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Review Article

Sorting Nexins: New Determinants for the Development of Hypertension

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Abstract

G protein-coupled receptors (GPCRs) are serpentine seven-transmembrane receptors that mediate the cellular responses to a myriad of hormones and neurotransmitters. As such, many of these receptors are crucial to the regulation of important physiological processes, such as blood pressure and renal sodium transport. The trafficking and signal transduction of GPCRs, including the dopamine receptors, are tightly regulated to ensure the accuracy of the intracellular signal and to limit the specificity and extent of the cellular response. A growing body of evidence has shown that the sorting and intracellular trafficking of agonist-activated receptors, including the GPCRs, appear to be mediated by the sorting nexins, among a few other proteins. The sorting nexin family consists of a diverse group of cytoplasmic and membrane-associated proteins that contain the canonical phox homology (PX) domain and are involved in the various aspects of protein trafficking after receptor endocytosis. Perturbation of the process and/or deficiency of the proteins involved in GPCR trafficking and signaling may lead to receptor dysfunction, impaired homeostatic responses, and possibly disease state. In this review, we provide an overview of GPCR trafficking, highlight the sorting nexins that impact the GPCRs that are involved in blood pressure control, and expound on the mechanisms of how the loss of certain sorting nexins may eventually lead to hypertension.

ABBREVIATIONS

AT_1R: Angiotensin II Type 1 Receptor; **D_1R, D_2R, D_3R, D_4R, D_5R:** Dopamine $D_{1\text{-}5}$ Receptor; **EEA1:** Early Endosome Antigen 1; **EGFR:** Epidermal Growth Factor Receptor; **ENaC:** Epithelial Na^+ channel; **GWAS:** Genome-Wide Association Study; **GPCR:** G Protein-Coupled Receptor; **GRK:** GPCR Kinase; **HEK293:** Human Embryonic Kidney ells; **hRPTCs:** human Renal Proximal Tubule Cells; **LAMP-1:** Lysosomal-Associated Membrane Protein 1; **(MMEP):** Microcephaly Microphthalmia Ectrodactyly, Prognathism; **NHE3:** Na^+/H^+ Exchanger isoform 3; **PX:** Phox homology; **PDZ:** Postsynaptic Density Protein-95/Discs-large, Zona-occludens-1; **RA:** Ras Association; **SNX:** Sorting Nexin; **TGF:** Transforming Growth Factor; **TGN:** Trans-Golgi Network; **USP10:** Ubiquitin-Specific Protease 10

INTRODUCTION

Hypertension is one of the most common and important health problems worldwide. Nearly 30% of middle-aged Americans have hypertension, but the prevalence is higher in non-Hispanic blacks and individuals >60 years of age (65%) [1]. In 2000, the worldwide prevalence of hypertension was estimated to be 26%, affecting approximately 1 billion people. It has been estimated that 29% of the world's adult population, or 1.56 billion people, will have hypertension by the year of 2025 [2]. Genetic and environmental factors and their interaction determine an individual's risk for hypertension [3,4]. Hypertension is a major risk factor for stroke, myocardial infarction, heart and kidney failure, and premature death globally [2,5,6].

G protein-coupled receptors (GPCRs) are a large and functionally diverse superfamily of cell-surface receptors that share a common architecture consisting of seven-transmembrane (TM) domains connected by extracellular and intracellular loops [7,8]. Upon ligand binding, GPCRs modulate a variety of cell functions by coupling to heterotrimeric G proteins and regulating

downstream effectors such as adenylyl cyclases, phospholipases, protein kinases, and ion channels [9-12]. The signal transduction that follows ligand occupation of a GPCR is tightly regulated to limit the specificity and extent of the cellular response. GPCR-mediated signal transduction is rapidly dampened via receptor desensitization, or the waning of the responsiveness of the receptor to agonist stimulation with time [13,14]. GPCRs, including the dopamine and angiotensin II receptors, elicit cellular responses to a myriad of stimuli, play essential roles in human health, and have important clinical implications in various diseases [15,16]. By far, GPCRs have been intensively studied as a key factor in the basic physiology and pathophysiology of hypertension and its complications. Identifying GPCRs associated with blood pressure advances our understanding of blood pressure regulation and highlights potential and novel strategies for the prevention and treatment of hypertension.

GPCR TRAFFICKING AND SIGNAL TRANSDUCTION

Agonist activation of a GPCR results into two simultaneous processes, i.e., receptor signal transduction and receptor trafficking. GPCR agonism induces a conformational change of the receptor which is followed by the uncoupling of the receptor from its cognate trimeric G protein and its disassembly into Gα and Gβγ subunits. The Gα subunit either activates or inhibits the enzyme adenylyl cyclase (or other signaling enzymes) to either increase or decrease the production of cAMP (or other signal transducers). The Gβγ subunit recruits G protein-coupled receptor kinases (GRKs), which then selectively phosphorylate serine and threonine residues in the receptor to promote the binding of the β-arrestins. Once internalized, the GPCRs, in vesicles termed as early (sorting) endosomes, are sorted and follow divergent pathways (Figure 1). The receptors are: (a) sorted into recycling endosomes for their return to the cell membrane (resensitization, recycling, and re-insertion); (b) accumulated in late endosomes and are passed on to the lysosomes for their subsequent degradation; or (c) transported initially to the perinuclear endosomes (trans-Golgi network [TGN]) and then to the late endosomes for eventual lysosomal degradation [17-20]. Additional proteolytic mechanisms, such as the proteasomes and cell-associated endopeptidases, are also implicated in mediating the down-regulation of certain GPCRs [21,22].

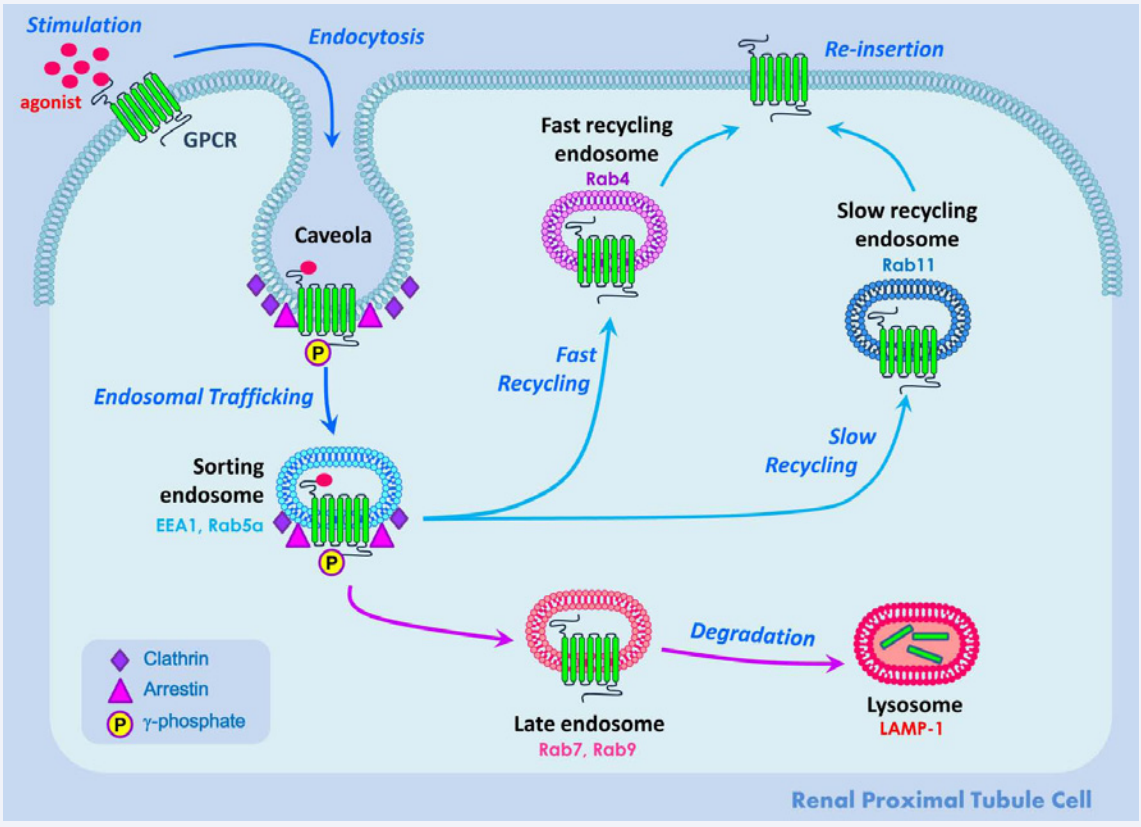

Figure 1 GPCR Trafficking GPCR internalization, sorting, and transport along the endosomal pathway are tightly controlled to ensure the accuracy of the intracellular signal and to limit the specificity and extent of the cellular response. The generally accepted paradigm for GPCR trafficking starts with the binding of a ligand to GPCRs followed by receptor desensitization through a change in receptor conformation, receptor dissociation from its G protein, modification via phosphorylation by G protein-coupled receptor kinases and binding of β–arrestins, and receptor endocytosis via caveolae or clathrin-coated pits. The receptors, in vesicles termed endosomes, are sorted and follow divergent pathways. The receptors are sorted into recycling endosomes for their return to the cell membrane (recycling and resensitization). This process may be fast (via the $Rab4^+$ early/fast recycling endosomes) or slow ($Rab11^+$ late/slow recycling endosomes). Alternatively, the receptors may accumulate in $Rab7^+$ and $Rab9^+$ late endosomes and are passed on to the $LAMP\text{-}1^+$ lysosomes for subsequent degradation, or they may be transported to the perinuclear endosomes (trans-Golgi network) and then to the late endosomes for eventual lysosomal degradation. Additional proteolytic mechanisms, such as proteasomes or cell-associated endopeptidases, are also implicated in down-regulating certain GPCRs. Perturbation of these steps may lead to receptor dysfunction, impaired homeostatic responses, and disease state, such as hypertension. Early endosome antigen 1 (EEA1), Lysosomal-associated membrane protein 1 (LAMP-1).

The signal transduction that follows GPCR occupation by its ligand is highly regulated to ensure the specificity of the cellular response, both temporally and spatially. GPCR-mediated signal transduction can be attenuated rapidly through a process known as desensitization or through a slower process of down-regulation after prolonged or repeated exposure to an agonist ligand. Rapid desensitization, or the waning of a receptor's responsiveness to the agonist with time, is carried out via at least two complementary mechanisms, i.e., the functional uncoupling of receptors from G proteins and the sequestration and internalization of cell surface receptors [23]. These processes occur within a time frame of seconds (uncoupling) to minutes (internalization) to hours (down-regulation).

SORTING NEXINS

The sorting nexin (SNX) family consists of a diverse group of cytoplasmic and membrane-associated proteins that are involved in various aspects of receptor endocytosis and trafficking through the endosomes [24,25]. To date, SNXs have been identified across phyla, from yeast to mammals, and currently 10 yeast and 33 mammalian SNXs have been identified [26]. All SNX family members contain the canonical 100-130-amino acid phox homology (PX) domain, which is responsible for binding to specific phosphoinositides [20,26]. Some of the SNXs also possess a C-terminal Bin/Amphiphysin/Rvs (BAR) domain that is important for both dimerization with a similar SNX and detection of membrane curvature, an important feature for proteins that monitor changes in membrane architecture [27,28]. SNXs play pivotal roles in the whole pathway of endocytic trafficking, including endocytosis, endosomal sorting, and endosomal signaling [24-26].

Increasing number of studies have shown that SNXs are associated with diseases in which endosomal function is adversely perturbed, such as cancer, Alzheimer's disease, Down's syndrome, and hypertension [29-34]. Specifically, recent studies have shed light into the molecular mechanisms by which SNXs regulate GPCRs, such as the dopamine receptors [29,30], β_1-adrenergic receptor [35], and other receptors like the transferrin receptor and transforming growth factor beta (TGF-β)receptor I [36,37]. In this paper, we review the physiological actions of SNXs in the regulation of GPCRs that are involved in the regulation of blood pressure and discuss the possible mechanisms by which hypertension develops when the function of SNXs is perturbed.

RENAL DOPAMINE RECEPTORS

The kidney plays a major role in the long-term control of blood pressure and is the major organ involved in the regulation of sodium homoeostasis [38-43]. Many studies have focused on the abnormal renal handling of salt in the pathogenesis of hypertension [39,40,44-47]. The sodium retention in hypertension results from an enhanced sodium transport *per se* and/or a failure to respond appropriately to signals that decrease sodium transport. Humans with polygenic essential hypertension have increased sodium transport in the renal proximal tubule and medullary thick ascending limb, which are regulated by numerous hormones and humoral factors, including the dopamine and angiotensin II, which exert their effects via GPCRs [48-51].

Dopamine, a well-known neurotransmitter in the central nervous system, has also been characterized as an important modulator of blood pressure, sodium balance, and renal and adrenal function, and is relevant to the pathogenesis and/or maintenance of hypertension [10,29,30,40,41,50,52-54]. Dopamine receptors are classified into the D_1- and D_2-like subtypes based on their structure and pharmacology. D_1-like receptors (D_1R and D_5R) couple to the stimulatory G protein $G\alpha_S$ and stimulate adenylyl cyclase activity, whereas D_2-like receptors (D_2R, D_3R, and D_4R) couple to the inhibitory G protein $G\alpha_i/G\alpha_o$ and inhibit adenylyl cyclase activity [41,50,55]. During conditions of moderate sodium balance, more than 50% of renal sodium excretion is regulated by the D_1-like receptors [41,50,56-59]. The D_1R increases cAMP production to a greater extent than the D_5R in renal proximal tubule cells [60]. However, the D_5R has a higher affinity for dopamine than the D_1R and exhibits constitutive activity [50,61]. Among the D_2-like dopamine receptors, the D_3R is the major receptor in the nephron and has 20 times higher affinity for dopamine than the D_2R.

All of the five dopamine receptor subtypes are expressed in the renal tubule and renal vasculature. Disruption of any of the dopamine receptor genes in mice results in hypertension, the pathogenesis of which is specific for each receptor subtype [10,50,61]. Disruption of the D_1R gene *Drd1* in mice results in the development of hypertension [62], while that of the D_2R gene *Drd2* leads to hypertension, in part, due to increased noradrenergic discharge [63]. The salt sensitivity of D_1R deficient mice remains to be determined but D_2R deficient mice may develop salt sensitivity [64]. Disruption of D_3R gene *Drd3* induces a renin-dependent form of hypertension accompanied by failure to excrete a sodium load [65] that may be dependent on the genetic background [66], while *Drd4* knockout mice exhibit hypertension, possibly through increased expression AT_1R [67] and also a failure to excrete a sodium load (unpublished data). Genetic ablation of the D_5R gene *Drd5* in mice also results in hypertension, presumably caused by increased activity of the sympathetic nervous system due to activation of oxytocin, V1 vasopressin, and non-N-methyl D-aspartate receptors in the central nervous system [68,69], although increased renal angiotensin II type I receptor (AT_1R) protein expression [21,40,70] may also play a significant role. D_5R-deficient mice are salt-sensitive and have increased oxidative stress [21,71].

SORTING NEXINS AND GPCRS

SNX1 and D_5R

There is now increasing evidence showing the importance of the D_5R in regulating blood pressure. The human D_5R gene *DRD5* locus at 4p15.1–16.1 is linked to essential hypertension [72,73]. Disruption of *Drd5* produces hypertension in (*Drd5*$^{-/-}$) mice and a high salt diet increases further the elevated blood pressure [21,40,71]. The renal expression of AT_1R and reactive oxygen species (ROS) are increased in *Drd5*$^{-/-}$mice [21,40,71,74]. Heydorn *et al* first reported the association of the C-terminal tail of D_5R, but not of the other dopamine receptors, with SNX1 [75].

SNX1 was originally identified as a protein that interacts with the cytoplasmic sequences of the epidermal growth factor receptor (EGFR), including the tyrosine kinase domain and the

adjacent lysosomal targeting signal [76,77]. SNX1 was the first mammalian sorting nexin to be characterized and is the ortholog of the yeast (vacuolar protein sorting) VPS5p, a protein involved in TGN trafficking. SNX1 can homodimerize or heterodimerize with SNX2 to form the membrane-targeting complex which, together with the cargo-recognition complex composed of Vps26, Vps29 and Vps35, forms the mammalian retromer, a protein complex that is involved in the retrograde trafficking between early endosomes and the TGN [78,79].

The human SNX1 consists of an N-terminal SNX region, a central PX domain, and a C-terminal BAR domain that binds to and/or induces membrane curvature via interactions with the lipid bilayer [80,81] (Figure 2A). It is distributed in both the plasma membrane and cytoplasm, where it exists in large complexes with other proteins [20]. Mutational analysis of SNX1 indicates that both an intact PX domain and an intact helical C-terminus are necessary for proper subcellular localization of SNX1 [82]. By way of "coincidence detection", the tandem PX and BAR domains efficiently direct SNX1 to membrane microdomains characterized by the presence of phosphoinositides and high curvature [81] (Figure 2B).

The role for SNX1 in endosome-to-lysosome trafficking was first proposed based on studies in which SNX1 overexpression enhances EGFR degradation and SNX1 deletion or point mutations inhibits EGFR degradation [76,82]. The endogenous SNX1 PX domain can specifically bind to specific phosphoinositides that are highly enriched in early endosomal membranes, such as phosphatidylinositol-3-phosphate and phosphatidylinositol-3,5-bisphosphate [83]. SNX1 is implicated in endosome-to-lysosome

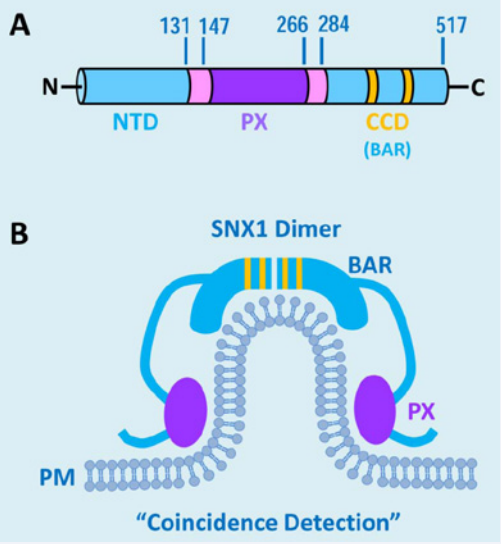

Figure 2 Functional domains of SNX1 and Coincidence Detection. A: Cartoon of the linear structure of SNX1. N-terminal domain (NTD), Phox homology domain (PX), coiled coil domains (CCD), and Bis-Amphyphysin-Rvs domain (BAR). The numbers indicate the amino acid residues that delineate the domains. The domains are not drawn to scale. **B:** Both the BAR and the PX domains are required for the simultaneous detection of membrane curvature and binding to phosphatidylinositol-3-phosphate and phosphatidylinositol-3,4,5-trisphosphate, respectively, by the functional SNX1 dimer in a process named "coincidence detection". PM = plasma membrane.

sorting of cell surface receptors, including several tyrosine kinase receptors (EGFR, PDGFR, insulin receptor, transferrin receptor, and long form of the leptin receptor), and serine-threonine kinase receptors (TGF-βtype I and II receptors) [84,85]. A protein-protein interaction screen using SNX1 and a library of C-terminal tails from 59 GPCRs revealed that SNX1 is capable of interacting with at least 10 distinct GPCRs *in vitro* [86]. SNX1 is essential for sorting protease-activated receptor-1 (PAR1) to a distinct lysosomal degradative pathway that does not require retromer activity [87,88].

We have recently reported that in human renal proximal tubule cells (hRPTCs) and human embryonic kidney cells heterologously expressing the human D_5R (HEK293-hD_5R), SNX1 is essential for the trafficking and function of the D_5R [30]. SNX1, but not its homolog SNX2, colocalizes and co-immunoprecipitates with the D_5R in these cells and in renal proximal tubules in the human kidney. RNAi-mediated, kidney-specific silencing of SNX1 results in the simultaneous impairment of three processes, i.e., (a) receptor internalization, (b) signal transduction, and (c) inhibition of AT_1R expression [30]. The failure of D_5R to internalize upon agonist stimulation prevents receptor resensitization, which is a prerequisite for sustained/long-term receptor response. Moreover, SNX1 depletion prevents the D_5R signal transduction by inhibiting the binding of GTP to $G\alpha_s$ in exchange for GDP to activate the D_5R-coupled $G\alpha_s$. This, in turn, leads to blunted cAMP response to agonist stimulation; $G\alpha_s$ cannot stimulate the enzyme adenylyl cyclase, which is needed to convert ATP to cAMP. Ultimately, SNX1 depletion leads to the failure of agonist-activated D_5R to inhibit sodium transport via Na^+,K^+-ATPase and the up-regulation of AT_1R expression [30]; D_5R negatively regulates the expression of AT_1R [21,40,70]. Silencing of renal *Snx1* results in increased AT_1R expression, elevated blood pressure, and impaired natriuretic response to D_1-like dopamine receptor agonist stimulation in two mouse strains, i.e., C57BL/6J and BALB/cJ mice[30]. We have proposed that SNX1 may initiate the sorting of the activated D_5R by tagging it for endocytosis and also serve as a scaffold or adaptor protein that facilitates the organization of the D_5R signaling complex [30].

SNX5 and D_1R

SNX5 is a 404-amino acid residue protein that contains a central PX domain and large C-terminal domain predicted to include a BAR domain [89]. SNX5 is distributed in both the plasma membrane and the cytoplasm where it partially colocalizes with the early endosomal marker EEA1 [90,91], the late endosomal marker Rab7 [92], and with the lysosomal marker LAMP-1, suggesting a potential role in protein degradation. Compared with other SNXs, the SNX5 PX domain is unique in both its structure and ligand binding [93] since it can bind phosphatidylinositol-3-phosphate and phosphatidylinositol-3,4-bisphosphate. This domain has been shown to be important in the ability of SNX5 to inhibit the degradation of EGFR [90].

SNX5 is expressed in many organs and cells. The highest levels of *SNX5* mRNA are found in skeletal muscle and kidney, as well as in the MoLT-4 (T cell leukemia), SW80 (colon adenocarcinoma), and A549 (lung carcinoma) cell lines. Very little *SNX5* mRNA is detected in the brain, placenta, lung, or liver, or in the HL60 (acute myelocytic leukemia), HeLa S3, and Raji (B cell leukemia) cell lines [94].

SNX5 was firstly identified by its interaction with the Fanconi anemia complementation group A protein [94]. Since then, SNX5 has been implicated in a myriad of cellular processes. SNX5 binds the clathrin heavy chain CHC22 and contributes to the specialization of CHC22 during myogenesis and muscle regeneration [95]. SNX5 colocalizes with the E3 ubiquitin ligase Mind bomb in early endosomal compartments and is important for its trafficking [96]. SNX5 also modulates the macropinocytic activity in primary mouse macrophages and influences the uptake and processing of soluble antigens [97,98]. SNX5 is necessary for the differentiation of alveolar epithelial type I cells. Disruption of *SNX5* gene can lead to neonatal mortality caused by respiratory failure due to impaired differentiation of alveolar epithelial type I cells [99].

SNX5 can interact with other sorting nexins, especially with SNX6 and SNX1. SNX5 and the closely related SNX6 are the functional equivalents of Vps17p, a component of the yeast retromer complex [100], and make up a protein complex that mediates the endosome-to-TGN retrograde transport of the mannose 6-phosphate receptor [101]. Both SNX5 and SNX6 colocalize with SNX1 in early endosomes [102]. Although it cannot homodimerize, SNX5 can associate with SNX1 through its C-terminal region [90] to form SNX5/SNX1 heterodimers [92]. This interaction allows the trans-regulation of SNX5 and SNX1 by one another. SNX1 can attenuate the inhibitory effect of SNX5 on EGFR degradation [90], while suppression of SNX5 and/or SNX6 can result in a significant loss of SNX1, an effect that seems to result from post-translational regulation of the SNX1 [100]. However, other studies showed that SNX5 does not always interact with SNX1. SNX5 is selectively recruited to membrane ruffles of activated cells and is not associated with SNX1 [91]. The absence of SNX1 has no effect on SNX5 localization and macropinosome biogenesis in macrophages from *SNX1* knockout mice [97]. A recent GWAS on a large cohort of European subjects revealed that the SNX5 single nucleotide polymorphism rs2328223 is associated increased LDL cholesterol levels [103].

We have recently identified the SNX5 as a novel binding partner for the C-terminus of D_1R [29]; its homolog SNX6 does not interact with D_1R. The D_1R is widely expressed in the kidney and plays a pivotal role in the regulation of sodium balance and maintenance of normal blood pressure [50,53]. Dopamine, via the D_1R, inhibits the activity of Na^+-K^+-ATPase in the basolateral membrane and the Na^+/H^+ exchanger isoform 3 (NHE3) in the apical membrane of renal proximal tubule cells [50,51,52,54,104,105]. Disruption of the D_1R gene *Drd1* in mice (*Drd1*$^{-/-}$) results in increased blood pressure [10,50,61].

SNX5 and D_1R colocalize in renal epithelial cells and in the human kidney (mainly in proximal tubules) and the mouse kidney (proximal tubules) and brain (caudate nuclei and putamen). Agonist stimulation of the D_1R enhances the colocalization with SNX5 in renal tubule cells. siRNA-mediated depletion of endogenous SNX5 in hRPTCs impairs receptor internalization, markedly delays recycling, and blunts the increase in cAMP production in response to agonist stimulation. SNX5 may also restrain the GRK4 from accessing the phosphorylation sites of agonist-activated D_1R, which may explain an earlier observation that the initial 20 min of D_1R desensitization in hRPTCs is not caused by GRK4 [102]; GRK4 plays an important role in the homologous desensitization and proper orientation of D_1R in the plasma membrane. In spontaneously hypertensive rats (SHR), kidney-restricted subcapsular infusion of *SNX5*-specific siRNA further increases the systolic and diastolic blood pressure, which is associated with a decrease in sodium excretion [29]. Depletion of renal SNX5 in the normotensive BALB/c mice results in the development of hypertension (unpublished data).

Other sorting nexins

A few other members of the sorting nexin family have been implicated to be involved in certain processes that are germane to blood pressure regulation and water and electrolyte homeostasis.

SNX3: SNX3 is a predominantly cytosolic protein [85] that is highly expressed in peripheral leukocytes, spleen, heart, and skeletal muscle, and much less in the kidney. Disruption of SNX3 has been described in a patient with microcephaly, microphthalmia, ectrodactyly, prognathism (MMEP) phenotype [106], but not in others [107]. It facilitates the recycling of transferrin receptor and is required for the proper delivery of iron to erythroid progenitors; silencing of SNX3 results in anemia and hemoglobin defects in vertebrates due to impaired transferrin-mediated iron uptake and its accumulation in early endosomes [36].

The amiloride-sensitive epithelial Na^+ channel (ENaC) in the distal nephron is involved in regulating Na^+ levels in the extracellular fluid compartment. The hormone vasopressin regulates ENaC by promoting its translocation to the plasma membrane and regulating its expression levels. Boulkroun *et al* have reported that vasopressin increases the expression of ubiquitin-specific protease 10 (USP10), which deubiquitinylates and stabilizes SNX3 to increase the channel's cell surface expression [108]. It has been suggested that USP10 and SNX3 act together to promote the export of ENaC via the secretory pathway to the plasma membrane, Alternatively, SNX3 may act as an adaptor for the channel and may engender its recycling via the retromer complex [108].

SNX19: SNX19 contains a central PX domain and non-BAR domains at the C-terminal region and its function is not clear. A few studies have shown that SNX19 is related to several diseases, including acute myeloid leukemia, thyroid tumors, and osteoarthritis [109,110,111]. However, SNX19 can interact with IA-2, a major autoantigen in type 1 diabetes and a regulator of insulin secretion [112]. Moreover, a variant of the SNX19 gene is associated with an increased risk of coronary heart disease [113].

SNX25: The full length SNX25 contains a typical PX domain, a PX-associated (PXA) domain, and a regulator of G protein Signaling (RGS) domain. The physiological role of SNX25 is unknown, although it is expressed in several tissues, including the brain and kidney [114]. SNX25 interacts with the TGF-β receptors and enhances the degradation of TGF-β receptor I via a clathrin-dependent endocytosis and endosome/lysosome degradation pathway [37]. The up-regulation of SNX25 is involved in the development of temporal lobe epilepsy [115]. SNX25 over-expression enhances the expression levels of both D_1R and D_2R, causes an increase in both D_1 and D_2 receptor-mediated signaling, and perturbs both endocytosis and recycling of the D_2R, but does

not affect D_1R desensitization [116]. Depletion of endogenous SNX25 using siRNA causes a subsequent decrease in the D_1R and D_2R expression [114]. These observations suggest that SNX25 plays a role in the D_1R and D_2R trafficking through intracellular membrane compartments and regulates both receptor expression and signaling.

SNX27: SNX27 contains several domains, i.e., the PX domain, Ras association (RA) domain, and the postsynaptic density protein-95/Discs-large, Zona-occludens-1 (PDZ) domain, which functions as a scaffold to organize various proteins. It is primarily localized to the cytoplasm and partly to the plasma membrane. It is particularly enriched in vesicles of the recycling endocytic pathway, where it colocalizes with Rab11 and the transferrin receptors. Its vesicular localization is dependent on its PX domain. SNX27 is implicated in the molecular etiology of Down's syndrome through its interaction with the ionotropic glutamate receptors (NMDA and AMPA receptors). *Snx27*$^{-/-}$ mice have severe neuronal deficits in the hippocampus and the cortex and exhibit defects in synaptic function, learning, and memory, and decreased NMDA and AMPA receptors [31], as well as growth retardation [117]. SNX27 also mediates the efficient recycling of the β_1-adrenergic receptor (β_1-AR) in monkey kidney-derived COS-1 cells [35] by linking to the retromer [118]. β_1-AR, the major subtype of adrenoceptor in cardiomyocytes, plays an important role in regulating cardiac output, an important determinant for blood pressure.

SUMMARY AND PERSPECTIVES

GPCRs are important for the regulation of blood pressure. The past few years have seen a rapidly growing appreciation of the importance of the sorting nexins in the biology and pathology of certain GPCRs, including the renal dopamine receptors. Recent studies have begun to highlight the pivotal roles of sorting nexins in the regulation of GPCR trafficking and signal transduction, and by extension, on water and electrolyte and blood pressure homeostasis. Further research using innovative silencing techniques and appropriate animal models will certainly lead to exciting advances in our understanding of the physiological functions of the sorting nexins and may demonstrate the sorting nexins as novel and crucial determinants for the pathogenesis of essential hypertension.

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