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REVIEW

CELLULAR CONTROL OF RENIN SECRETION

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Summary

Renin secretion at the level of renal juxtaglomerular cells appears to be controlled mainly by classic second messengers such as Ca^{2+}, cyclic AMP and cyclic GMP, which in turn exert their effects through oppositely acting protein kinases and probably also by affecting the activity of ion channels in the plasma membrane. Thus, protein kinase A stimulates renin secretion, whilst protein kinase C and protein kinase G II inhibit renin secretion. Moreover, Cl^- channels could be involved in the mediation of the inhibitory action of Ca^{2+} on renin secretion. This review summarizes our present knowledge about the possible actions of these kinases in renal juxtaglomerular cells and considers pathways in the organ control of renin secretion.

Key words: juxtaglomerular cell, protein kinase A, protein kinase G, calcium, kidney, renin, secretion.

Introduction

The renin system

The renin–angiotensin–aldosterone system plays an important role in maintaining blood pressure, in electrolyte and fluid homeostasis of organisms, in activating the system leading to an increase in blood pressure and in enhancing (re)absorption of Na^+. The activity of the renin–angiotensin system in the circulation depends on the concentration of the protease renin, which is considered to be the key regulator of the system. Renin cleaves the decapeptide angiotensin I from angiotensinogen, which in turn is processed to the octapeptide angiotensin II by the action of angiotensin-converting enzyme. Renin found in the circulation comes from the kidneys, where it is produced by the juxtaglomerular epithelioid (JGE) cells. These cells are located in the medial layer of the afferent arteriole adjacent to the vascular poles of the glomeruli (Barajas, 1979; Taugner et al., 1984a).

JGE cells develop from vascular smooth cells by a reversible metaplastic transformation (Barajas, 1979; Taugner et al., 1984a). This particular differentiation of smooth muscle cells is associated with a marked change in cell morphology such that numerous granular (renin storage) vesicles of various sizes and shapes appear in the cells, while the number of myofilaments decreases (Taugner et al., 1984a). The cells become more epithelioid in appearance. The number of renal renin-producing cells is not constant. In general, the number decreases with increasing cellular age, but is at any time subject to rapid changes in response to an altered requirement for renin. Thus, during states of chronic renin stimulation, additional smooth muscle cells in the afferent arterioles transform to become renin-producing cells; during states of chronic renin suppression, the opposite transformation occurs. The intracellular events that trigger and control the transformation of smooth muscle cells to JGE cells and *vice versa* is not yet understood, but may be related to the cellular control of renin synthesis and renin secretion.

Regulation of renin secretion from the kidney

At the level of the whole kidney, renin secretion from JGE cells is controlled by a variety of factors. Renal nerve activity represents a stimulatory signal for renin secretion that is transmitted *via* β_1-adrenoreceptors (Hackenthal et al., 1990). Other neurotransmitter-like factors such as dopamine, calcitonin-gene-related peptide (Kurtz, 1989) and adrenomedullin (Jensen et al., 1997) also stimulate renin secretion. The level of renin secretion is also determined by the perfusion pressure in the renal arterial tree, in particular in the afferent arterioles, the rate of renin secretion increasing with a reduction in the perfusion pressure (Hackenthal et al., 1990). The mechanism linking perfusion pressure and renin secretion has been operationally defined as the ‘renal baroreceptor’. It has long been known that Na^+ intake and, in consequence, the Na^+ balance of the organism are important determinants of renin secretion, the rate of renin secretion being inversely related to the Na^+ balance (Hackenthal et al., 1990). In view of the effects of the renin–angiotensin–aldosterone system on blood pressure and on Na^+ balance, it appears that renin secretion is subject to negative feedback regulation mediated indirectly by blood pressure and by extracellular [Na^+]. Angiotensin II exerts a

direct negative feedback regulation of renin secretion and directly inhibits renin secretion at the level of JGE cells (Hackenthal et al., 1990). Apart from these more systemically determined factors, locally generated factors also appear to influence renin secretion: an undefined signal from neighbouring macula densa cells exerts an inhibitory effect on renin secretion (Schnermann, 1998). Endothelial autacoids, such as prostaglandin E_2, prostacyclin and nitric oxide, stimulate renin secretion, whilst endothelins inhibit renin secretion (Wagner et al., 1998a). Taken together, renin secretion from JGE cells at the level of the whole kidney is controlled by a variety of identified factors, such as neurotransmitters, angiotensin II and endothelial autacoids, whilst the nature of other mediator signals, such as perfusion pressure, extracellular [Na^+] and macula densa cells, remains elusive. Nonetheless, it appears reasonable to assume that all these different factors influencing renin secretion feed into either stimulatory or inhibitory pathways controlling the secretion of renin within JGE cells.

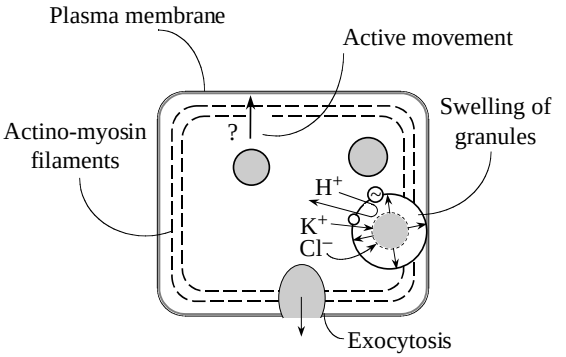

Fig. 1. Intracellular events regulating the exocytosis of renin from renal juxtaglomerular epithelioid cells. Active movement of renin storage granules towards the plasma membrane for induction of exocytosis appears less likely, but swelling of the storage granules due to an influx of KCl driven by the activity of a proton pump appears to be important. The actino-myosin filaments could also play a role in renin secretion by influencing the access of the storage vesicles to the plasma membrane.

Exocytosis of renin

The rate of renin release from JGE cells can change rapidly within a few minutes. Although the mechanism of release of renin from JGE cells is the subject of controversy, it appears reasonable to assume that renin secretion involves an exocytotic process similar to that for other secretory cells that contain storage vesicles for their secretion products. Arguments for exocytosis in JGE cells derive from the observation that renin secretion occurs in 'quanta' rather than continuously (Skott, 1986) and that fusion between renin vesicles and plasma membranes has been demonstrated for JGE cells (Taugner et al., 1984b).

An important step in the initiation of exocytosis in JGE cells appears to be swelling of the renin storage granules (Fig. 1) in a manner similar to the well-known vesicle swelling during exocytosis in other secretory cells. A peculiarity of JGE cells appears to be that granule swelling is required before the formation of the fusion pore (Skott and Taugner, 1987).

Renin secretion from JGE cells is sensitive to changes in extracellular osmolality, such that the rate of renin secretion is inversely related to the extracellular osmolality (Skott, 1988). Since the sensitivity of renin secretion to changes in osmolality is maintained in permeabilized JGE cells (Jensen and Skott, 1993), one may assume that it is the vesicle volume rather than the cell volume that is important for renin secretion. It has been suggested that the vesicle volume is subject to chemiosmostic control, with an influx of KCl from the cytosol into the granular matrix being the essential determinant of the vesicle volume (King and Fray, 1994). Important regulators of KCl influx into the granules could be the activities of a proton pump and of a K^+/H^+ exchanger in the vesicle membrane (King and Fray, 1994; Fig. 1).

Apart from vesicle volume, the cytoskeleton of JGE cells may also play a role in the control of exocytosis, but in a way quite different from that in other secretory cells. Since JGE cells transform from vascular smooth muscle cells, they contain actin and myosin filaments that are displaced to the subplasmalemmal space, where they form a subplasmalemmal shield that could regulate the access of renin storage granules to the plasma membrane by its state of contraction, just as contraction of the actin–myosin network inhibits renin secretion and *vice versa* (Taugner et al., 1988; Fig. 1). In line with this proposal, it has been suggested that activation of the myosin light chain kinase and JGE cell contraction inhibit renin secretion (Park et al., 1996a,b). Conversely, it has been suggested that actin disassembly stimulates renin secretion (Ogawa et al., 1995).

In summary, the intracellular regulation of renin secretion from JGE cells may occur on at least three levels: vesicle volume, the state of contraction of the actin–myosin complex, and the docking process of the vesicles with the cell membrane. Since it is reasonable to assume that these processes are regulated by intracellular signal cascades, the role of established second-messenger molecules in the cellular control of renin secretion will be considered next.

Intracellular signals involved in the control of renin secretion

Cyclic AMP

Among the intracellular signal pathways involved in the regulation of renin secretion, the cyclic AMP pathway is the best established (Hackenthal et al., 1990). It has been found using a variety of experimental models, ranging from *in vivo* experiments to experiments with isolated cells, that an elevation of cyclic AMP concentrations in JGE cells causes a rapid stimulation of renin secretion. Cyclic AMP thus mediates the stimulation of renin secretion induced by β-adrenoreceptor activation, dopamine, calcitonin-gene-related peptide, prostaglandin E_2 (PGE_2) and prostacyclin, all of which increase cyclic AMP levels in JGE cells (Kurtz, 1989), presumably by stimulating adenylate cyclase activity. There is

mounting evidence that cyclic AMP phosphodiesterases, in particular PDE-3 and PDE-4 (Beavo, 1995), are involved in the control of cyclic AMP levels in JGE cells and consequently in renin secretion (Chiu and Reid, 1996; Kurtz et al., 1998b). PDE-3, the level of which is regulated by cyclic GMP (see below), may play an important regulatory role in renin secretion. How cyclic AMP acts to stimulate renin secretion is less clear (Fig. 2). Since the renin stimulatory effect of β-adrenoreceptors on renin secretion was found to be reversibly attenuated by an inhibitor of protein kinase A (Kurtz et al., 1998a), it appears likely that cyclic AMP stimulates renin secretion by a process involving protein kinase A, which would be in accordance with the mode of action of cyclic AMP in other cells. There is some evidence that cyclic AMP could interfere with the regulation of the cytosolic Ca^{2+} concentration in JGE cells (Kurtz, 1989) and, in consequence, reduce the inhibitory effect exerted by Ca^{2+} on renin secretion (see below). It has also been suggested that protein kinase A activity could activate the proton pump in the renin storage vesicle membrane, thus increasing the transmembrane proton gradient and therefore the driving force for K^+ entry *via* the K^+/H^+ exchanger (King and Fray, 1994), which would be expected to cause vesicle swelling. Since cyclic AMP relaxes smooth muscle cells by inhibiting the contractile machinery, it is also conceivable that cyclic AMP activates renin secretion by relaxing the subplasmalemmal actino-myosin shield. Whether cyclic AMP also directly influences the docking of renin storage vesicles with the plasma membrane in JGE cells is unknown. Although it is well established that cyclic AMP stimulates renin secretion, the precise mechanism of this effect remains to be clarified.

Ca^{2+} and protein kinase C activity

The cytosolic Ca^{2+} concentration, either alone or in conjunction with the activity of protein kinase C (PKC), is an important intracellular regulator of secretion. In contrast to other secretory cells, however, in which Ca^{2+} and/or PKC initiate, support or maintain secretion, this pathway appears to inhibit renin secretion from JGE cells (Fig. 3). The concept of such an unusual role of Ca^{2+}/PKC in secretion, also termed the 'calcium

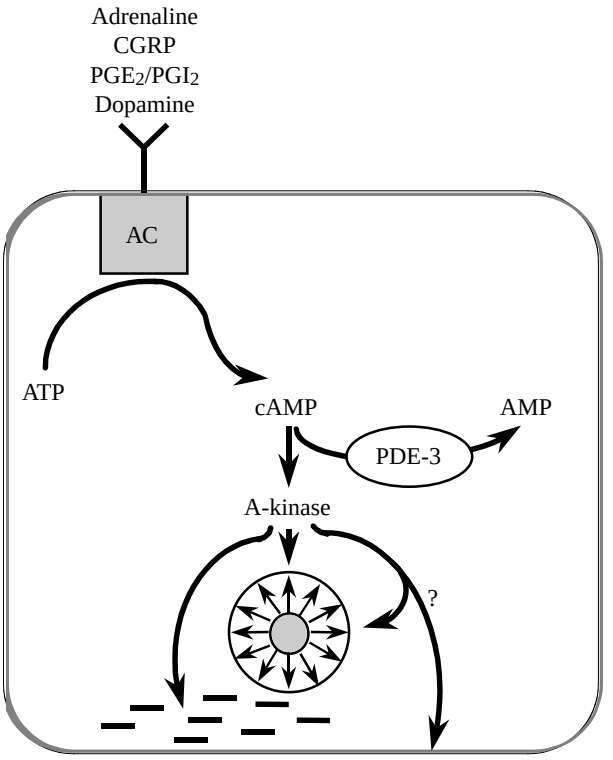

Fig. 2. Diagram summarizing the potential intracellular pathways involved in the stimulation of renin secretion by cyclic AMP (cAMP). Membrane-bound adenylate cyclase (AC) in renal juxtaglomerular epithelioid cells can be activated by various factors as indicated. Cyclic AMP stimulates renin secretion through activation of cyclic-AMP-dependent protein kinase (A-kinase), which could stimulate renin secretion by weakening the actino-myosin shield, by inducing swelling of renin storage granules or by other as yet unknown events. The effect of cyclic AMP is dependent on the activity of cyclic AMP phosphodiesterases (PDE-3), which generate AMP from cyclic AMP. CGRP, calcitonin-gene-related peptide; PGE_2, prostaglandin E_2; PGI_2, prostaglandin I_2.

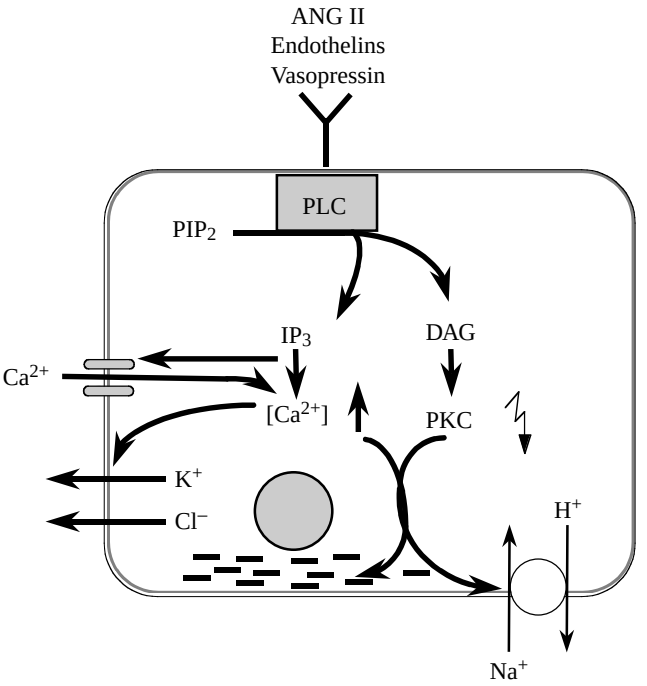

Fig. 3. Diagram summarizing the potential intracellular pathways involved in the inhibition of renin secretion by Ca^{2+} and protein kinase C (PKC) activity. Membrane-bound phospholipase C (PLC), generating inositol trisphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol bisphosphate (PIP_2), can be activated by various factors as indicated. Raised levels of IP_3 lead to an increase in the cytosolic Ca^{2+} concentration *via* release of Ca^{2+} from internal stores and by indirectly triggering transmembrane Ca^{2+} influx. Ca^{2+} could inhibit renin secretion by promoting efflux of KCl and/or by stabilizing the subplasmalemnal actino-myosin shield. DAG stimulates PKC activity, which could inhibit renin secretion by activating Na^+/H^+ antiport or by stabilizing the actino-myosin shield. ANG II, angiotensin II.

paradox of renin secretion', derives from several lines of evidence. Hormones activating phospholipase C, such as angiotensin II (Hackenthal et al., 1990), leading to intracellular Ca^{2+} mobilization and PKC activation in JGE cells, vasopressin (Kurtz et al., 1986) and endothelins (Ritthaler et al., 1995), inhibit renin secretion. The inhibitory effect of these hormones on renin secretion is attenuated by a reduction in the extracellular Ca^{2+} concentration to the submicromolar range (Ritthaler et al., 1995; Scholz et al., 1994; Vandongen and Peart, 1974; Naftilan and Oparil, 1982; Churchill, 1980). Conversely, lowering the extracellular Ca^{2+} concentration causes a marked stimulation of renin secretion in a variety of experimental preparations (Hackenthal et al., 1990; Ritthaler et al., 1995; Scholz et al., 1994; Vandongen and Peart, 1974; Naftilan and Oparil, 1982; Churchill, 1980; Antonipillai and Horton, 1985; Jensen and Skott, 1994). It is likely, therefore, that both the release of Ca^{2+} from internal stores and the enhancement of transmembrane Ca^{2+} influx inhibit the exocytosis of renin. Consistent with this conclusion, inhibitors of Ca^{2+}/calmodulin activity were found to be potent stimulators of renin secretion *in vitro* (Schwertschlag and Hackenthal, 1983; Churchill and Churchill, 1983; Della Bruna et al., 1992; Park et al., 1986), suggesting that a reaction triggered by Ca^{2+}/calmodulin could also be involved in the Ca^{2+}-mediated inhibition of renin secretion. The inhibitory effect of cytosolic Ca^{2+} on renin secretion appears to require that the JGE cells be electrically intact, because an increase in the Ca^{2+} concentration in permeabilized JGE cells fails to inhibit renin secretion (Jensen and Skott, 1994), whilst higher Ca^{2+} concentrations actually stimulate renin secretion from permeabilized JGE cells (Jensen and Skott, 1994), a response resembling the typical effect of Ca^{2+} on secretion. Similar observations were made in intact JGE cells exposed to increased extracellular Ca^{2+} concentrations for a period of hours, which led to a marked stimulation of renin secretion (Schricker et al., 1993). A link between the cytosolic Ca^{2+} concentration and the electrical properties of JGE cells is provided by the existence of Ca^{2+}-activated Cl^- channels (Kurtz and Penner, 1989) and probably also of Ca^{2+}-activated K^+ channels. Since the resting membrane potential of JGE cells is more positive than the K^+ equilibrium potential, but more negative than the Cl^- equilibrium potential (Bührle et al., 1985; Loutzenhiser et al., 1997), one may assume that an electroneutral efflux of KCl from JGE cells is directly triggered by the cytosolic Ca^{2+} concentration. Thus, an increase in the cytosolic Ca^{2+} concentration will lower the cytosolic concentrations of Cl^- and of K^+, which in turn are relevant for vesicle swelling. The role of Cl^- in the exocytosis of renin is supported by the observations that Cl^- stimulates renin secretion in both intact (Skott and Jensen, 1992) and permeabilized (Jensen and Skott, 1994) JGE cells and that the inhibitory effect of Ca^{2+} on renin secretion is markedly attenuated by blockade of Cl^- channels (Jensen and Skott, 1996).

Ca^{2+}-related changes in $[K^+]$ and $[Cl^-]$ do not account fully for the inhibitory effect of Ca^{2+} on renin secretion (Jensen and Skott, 1996) and they do not explain the inhibitory effect of calmodulin activity on renin secretion. It has been suggested, therefore, that a calmodulin-mediated reaction may directly inhibit vesicle swelling (Park et al., 1992) by impairing KCl influx into the vesicles and thus preventing renin secretion (King and Fray, 1994). Another action of Ca^{2+}/calmodulin in JGE cells relevant to renin secretion could be the activation of myosin light chain kinase (Park et al., 1996a,b). Whether the initiation of actin–myosin sliding in JGE cells inhibits renin secretion by forming a subplasmalemmal actin–myosin shield that impedes the access of the renin storage vesicles to the plasma membrane or by a mechanism acting directly on renin storage granules remains to be clarified.

Ca^{2+} is also required for the activation of PKC, which exerts a negative effect on renin secretion. It has been shown that phorbol esters stimulating PKC inhibit renin secretion (Churchill and Churchill, 1984; Kurtz et al., 1986; Hano et al., 1990; Ritthaler et al., 1996) and that PKC inhibitors attenuate the inhibitory effect on renin secretion of hormones acting *via* stimulation of phospholipase C in JGE cells (Munter and Hackenthal, 1989; Ritthaler et al., 1996). PKC could also inhibit renin secretion by contracting the actin–myosin network. Another inhibitory effect of PKC could be on Na^+/H^+ exchange. There is evidence that PKC can stimulate Na^+/H^+ exchange in the plasma membrane of vascular smooth muscle cells (Berk et al., 1987). Inhibition of this exchange process was found to stimulate basal rates of renin release and to attenuate the inhibitory effect of angiotensin II on renin release from isolated JGE cells (Kurtz et al., 1991).

It is not clear at present whether Ca^{2+} and/or PKC exert direct inhibitory effects on the protein machinery required for the docking and fusion events between renin storage vesicles and the plasma membrane in JGE cells. Nonetheless, from our present state of knowledge, it appears that the atypical inhibitory effects of phospholipase C activation and of Ca^{2+} on exocytosis in JGE cells are related to indirect cell-specific mechanisms such as vesicle swelling and the accessibility of the plasma membrane rather than to a novel direct inhibitory effect of Ca^{2+} on exocytosis.

Physiological regulators of renin secretion that act along the phospholipase C/ Ca^{2+} pathway in JGE cells include vasoconstrictor peptides such as angiotensin II and endothelins. Moreover, the control of renin secretion by renal perfusion pressure also appears to be related to the Ca^{2+} pathway, because the classic inverse relationship between the rate of renin secretion and renal perfusion pressure is reversed if the extracellular Ca^{2+} concentration is lowered to the submicromolar range (Scholz et al., 1994).

Cyclic GMP

There is evidence to suggest that cyclic GMP may participate in the control of renin secretion (Kurtz, 1989; Reid and Chiu, 1995; Romero et al., 1992). The precise role of cyclic GMP in this context is, however, the subject of controversy. The effects of factors elevating cyclic GMP levels in JGE cells, such as endothelium-derived nitric oxide or atrial natriuretic peptide, provide contradictory results (Kurtz and Wagner, 1998): nitric oxide has been implicated both as a stimulator and as an inhibitor of renin secretion *in vivo* and *in vitro*. Similar

controversial data reporting stimulation or inhibition of renin secretion have been reported for atrial natriuretic peptide. The data become more consistent if the effects of membrane-permeable cyclic GMP analogues are considered. Inhibition of renin secretion from isolated perfused kidneys, from kidney slices or from isolated JGE cells has been reported (Kurtz et al., 1998a; Greenberg et al., 1995; Henrich et al., 1988; Noble et al., 1994; Schricker and Kurtz, 1993). This puzzling situation could be resolved by assuming that native cyclic GMP, but not membrane-permeable cyclic GMP analogues, interferes with more than one pathway relevant to renin secretion, the overall effect on renin secretion being the sum of several actions. At present, three pathways along which cyclic GMP can exert cellular effects have been characterized (Schmidt et al., 1993). The most typical pathway is the activation of cyclic-GMP-dependent protein kinases, for which two subtypes (termed cGKI and cGKII) are known (Schmidt et al., 1993). A second effect is the activation of cyclic-nucleotide-triggered ion channels. Finally, cyclic GMP may also act along the cyclic AMP pathway by transactivation of cyclic-AMP-dependent protein kinase (Butt et al., 1992) or by inhibition and by activation of cyclic AMP phosphodiesterases (Beavo, 1995). Commonly used membrane-permeable cyclic GMP analogues have a high affinity for protein kinase G, a moderate affinity for cyclic-GMP-gated ion channels and a low affinity for protein kinase A or cyclic AMP phosphodiesterases (Butt et al., 1992). Since there is no evidence for the presence of cyclic-GMP-gated ion channels in JGE cells, it appears reasonable to assume that the inhibitory effect of cyclic GMP analogues on renin secretion is mediated by protein kinase G. This assumption is supported by the observation that protein kinase G inhibitors increase basal rates of renin secretion from isolated perfused rat kidney (Kurtz et al., 1998a). JGE cells contain both cGKI and cGKII with strikingly different intracellular distributions (Gambaryan et al., 1996). Whilst cGKI is localized to the cytosol, cGKII is predominantly found in association with renin storage granules or the plasma membrane. Since the inhibitory effect of membrane-permeable cyclic GMP analogues is normal in JGE cells lacking cGKI, but is fully restored in JGE cells lacking cGKII (Wagner et al., 1998b), it is probably cGKII that causes inhibition of renin secretion. Thus, cGKII appears to be a natural antagonist of cyclic AMP in the cellular regulation of renin secretion in JGE cells. Since cGK activation attenuates not only cyclic-AMP-stimulated renin secretion but also renin secretion stimulated by low external [Ca^{2+}] (Wagner et al., 1998b), it is more likely that cGKII inhibits renin secretion by a mechanism not utilizing the inhibitory Ca^{2+} pathway.

As mentioned above, cyclic GMP can also stimulate renin secretion; this stimulation occurred in the majority of investigations using native stimulators of cyclic GMP formation. This seeming contradiction may be resolved by the relatively strong expression of cyclic AMP phosphodiesterase 3 (PDE-3) in renal afferent arterioles (Sandner et al., 1999). The cyclic-AMP-degrading activity of PDE-3 is inhibited by cyclic GMP (Beavo, 1995), and increases in cyclic GMP concentration will therefore elevate cyclic AMP levels in JGE cells, which in turn should stimulate renin secretion. In fact, pharmacological inhibition of PDE-3 stimulates renin secretion and blunts the stimulatory effect of cyclic GMP (Kurtz et al., 1998b). As a consequence, the overall effect of intracellular cyclic GMP on renin secretion is the result of the difference between inhibition *via* cGKII and stimulation by cyclic AMP *via* inhibition of PDE-3. Whether and how the overall effects of cyclic GMP on renin secretion are physiologically regulated remains to be elucidated.

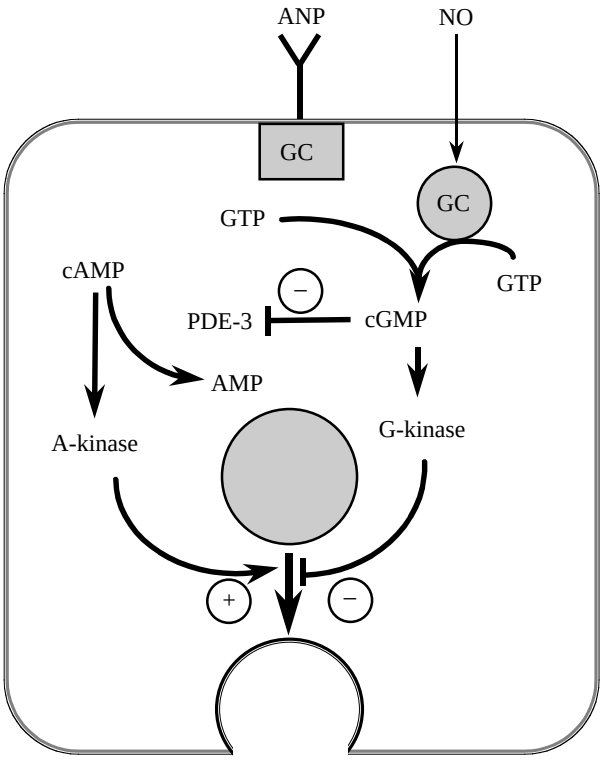

Fig. 4. Diagram summarizing the potential intracellular pathways involved in the effects of cyclic GMP (cGMP) on renin secretion. Membrane-bound guanylate cyclase (GC) in renal juxtaglomerular cells can be activated by atrial natriuretic peptide (ANP) and soluble GC can be activated by nitric oxide (NO). Cyclic GMP probably exerts two oppositely directed effects on renin secretion, a stimulatory effect (+) through inhibition of cyclic AMP (cAMP) degradation *via* inhibition of cyclic AMP phosphodiesterase 3 (PDE-3), and an inhibitory effect (–) *via* activation of cyclic-GMP-dependent protein kinase (G-kinase). A-kinase, cyclic-AMP-dependent protein kinase.

Nonetheless, it appears that the stimulatory effect on renin secretion of cyclic GMP mediated through PDE-3 inhibition is related to adenylate cyclase activity in JGE cells. From a theoretical point of view, one would expect the stimulatory effect of cyclic GMP on renin secretion to be reduced if the rate of cyclic AMP formation is low, but also to be lower at high adenylate cyclase activities, because of saturation of the cyclic AMP pathway. Thus, cyclic GMP appears to exert a dual control on renin secretion, an inhibitory effect *via* cGKII and a stimulatory effect *via* cyclic AMP (Fig. 4). Physiological

factors influencing renin secretion *via* the cyclic GMP pathway include nitric oxide and atrial natriuretic peptide.

Future perspectives

From our present state of knowledge, renin secretion at the cellular level appears to be controlled by classic signalling systems, including the cyclic AMP, Ca^{2+}/PKC and cyclic GMP pathways. Whilst cyclic AMP and Ca^{2+}/PKC appear to be direct antagonists in the regulation of renin secretion, cyclic GMP plays a more versatile role by directly inhibiting renin secretion *via* protein kinase G II and by indirectly stimulating renin secretion *via* inhibition of cyclic AMP degradation.

Future work is required to characterize the actions of protein kinase A, protein kinase G and protein kinase C at the molecular level in JGE cells.

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