Renal and cardiovascular sensory receptors and blood pressure regulation

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Sensory Receptors and Blood Pressure Regulation

Blood pressure homeostasis is regulated by a variety of inputs (23) including baroreceptors, chemoreceptors, sympathetic nerve activity, and hormones. Although these inputs are important regulators of blood pressure on a timescale of seconds (neural) or minutes (hormonal), long-term blood pressure control is dominated by the kidney (10, 22, 24, 76) via regulation of extracellular fluid volume. When blood pressure is high, the excess pressure promotes renal salt and water excretion and thus returns blood volume, and blood pressure, toward normal. Conversely, if blood pressure is low, extracellular fluid volume will be increased, thereby increasing both blood volume and blood pressure.

Recently, studies have highlighted roles that sensory receptors, particularly in the kidney, play in the regulation of blood pressure. Indeed, the idea that sensory receptors modulate blood pressure regulation is not new; chemoreceptors in the carotid and aortic bodies have long been known to play important roles in blood pressure regulation. However, as recent studies have demonstrated, sensory receptors, olfactory receptors (ORs), taste receptors, and other G protein-coupled receptors (often of the GPR family) play functional roles in traditionally “nonsensory” processes in many different tissues (13, 14, 25, 28, 30, 33, 34, 38, 39, 60, 64, 65, 73). Often, the ligands for these “sensory” receptors are metabolites produced by metabolic pathways or other physiological processes (25, 28, 33, 72). This review will focus on recent studies highlighting the roles that renal and cardiovascular sensory receptors play in blood pressure regulation, focusing on the role of adenylate cyclase 3 (AC3), as well as receptors that have been shown to be sensors for two important metabolites: succinate and short-chain fatty acids.

Succinate

Succinate is a metabolic intermediate of the citric acid cycle that is present in the plasma in the low micrometer range (25). In the 1980s, it was demonstrated that succinate alters various aspects of metabolism and transport in the proximal tubule (3, 7, 19–21). However, it was not until 2004 that G protein-coupled receptor 91 (Gpr91) was identified as a succinate receptor by He et al. (25); subsequently, Gpr91 is now also referred to as succinate receptor 1 (or SuciR1). In agreement with earlier work on the effect of succinate in the kidney, Gpr91 was localized to the proximal tubule as well as the juxtaglomerular apparatus (JGA) and distal tubule. A subsequent study localized Gpr91 to the glomerulus (likely glomerular endothelial cells) and to the apical membranes of multiple distal segments, including the thick ascending limb, the macula densa (MD), and the principal cells of the cortical and medullary collecting ducts (56).

In the study of He et al. (25), activation of Gpr91 by succinate was identified as a novel stimulus for renin secretion. This study demonstrated that succinate delivery could induce hypertension in wild-type but not Gpr91−/− animals (although angiotensin II induced hypertension similarly in both geno-
types). This group also reported that succinate delivery increased plasma renin levels and that the succinate-induced blood pressure increase in wild-type animals could be blocked by angiotension-converting enzyme inhibitors, implicating the activation of the renin-angiotension system. On a cellular level, it is thought that succinate activates Gp91 on the apical membrane of MD cells to activate mitogen-activated protein kinases as well as cyclooxygenase-2 (72). This leads to increased synthesis and release of prostaglandin E2, which is both a vasodilator and an important paracrine mediator of renin release from the juxtaglomerular apparatus (63). In further support of the role of succinate to mediate renin release, it was shown that succinate induces renin release from ex vivo glomerul/i/JGA preparations in Gpr91+/+ but not Gpr91−/− mice (72). Interestingly, however, Gpr91−/− mice have normal baseline blood pressures (25), likely due to long-term blood pressure counterregulatory mechanisms (23). Because renin is a key part of the ability of the kidney to increase blood pressure in the face of low blood volume, it is tempting to speculate that succinate may be acting via Gpr91 to support increases in blood volume (and therefore blood pressure).

Recent studies have also tied the succinate-GPR91-renin pathway to various aspects of pathophysiology. Tissue succinate levels are known to be increased during ischemic hypoxia (whereas other TCA intermediates decrease; Refs. 17, 49); thus, an increase in succinate levels may indicate ischemia, oxidative stress, or renal energy deprivation. In addition, it has been suggested that accumulation of succinate in renal ischemia could contribute to stenosis-associated hypertension (25).

It has also been demonstrated (57) that circulating succinate levels are elevated in several rodent models of hypertension and metabolic disease, including the spontaneously hypertensive rats rat, ob/ob mice, and db/db mice. However, in humans, neither hypertensive nor diabetic patients presented with elevated succinate in the blood. As the authors note, however, this does not preclude a local signaling role of succinate, which is not reflected in the circulating levels. In the same vein, it has been suggested that localized succinate signaling may be relevant in the case of diabetic nephropathy, as hyperglycemia can lead to the local accumulation of succinate, which then can induce renin release from the JGA (49–51, 67). In addition, there is interest in urinary succinate as a potential early biomarker for diabetic nephropathy, as urinary succinate is increased one- to twofold in diabetic mice (67). Although much work remains to be done, succinate is clearly an important signaling molecule that plays important roles in both the physiology and pathophysiology of blood pressure control.

AC3 and the MD

AC3 is the “olfactory” isoform of adenylate cyclase and is a necessary component of OR signaling in the nose. In the nose, when an OR binds to its ligand, it activates downstream signaling by activating a specific subtype of G protein (Golfactory, or Golf) and subsequently, AC3. Golf and AC3 are obligatory for OR downstream signaling in the olfactory epithelium, as demonstrated by the fact that both Golf−/− and AC3−/− mice cannot smell (5, 77). In the kidney, Golf and AC3 colocalize with one another in both the distal convoluted tubule and in the MD (53). AC3−/− mice have a renal phenotype that is consistent with a dysregulation of MD function: decreased plasma renin and decreased glomerular filtration rate (GFR). Despite the decrease in plasma renin, however, blood pressure is normal in AC3−/− mice. Although a decrease in both plasma renin and GFR is consistent with an impairment in tubuloglomerular feedback (TGF), TGF (measured by stop-flow using an artificial perfuse) was normal in these animals (53). However, it is important to note that the ligand, and the OR, which mediate this signaling pathway in the MD, have not yet been identified. Therefore, it seems likely that TGF appeared normal in AC3+/+ and AC3−/− animals only because the artificial tubular fluid used for these studies was “missing” the ligand that activates this pathway (artificial tubular fluid is similar in electrolyte composition to tubular fluid but is missing other small molecule components). In the absence of the ligand, AC3+/+ and AC3−/− would indeed be expected to have similar TGF. Therefore, future studies must yet be done to understand if the GFR phenotype in AC3−/− is indeed due to altered TGF.

If AC3 does act on the TGF pathway, where might it impinge on this pathway to result in a chronic lowering of GFR? TGF is thought to be initiated by elevations in luminal NaCl, which leads to increased transport function (signaling) of the Na+/K+−2Cl− transporter (NKCC2) on the apical membrane of the MD (70). The MD isoform of NKCC2 is known to be inhibited by cAMP (35). AC3 is a potential source of this cAMP, thereby mediating a tonic “brake” on TGF by preventing NKCC2 from maximal signaling and keeping TGF in check. In an AC3−/− mouse, the brake on the pathway may be gone; if so, NKCC2 would be free to signal maximally. This would result in inappropriately high TGF, excess afferent arteriolar constriction, and therefore lowered GFR. Additionally, unregulated NKCC2 signaling and excess TGF would decrease renin secretion, another phenotype seen in AC3−/− mice. In addition, the fact that AC3 is inhibited by increased intracellular Ca2+ concentrations (74) is consistent with reports in the literature that increased intracellular Ca2+ is required for the TGF response (55) and that the cAMP inhibition of NKCC2 is reversed by calcium ionophores (4). In this scenario, if GFR becomes elevated, then a higher flow rate near the MD will increase TGF both directly and indirectly via AC3: first, an increased GFR will result in increased NaCl delivery to the MD, which will increase NKCC2 signaling and will directly increase TGF. In addition, a high flow rate will increase intracellular Ca2+ concentration in the MD cells because 1) an increase in luminal NaCl transport would inhibit activity of the basolateral Na+/Ca2+ exchanger and therefore inhibit Ca2+ efflux, and 2) because distal segments are generally believed to respond to increased flow or shear stress with an increase in intracellular calcium (37, 66). This increase in intracellular calcium would serve to inhibit AC3 and release the brake on TGF, allowing TGF to increase and therefore for GFR to decrease (an appropriate response to the initially high GFR). Therefore, although much work remains to be done, it appears that previously published studies of TGF regulation fit well with a model in which AC3 acts as a modulator of TGF.

Short-Chain Fatty Acids

The aforementioned study examining the role of AC3 in the kidney also identified several ORs that are expressed in murine kidney, including olfactory receptor 78 (Olf78; Ref. 53). More recently, the localization, ligand, and subsequently the physi-
The identification of Olfr78 as novel SCFA receptor (52), and the localization of Olfr78 to both the afferent arteriole and to vascular resistance beds (52), led to the novel hypothesis that Olfr78 may be playing a role in blood pressure regulation in response to SCFAs. Given the localization of Olfr78 to the afferent arteriole, it was hypothesized that SCFAs play a role in blood pressure regulation via Olfr78-mediated renin secretion. Consistent with this, propionate stimulated exocytosis from renin-containing juxtaglomerular cells in an Olfr78-dependent manner (52), and Olfr78−/− mice were found to have significantly lower plasma renin levels and baseline blood pressure compared with wild-type littermates (52).

Second, given the localization of Olfr78 to vascular resistance beds, it was hypothesized that SCFAs may also play a role in resistance vessels to acutely regulate blood pressure. Previous studies have shown that SCFAs, including propionate, cause vasodilation of ex vivo vascular ring preparations from both rodents and humans (41–43) and that the inclusion of acetate in hemodialysis buffers causes hypotension in patients (31, 47). To test whether there is a systemic consequence of the reported ex vivo vasodilatory effect (41–43), blood pressure was assayed in mice during delivery of an intravenous dose of propionate. Upon propionate delivery, there was a rapid and dose-dependent drop in blood pressure (52) over a ~1- to 2-min period, which recovered over ~5 min (for a calculated plasma dose of 10 mM, the hypotensive response was ~14 mmHg). This effect is consistent with the previously reported acute vasodilation of vascular ring preparations (41–43), and we therefore hypothesize that acute vasodilation of resistance vessels underlies the acute drop in blood pressure upon propionate administration. SCFAs have been reported to be in the 0.1- to 10-mM range in plasma (36,
fact, Gpr41 activation is accentuated in the systolic, diastolic, and mean blood pressure in microbiota. This antibiotic treatment resulted in an increase in these effects, antibiotic treatment was used to dramatically reduce gut microbiota can play a role in blood pressure regulation and that these effects are mediated in a complex manner via at least two microbiota. As noted above, the effect of propionate on renin release is absent in Olfr78−/− mice. In contrast to this, however, the acute hypotensive effect of propionate (presumably vasodilation) is accentuated in Olfr78−/− mice, indicating that Olfr78 activation antagonizes (rather than mediates) the acute hypotensive effects of propionate. In both the case of renin release and that of the smooth muscle cell responses, Olfr78 appears to be acting to support blood pressure in response to propionate. Therefore, Olfr78 acts to oppose the powerful hypotensive effects of propionate mediated by other receptors or pathways (the bulk of the acute hypotensive response must be mediated by a receptor other than Olfr78, as the hypotensive response is still present in Olfr78−/−). A likely candidate for these other receptors is Gpr41 and/or Gpr43, previously characterized SCFA receptors that also respond to gut flora-derived propionate to mediate physiological responses, such as adiposity (Gpr41; Ref. 60) and inflammatory responses (Gpr43; Refs. 36, 39).

RT-PCR experiments demonstrated that both Gpr41 and Gpr43 colocalize to blood vessels, along with Olfr78 (52). It was therefore hypothesized that Gpr41 and/or Gpr43 act to mediate the bulk of the hypotensive response, while Olfr78 opposes this response. In this case, the contrasting responses of Olfr78 and Gpr41/43 would produce a “buffering” effect to guard against wide swings in blood pressure (Fig. 1). In support of this hypothesis, it was found that 10 mM propionate (a concentration at the high end of the physiologically relevant range; Ref. 39) produce a decrease in blood pressure of 13.9 mmHg in wild-type mice, this effect is attenuated in Gpr41−/− animals and is absent in Gpr41−−/− (in fact, Gpr41−/− animals have a modest hypertensive response; Ref. 52). These data indicate that Gpr41 likely mediates the hypotensive effects of propionate, whereas Olfr78 functions to raise blood pressure and to antagonize the hypotensive effects of propionate.

To implicate gut microbiota more directly in these processes, antibiotic treatment was used to dramatically reduce gut microbiota. This antibiotic treatment resulted in an increase in the sympathetic, diastolic, and mean blood pressure in Olfr78−/− mice but did not significantly affect blood pressure in wild-type littermates (52). This is consistent with the idea (Fig. 1) that Olfr78 and Gpr41 respond to SCFAs to effect opposing changes in blood pressure. This model predicts that when the activation of both Olfr78 and Gpr41 are decreased simultaneously (via antibiotic treatment suppression of SCFA production), there is little effect in a wild-type animal (see Fig. 2). However, in an Olfr78−/−/Gpr41−− animal, propionate is acting solely on Gpr41 to lower blood pressure; therefore, removing the source of this ligand would allow for a relative rise in blood pressure. Although future studies must be done to better understand these pathways, it is clear that metabolites of gut microbiota can play a role in blood pressure regulation and that these effects are mediated in a complex manner via at least two SCFA receptors.

It is intriguing to consider “why” the metabolites of gut flora would affect vascular resistance. One possibility is that this facilitates nutrient absorption after a meal. The majority of absorption occurs in the small intestine; however, a significant quantity of nutrients (including starches, lactose, and lactulose) is absorbed from the large intestine in animals (2, 9, 11, 12, 27, 32, 44–46, 68) and in humans (1, 6, 15, 40, 48, 54, 61, 62, 75). After a meal, SCFA concentrations in the vessels serving the large intestine would peak, and the resulting vasodilation would facilitate efficient absorption from the gut into the circulation, ensuring that nutrients are not lost in the stool. Although it unclear whether there is a beneficial effect of having a systemic change in BP after a meal, it is interesting to note that there is evidence for this drop in BP in humans: postprandial hypotension is common among the elderly, even among healthy elderly populations (71).

As alluded to above, the opposing actions of Gpr41 and Olfr78 in response to propionate may act to buffer blood pressure changes. Specifically, Gpr41 (EC50 11 μM for propionate; Refs. 8, 36) would be expected to be tonically active under basal conditions (plasma SCFAs are 0.1–10 mM; Refs. 36, 39, 59). Therefore, although a transient hypotensive response is observed after the delivery of a bolus of propionate, it may in fact be that Gpr41 is exerting a tonic hypotensive influence, involved in setting blood pressure. When plasma SCFA concentrations begin to rise (i.e., after a meal), Gpr41 would further lower blood pressure; however, as plasma SCFAs elevate further, Olfr78 (EC50 0.9 mM for propionate; Ref. 52) would activate as well, acting as a homeostatic brake to prevent an inappropriate level of hypotension.

Summary

In summary, although the complexity of extracellular fluid volume and blood pressure regulation has been long appreciated (23), recent studies have revealed new roles for sensory receptors in these processes. The examples reviewed here highlight the fact that fluid, electrolyte, and blood pressure regulation is complex and that it is affected by the metabolism of not only the host (succinate) but also of the gut microbiota (SCFAs). Clearly, future studies are needed to better understand not only each individual pathway, but how these pathways, and others, interact in the integrative control of extracellular fluid volume and blood pressure.

GRANTS

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