Gap junctional intercellular communication in the juxtaglomerular apparatus

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Yao J, Oite T, Kitamura M. Gap junctional intercellular communication in the juxtaglomerular apparatus. Am J Physiol Renal Physiol 296: F939–F946, 2009. First published December 10, 2008; doi:10.1152/ajprenal.90612.2008.—The juxtaglomerular apparatus (JGA) is a specialized contact region between the glomerulus and the cortical thick ascending limb that plays an active role in the maintenance of ion homeostasis and control of blood pressure. The JGA accommodates several different cell types, including vascular smooth muscle cells, endothelial cells, mesangial cells, macula densa cells, and renin-secreting juxtaglomerular granular cells. These cells, with the exception of the macula densa cells, are tightly coupled by gap junctions. Gap junction-mediated intercellular communication in the JGA provides a pathway for signal transduction and coordination of multicellular functions. Disruption of cell-to-cell communication in the JGA results in altered preglomerular vascular tone and renin secretion. This review summarizes recent data about the roles of gap junctions in the JGA and illustrates how gap junction-mediated intercellular Ca\textsuperscript{2+} signals determine physiological responses in the JGA.

gap junction; intercellular calcium signal; renal autoregulation

Maintenance of renal structure and function requires coordinated intercellular communication, which is mediated by autocrine and paracrine factors including neurotransmitters, hormones, growth factors, and vasoactive substances (41, 48, 65, 70). In addition to these paracellular mediators, direct cell-to-cell communication through gap junctions has been recognized as another important mechanism in the regulation of renal function, and especially in the function of the juxtaglomerular apparatus (JGA) (23, 28, 29, 52, 53, 81, 88). The JGA is a specialized contact region between the glomerulus and the cortical thick ascending limb that plays an active role in the maintenance of ion homeostasis and control of blood pressure (36, 39, 48, 50, 65). The JGA is composed of a tubular component, the macula densa, and a vascular component consisting of the afferent and efferent arterioles as well as the extraglomerular mesangium. The JGA accommodates several different cell types including vascular smooth muscle cells (VSMCs), endothelial cells, mesangial cells, macula densa cells, and renin-secreting juxtaglomerular granular cells (renin-secreting cells) (Fig. 1A). Of these cells, the macula densa cells and endothelial cells act as sensors that perceive changes in Na\textsuperscript{+} concentration and blood pressure, respectively, send signals to the effector cells (VSMCs and renin-secreting cells) in the afferent arteriole, and thereby regulate preglomerular vascular tone and renin secretion (Fig. 1B). This physiological response is termed renal autoregulation. It involves several different cell types and requires sophisticated intercellular communication and functional coordination.

There is an abundance of gap junction channels in the vascular cells of the JGA (10, 21, 76), which are situated ideally to perceive and integrate signals triggered by pressure, hormones, and ions and to transmit the information to the effector cells. Acting as a sophisticated cellular communication system, gap junctions interconnect individual vascular cells and allow the JGA to function as a synchronized syncytium (23, 28, 29, 53, 76, 81, 88) (Fig. 1). In this article, we summarize the current knowledge of gap junctions in the JGA, focusing especially on the roles of gap junction-mediated intercellular Ca\textsuperscript{2+} waves in renal autoregulation.

Gap Junction Channels

Gap junctions are intercellular channels that allow the direct exchange of small molecules such as ions (Na\textsuperscript{+}, K\textsuperscript{+}, Ca\textsuperscript{2+}, H\textsuperscript{+}) and low-molecular-weight metabolites [e.g., cyclic nucleotides, inositol 1,4,5-trisphosphate (IP\textsubscript{3})] (20, 24, 43, 59) (Fig. 2A). Gap junctions are formed by a family of special proteins termed connexins (Cx). Six Cx subunits form a connexon, a hemichannel that docks to its counterpart in the plasma membrane of neighboring cells, resulting in the formation of a gap junction channel (Fig. 2B). Each Cx has four transmembrane domains, one intracellular loop, and two extracellular loops (Fig. 2C). The extracellular regions are responsible for interacting with their counterparts on neighboring cells. The intracellular domains, containing the COOH and NH\textsubscript{2} termini, are subjected to posttranslational modifications that control channel activity.

To date, more than 20 different Cx proteins have been identified. The members of the Cx family share a conserved NH\textsubscript{2} terminus, whereas the intracellular cytoplasmic loop and
the COOH terminus differ from molecule to molecule. Individual Cxs are designated according to their molecular weight (e.g., Cx43, Cx40, Cx30, Cx26) (20, 24, 43). Expression of Cx is tissue and cell type specific, although more than one isoform can exist within a single cell. If interacting cells express multiple Cxs, different combinations of Cxs form three types of channels: homotypic channels assembled by the same Cx; heterotypic channels composed of homomeric hemichannels in which the two hemichannels contain different Cxs; and heterotypic channels formed by heteromeric hemichannels in which different Cxs are included within the hemichannels (37, 43, 80) (Fig. 2D). Different homotypic channels have distinct electrical and biochemical properties (7, 40, 49). In addition, heterotypic channels composed of different Cxs display different selectivity and permeability of second messengers such as IP₃ and cyclic nucleotides (79).

Gap junctions are involved in a wide range of cell functions including transmission of intercellular signals, synchronization of multicellular functions, and transport of nutrients (14, 22, 47, 59). These junctions also regulate cell proliferation, differentiation, migration, and survival (2, 88). The majority of the biological effects of gap junctions are mediated by the direct transmission of signaling molecules among neighboring cells (20, 24, 59). Some function of gap junctions may involve the release of metabolites (ATP, NAD⁺, glutamate) into the extracellular space by nonjunctional hemichannels (11, 15, 56). It also has been reported that gap junctions exert their biological effects by mechanisms independent of cell-to-cell communication (56, 71). For example, Cx43 is reported to mediate transforming growth factor (TGF)-β signaling via competition with Smads for binding to microtubules. Gap junctions may regulate cell growth in a manner independent of their channel-based functions (16).
**Interconnection of the Vascular Cells by Functional Gap Junction Channels in the JGA**

Freeze-fracturing studies have demonstrated that cells in the vascular components of the JGA are tightly coupled by gap junctions. Gap junctions physically link mesangial cells, VSMCs, endothelial cells, and renin-secreting cells, allowing them to function as a unified system (10, 21, 76). Immunohistochemical staining has revealed that at least four different Cxs are present in the vascular components of the JGA, including Cx37, Cx40, Cx43, and Cx45, all of which are expressed predominantly in the cells of the vascular system (18, 64). Among these isofoms, renin-secreting cells express Cx37, Cx40, and Cx45 (27, 30, 74, 82, 90). Glomerular endothelial cells express Cx37, Cx40, and Cx43 (27, 74, 90), whereas preglomerular VSMCs (30, 32, 90) and extraglomerular mesangial cells express Cx37, Cx40, Cx43, and Cx45 (6, 25, 30–32, 74, 88, 90). The expression pattern of different isoforms of Cxs in distinct cell types in the JGA is summarized in Table 1.

The presence of gap junction proteins in the vascular components also has been documented in vitro. Expression of Cx40 and Cx43 proteins has been observed in cultured mesangial cells (85, 88), whereas Cx40 is expressed in glomerular endothelial cells (77) and Cx45 in preglomerular VSMCs (30). At the mRNA level, expression of Cx37, Cx40, Cx43, and Cx45 is observed in immortalized renin-producing As4.1 cells (58), and expression of Cx37, Cx37, Cx40, Cx43, and Cx45 is detectable in preglomerular VSMCs (3). In cultured cells, Cx molecules are localized at the cell-to-cell contacts and/or the perinuclear regions (3, 85). Using a dye-transfer assay, several studies have confirmed that the gap junctions expressed in the cultured cells are functional (30, 58, 83–86, 88). In a heterocellular coculture system, bidirectional communication among renin-secreting cells, endothelial cells, and VSMCs has been documented (58). These studies suggest that the cells in the JGA are tightly interconnected by functional gap junction channels.

**Roles of Gap Junction Channels in the JGA**

**Transmission of intercellular Ca\(^{2+}\) signal.** Gap junctions provide a pathway for the intercellular transmission of signaling molecules. In contrast to the extracellular regulatory pathway of growth factors, hormones, or neurotransmitters, the intercellular pathway bypasses signal transduction across the cell membrane. Signaling molecules of <1.2 kDa pass through gap junctions, and most second messengers such as cAMP, ATP, IP\(_3\), and Ca\(^{2+}\) can be transferred (20, 24, 59). Among these molecules, the transmission of Ca\(^{2+}\) signals via gap junctions has been extensively investigated. As a versatile second messenger, Ca\(^{2+}\) is critically involved in the control of many cellular functions (8, 36, 85, 87). Gap junction-mediated intercellular Ca\(^{2+}\) waves have been characterized in a variety of cell types and are presumably responsible for multicellular processes such as bile expulsion in the liver (55), hormone secretion in the pancreas (47), and information processing in neural cells (14, 63). The mechanisms underlying the propagation of intercellular Ca\(^{2+}\) waves involve the diffusion of intracellular messengers through gap junctions and/or the paracrine effects of extracellular nucleotides such as ATP and UTP (15, 38, 57, 60, 62, 68).

In the JGA, vascular tone and renin secretion are regulated by a variety of stimuli such as blood pressure, hormones, neurotransmitters, and vasoactive substances (26, 48, 65). Although underlying signaling may be different between the stimuli, changes in intracellular Ca\(^{2+}\) are considered to represent the common event through which vascular tone and renin secretion are governed (8, 12, 26, 36, 45, 48).

**HOMOCELLULAR CA\(^{2+}\) SIGNALING IN THE JGA.** Using an in vitro model of mechanical stimulation, several investigators have examined homocellular propagation of Ca\(^{2+}\) in different JGA cell types (30, 77, 85, 87). In this model, a single cell is stimulated mechanically with a micropipette, and elevation in the intracellular Ca\(^{2+}\) in the target cell, as well as in the surrounding cells, is monitored. Involvement of gap junctions in Ca\(^{2+}\) wave formation is evaluated by pretreatment of the cells with chemical gap junction uncouplers, inhibitory mimetic peptides, or small interfering RNAs against particular Cxs. Involvement of ATP is assessed using blockers of purinergic receptors, ATP-degrading enzymes, or high doses of ATP to desensitize purinergic receptors. Cell-to-cell propagation of Ca\(^{2+}\) waves without physical contact and in the context of increased extracellular ATP concentrations also suggests the involvement of the extracellular pathway.

With the use of the mechanical stimulation model, propagation of intercellular Ca\(^{2+}\) signals in the cells of the JGA has been characterized. In mesangial cells and VSMCs of the afferent arterioles, intercellular transmission of Ca\(^{2+}\) signals is mediated by gap junctions (30, 85). The messenger responsible for the transmission has been identified as IP\(_3\) in mesangial cells. In glomerular endothelial cells, which share many properties of endothelial cells in the afferent arterioles, Cx40 hemichannels and extracellular ATP play crucial roles in the propagation of the Ca\(^{2+}\) wave. In this case, intercellular Ca\(^{2+}\) signals are transmitted by Cx40 hemichannels that release ATP and thereby activate purinergic receptors (77). In primary cultures of renin-secreting cells, ATP is also a mediator that is responsible for the propagation of intercellular Ca\(^{2+}\) signals. Given, expression of gap junctions is rapidly lost in cultured renin-secreting cells, and the roles of gap junctions in the propagation of Ca\(^{2+}\) signals cannot be determined in vitro (87). The fact that renin secretion is altered in gap junction-deficient mice (30, 82) indicates that gap junctions may be involved in the transmission of intercellular Ca\(^{2+}\) signals in renin-secreting cells in vivo.

**HETEROCELLULAR CA\(^{2+}\) SIGNALING IN THE JGA.** In addition to homocellular Ca\(^{2+}\) signals, a heterocellular Ca\(^{2+}\) wave in the JGA has also been documented (53). Using a JGA-glomerulus complex isolated from rabbit kidneys, Peti-Peterdi (53) demonstrated that activation of tubuloglomerular feedback (TGF) by increasing tubular flow at the macula densa leads to a significant elevation in intracellular Ca\(^{2+}\) in extraglomerular mesangial cells and renin-secreting cells. Cell-to-cell propaga-

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**Table 1. Distribution of connexins in the cells of the JGA**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Connexin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraglomerular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mesangial cells</td>
<td>Cx37, Cx40, Cx43, Cx45</td>
<td>6, 25, 30–32, 74, 88, 90</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Cx37, Cx40, Cx43, Cx45</td>
<td>30, 32, 90</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Cx37, Cx40, Cx43</td>
<td>27, 74, 90</td>
</tr>
<tr>
<td>Renin-secreting cells</td>
<td>Cx37, Cx40, Cx45</td>
<td>27, 30, 74, 82, 90</td>
</tr>
<tr>
<td>JGA, juxtaglomerular apparatus.</td>
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<td></td>
</tr>
</tbody>
</table>
tion of the Ca\textsuperscript{2+} signals is further transmitted toward proximal segments of the afferent arterioles and adjacent glomeruli, as well as toward intraglomerular elements, including podocytes. Disturbance of gap junction coupling, scavenging of ATP, and pharmacological inhibition of purinergic receptors abolish the changes in Ca\textsuperscript{2+} and stop the propagation of the Ca\textsuperscript{2+} wave, indicating the involvement of both gap junction-mediated intercellular communication and extracellular ATP in Ca\textsuperscript{2+} wave propagation (53).

Using microperfusion of the rabbit afferent arterioles, Uhrenholt et al. (78) demonstrated that elevated levels of extracellular KCl lead to a rapid elevation of intracellular Ca\textsuperscript{2+} in VSMCs. This signal is subsequently transmitted to adjacent endothelial cells and propagates in the endothelium in both upstream and downstream directions. Although the underlying mechanisms for the transmission of Ca\textsuperscript{2+} signals in the afferent arterioles have not been fully addressed, involvement of myoendothelial coupling via the gap junctions is likely (3, 27, 75, 78).

The roles of gap junctions in the transmission of Ca\textsuperscript{2+} signals in the JGA are summarized in Table 2. Gap junctions transmit Ca\textsuperscript{2+} signals triggered by various stimuli (mechanical, chemical, and physiological) in different cell types in the JGA. The propagation of intercellular Ca\textsuperscript{2+} signals by gap junction channels involves both intra- and extracellular mechanisms. In the intracellular model, gap junction channels are responsible for the intercellular passage of IP\textsubscript{3} (85). In the extracellular model, gap junctions are involved in the release of ATP via gap junction hemichannels (77). Potential mechanisms for each of these processes are depicted in Fig. 3.

**Table 2. Intercellular Ca\textsuperscript{2+} signaling in the cells of the JGA**

<table>
<thead>
<tr>
<th>Cell Type/Tissue</th>
<th>Stimulation</th>
<th>Mechanism</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial cells</td>
<td>Depolarization [KCl]</td>
<td>GI dependent\textsuperscript{a}</td>
<td>Functional syncytium in mesangium; MCs in</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Mechanical</td>
<td>GI/P\textsubscript{3} dependent\textsuperscript{a}</td>
<td>mediating TGF signaling</td>
<td>85</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Mechanical</td>
<td>GI/Cx45 dependent\textsuperscript{a,b}</td>
<td>Cx45 in JGA function</td>
<td>30</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Mechanical</td>
<td>Cx40 and ATP dependent\textsuperscript{a,c}</td>
<td>Cx40 hemichannel in JGA function</td>
<td>77</td>
</tr>
<tr>
<td>Renin-secreting cells</td>
<td>Mechanical</td>
<td>ATP dependent\textsuperscript{d}</td>
<td>ATP in inhibition of renin secretion</td>
<td>87</td>
</tr>
<tr>
<td>Isolated JGA-glomerulus</td>
<td>Increased tubular flow</td>
<td>GI and ATP dependent\textsuperscript{e}</td>
<td>GJs and ATP as integral parts of TGF response</td>
<td>53</td>
</tr>
<tr>
<td>Isolated afferent arteriole</td>
<td>Depolarization [KCl]</td>
<td>Myoendothelial coupling\textsuperscript{f}</td>
<td>NO feedback mechanism on vasoconstriction in afferent arteriole</td>
<td>78</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Blocked with putative gap junction (GJ) uncoupler. \textsuperscript{b}Inhibited in smooth muscle cells from Cx45-deficient mice. \textsuperscript{c}Abolished by treatment of cells with Cx40 small interfering RNA. \textsuperscript{d}Expression of GI is lost in cultured renin-secreting cells, and roles of GJs in the propagation of Ca\textsuperscript{2+} signals cannot be determined in vitro. \textsuperscript{e}Putative mechanism. MCs, mesangial cells; NO, nitric oxide.
studies are needed to clarify how different signals in the JGA are integrated via gap junctions.

**Gap junction-mediated Ca\(^{2+}\) signal in the coordination of the vascular contractile response.** The transmission of the intercellular Ca\(^{2+}\) wave in the JGA may lead to synchronized cell behavior. In the cardiovascular system, gap junctions are known to control coordinated vascular responses in concert with hormones, neurotransmitters, and other factors (13, 59).

The contractile response of glomerular mesangial cells also are regulated by gap junction-mediated Ca\(^{2+}\) signals. Single-cell injection of IP\(_3\), a mediator responsible for the propagation of the Ca\(^{2+}\) wave in mesangial cells, leads to contraction of not only the injected cell but also neighboring mesangial cells (85). Propagation of the TGF Ca\(^{2+}\) wave is closely associated with contractions of the afferent arterioles and the glomerular tuft, and blockade of the calcium wave abolishes the contractile response (53). Gap junctions also may regulate vascular responses via integration and amplification of Ca\(^{2+}\) signals elicited by various stimuli. In mesangial cells and fibroblasts, dysfunction of gap junctional intercellular communication significantly attenuates serum-induced cell contraction (19, 85). In addition, both agonist-induced vascular contraction and relaxation processes are interfered by disruption of gap junctional intercellular communication (13). The Ca\(^{2+}\) wave also may help balance the vasoconstrictive response in the afferent arterioles during renal autoregulation. Propagation of the Ca\(^{2+}\) signal from VSMCs to the endothelium in the afferent arterioles has been reported by two separate studies using isolated JGA and afferent arterioles (53, 78). The Ca\(^{2+}\) wave in the endothelium initiated by contracting VSMCs triggers the release of nitric oxide, which provides a negative feedback mechanism to avoid excessive vasoconstriction. It is conceivable that inhibition of gap junctional intercellular communication in the JGA may lead to desynchronization of the Ca\(^{2+}\) signals, resulting in less coordinated vascular responses.

**Gap junction-mediated Ca\(^{2+}\) signaling in renin secretion.** Renin secretion is normally regulated in response to mechanical, osmotic, and electrochemical stimuli that act on different cells of the JGA (26). Signals triggered by different stimuli are converged and transmitted to renin-secreting cells via gap junctions. Thus impairment of the intercellular signaling pathway should lead to dysregulated renin secretion. Indeed, Cx40 null mice exhibit hypertension, which is accompanied by marked increases in the number of renin-secreting cells, renin biosynthesis, and plasma renin levels (17, 42, 46). In addition, increased renin expression and plasma renin activity also have...
been reported in Cx45-deficient (Cx45fl/fl:Nestin-Cre) mice (30). Intrarenal infusion of peptides that specifically block Cx37, Cx43, or Cx40 also cause elevation in blood pressure, plasma renin activity, and angiotensin II levels (74). Furthermore, genetic replacement of Cx43 (which is not expressed in renin-secreting cells) with Cx32 leads to diminished renin secretion, even under stimulated conditions (28). These data collectively suggest that gap junction is a major and essential player in the control of renin secretion.

The mechanisms underlying increased renin levels in mice with disrupted Cx40, Cx45, or Cx37 signaling in the JGA have not been fully elucidated. However, the fact that disruption of Cx signaling leads to increased renin secretion (30, 42, 74, 82) indicates that signals transmitted to renin-secreting cells by gap junctions inhibit renin secretion. Gap junction-mediated intercellular Ca\(^{2+}\) signaling may contribute to this inhibitory effect. Previous studies have indicated that Ca\(^{2+}\) is a potent inhibitor of renin secretion. This is supported by several lines of experimental evidence: 1) Ca\(^{2+}\)-mobilizing agents inhibit renin secretion (26); 2) Ca\(^{2+}\) influx via store-operated Ca\(^{2+}\) channels suppresses renin secretion (67); and 3) depletion of extracellular Ca\(^{2+}\) stimulates renin secretion (66). Wagner et al. (82) demonstrated that in Cx40-deficient kidneys or wild-type kidneys treated with a nonselective gap junction blocker, renin secretion is enhanced, similar to what is seen in wild-type kidneys in the absence of extracellular Ca\(^{2+}\). The regulation of renin secretion from both the endothelium and the macula densa sides is disrupted in the absence of Cx40 (42, 46, 82). It has been documented that pressure- and angiotensin II-induced suppression of renin secretion, as well as stimulatory effects of loop diuretics on renin secretion, are abrogated in the absence of Cx40 (42, 46, 82). These observations indicate that disruption of gap junction-mediated intercellular Ca\(^{2+}\) signals interferes with the physiological feedback loop and the pressure-sensing machinery in the JGA, resulting in dysregulated renin secretion.

**Regulation of Gap Junction in the JGA**

Gap junction proteins have a very short half-life of ~1–5 h. This property is advantageous for their roles in signal transduction, i.e., rapid and dynamic regulation of gap junctions by various factors allows for more finely tuned regulation of signal transduction pathways. The function of gap junction channels is regulated by phosphorylation, synthesis, assembly, trafficking, and degradation of Cx proteins (59).

Currently, molecular mechanisms involved in the regulation of gap junctions in the cells of the JGA are not well understood, and the majority of previous studies have utilized cultured rat mesangial cells. We previously reported that platelet-derived growth factor disrupts gap junctional intercellular communication in mesangial cells via mechanisms related to Cx43 phosphorylation (86, 88). We also identified that vasoactive substances are potent regulators of gap junction expression and function in mesangial cells. For example, vasoconstrictors such as nitric oxide and cAMP-elevating agents promote Cx43 expression and gap junctional intercellular communication (83, 84, 89). However, vasoconstrictors angiotensin II and endothelin strongly suppress Cx43 expression and gap junctional intercellular communication (unpublished observations). Other factors, such as high glucose, the protein kinase C activator phorbol myristate acetate, the Ca\(^{2+}\) ionophore ionomycin, reactive oxygen intermediates, and cellular acidification, also disrupt gap junctional intercellular communication in mesangial cells (33, 91). Because most of these factors are implicated in various renal physiopathologies, regulation of gap junctions could be an important mechanism by which these factors affect renal hemodynamics.

Regulation of renal gap junctions in pathological scenarios also has been investigated in vivo. In two-kidney, one-clip hypertensive rats, increased levels of Cx40 mRNA were observed in both clipped and unclipped kidneys, whereas an increase in Cx43 mRNA was observed only in the unclipped kidney. Immunohistochemical staining showed that the increase in the level of Cx40 was primarily localized to renin-secreting cells in the hypertensive rats (27, 29). This observation suggests differential regulation of Cx40 and Cx43 under hypertension. In addition, cell-to-cell communication mediated by Cx40 may be implicated in the function of renin-secreting cells and thereby participates in the control of blood pressure.

In cell cultures, high glucose concentrations suppress the expression and function of Cx43 in various types of vascular cells (mesangial cells, endothelial cells, and VSMCs) (44, 61, 91). Zhang et al. (90) reported altered distribution and expression of Cx40 and Cx43 proteins in the cells of the afferent arterioles in streptozotocin-induced diabetic mice. They found that Cx40 and Cx43 are expressed abnormally in VSMCs and renin-secreting cells, respectively. Moreover, the level of Cx43 protein in endothelial cells of the efferent arteriole is markedly reduced in this diabetic model. These results suggest that altered gap junction expression and function may contribute to glomerular hyperfiltration as observed in diabetes mellitus.

**Conclusion**

Cells in the JGA are tightly interconnected by gap junction channels. Gap junctions within the JGA play important roles in renal autoregulation through the transmission of intercellular signals and coordination of multicellular functions. Despite extensive recent investigations on gap junctions, our understanding of gap junctions in the JGA remains limited. Elucidation of gap junction-mediated signaling mechanisms in the control of renin secretion and hypertension is an exciting and challenging field for further studies. In addition, the properties of channels formed, signal molecules transmitted, and regulatory mechanisms involved in the JGA should be explored in the future. The specific roles of different isoforms of Cx proteins in the JGA also need to be clarified. Unraveling the precise mechanisms by which gap junctions regulate the function of the JGA may lead to the development of novel therapeutic strategies for the prevention and treatment of certain renal diseases.

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**Review**

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