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Connexins, renin cell displacement and hypertension

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Vascular gap junctions formed by specific connexins proteins Cx37, 40, 43 and 45 are important for proper vascular function. This review outlines that defects of the connexin 40 protein leads to hypertension because of dysfunction of renin secreting cells of the kidney. Thus defects of Cx40 but not of other vascular connexins blunt the negative feedback control of renin secretion by the blood pressure, and moreover, lead to a shift of renin expression from the juxtaglomerular vessels walls into the periglomerular interstitium. Evidence exists to indicate that those findings which were primarily obtained with mice are also relevant for humans.

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Introduction

Hypertension is meanwhile a common disease with a high prevalence in industrial societies. The causes for hypertension are multifactorial. A substantial part of hypertensive diseases can be attributed to a dysfunction of the renin–angiotensin–aldosterone-system (RAAS), which normally plays an essential physiological role for the maintenance of normal sodium balance and of normal blood pressure [1]. The activity of the RAAS is triggered by the release of the protease renin from the kidneys. Inadequate secretion of renin is therefore a known reason of hypertension. During the last seven years a novel cellular mechanism has been identified that leads to hypersecretion of renin and to hypertension. This mechanism is related to disturbed intercellular communication of renin cells via gap junctions. It is the aim of the review to summarize the present state of knowledge how gap junctional coupling and control of renin secretion could be linked and how defective coupling could lead to hypertension.

Connexins

Gap junctions (GJs) are intercellular channels with a high permeability [2]. They serve to electrical impulse propagation and also to the exchange of signaling molecules with a molecular mass below 1 kD. GJs are formed by docking of two hemichannels (connexons) expressed by the two neighbored cells to be connected [2]. Beyond this classical view of GJs there is emerging evidence that also nonconnected hemichannels which allow communication between the intra-cellular and the extracellular space may play important physiological roles by the release of signaling molecules such as ATP [3]. Connexons are built up by six connexin proteins which assemble around a central pore. There exist 21 different connexin proteins in man and 20 in mice [4]. A connexon is normally formed by connexins of the same isoform (homomeric connexon), but also a mixture of two connexin isoforms within the same connexon may occur (heteromeric connexon). The type of the connexins determines the biophysical function of the connexon and if connected of the GJ.

Within the cardiovascular system GJs and connexons play an important role for intercellular communication in the heart, in the vascular endothelium, between vascular smooth muscle cells and between endothelial and smooth muscle cells. The cardiovascular GJs are mainly formed by Cx40, 43 and 45 in the heart [5–7] and by Cx37, 40, 43 and 45 in the vasculature [5,8–10]. Although there exist some regional heterogeneities within the vasculature, the endothelium normally expresses Cx37, Cx40 and also Cx43 [5,11,12], whereas smooth muscle cells mainly express Cx45 and Cx43 [8,13]. Myoendothelial junctions are probably formed by Cx37, Cx40 and Cx43 [14,15]. On the other hand interendothelial spreading of vasodilatory signals is dependent on Cx40 GJs [16,17].

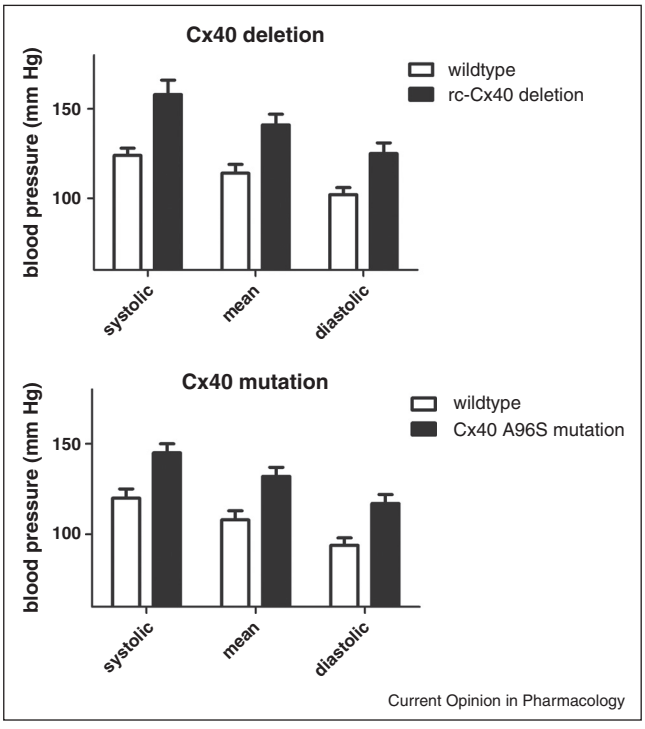
Connexins and hypertension

The regulation of GJ function either by modulation of connexon insertion into the membrane or by the physiological modulation of permeability of membrane inserted connexons in blood vessels is subject of increasing interest, but is still only poorly understood. There are findings that the expression of vascular connexins change in response to hypertension in a region dependent fashion suggesting secondary alterations of vascular functions induced by high blood pressure [18–20]. If connexins are important for proper vascular function [10] then primary alterations in the functions of vascular connexins would be expected to also alter vascular function [21••]. This issue was addressed by generation of genetically engineered mice lacking these individual vascular connexin proteins. Whilst mice with conditional deletion of

Cx43 and of Cx45 are not viable because of defective cardiovascular development [4], do mice lacking either Cx37 or Cx40 survive and reach normal age. Cx37 deficient mice are normotensive but Cx40 deficient mice are hypertensive [22–24]. As Cx40 is essential for the spreading of vasodilatory signals along the endothelium [23••,25•] block of this spreading may cause the hypertension in these animals. However, it turned out that endothelium specific deletion of Cx40 exerts no influence on blood pressure [26•].

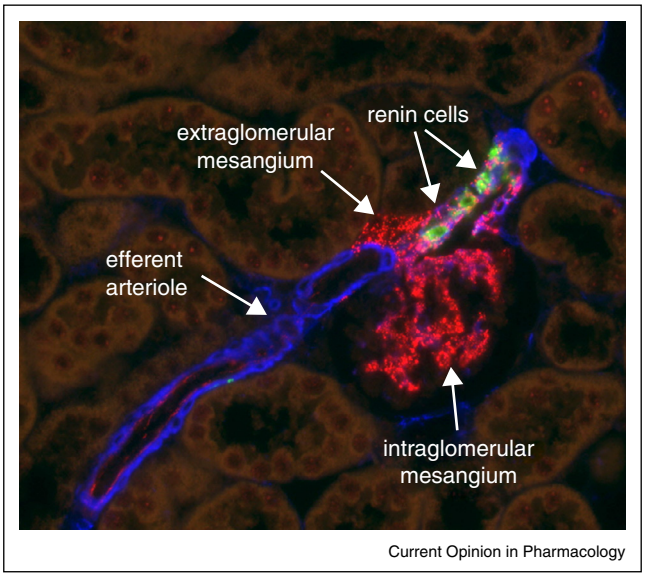
The hypertension of Cx40 deficient mice is systolic and diastolic [25•,26•] (Figure 1) but is not salt sensitive, meaning that lowering or increasing salt intake does not change blood pressure [22,24]. Instead it turned out that inhibitors of the renin–angiotensin–aldosterone system (RAAS) such as ACE-inhibitors or inhibitors of angiotensin II-type 1 receptors (sartans) effectively rendered hypertensive Cx40 knockout mice normotensive [22,24]. In line, deletion of the angiotensin II-AT1a receptors in Cx40 deficient mice also makes them normotensive [27]. The conclusion from these findings, namely that the RAAS plays an important role for hypertension in Cx40 deficient mice, was corroborated by the findings that Cx40 deficient mice have high plasma renin concentrations [22,24] and also increased plasma aldosterone levels [27]. A causal role of renin and the RAAS for the hypertension in Cx40 deficient mice was further supported by the observation, that the hypertensive phenotype of Cx40 deficient mice could be mimicked by cell specific deletion of Cx40 in renin cells only [26•], what is in line with the observation that intrarenal infusion of Cx40 mimetic peptides increases blood pressure [28]. In accordance with these findings it turned out that renin cells display strong expression of Cx40 [29–32] (Figure 2). The strong expression of Cx40 in renin cells and in the neighbored mesangial cells explained previous electron-microscopical findings about a high density of gap junctions between renin cells and mesangial cells [33,34•]. In line, specific reintroduction of Cx40 in renin cells in mice with a global Cx40 deletion significantly ameliorates hypertension [35]. Whilst the demonstration of Cx40 renin cells was unequivocal, was a possible expression of other vascular connexins such as Cx37, 43 and 45 in renin cells more subject to discussion [30,31,36,37]. Regardless, specific deletion of any of these other connexins in renin cells produced no change of plasma renin activity or of blood pressure [36,38,39]. Conversely, the effect of Cx40 deletion on plasma renin and on blood pressure was mimicked by a mutation of the Cx40 protein, that strongly reduces the permeability of the Cx40 connexon [40••,41]. This mutation leading to the exchange of serine at position 96 to alanine in the Cx40 protein was discovered in humans suffering from cardiac arrhythmia [40••]. When inserted into mice the mutation caused increased plasma renin concentrations and hypertension [41]. In summary, there is convincing evidence to indicate

Figure 1



Telemetry measurements of blood pressure in conscious mice lacking either connexin 40 selectively in renin cells (upper panel) or harboring a less of function mutation of Cx40 (lower panel). For details see text.Data are adapted from Refs. [24,25•].

Figure 2



Mouse kidney section stained for connexin 40 (red color). There is intense Cx40 immunoreactivity in glomeruli, in particular in the intra- and extraglomerular mesangium and in the renin cells (green color) located in the wall of the afferent arteriole. Blue color marks alpha-smooth muscle actin delineating arteriolar vessel walls.