COMMENTARY

Histamine provides an original vista on cardiorenal syndrome

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Cardiac and renal dysfunction frequently go hand in hand in hospitalized patients, and epidemiological studies have suggested an inverse correlation between renal function and cardiovascular morbidity and mortality. This relationship exists regardless of what organ is first affected (1). It reflects upon a complex interplay between heart and kidneys, with dysfunction of one organ often impairing the function of the other. The causal association between chronic kidney disease (CKD) and cardiovascular risk was initially discussed by Bright in 1836. The notion of passive renal congestion arising from cardiac dysfunction was coined "rein cardiaque" by French pathologist Frédéric Justin Collet in 1903, while "cardiorenal syndrome" (CRS) was introduced in the 1940s to describe the bidirectional interactions between heart and kidneys (2).

Kidney injury will stress both the heart and the circulatory system and cardiac dysfunction can, reciprocally, inflict injury on the kidney. Determinants of CRS include hemodynamic parameters such as central venous pressure, extracellular fluid volume, cardiac output, arterial pressure, pulmonary hypertension, and edema. Reduced cardiac performance ultimately limits blood perfusion of all organs including the kidneys and thereby contributes to renal injury. Altered tissue perfusion with disproportionate effects on the kidney leads to overactivation of both the sympathetic nervous and renin–angiotensin systems (RAS) reported in CRS. Inadequate renal extracellular fluid handling may have deleterious effects on the heart with an ensuing increase in volume preload and afterload and thus myocardial oxygen demand and vasoconstriction—including of coronary vessels—and an increase in inflammation, reactive oxygen species, and fibrosis (3).

Clinical and epidemiological studies support a causal relationship between CKD, cardiovascular risk, and heart failure (4, 5). In patients with congestive heart failure, a moderate elevation in serum creatinine levels (e.g., by 26.5 μmol/L [0.3 mg/dL]) will significantly increase cardiovascular mortality (6). Thus, even subtle alterations in renal function may have substantial impact on a stressed heart. This is illustrated by the fact that more than 50% of all patients presenting with CKD succumb to cardiovascular disease, at rates 10- to 20-fold higher than an age-matched non-CKD population. The processes by which primary kidney disease increases cardiovascular risk are not well defined.

Thus, despite the magnitude of the public health problem of CRS, the mechanisms underlying this "cardiorenal syndrome" or "renocardiac syndrome" are incompletely understood and effective intervention unavailable. The development of novel animal models that recapitulate more closely the clinical CRS and that might help explore the molecular basis of this condition further would be of great benefit.

In PNAS, Noguchi et al. (7) characterize a recently developed mouse model of CRS (8) that combines a reduction in renal functional reserve induced by unilateral nephrectomy with a high-salt diet and chronic infusion of angiotensin II, together mimicking the overactivation of the RAS described in CRS. Although this "ANS" model was previously described as a mouse model of hypertension-induced heart failure, Noguchi et al. (7) demonstrate its broader utility by providing mechanistic insight into the kidney–heart interplay in the context of hypertension. They describe that the model induces a CRS with heart failure and fibrosis associated with features of acute kidney injury (AKI) and a gradual increase in circulating histamine.

Histamine is exclusively synthesized by catalytic decarboxylation of histidine by L-histidine decarboxylase (HDC, encoded by *Hdc*) (EC 4.1.1.22). *Hdc* expression is regulated by lineage-specific transcription factors and has not been reported to respond to angiotensin II. Noguchi et al. (7) uncover an overall protective role for histamine in the ANS model, as HDC-deficient mice display accentuated cardiorenal damage with increased cardiac hypertrophy, decreased left ventricular fractional shortening, and exaggerated deterioration of the renal function as typified by a lower glomerular filtration rate and increased albuminuria compared to

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their wild-type counterparts. Importantly, heart and renal failure occurred at similar levels of high blood pressure, suggesting that histamine deficiency potentiated injury independent of systemic hemodynamics.

The Quest for Histamine Source

The source of elevated plasma histamine in experimental CRS remains to be identified. Classic main sources of histamine include mast cells, basophils, enterochromaffin-like cells, and neurons. Histamine is synthesized in the cytosol and transported into cellular granules, where it binds to heparin in the granule matrix and is released upon cell activation. While analysis of whole blood of healthy individuals suggests that activation of basophils and eosinophils can prominently contribute histamine to plasma, activation of perivascular mast cells can yield a further increase in circulating levels.

In order to determine the source of histamine in CRS, Noguchi et al. (7) explored mast cell and basophil infiltration into heart and kidneys. Assessment of the enrichment of mast cell- and basophil-specific gene expression and mast cell infiltration both proved inconclusive, which may point either to a different cell type or to paracrine effects of histamine released from circulating basophils or perivascular mast cells in distal organs. Importantly, in the absence of specific granules for storage, other myeloid cells distinct from mature mast cells or basophils as well as nonmyeloid cells display a high HDC enzymatic activity and low intracellular levels of histamine, which may suggest secretion immediately after synthesis (9). HDC activity in the aorta and in the kidney as reported in diabetes, hypertension, and in response to high shear stress may be relevant to CRS (10, 11). Histamine concentrations measured in the mouse kidney are well above circulating levels despite a scarcity of resident mast cells (11). Glomeruli produce large amounts of histamine, and HDC is expressed in proximal tubule cells of mice as well as in the human kidney. Renal HDC activity is high in diabetic rats and is also markedly up-regulated in the mouse kidney during pregnancy (11).

Exploring H3-Mediated Protection in CRS

Histamine exerts its actions through four G protein-coupled receptors, H1R, H2R, H3R, and H4R. Noguchi et al. (7) evaluated the effect of H1, H2, and H3 antagonists on the development of experimental CRS. Blockade of H1 or H2 had no impact on the deterioration of cardiac and renal function in the CRS model. By contrast, the H3 antagonist carcinine mimicked the effect of global histamine deficiency in HDC-deficient mice as shown by exaggeration of cardiac dysfunction and renal tubular injury markers, assigning an important function to H3. Conversely, the histamine H3-specific agonist immethridine prevented kidney inflammation and injury and left-ventricle fibrosis and dysfunction. Beneficial effects on organ damage were independent of high blood pressure, again suggesting a local effect of histamine on tissue injury mechanisms. These findings assign an important protective function to H3 in this setting and raise questions about the cellular targets of histamine and effectors of H3-mediated cardio-renoprotection in both heart and kidney.

Previous reports indicated that H3 activation affords cardioprotection by preventing excessive norepinephrine release in experimental myocardial ischemia (MI). Pivotal to this action is the inhibition of the neuronal Na^+/H^+ exchanger (NHE) by H3 agonism. Relevant to the ANS model of CRS, angiotensin II stimulates NHE via angiotensin II type 1 (AT_1) receptors, facilitating norepinephrine release. Seminal work by Levi and coworkers (12) suggests that H3-mediated NHE inhibition in ischemia/reperfusion not only opposes the angiotensin II-induced stimulation of NHE in cardiac sympathetic neurons but also down-regulates AT_1 expression. Similarly, H3 agonism attenuated isoproterenol-induced RAS and sympathetic nervous system overactivity in MI of rats (13). Another study had demonstrated that histamine inhibited cardiac fibroblast proliferation and that HDC-deficient mice exhibit worse cardiac fibrotic remodeling and dysfunction following MI (14). The relevance of post-MI condition or isoproterenol-induced toxicity to CRS remains to be determined.

In addition to a potential direct protective role in the heart, activation of the H3 receptor may have conferred a general improvement of cardiorenal perfusion. H3 agonism was indeed shown to promote endothelium-dependent vasodilation through release of NO, prostacyclin, and endothelium-derived hyperpolarizing factors (15).

In PNAS, Noguchi et al. characterize a recently developed mouse model of CRS that combines a reduction in renal functional reserve induced by unilateral nephrectomy with a high-salt diet and chronic infusion of angiotensin II, together mimicking the overactivation of the RAS described in CRS.

H3 is expressed at high levels on histaminergic neurons, particularly in the basal ganglia, cortex, and hippocampus. The possibility that H3 agonism influences the neural command of renal and cardiac physiology is intriguing. Lateral cerebral ventricular injection of histamine in anesthetized rats demonstrated that low dose suppresses renal sympathetic nerve activity with corresponding effects on blood pressure (16). Inhibitory effects of low-dose histamine were eliminated by lateral cerebral ventricular preinjection of an H3 antagonist. These effects suggest that central nervous system actions of the histaminergic system can influence renal noradrenergic neurotransmission. Further data suggest that H3 receptors, possibly located on renal noradrenergic nerve endings, may serve as inhibitory modulators of renal noradrenergic neurotransmission, since administration of an H3 antagonist evoked an antidiuretic effect and increased the noradrenaline overflow rate (17). Thus, both the renal noradrenergic activity and the modulation of sodium and fluid handling by the kidney are affected by the histaminergic system with an H3 component. Although neither HDC deficiency nor pharmacological H3 modulation impacted blood pressure elevation despite differences in CRS development, H3-dependent modulation of intrarenal microcirculation is not ruled out. The prevention of glomerular enlargement and albuminuria in ANS/CRS mice reported by Noguchi et al. (7) may indeed suggest an alleviation of glomerular capillary pressure by H3 agonism.

Outside the acute setting, several studies have identified the common coexistence of chronic heart disease and CKD. In many patients, it is not possible to determine which affection is primary (5). The analysis of the kinetics of the cardiorenal failure may help position the histamine–H3 cascade and inform this interplay. Noguchi et al. (7) demonstrate that histamine first limits kidney inflammation and injury and subsequently heart failure. ANS mice displayed renal dysfunction 1 wk after disease induction, while cardiac affection was evident only after 4 wk. According to the most commonly used classification of CRS (2), which breaks it

down into five categories on the basis of the direction and chronicity of interaction between the heart and kidneys, the ANS model used by Noguchi et al. (7) is a type 3 CRS with AKI producing rapid functional changes in the heart. The ANS model of CRS may be considered a model of type 3 CRS transitioning to type 4 according to the timing when these mice are analyzed.

Noguchi et al. (7) reveal that reduced but undetectable alteration of kidney function, as exemplified by unilateral nephrectomy, suffices to provoke kidney inflammation and heart failure in a condition of volume overload stress. As such a combination of disease-sensitizing factors may be seen in patients, this underscores the need to develop strategies to detect early mild renal defect putting patients at risk for developing CRS. Notably, the ANS model displayed an early rise in plasma histamine and urinary markers of kidney injury such as NGAL/lipocalin 2 and beta2 microglobulin whose levels can be reliably and cost-effectively measured.

This study adds histamine to the neuroinflammatory systems that play an important modulating role in physiopathology of type 3 CRS. How histamine production is triggered and where protective H3 signaling is acting remain to be understood. Nonetheless, this study provides insight into cardiorenal pathophysiology and characterizes a tool for developing new therapeutic strategies for CRS. It may serve as a basis for repositioning H3 agonists to inflammatory renal and cardiac diseases.

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