

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Histamine in the kidneys: what is its role in renal pathophysiology?

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1721866> since 2020-08-25T23:48:15Z

Published version:

DOI:10.1111/bph.14619

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This is the author's final version of the contribution published as:

Cristina Grange, Maura Gurrieri, Roberta Verta, Roberto Fantozzi, Alessandro Pini, Arianna Carolina Rosa. Histamine in the kidneys: what is its role in renal pathophysiology? *British Journal Of Pharmacology*, 2019, 1-13, 10.1111/bph.14619

The publisher's version is available at:

[http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1476-5381](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1476-5381)

When citing, please refer to the published version.

Link to this full text:

<https://bpspubs.onlinelibrary.wiley.com/doi/epdf/10.1111/bph.14619>

Histamine in the kidneys: what is its role in renal pathophysiology?

Running Title: Histamine, kidneys and renal disease

Cristina Grange*¹, Maura Gurrieri*², Roberta Verta², Roberto Fantozzi², Alessandro Pini³ and Arianna Carolina Rosa²

*Authors contributed equally to this work

¹Department of Medical Sciences, University of Turin, C.So Dogliotti 14, 10126 Turin, Italy;

²Department of Scienza e Tecnologia del Farmaco, University of Turin, Via P. Giuria 9, 10125,

Turin, Italy; ³Department of Experimental and Clinical Medicine, University of Florence, Viale Pieraccini 6, 50139, Florence, Italy

Corresponding author: Arianna Carolina Rosa, PhD

Department of Scienza e Tecnologia del Farmaco,

Università di Torino,

Via P. Giuria 9, 10125, Turin, Italy

Phone: +390116707152

e-mail: ariannacarolina.rosa@unito.it

Author's Contribution to the Manuscript

ACR and CG conceived and designed the study; ACR, CG and MG drafted the article; ACR, RF and AP critically revised the article for important intellectual content; MG and RV performed literature searches.

Word count 5530

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org> , the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017).

Acknowledgements

We acknowledge Dr. Dale Lawson for his English language revision and editorial assistance, and Sara Borgia for her moral support. This work was supported by funds from the Università degli Studi di Torino, Ricerca Locale Ex 60% 2016-2017 provided to ACR.

Conflict of Interest Statement

None

Abstract

Starting from the histamine role in the renal haemodynamic, over time, spare evidence suggested a wider range of action on renal function and renewed the interest on the pathophysiological role of histamine in the kidney. This review intends to provide an up-to-date focus on this topic. According to the intrarenal production of histamine and the renal presence of its receptors, the histaminergic machinery appears to be well suited. The distribution of histamine receptors supports their differential effects but do not exclude the redundancy of H₁ and H₂ receptors in renal haemodynamics, the complementary role of H₁ and H₄ receptors in renal filtration and reabsorption, and the dichotomy between local and neuronal H₁ and H₃ receptors. Experimental models of renal diseases rise the hypothesis of new therapeutic approaches histamine based. A complete elucidation of the influence of the renal regulation by histamine is still ongoing.

Keywords: renal pathophysiology, histamine, histamine receptors, kidneys, renal disease

Abbreviations: alpha-HH = alpha-hydrazinohistidine; AQP = aquaporin; DAO = diaminoxidase; GBM = glomerular basement membrane; GFR = glomerular filtration rate; HDC = histidine decarboxylase; HNMT = histamine-N-methyltransferase; K_f = ultrafiltration coefficient; OCT = organic cation transporter; PA = puromycin aminoglycoside; TGF = transforming growth factor; ZO = zonula occludens

Douglas (1971) wrote “*the core of the matter is that, while the autacoids possess an astonishingly wide range of pharmacological activities [...], there are comparatively few instances where a physiological role can be stated with assurance*”. Compared to its pleiotropic effects, the therapeutic strategies based on histamine targeting are very few: H₁ receptor antihistamines for the treatment of allergy (Simons and Simons, 2011), H₂ receptor antagonists for peptic ulcer (Singh *et al.*, 2018) and the H₃ receptor inverse agonist pitolisant for narcolepsy (Kollb-Sielecka *et al.*, 2017).

Other effects exerted by histamine cannot be translated to therapeutic approaches till the contribute of the amine to a specific pathophysiological event is not functionally weighed. Therefore, looking at the kidney, the goal is to define the role of the amine in the renal pathophysiology. The evidence for histamine playing a role in this organ has been scanty investigated over the years. In renal plethysmographic studies (Dale and Laidlaw, 1910; Dale and Richards, 1918) histamine injection evoked the renal arteriolar constriction. Renal arteriolar constriction triggers the alteration of the glomerular hydrostatic pressure and causes the reduction of the renal blood flow. These events culminate in the modulation of the glomerular filtration rate (GFR): reduced by renal afferent arteriolar constriction and increased by renal efferent arteriolar constriction (Dalal and Sehdev, 2018). The changes induced by the amine on the renal circulation could account for the drop in both urea and creatinine clearance observed after histamine injections in human subjects with various cardiovascular and renal pathologies (Bjering, 1937). These acute effects were observed after a high loading dose of histamine (1 mg s.c.) and were accompanied by a simultaneous fall in blood pressure, therefore might be due to a systemic vascular event elicited by the amine. However, Bjering (1937) stressed that it is reasonable to assume that histamine affects both the glomerular and tubular function. Indeed, an increase in protein concentration causes the rise of the glomerular capillary oncotic pressure with a consequent decrease in GFR (Dalal and Sehdev, 2018). It was noted that in dogs histamine injection was able to acutely induced albuminuria (1 day after histamine load), and degenerative tubules changes after 7 days (Bjering, 1937). Anyway, since that time, histamine's contribution to renal function was always linked to its vasoactive properties, relegating histamine to

the sole role of haemodynamic regulation (Pini *et al.*, 2016b). Some time later, between the '70s-'80s, the possibility that histamine played a role in renal immune-mediated diseases was explored, but no conclusive data was provided. In the last decade the discovery of the presence of all the known histamine receptors [H_{1-4} receptors; as designated by International Union of Pharmacology – IUPHAR; Alexander *et al.*, 2017)] on residential renal cells renewed the interest for the possible role of histamine in renal function. Therefore, this review intends to provide an up-to-date focus on data supporting the possible pathophysiological role of histamine in the mammalian kidney.

The histaminergic machinery in the kidneys

The presence of the histamine metabolic enzymes diaminoxidase (DAO, whose metabolic product is the imidazole-4-acetaldehyde) (Wolvekamp and de Bruin, 1994) and histamine-N-methyltransferase (HNMT, producing the N-methyl-histamine) (Brown *et al.*, 1959) in the cytoplasm of renal residential cells highlights that histamine is handled by the kidney, but the source of the amine in this organ has been the subject of some discussion. Histamine enters the intracellular system through active transport by the organic cation transporter (OCT)-2 (Ogasawara *et al.*, 2006), expressed exclusively in renal tissue (Aoki *et al.*, 2008). However, the hypothesis that histamine in the kidney could derive only from the circulatory system may be retained unlikely. A first observation in keeping with this theory is the ipsilateral histamine synthesis following the infusion of L-histidine, the aminoacid precursor of histamine, into the renal arteries of dogs (Lindell and Schayer, 1958). Nevertheless, the histidine decarboxylase (HDC) enzyme, which is responsible for histamine synthesis, was purified from the kidneys of thyroxine-treated mice in 1986 (Martin and Bishop, 1986). A significant increase in histamine content in the human glomerular suspension was observed when the isolated glomeruli and tubules were incubated with L-histidine 1mM but not with D-histidine 1mM, used as negative control. The challenge of isolated glomeruli with the HDC inhibitor brocresine blocked the accumulation of histamine evoked by L-histidine (Sedor and Abboud, 1984). It could be questioned that brocresine is not selective to HDC, being able to inhibit also the nonspecific aromatic L-amino acid decarboxylase (Hakanson and Liedberg, 1972), as well as to affect histamine catabolism (Binder and Sewing, 1973).

However, a demonstration of the presence of specific HDC enzyme in the glomeruli came already from Heald and Hollis (1976) who purified a glomerular enzyme with an apparent Michaelis-Menten constant (K_m) for histidine of 240 μ M and an optimal pH of 6.2 for histidine 10 mM. On the contrary, the nonspecific aromatic L-amino acid decarboxylase has a higher K_m (100-10 mM) and an optimum pH independent from histidine concentration.

The observation by Sedor and Abboud (1984) was the first clear evidence of the production and presence of histamine in the kidneys despite the absence of mast cells, the professional source of histamine, in human glomeruli (Li *et al.*, 2007). Mast cells have been found to be present in very low constitutive number in the whole kidney (Li *et al.*, 2007). Despite the number of mast cells, kidneys have been reported to contain a concentration of histamine ranging from about 2 pmol/mg organ weight (5- to 9-week-old mice) to about 5 pmol/mg organ weight (10- to 14-week-old mice) (Zimmermann *et al.*, 2011). Notably, these values are comparable with previously reported amounts (Burtin *et al.*, 1982; Sedor and Abboud, 1984) and are far above circulating levels in humans (< 10 nM). This content was paralleled by levels of the histamine metabolite, N-methylhistamine, in urine (Zimmermann *et al.*, 2011). Collectively, this evidence points out the possibility of a local intrarenal production and secretion of histamine. The wide distribution of HDC enzyme other than in mast cells, is now well recognised. It is ubiquitously expressed in the proximal tubules of both mice and humans, both in foetuses and adults (Morgan *et al.*, 2006). Notably, the enzyme expression is up-regulated in physiological/adaptive processes. Indeed, HDC is over-expressed in the kidneys of pregnant mice, especially in the superficial cortical zone. These findings suggest that intrarenal produced histamine may increase renal blood flow and recruit superficial cortical nephrons during pregnancy (Morgan *et al.*, 2006). However, histamine is also known to exert mitogenic effects, thus potentially contributing to the lengthening of the proximal tubule (Morgan *et al.*, 2006).

Whereas the presence of intrarenal produced histamine in the kidneys is now established and documented, which histamine receptor is present and where it is located is still a matter for debate. Indeed, the immunological detection of histamine receptors is biased by antibodies, whose specificity

is often questioned. H₁ receptor and H₂ receptor expression on renal vessels has long been established (Banks *et al.*, 1978). More recently, an *in vitro* pharmacological approach performed on both primary and immortalised selected renal cell types from different mammals (Table 1), allowed to identify in the nephron and collecting ducts not only the H₁ receptor and H₂ receptor, but also the more recently discovered H₃ receptor and H₄ receptor (Rosa *et al.*, 2013; Pini *et al.*, 2015; Veglia *et al.*, 2015; Veglia *et al.*, 2016). A differential distribution of histamine receptors can be observed in the nephron and collecting duct (Figure 1 and Table 1). H₁ receptor is the most prevalent, as it is localised on both the glomerular and tubular levels. It was described in the glomerulus for the first time in 1985, when the H₁ receptor antagonist diphenhydramine (100 µM) suppressed the contractile effects evoked by histamine (5 µM to 100 µM) in a primary culture of mesangial cells from Sprague-Dewley rats (Sedor and Abboud, 1985). Only H₁ receptor and H₂ receptor were known at that time, and the presence of H₂ receptor was demonstrated in the same cells via the measurement of the accumulation of the second messenger cAMP following histamine challenge. The H₂ receptor antagonists cimetidine (Sedor and Abboud, 1985) and metiamide (Torres *et al.*, 1978) blunted histamine-induced second messenger production. More recently, a better insight of glomerular histamine receptor presence was provided. Four different cell types can be distinguished within the glomerulus: glomerular endothelial cells, podocytes, mesangial cells and parietal epithelial cells. Podocytes are the most differentiated of these cells and are a crucial component of the glomerular filtration barrier. H₁ receptor expression on human immortalised podocytes was demonstrated by complementary immunohistochemical and pharmacological approaches (Veglia *et al.*, 2016). The confocal analysis revealed that in human podocytes only H₁ receptor is localised on the cell membrane. H₁ receptor expression was confirmed by the saturation binding analysis (Veglia *et al.*, 2016). Moreover, histamine challenge evoked a sigmoidal dose-dependent increase in IP₃, the second messenger involved in the H₁ receptor signaling pathway, but not in cAMP, downstream signal of the histamine receptors (Veglia *et al.*, 2016). The presence of H₁ receptor has also been demonstrated in both the proximal and distal tubules with a similar experimental approach using human primary and immortalised tubular epithelial cells

(TECs) from the renal cortex and the proximal tubular epithelial cell line HK-2 (Veglia *et al.*, 2015). This study demonstrated also that H₂ receptor coexists with H₁ receptor in the distal tubules (Veglia *et al.*, 2015). Even the H₄ receptor and H₃ receptor subtypes have been found in the kidneys. By immunolabeling and gene expression analyses, the presence of H₄ receptor has been revealed. H₄ receptor shows partial species-dependent distribution (Table 1), with rats expressing it mostly in the ascending limb of Henlé's loop (Rosa *et al.*, 2013), and humans and mice mostly on the proximal tubule (Veglia *et al.*, 2015; Pini *et al.*, 2018). The interspecies variability is in line with previous data on H₄ receptor expression (Liu *et al.*, 2001).

The data by immunoassay were confirmed at least in humans by the functional assay evaluating cAMP accumulation following histamine challenge alone or with histamine receptor selective antagonists (Veglia *et al.*, 2015). H₃ receptor has surprisingly been found on the principal cells of the collecting duct, both in humans (Veglia *et al.*, 2015) and in rats (Pini *et al.*, 2015). Again the data were obtained by both immunodetection and gene expression in both *ex-vivo* and *in-vitro* studies (Pini *et al.*, 2015; Veglia *et al.*, 2015) and were confirmed *in vitro* on human renal cells (Veglia *et al.*, 2015), as described above.

The role of histamine in the kidneys

Despite high amount of histamine in kidneys, only few independent data provide evidence of the role that histamine plays in renal haemodynamic and, even less, suggest that it has effects far beyond its vasoactive properties. The data currently available on the role of histamine on renal function do not allow a clear differentiation between the physiological and the pathophysiological effects of histamine and its role in renal diseases. Similarly, is not possible to really discriminate between the effect of the extrarenal and the intrarenal produced histamine. Indeed, the possible role of the amine on kidney function mostly derives from studies in which histamine has been exogenously administered.

Figure 2 summarises the proposed effects of histamine on renal function and the potential contribution of the receptor subtypes. The relative contribution is mostly due to the localisation of the histamine

receptors on different renal cell types (Figure 1) and is consistent with the pharmacological characterisation of the histaminergic system in various mammals. Changes in renal circulation have been observed both in normotensive and hypertensive subjects without any history of renal disease challenged with histamine s.c. in the 0.3-0.5 mg range. Both groups showed an elevation in filtration fraction and a reduction in renal plasma flow that were ascribed to the efferent arteriolar constriction, observed in the majority of them (Reubi and Futcher, 1949). On the other side, a higher dose of histamine (1 mg s.c.) caused a fall in blood pressure and a drop in creatinine and urea clearance (Bjering, 1937). It is known that renal blood flow autoregulation is a defensive mechanism that protects the kidney from elevation in arterial pressure and that allows the kidney to maintain a relatively constant GFR (Burke *et al.*, 2014). The experimental data are in favour of an active role of at least the extrarenal histamine in regulating GFR, eventually as a possible effector of the renal blood flow autoregulation via H₁ receptor (Banks *et al.*, 1984). Indeed, after the intrarenal infusion of chlorpheniramine 10⁻⁵ mol/min or other H₁ receptor antagonists/inverse agonists, with a variety of chemical structures (terfenadine, diphenhydramine and mepyramine), attenuated the hyperaemia evoked by aortic clamping. Furthermore, a drop in the GFR was measured in parallel (Banks *et al.*, 1984). A similar effect was observed when H₁ receptor antagonists were used to counteract histamine infusion-induced renal vasodilation (Banks *et al.*, 1978). Interestingly, this study, in accordance with the one by Campbell and Itskovitz (1976) on isolated blood-perfused canine kidneys, failed to demonstrate the involvement of H₂ receptor. However, other reports have published opposing results, in which ranitidine (Laight *et al.*, 1995) and cimetidine, but not tripelennamine (Radke *et al.*, 1985), blunted histamine-induced vasodilation.

Despite contrasting evidence was provided for the relative contribute of H₁ receptor and H₂ receptor in vasodilation, H₂ receptor has been associated with histamine-induced renin release. Histamine and dimaprit, at that time thought to be an H₂ receptor agonist, induced a significant increase in renin release in dogs, while the H₁ receptor agonist 2-pyridylethylamine had no effect (Gerber and Nies, 1983). Similar conclusions were reached by *ex vivo* studies on isolated perfused rat kidneys. In this

model histamine induced renin release in a concentration range 0.5-10 μM , and vasodilation appears only at 100 μM . The H_2 receptor antagonist ranitidine inhibited the renin release induced by histamine. In this study the H_1 receptor agonist 2-pyridylethylamine demonstrated a low stimulatory activity, but only at 10 μM , a dose at which partial H_2 receptor agonism was shown (Schwertschlag and Hackenthal, 1982). cAMP accumulation, evoked by H_2 receptor stimulation in cultured rat mesangial cells (Sedor and Abboud, 1984), was hypothesised to be the underlying mechanism. Indeed, any increase in cAMP in renin-secreting cells, such as juxtaglomerular cells, has been reported to stimulate renin secretion (Castrop *et al.*, 2010). Therefore, on the basis of the role of the renin-angiotensin-system in vasoconstriction, histamine can contribute to the efferent arteriolar constriction, at least via the H_2 receptor-renin axis.

Due to the role of the sympathetic nerve activity in renal haemodynamic, the noradrenergic transmission was the other mediator of vasoconstriction for which an interplay with histamine has been investigated. The possibility that indirect effects could involve the noradrenergic transmission was discounted after negative results were obtained in an atenolol 1 μM infusion test. However, the histaminergic system may be involved in the regulation of renal noradrenergic neurotransmission, like in the uterus (Montesino *et al.*, 1995). Lateral cerebral ventricular injection of histamine in anaesthetised rats demonstrated opposite effects on renal sympathetic nerve activity, in a dose-dependent manner: 100 nM suppressed and 100 mM stimulated the renal sympathetic nerve activity (Tanida *et al.*, 2007). These effects suggest that the renal noradrenergic neurotransmission can be affected by the central histaminergic system. H_1 receptor and H_3 receptor were both implicated, with H_1 receptor involved in the high-dose effects of histamine, and the H_3 receptor involved in the low-dose effects, consistently with the differential affinity of the two receptors for the natural ligand [histamine $p\text{K}_i$ reported for H_1 receptor is 4.7 – 5.9 and for H_3 receptor is 7.8 - 8.3 (Alexander *et al.*, 2017)]. Nevertheless, in anaesthetised dogs, following renal nerve stimulation (0.5–2.0 Hz) a decrease in urine flow and urinary sodium excretion and an increase in norepinephrine overflow rate were observed. These effects were reduced by intravenous infusion of the H_3 receptor agonist (R)-

alpha-methylhistamine (1 µg/kg/min), while the administration of the H₃ receptor antagonist thioperamide (5 µg/kg/min) evoked an antidiuretic effect and increased the norepinephrine overflow rate (Yamasaki *et al.*, 2001).

These effects were ascribed to a possible localisation of the H₃ receptor on renal noradrenergic nerve endings. However, data obtained from rats and humans indicated that H₃ receptors are present in the resident epithelial cells of the collecting duct and that they are colocalised with the vasopressin water channel aquaporin (AQP)-2 (Pini *et al.*, 2015; Veglia *et al.*, 2015). This localisation renews interest in histamine's effect on diuresis. A role for central histamine in regulating diuresis has, in fact, been postulated. Histamine was found to depolarise supraoptic neurons that contain vasopressin, causing vasopressin release from axonal endings in the neurohypophysis (Selbach and Haas, 2008). High doses of histamine (25-500 µg i.c.v.) have been observed to elicit a dose-dependent antidiuretic response with a concomitant rise in blood vasopressin in dogs (Bhargava *et al.*, 1973), although tachyphylaxis occurred after four doses of histamine 400 µg i.c.v. Mepyramine 5 mg i.c.v. prevented these effects. H₃ receptor had not yet been discovered at the time of this study, and its potential contribution has never been investigated. Nevertheless, its colocalisation with AQP-2 suggests that H₃ receptor and AQP-2 may cooperate in the vasopressin response of the principal cells in the collecting duct. Although there is evidence for an antidiuretic effect of histamine (Dale and Laidlaw, 1910; Dale and Richards, 1918; Reubi and Futcher, 1949; Blackmore and Cherry, 1955), there is also contrasting evidence to suggest that histamine does not affect urine outflow (Campbell and Itskovitz, 1976), or even increase water excretion (Sinclair *et al.*, 1974a; Banks *et al.*, 1978; Ichikawa and Brenner, 1979). Similarly, conflicting data also exist on the histamine receptor subtype involved. Banks *et al.* (1978) demonstrated that histamine infusion in dogs (1 µg/min per kg) increased urine outflow; dimaprit produced a similar effect and the 2-pyridylethylamine reduced the urinary flow rate. These data led to the hypotheses that H₂ receptor has an active role in water excretion; however, we must remember that dimaprit is not an H₂ receptor agonist, thought to act on both H₂ receptor and H₄ receptor (Lim *et al.*, 2009), now has been classified as H₃ receptor [$pK_i = 6.1$] (Alexander *et*

al., 2017)] and H₄ receptor agonist [$p_{ki} = 4.9 - 6.5$ (Alexander *et al.*, 2017)]. *In vivo* experimental models of renal disease with polyuric phenotype, such as diabetic nephropathy, demonstrated that pre-treatment with the H₄ receptor antagonist JNJ-39758979 reduces the urine outflow of diabetic animals in a dose-dependent manner (Pini *et al.*, 2018). Convergent evidence comes from unpublished data demonstrating the involvement of H₄ receptor in the AQP_s pattern of expression (Pini, 2018, unpublished data; Verta, 2018, unpublished data). Moreover, the pre-treatment of animals with the H₁ receptor antagonist tripeleminamine has been shown to significantly reduce renal responses to histamine infusion, including diuresis (O'Brien and Williamson, 1971). Accordingly, polyuria has been reduced by the administration of (R)-cetirizine at 0.5 mg/kg/day in a model of diabetic nephropathy in rats (Anbar *et al.*, 2016).

H₁ receptor was found to be correlated with a decrease in the ultrafiltration coefficient (K_f) induced by histamine (Ichikawa and Brenner, 1979). These data are consistent with the localisation of H₁ receptor on podocytes (Veglia *et al.*, 2016). Interestingly, it has been demonstrated that histamine affects the disruption of cell-to-cell contact, via H₁ receptor activation, in an *in vitro* model of human immortalised podocytes. In particular, histamine was found to downregulate the expression of two key molecular components of the slit diaphragm, zonula occludens (ZO)-1 and P-cadherin, leading to a dose- and time-dependent efflux of albumin. Chlorpheniramine, at 10 μ M, was able to restore junctional integrity (Veglia *et al.*, 2016). These data are consistent with the theory that histamine affects the glomerular pore density with a reduction in total filtration surface area (Ichikawa and Brenner, 1979). Nonetheless, histamine i.p. injection at 0.5 mg/kg has been observed to cause foot processes loss in fasting rats (Gurgen *et al.*, 2013). These glomerular changes correlate with the filtration capacity of the kidneys and affect creatinine and urea clearance. In fact, the effect of H₂ receptor antagonists on creatinine clearance has been extensively studied, and cimetidine has been reported to significantly decrease this parameter after 7 days of treatment. This effect is not a class-effect as it was not reported for other H₂ receptor antagonists, such as famotidine (Ishigami *et al.*, 1989), and is therefore histamine-independent. However, *in vivo* models of diabetic nephropathy in

mice and rats have demonstrated that both (R)-cetirizine (Anbar *et al.*, 2016) and JNJ-39758979 (Pini *et al.*, 2018) dramatically restored creatinine clearance in diabetic animals.

Histamine challenge may be directly responsible for the appearance of albuminuria and proteinuria (Bjering, 1937). Interestingly, H₁ receptor antagonism has been reported to reduce the degree of proteinuria in an experimental model of glomerular nephritis (Bolton *et al.*, 1974) and in diabetes, where also an amelioration of albuminuria has also been reported (Anbar *et al.*, 2016). These effects are consistent not only with the vascular events associated with histamine receptors, but also with the localisation of H₁ receptor on glomeruli, and, more precisely, on podocytes. Indeed, the reduction in filtration area, caused for instance by fenestration and podocyte loss, is a direct contributor to hyper-filtration and the consequent albuminuria (Nagata, 2016). However, glomerular hyper-filtration could be also triggered by hyper-reabsorption at the proximal tubule, through the decreases of electrolyte load to the macula densa, causing an increase in the colloid osmotic pressure of the glomerular capillaries (Palatini, 2012). The proximal tubules, where both H₁ receptor and H₄ receptor (Figure 1) are present, are specialised for albumin and protein reabsorption. In particular, the megalin/cubilin pathway mediates albumin reabsorption. Interestingly, the H₄ receptor antagonist JNJ-39758979 has been found to prevent megalin loss in a model of experimental diabetic nephropathy (Pini *et al.*, 2018). The dysregulation of the reabsorptive process at the different levels of the nephron may account for the excretion of electrolytes, particularly sodium, excretion induced by histamine via H₁ receptor (Sinclair *et al.*, 1974b; Banks *et al.*, 1978; Ichikawa and Brenner, 1979; Gerber and Nies, 1983; Laight *et al.*, 1995). Furthermore, a potential role for H₄ receptor should be considered, even if it has yet to be investigated.

Despite the evidence of functional effects of histamine in the kidney, the actual relevance of the contribute of this amine cannot be conclusive demonstrated. Currently, the experimental data are in favour of at least an additive role.

Histamine and renal disease

The role of histamine in renal disease can be extrapolated in accordance with the above-reported analysis. Moreover, the relative contribution of each histamine receptor reflects their distribution, with histamine triggering both degenerative glomerular and tubular changes (Bjering, 1937; Gurgen *et al.*, 2013), via different histamine receptor pathways.

The correlation between histamine and renal disease in humans comes from the observation that, compared to healthy subjects, plasma levels of histamine are significantly higher in patients that have nephrotic syndrome, end stage renal failure, and undergoing haemodialysis or peritoneal dialysis than in the healthy ones (Gill *et al.*, 1991). In particular, high plasma histamine levels have been found in patients with renal insufficiency and uremic pruritus (Stockenhuber *et al.*, 1990). This data is consistent with histamine's ability to reduce urea clearance (Bjering, 1937). Histamine may therefore have detrimental effects on renal function. This hypothesis is supported by a number of *in vivo* studies reported in Table 2. However, the role of histamine in renal diseases can also be hypothesised in terms of the presence of mast cells in several kidney diseases with a prominent fibrotic component. Regardless of the underlying disease, the presence of mast cells has been found to correlate with the progressive loss of renal function (Holdsworth and Summers, 2008). An increase in mast cells was found to parallel renal function in primary and secondary forms of membranous, diabetic and IgA nephropathy, and in allograft rejection (Roberts and Brenchley, 2000), as well as in amyloidosis, renovascular ischemia, reflux nephropathy, polycystic kidney disease and drug induced nephropathy (Holdsworth and Summers, 2008). The inhibition of mast cells has also been proposed as a possible target in tubulointestinal fibrosis (Li *et al.*, 2007). Mast cells liberate a variety of well-characterized profibrotic mediators, including transforming growth factor (TGF)- β . Nevertheless, histamine has been shown to induce a profibrotic response via H₄ receptor activation. Indeed, the H₄ receptor antagonist prototype JNJ 7777120 was found to blunt the fibrotic response by down-regulating the TGF- β -Smad3/4 pathway in a model of pulmonary fibrosis induced by bleomycin, in mice (Rosa *et al.*, 2014; Lucarini *et al.*, 2016). Moreover, the H₄ receptor antagonist JNJ-39758979 [$p_{ki} = 7.9$ (Alexander *et al.*, 2017)] prevented collagen deposition and fibrosis development in the kidneys of

diabetic animals (Pini *et al.*, 2018). However, Kim *et al.* (2009) hypothesised that mast cells may exert a protective role in renal fibrosis secondary to obstructive uropathy in a mouse model genetically deficient in mast cells.

As shown in Table 2, the majority of the publications are based on streptozotocin-induced type 1 diabetes, which causes long term renal damage, that is consistent with diabetic nephropathy. Results in mice and rats were comparable, indicating that histaminergic tone is higher in diabetic animals than in controls (Markle *et al.*, 1986; Gill *et al.*, 1988; Gill *et al.*, 1990; Rosa *et al.*, 2013). In particular, HDC expression has been noted to occur in the tubular and peritubular areas in the diabetic kidney of mice (Pini *et al.*, 2018). This evidence is consistent with previous studies reporting an over-activity of HDC. In diabetic rats the increase in renal histamine content was blunted by the administration of the selective HDC inhibitor alpha-hydrazinohistidine (alpha-HH) (Levine *et al.*, 1965), but not by insulin (Markle *et al.*, 1986). Based on these results, the authors proposed a possible increase in renal HDC activity in diabetic animals. However, being the alpha-HH administered at 25 mg/kg/day i.p. via an intra-abdominally implanted pump, a systemic effect could not be ruled out. The data from Gill *et al.* (1990) supported the hypothesis of an increase in renal HDC activity in diabetes. Indeed, comparing the HDC activity, the histamine content and the DAO activity in different tissue from diabetic rats, the kidney was found to be the second (aorta the first) for HDC activity and histamine levels, with an increase of 70 % over control. Any concomitant decrease in DAO activity was observed in kidney of diabetic animals. All these data are in favour of a net increase in the local synthesis of histamine. Besides an increase in the renal histamine content, some evidence has been provided in favour of a general up-regulation of the histaminergic system in the kidney of diabetic mice. Indeed, the immunolabeling and the gene expression analyses revealed that at least H₄ receptor (Rosa *et al.*, 2013) and H₃ receptor (Pini *et al.*, 2015) expression is up-regulated in the kidney of diabetic rats. Moreover, preliminary data report that renal H₄ receptor expression parallel the hierarchical susceptibility to diabetic nephropathy induced by streptozotocin injection in different strain of mice (Gurley *et al.*, 2006): absent in Balb/c (not susceptible), medium in C57BL/6 and higher

in DBA2/J (most susceptible). Also H₁ receptor and H₂ receptor expression was increased in diabetic mice from both C57BL/6 and DBA2/J strain (Pini *et al.*, 2016a). However, the functional meaning of these changes is still far to be completely elucidated. Two pharmacological approaches were tested in the streptozotocin-induced diabetic nephropathy model: one was based on H₁ receptor, while the other on H₄ receptor antagonism (Table 2). The two strategies can be considered complementary: H₁ receptor were directed to the glomerulus and H₄ receptor to the tubules, according to their localisation. It is currently thought that the antagonism of H₁ receptor may prevent the integrity of the filtration barrier and reduce the mechanical damage caused by hyperglycaemia, as it is consistent with preserved junctional integrity at the slit diaphragm level (Veglia *et al.*, 2016). Nevertheless, the detrimental effect of histamine on the filtration slit is in keeping with previous observations. In particular, Abboud *et al.* (1982), using a model of nephrosis with predominantly direct podocyte damage, the puromycin aminoglycoside (PAN)-induced nephrosis, stated that histamine levels are significantly increased in in the renal cortex of nephrotic rats. Notably, (R)-cetirizine have been demonstrated to reduce the focal segmental glomerulosclerosis, interstitial fibrosis and the thickening of the glomerular basement membrane (GBM) shown by diabetic rats, with a significant improvement in renal function. These changes were accompanied by a reduction in the renal inflammatory response (Anbar *et al.*, 2016). On the other hand, in a model of diabetic mice, the H₄ receptor antagonist JNJ-39758979 has been demonstrated to preserve the tubular reabsorptive machinery, triggering protective effects on glomerular integrity and a positive outcome on renal function. Once again, a reduction in the renal inflammatory response was observed (Pini *et al.*, 2018). The role of histamine in inflammatory and immune response has long been the main subject of evaluation. However, only a few studies have aimed to evaluate histamine's contribution in models of renal diseases with a high immune component (Table 2). Notably, interesting but conflicting evidence has been reported. Two out of three studies on the anti-GBM-induced glomerulonephritis model failed in demonstrate an active role for histamine. However, in the late stage of glomerulonephritis the infiltration by histamine containing cells and, consequently, the histamine levels, in kidney of rats were reduced (Kossi and

Nahas, 2006). Moreover, both diphenhydramine and cimetidine prevented the GFR decrease, without influencing the anti-GBM antibodies ability to induce the glomerular pathological changes (Wilson *et al.*, 1981). Therefore, the hypothesis that histamine can trigger the associated fibrotic response was discounted. By contrast, a study by Tanda *et al.* (2007) suggested that H₄ receptor agonism may provide beneficial effects by suppressing the immune response. However, clozapine was used as the H₄ receptor agonist [$p_{ki} = 6.2 - 6.7$ (Alexander *et al.*, 2017)] in this study, but this antipsychotic drug binds many other different receptors, H₁ receptor and H₃ receptor included [$p_{ki} = 8.8 - 9.6$ and $p_{ki} = 5.8$ for H₁ receptor and H₃ receptor, respectively (Alexander *et al.*, 2017)]. Another study demonstrated that cyproheptadine, blocking H₁ receptor, delayed the onset and reduced the degree of proteinuria (Bolton *et al.*, 1974) in a model of autologous immune complex glomerulonephritis, which mimics human membranous glomerulopathy. These effects were, at least partially, ascribed to the vasoactive properties of histamine, but a partial serotonin-dependent effect could not be ruled out. The contribute of histamine in renal haemodynamics led to evaluate its role in ischemia-induced acute renal failure. Almost convergent lines of evidence was provided to indicate that beneficial effects can be achieved following an anti-histaminergic approach. Indeed, DAO administration (0.5 U/kg i.v.) inhibited the induced vascular permeability, as well as preserved renal function and structure integrity in a model of ischemia (30 min)/reperfusion (24 h) and in another of unilaterally nephrectomy in rats. The combined administration of diphenhydramine and ranitidine (each at 10 mg/kg) evoked similar effects (Kaneko *et al.*, 1998). Nonetheless, the histamine-release inducer compound 48/80 has been demonstrated to worsen kidney injury induced by bilateral renal artery and vein occlusion for 45 min, followed by 24 h of reperfusion. Consistently, a beneficial effect was obtained with the administration of cromoglicic acid (Tong *et al.*, 2016). The suggested contribution of H₂ receptor was confirmed by pretreating rats for 7 days with ranitidine 10 mg/kg/day in drinking water before left vascular pedicle clamping for 50 min in uninephrectomised animals. The drug significantly reduced the mortality at day 7 (Vannay *et al.*, 2004). However, Kurata *et al.* (2006), obtained contrasting results as they demonstrated the protective effect of carosine (15 nmol i.v.) 2-weeks after the occlusion of the left

renal artery and vein for 45 min. carnosine is a precursor of L-histidine and, consequently, of L-histamine. Notably, the H₃ receptor agonist (R)alpha-methylhistamine (5 pmol i.c.v.) mimicked the effects of carnosine, while the use of the H₃ receptor antagonist thioperamide (30 nmol i.c.v.) abolished them (Kurata *et al.*, 2006). The influence of H₃ receptor activation in the central nervous system on the observed effects therefore suggests that a dichotomy may exist between peripheral and central histamine in the pathogenesis of ischemic renal failure.

Conclusion

In conclusion, looking at the histaminergic machinery in the kidney, it can be stated that histamine can act on this organ in an autocrine manner under physiological conditions, and in both an autocrine and paracrine manners in pathological conditions, in which either the renal inducible pool of histamine, or an extrarenal source, like mast cells, could occur. The presence of all four histamine receptors, with differential distribution, suggests and further confirms the multiple actions that histamine presents, but may also hint at possible histamine receptor redundancy. The overall data reported in the literature raise the intriguing hypothesis of redundancy between H₁ receptor and H₂ receptor in renal haemodynamics; both mediating the increase in renal blood flow and reducing vascular resistance (Banks *et al.*, 1978; Banks *et al.*, 1984; Laight *et al.*, 1995). Moreover, both H₁ receptor and H₄ receptor have been demonstrated to participate in the complex process of urine formation, with H₁ receptor mostly being involved in glomerular filtration (Anbar *et al.*, 2016; Veglia *et al.*, 2016) and H₄ receptor in tubular reabsorption (Pini *et al.*, 2018). These two receptors therefore appear to possess complementary function(s). However, data from the peripheral and central activation of the histaminergic system, H₁ receptor and H₃ receptor seem to present a dichotomy. The effect of histamine on vasopressin regulation (Bhargava *et al.*, 1973; Selbach and Haas, 2008) against increases in water excretion (Sinclair *et al.*, 1974a; Banks *et al.*, 1978; Ichikawa and Brenner, 1979), as well as targeting at either peripheral or central histamine in ischemic acute renal failure, are

examples of this issue. These considerations should be taken into account when exploring possible therapeutic strategies for renal disease.

Preclinical studies of renal injury models point out at the intriguing hypothesis of new therapeutic approaches directed to the histaminergic modulation in kidney diseases. However, the functional influence of histamine in kidney pathophysiology still needs to be completely elucidated before experimental data can be translated to therapeutic applications.

References

Abboud HE, Ou SL, Velosa JA, Shah SV, Dousa TP (1982). Dynamics of renal histamine in normal rat kidney and in nephrosis induced by aminonucleoside of puromycin. *J Clin Invest* 69: 327-336.

Alexander SP, Christopoulos A, Davenport AP, Kelly E, Marrion NV, Peters *et al.* (2017). The concise guide to PHARMACOLOGY 2017/18: G protein-coupled receptors. *Br J Pharmacol* 174: S17-S129.

Anbar HS, Shehatou GS, Suddek GM, Gameil NM (2016). Comparison of the effects of levocetirizine and losartan on diabetic nephropathy and vascular dysfunction in streptozotocin-induced diabetic rats. *Eur J Pharmacol* 780: 82-92.

Aoki M, Terada T, Kajiwara M, Ogasawara K, Ikai I, Ogawa O *et al.* (2008). Kidney-specific expression of human organic cation transporter 2 (OCT2/SLC22A2) is regulated by DNA methylation. *Am J Physiol Renal Physiol* 295: F165-170.

Banks RO, Fondacaro JD, Schwaiger MM, Jacobson ED (1978). Renal histamine H1 and H2 receptors: characterization and functional significance. *Am J Physiol* 235: F570-575.

Banks RO, Inscho EW, Jacobson ED (1984). Histamine H1 receptor antagonists inhibit autoregulation of renal blood flow in the dog. *Circ Res* 54: 527-535.

Bhargava KP, Kulshrestha VK, Santhakumari G, Srivastava YP (1973). Mechanism of histamine-induced antidiuretic response. *Br J Pharmacol* 47: 700-706.

Binder B, Sewing K (1973). The effect of brocresine (NSD-1055) on diamine oxidase activity in plasma, liver, stomach and upper small intestine of rats. *Naunyn Schmiedebergs Arch Pharmacol* 278: 425-430.

Bjering T (1937). The Influence of Histamine on Renal Function. *Acta Medica Scandinavica* 91: 12.

Blackmore WP, Cherry GR (1955). Antidiuretic action of histamine in the dog. *Am J Physiol* 180: 596-598.

Bolton WK, Spargo BA, Lewis EJ (1974). Chronic autologous immune complex glomerulopathy: effect of cyproheptadine. *J Lab Clin Med* 83: 695-704.

Brown DD, Tomchick R, Axelrod J (1959). The distribution and properties of a histamine-methylating enzyme. *J Biol Chem* 234: 2948-2950.

Burke M, Pabbidi MR, Farley J, Roman RJ (2014). Molecular mechanisms of renal blood flow autoregulation. *Curr Vasc Pharmacol* 12: 845-858.

Burtin C, Scheinmann P, Paupe J, Canu P, Goy J (1982). Tissue histamine levels in male and female normal and nude mice. *Agents Actions* 12: 199-200.

Campbell WB, Itskovitz HD (1976). Effect of histamine and antihistamines on renal hemodynamics and functions in the isolated perfused canine kidney. *J Pharmacol Exp Ther* 198: 661-667.

Castrop H, Hocherl K, Kurtz A, Schweda F, Todorov V, Wagner C (2010). Physiology of kidney renin. *Physiol Rev* 90: 607-673.

Dalal R, Sehdev JS (2018). Physiology, Renal, Blood Flow and Filtration. In StatPearls. Treasure Island (FL).

Dale HH, Laidlaw PP (1910). The physiological action of beta-aminazolyethylamine. *J Physiol* 41: 318-344.

Dale HH, Richards AN (1918). The vasodilator action of histamine and of some other substances. *J Physiol* 52: 110-165.

Douglas W (1971). Autacoids. In *The Pharmacological Basis of Therapeutics*. eds Goodman L., and Gilman A. THE MACMILLAN COMPANY: London, pp 620-675.

Ennis M (1992). Laboratory histamine measurements to study type I adverse allergic/pseudoallergic reactions to agents used in anaesthesia and surgery. *Monogr Allergy* 30: 74-93.

Gerber JG, Nies AS (1983). The role of histamine receptors in the release of renin. *Br J Pharmacol* 79: 57-61.

Gill DS, Fonseca VA, Barradas MA, Balliod R, Moorhead JF, Dandona P (1991). Plasma histamine in patients with chronic renal failure and nephrotic syndrome. *J Clin Pathol* 44: 243-245.

Gill DS, Thompson CS, Dandona P (1988). Increased histamine in plasma and tissues in diabetic rats. *Diabetes Res* 7: 31-34.

Gill DS, Thompson CS, Dandona P (1990). Histamine synthesis and catabolism in various tissues in diabetic rats. *Metabolism* 39: 815-818.

Gurgen SG, Erdogan D, Take-Kaplanoglu G (2013). The effect of histamine on kidney by fasting in rats. *Bratisl Lek Listy* 114: 251-257.

Gurley SB, Clare SE, Snow KP, Hu A, Meyer TW, Coffman TM (2006). Impact of genetic background on nephropathy in diabetic mice. *Am J Physiol Renal Physiol* 290: F214-222.

Hakanson R, Liedberg G (1972). Effects of brocresine (NSD-1055) and cycloheximide on amino acid decarboxylase activities in gastric mucosa of normal and vagally denervated rats. *Br J Pharmacol* 46: 688-695.

Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S et al. (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucl Acids Res* 46: D1091-D1106.

Heald JI, Hollis TM (1976). Histidine decarboxylase-mediated histamine synthesis in glomeruli from rat kidneys. *Am J Physiol* 230: 1349-1353.

Holdsworth SR, Summers SA (2008). Role of mast cells in progressive renal diseases. *J Am Soc Nephrol* 19: 2254-2261.

Ichikawa I, Brenner BM (1979). Mechanisms of action of hisamine and histamine antagonists on the glomerular microcirculation in the rat. *Circ Res* 45: 737-745.

Ishigami M, Sezai Y, Shimada Y, Maeda T, Yabuki S (1989). Effects of famotidine, a new histamine H₂-receptor antagonist, on renal function. *Nihon Jinzo Gakkai Shi* 31: 687-691.

Kaneko H, Koshi S, Hiraoka T, Miyauchi Y, Kitamura N, Inoue M (1998). Inhibition of post-ischemic reperfusion injury of the kidney by diamine oxidase. *Biochim Biophys Acta* 1407: 193-199.

Kim DH, Moon SO, Jung YJ, Lee AS, Kang KP, Lee TH *et al.* (2009). Mast cells decrease renal fibrosis in unilateral ureteral obstruction. *Kidney Int* 75: 1031-1038.

Kollb-Sielecka M, Demolis P, Emmerich J, Markey G, Salmonson T, Haas M (2017). The European Medicines Agency review of pitolisant for treatment of narcolepsy: summary of the scientific assessment by the Committee for Medicinal Products for Human Use. *Sleep Med* 33: 125-129.

Kossi M, Nahas A (2006). kidney histamine levels in an experimental model of glomerulonephritis. *Al-Azhar Assiut Medicla Journal* 4: 10.

Kurata H, Fujii T, Tsutsui H, Katayama T, Ohkita M, Takaoka M *et al.* (2006). Renoprotective effects of l-carnosine on ischemia/reperfusion-induced renal injury in rats. *J Pharmacol Exp Ther* 319: 640-647.

Laight DW, Woodward B, Waterfall JF (1995). Renal vasodilation to histamine in vitro: roles of nitric oxide, cyclo-oxygenase products and H2 receptors. *Inflamm Res* 44: 116-120.

Levine RJ, Sato TL, Sjoerdsma A (1965). Inhibition of Histamine Synthesis in the Rat by Alpha-Hydrazino Analog of Histidine and 4-Bromo-3-Hydroxy Benzyloxyamine. *Biochem Pharmacol* 14: 139-149.

Li Y, Liu FY, Peng YM, Li J, Chen J (2007). Mast cell, a promising therapeutic target in tubulointerstitial fibrosis. *Med Hypotheses* 69: 99-103.

Lim HD, Adami M, Guaita E, Werfel T, Smits RA, de Esch IJ *et al.* (2009). Pharmacological characterization of the new histamine H4 receptor agonist VUF 8430. *Br J Pharmacol* 157: 34-43.

Lindell SE, Schayer RW (1958). Formation of histamine in the kidney of the dog. *Br J Pharmacol Chemother* 13: 89-90.

Liu C, Ma X, Jiang X, Wilson SJ, Hofstra CL, Blevitt J *et al.* (2001). Cloning and pharmacological characterization of a fourth histamine receptor (H(4)) expressed in bone marrow. *Mol Pharmacol* 59: 420-426.

Lucarini L, Pini A, Rosa AC, Lanzi C, Durante M, Chazot PL *et al.* (2016). Role of histamine H4 receptor ligands in bleomycin-induced pulmonary fibrosis. *Pharmacol Res* 111: 740-748.

Markle RA, Hollis TM, Cosgarea AJ (1986). Renal histamine increases in the streptozotocin-diabetic rat. *Exp Mol Pathol* 44: 21-28.

Martin SA, Bishop JO (1986). Purification and characterization of histidine decarboxylase from mouse kidney. *Biochem J* 234: 349-354.

Montesino H, Villar M, Vega E, Rudolph MI (1995). Histamine, a neuromodulator of noradrenergic transmission in uterine horns from mice in diestrus. *Biochem Pharmacol* 50: 407-411.

Morgan TK, Montgomery K, Mason V, West RB, Wang L, van de Rijn M *et al.* (2006). Upregulation of histidine decarboxylase expression in superficial cortical nephrons during pregnancy in mice and women. *Kidney Int* 70: 306-314.

Nagata M (2016). Podocyte injury and its consequences. *Kidney Int* 89: 1221-1230.

O'Brien KP, Williamson HE (1971). The natriuretic action of histamine. *Eur J Pharmacol* 16: 385-390.

Ogasawara M, Yamauchi K, Satoh Y, Yamaji R, Inui K, Jonker JW *et al.* (2006). Recent advances in molecular pharmacology of the histamine systems: organic cation transporters as a histamine transporter and histamine metabolism. *J Pharmacol Sci* 101: 24-30.

Palatini P (2012). Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. *Nephrol Dial Transplant* 27: 1708-1714.

Pini A, Chazot PL, Rosa AC (2016a). Parallel hierarchical intra-strain difference between the susceptibility to diabetic nephropathy and renal histamine receptor expression. *Inflammation research : official journal of the European Histamine Research Society [et al]* 65: 1.

Pini A, Chazot PL, Veglia E, Moggio A, Rosa AC (2015). H3 receptor renal expression in normal and diabetic rats. *Inflamm Res* 64: 271-273.

Pini A, Grange C, Veglia E, Argenziano M, Cavalli R, Guasti D *et al.* (2018). Histamine H4 receptor antagonism prevents the progression of diabetic nephropathy in male DBA2/J mice. *Pharmacol Res* 128: 18-28.

Pini A, Obara I, Battell E, Chazot PL, Rosa AC (2016b). Histamine in diabetes: Is it time to reconsider? *Pharmacol Res* 111: 316-324.

Radke KJ, Selkurt EE, Willis LR (1985). The role of histamine H1 and H2 receptors in the canine kidney. *Ren Physiol* 8: 100-111.

Reubi FC, Fitcher PH (1949). The Effects of Histamine on Renal Function in Hypertensive and Normotensive Subjects. *J Clin Invest* 28: 440-446.

Roberts IS, Brenchley PE (2000). Mast cells: the forgotten cells of renal fibrosis. *J Clin Pathol* 53: 858-862.

Rosa AC, Grange C, Pini A, Katebe MA, Benetti E, Collino M *et al.* (2013). Overexpression of histamine H(4) receptors in the kidney of diabetic rat. *Inflamm Res* 62: 357-365.

Rosa AC, Pini A, Lucarini L, Lanzi C, Veglia E, Thurmond RL *et al.* (2014). Prevention of bleomycin-induced lung inflammation and fibrosis in mice by naproxen and JNJ7777120 treatment. *J Pharmacol Exp Ther* 351: 308-316.

Schwertschlag U, Hackenthal E (1982). Histamine stimulates renin release from the isolated perfused rat kidney. *Naunyn Schmiedebergs Arch Pharmacol* 319: 239-242.

Sedor JR, Abboud HE (1984). Actions and metabolism of histamine in glomeruli and tubules of the human kidney. *Kidney Int* 26: 144-152.

Sedor JR, Abboud HE (1985). Histamine modulates contraction and cyclic nucleotides in cultured rat mesangial cells. Differential effects mediated by histamine H1 and H2 receptors. *J Clin Invest* 75: 1679-1689.

Selbach O, Haas HL (2008). Histamine as a Neurotransmitter. In *The Third Histamine Receptor: Selective Ligands as Potential Therapeutic Agents in CNS Disorders*. ed Vohora D. CRC Press.

Simons FE, Simons KJ (2011). Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol* 128: 1139-1150 e1134.

Sinclair MC, Lemmi CA, Moore TC (1974a). Elevation in urinary excretion of histamine following renal allografting in rats. *J Surg Res* 17: 43-44.

Sinclair RJ, Bell RD, Keyl MJ (1974b). Effects of prostaglandin E2 (PGE2) and histamine on renal fluid dynamics. *Am J Physiol* 227: 1062-1066.

Singh V, Gohil N, Ramirez-Garcia R (2018). New insight into the control of peptic ulcer by targeting the histamine H2 receptor. *J Cell Biochem* 119: 2003-2011.

Slorach SA, Uvnas B (1968). Amine formation by rat mast cells in vitro. *Acta Physiol Scand* 73: 457-470.

Stockenhuber F, Kurz RW, Sertl K, Grimm G, Balcke P (1990). Increased plasma histamine levels in uraemic pruritus. *Clin Sci (Lond)* 79: 477-482.

Tanda S, Mori Y, Kimura T, Sonomura K, Kusaba T, Kishimoto N *et al.* (2007). Histamine ameliorates anti-glomerular basement membrane antibody-induced glomerulonephritis in rats. *Kidney Int* 72: 608-613.

Tanida M, Kaneko H, Shen J, Nagai K (2007). Involvement of the histaminergic system in renal sympathetic and cardiovascular responses to leptin and ghrelin. *Neurosci Lett* 413: 88-92.

Taylor KM, Snyder SH (1972). Dynamics of the regulation of histamine levels in mouse brain. *J Neurochem* 19: 341-354.

Tong F, Luo L, Liu D (2016). Effect of Intervention in Mast Cell Function Before Reperfusion on Renal Ischemia-Reperfusion Injury in Rats. *Kidney Blood Press Res* 41: 335-344.

Torres VE, Northrup TE, Edwards RM, Shah SV, Dousa TP (1978). Modulation of cyclic nucleotides in isolated rat glomeruli: role of histamine, carbamylcholine, parathyroid hormone, and angiotensin-II. *J Clin Invest* 62: 1334-1343.

Vannay A, Fekete A, Muller V, Strehlau J, Viklicky O, Veres T *et al.* (2004). Effects of histamine and the h2 receptor antagonist ranitidine on ischemia-induced acute renal failure: involvement of IL-6 and vascular endothelial growth factor. *Kidney Blood Press Res* 27: 105-113.

Veglia E, Grange C, Pini A, Moggio A, Lanzi C, Camussi G *et al.* (2015). Histamine receptor expression in human renal tubules: a comparative pharmacological evaluation. *Inflamm Res* 64: 261-270.

Veglia E, Pini A, Moggio A, Grange C, Premoselli F, Miglio G *et al.* (2016). Histamine type 1-receptor activation by low dose of histamine undermines human glomerular slit diaphragm integrity. *Pharmacol Res* 114: 27-38.

Wilson CB, Gushwa LC, Peterson OW, Tucker BJ, Blantz RC (1981). Glomerular immune injury in the rat: effect of antagonists of histamine activity. *Kidney Int* 20: 628-635.

Wolvekamp MC, de Bruin RW (1994). Diamine oxidase: an overview of historical, biochemical and functional aspects. *Dig Dis* 12: 2-14.

Yamasaki T, Tamai I, Matsumura Y (2001). Activation of histamine H3 receptors inhibits renal noradrenergic neurotransmission in anesthetized dogs. *Am J Physiol Regul Integr Comp Physiol* 280: R1450-1456.

Yousif MH (2005). Histamine-induced vasodilation in the perfused kidney of STZ-diabetic rats: role of EDNO and EDHF. *Pharmacol Res* 51: 515-521.

Zimmermann AS, Burhenne H, Kaefer V, Seifert R, Neumann D (2011). Systematic analysis of histamine and N-methylhistamine concentrations in organs from two common laboratory mouse strains: C57Bl/6 and Balb/c. *Inflamm Res* 60: 1153-1159.

Figure legends

Figure 1. Differential histamine receptor distribution in the mammalian nephron and collecting duct.

Histamine receptors topology within the mammalian kidney based on current knowledge (Sedor and Abboud, 1984; Sedor and Abboud, 1985; Rosa *et al.*, 2013; Pini *et al.*, 2015; Veglia *et al.*, 2015; Veglia *et al.*, 2016). H₁ receptor and H₂ receptor have been identified within the renal corpuscle (H₁ receptor in the glomerulus and H₂ receptor in glomerulus and in glomerular capsule) and in the distal tubule. H₁ receptor and H₄ receptor are both present on the renal proximal convoluted tubule. H₄ receptor is also expressed in the ascending limb of the loop of Henlé. H₃ receptor have been localised in the collecting duct.

Figure 2. Histamine and histamine receptor contribution to renal function.

Proposed summary of the data reported on the effects of histamine on renal function. The amine mediates a range of effects through the differential contribution of all the histamine receptors. The increases in albuminuria, and water and salt excretion, as well as the reductions in creatinine and urea clearance are mediated by both H₁ receptor and H₄ receptor. Moreover, H₁ receptor also participate in the reduction of the ultrafiltration coefficient as well as the modulation of renal blood flow and vascular resistance. The vasoactive properties of H₁ receptor are shared by H₂ receptor, whose activation also evokes renin release. The role of H₂ receptor in the distal tubule is still unknown. Finally, H₃ receptor activation may be involved in polyuria.