphodiesterase 3 (PDE₃), a cAMP-degrading phosphodiesterase that is sensitive to cGMP [48]. This notion is consistent with an early report showing that the PDE₃ inhibitor milrinone increased basal and isoproterenol-stimulated renin release in conscious rabbits [49]. In the isolated perfused rat kidney, Na nitroprusside increased renin secretion, and this increase was attenuated by the protein kinase A inhibitor Rp-8-CPT-cAMPS. Since membrane-permeable cGMP analogs also reduced the stimulatory effect of Na nitroprusside, stimulation of renin secretion by NO was clearly related to the A kinase, and not the G kinase pathway [50]. PDE₃ inhibition by cGMP as the cause for the increase in cAMP is suggested by the observation that two inhibitors of this enzyme, milrinone and trequinsin, markedly elevated renin secretion, and that a specific guanylate cyclase inhibitor abolished the stimulatory effect of nitroprusside [51]. Furthermore, trequinsin elevated cellular cAMP

content in JG cells, and enhanced renin secretion, an effect that was abolished by PKA inhibition [52]. Inhibition by zaprinast of phosphodiesterase type 5 (PDE₅), a cGMP-degrading phosphodiesterase, also stimulated renin secretion, and this effect was reduced by nNOS-specific inhibitor 7-nitroindazole indicating that nNOS contributed to the cGMP generation [53]. Thus, the stimulatory pathway of NO is initiated by guanylate cyclase-dependent generation of cGMP, inhibition of PDE₃-dependent degradation of cAMP, and activation of the PKA pathway. Since NO can also inhibit renin through activation of cyclic GMP-dependent protein kinase it remains to be clarified why under normal conditions the PKA pathway predominates [54–56].

Beta-adrenergic receptors in renin secretion

There is solid experimental evidence that renal sympathetic nerves are critically involved in the homeostatic control of sodium excretion and of the regulation of renin–angiotensin system [57]. The effects on renin secretion are mediated by activation of β_1 - and β_2 -adrenergic receptors (β_1/β_2 ADR) expressed pre- and postjunctionally at various sites in the kidney including the glomerular vascular pole where they co-localize with renin [57, 58]. Activation of β -adrenergic receptors increases renin secretion without an involvement of changes in renal vascular tone or MD signals [57], and this stimulation is doubtlessly mediated through the cAMP/PKA pathway activated by the Gs-coupled β -receptors.

The availability of mice with genetic deletions of β_1/β_2 ADR has opened a new way to study the adrenergic regulation of renin release [59, 60]. In a recent study we demonstrated that PCR under basal conditions was markedly reduced in β_1/β_2 ADR-deficient compared to wild-type mice [61]. Thus, renin synthesis and renin secretion appear to be tonically activated by renal sympathetic nerve activity and circulating catecholamine levels prevailing under our basal experimental conditions. For reasons that are not entirely clear, the reduction of plasma renin in β_1/β_2 ADR knockout mice is larger than that usually observed with pharmacological blockade or observed in denervated kidneys [8, 62, 63]. Mean arterial blood pressure was found to be significantly reduced in the β_1/β_2 ADR^{−/−} mice over the entire 24 h cycle so that renal baroreceptors cannot be invoked as contributing to the inhibition of renin observed in the β_1/β_2 ADR-deficient animals [64]. The reduced effect of isoproterenol on renin release from JG cells isolated from β_1/β_2 ADR knockout mice suggests that the inhibition of renin by β_1/β_2 ADR-deficiency is a reflection of the loss of direct activation of JG cells.

In addition to reduced plasma renin, mice with β_1/β_2 ADR-deficiency also have a significantly lower expression of renin mRNA [61, 65]. Changes of plasma renin in response to an acute blood pressure reduction with hydralazine were found to be markedly smaller in β_1/β_2 ADR-deficient than in wild-type mice [65]. The reduced secretory response may suggest that the effect of the reflex activation of the renal sympathetic tone during the blood pressure reduction is ineffective in the absence of β_1/β_2 ADR. However, the absolute change of renin release in response to furosemide was also reduced by about 50% in β_1/β_2 ADR knockout compared to wild-type mice arguing for the non-specific nature of the effect of the renin pool size on the acute secretory response [61]. In addition, there were also drastic reductions in the acute effects of captopril, quinapril, and candesartan on renin release in β_1/β_2 ADR knockout mice. The uniform reduction of a number of acute release responses in the relatively renin-depleted mice with COX-2 or β_1/β_2 ADR deficiencies seems to permit the generalization that the size of the releasable renin pool is a modulating and limiting factor for acute renin release.

Role of the cAMP/PKA pathway in the stimulation of renin by ATII inhibition

A striking example of the interaction between various pathways converging on the *Gsa*/cAMP/PKA pathway is new evidence that this pathway is critical for the profound stimulation of renin secretion and expression by pharmacological inhibition of either ACE or AT receptors (Fig. 2). Classically, the effect of these agents on renin release has been attributed to direct effects of ATII withdrawal on JG cells, releasing renin secretion from a negative feedback mechanism exerted by ATII that has been called the 'short feedback loop' [66]. There is good evidence that the acute inhibition of renin secretion by ATII is in fact a direct effect of the peptide on the granular cells, and an increase of cytosolic calcium is the likely cellular transduction mechanism [66–68]. However, it has been unclear if the regulation of renin by ATII is symmetrical, i.e., if the increase of renin in response to ATII blockade is caused by withdrawal of ATII effects from JG cells and the resulting fall of cytosolic calcium. Asymmetric mechanisms are suggested because the stimulation of renin by ATII blockade is quantitatively much more pronounced than its inhibition by angiotensin excess.

In mice with cell-specific deletion of *Gsa* from JG cells we have observed that the stimulation of renin release normally elicited by acute or chronic inhibition of ACE or AT subtype 1A (*AT_{1A}*) receptors was virtually abolished, indicating that *Gsa* is required for the stimulation of renin release caused by blockade of the *AT_{1A}* receptor interaction with its ligand. The implication of this finding is that an acute or chronic decrease in the occupation of *AT_{1A}* receptors in vivo leads to *Gsa*-mediated stimulation of AC in JG cells. We suspect that this stimulation of AC by AT withdrawal in vivo is mostly indirect and involves the participation of other cell types and the concerted action of ligands that require *Gsa* signaling. Several pathways have been identified along which ATII can exert inhibitory effects on renin release and expression. For example, inhibition or genetic deletion of COX-2 markedly attenuates the stimulatory effect of ATII blockade on renin [13, 33, 35]. Thus, a reduction in ATII signaling, probably at the level of the MD and/or TAL cells, appears to lessen COX-2 inhibition. This is strongly supported by the observation that COX-2 expression is markedly upregulated in ATII-blocked or -deficient mice [13, 69, 70]. A five-fold upregulation of COX-2 and of urinary PGE₂ excretion has also been observed in the *Gsa*-deficient mice used in these experiments [3]. Increased COX-2-mediated generation of PGE₂ upon withdrawal of ATII inhibition could then stimulate renin release through the *Gsa*-coupled EP₄ receptors, a mechanism that would be disrupted in *Gsa*-deficient mice. A second pathway that may be disinhibited by ATII blockade is the NO-dependent regulation of renin release. Up-regulation of neuronal NOS in mice with *AT_{1A}* receptor or angiotensinogen deletions indicates that ATII exerts a suppressing effect on nNOS expression [71, 72]. Increased levels of NO may stimulate COX-2 and thereby indirectly enhance renin expression and release in a *Gsa*-dependent fashion [73]. This action would be expected to be magnified by the effect of NO to inhibit PDE₃ and thereby to stabilize cAMP [50, 51]. Finally, ATII removal is usually associated with a decrease of arterial blood pressure, and reflex activation of the sympathetic nervous system. As has been pointed out above, the effects of both of these changes appear to be mediated by ligands that signal through *Gsa* since the plasma renin response to a blood pressure reduction by hydralazine and to the β -adrenergic agonist isoproterenol are drastically curtailed in *Gsa*-deficient mice [3]. The stimulatory effect of ACE inhibitors and angiotensin receptor blockers on the renin system being the result of the activation of several pathways that all converge on cellular cAMP is also supported by our observation that the simultaneous inhibition of the prostaglandin, catecholamine and NO inputs by indomethacin, propranolol, and L-NAME fully mimics the effect of *Gsa* deletion whereas inhibition of individual pathways does not.

Acknowledgments

The experimental work of the authors was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH.

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Fig. 1.

a Relationship between luminal Cl concentration and renin secretion in an isolated perfused JG apparatus preparation; data are from He et al. [2]. **b** Relationship between luminal NaCl concentration and PGE₂ release; PGE₂ release is expressed as equivalent increase of cytosolic calcium in EP₁ receptor-transfected HEK cells [18]

Fig. 2. Scheme describing feedforward effects on renin secretion and renin expression mediated by Gs α -coupled receptors and cAMP/PKA signaling. Renin secretion is also controlled by angiotensin II feedback effects that negatively affect levels of JG cell cAMP. *Solid arrows* indicate direct (stimulatory) relationships, and *broken arrows* indicate inverse (inhibitory) relationships. The *rectangle* represents MD cells while the *oval* represents the entire population of JG cells