Histamine Receptor Distribution Along The Nephron

E. Veglia[1], A. Pini[2], A. Moggio[1], C. Grange[3], P.L. Chazot[4], R. Fantozzi[1], A.C. Rosa[1]

[1]Dip. di Scienza e Tecnologia del Farmaco, Università di Torino, Turin, Italy
[2]Dip. di Medicina Sperimentale e Clinica Sezione di Anatomia e Istologia Università degli Studi di Firenze, Florence, Italy
[3]Dip. di Scienze Mediche, Università di Torino, Turin, Italy
[4]School of Biological and Biomedical Sciences and Wolfson Research Institute, Durham University, South Road, Durham DH1 3LE, UK

Recently, we demonstrated the presence of the histamine H4 receptor (H_4R) in rat resident renal cells of the loop of Henle and its profound upregulation in the kidney of diabetic animals (Rosa et al., 2013), where the levels of histamine have been reported to be increased compared with controls (Markle et al., 1986). Our observation provides new evidence for a role of histamine in renal (patho)physiology.
The aim of this study was to extend our previous observation on H_4R in healthy and diabetic rats, firstly evaluating in the same specimens the renal expression of the other histamine receptor subtypes; furthermore, in order to translate to humans, a comparative evaluation of four histamine receptor expression in specimens from human kidney and in different human epithelial cell lines was performed.
Immunohistochemical and biomolecular studies were performed on both kidney specimens from 24 8-week-old male Wistar rats (12 control and 12 diabetic animals) and 12 non-diabetic patients who underwent elective nephrectomy. Moreover, the expression of the 4 histamine receptors was evaluated at gene and protein levels in different human tubular epithelial cells (HK-2, immortalized iTECs and primary pTECs). The pharmacological analysis was performed by TR-FRET measurements of second messenger (IP3 and cAMP) production induced by histamine with or without selective antagonists.
In the kidney of rats, the immunohistochemical analysis revealed a clear H_3R-like immunoreactivity in control rats, predominantly in renal medulla and papilla, colocalised with aquaporin 2, AQP2, consistent with a predominant H_3R expression at the apical membrane of epithelial cells of collecting ducts. Notably, differently from H_1R and H_2R, H_3R expression was profoundly upregalated in diabetic rats.
Comparatively with rats, also humans showed specific H_1R, H_2R and H_4R immunoreactivities at tubular level, with a predominant expression of H_4R at basal and H_3R at apical membrane of some tubular epithelial cells.
When different tubular epithelial cells were evaluated, single transcript corresponding to the size predicted for H_1R, H_2R, H_3R and H_4R was obtained in both pTECs and iTECs. In comparison to all TECs tested, only the single transcripts corresponding to the size predicted for H_1R and H_4R were observed in HK-2. Consistent results were obtained when the protein expression was evaluated by immunofluorescence.
Cells exposed for 1 h to histamine, 3 pM–300 nM, showed a concentration-dependent decrease in TR-FRET signal, which indicates an increase of IP1; the pretreatment for 10 min with the selective H_1R antagonist chlorpheniramine (1 or 10 μM) shifted in a concentration dependent manner the curves evoked by histamine, confirming the functional expression of H_1R in the renal cell.
iTECs exposed for 30 min to histamine produced a double bell-shaped dose–response curve for cAMP production. When singly tested, the selective antagonists, ranitidine (H_2R), GSK189254 (H_3R) or JNJ7777120 (H_4R), 1 or 10 μM, affected differently the dose-response curve, while the co-administration of all antagonists blunted the effect evoked by histamine.
In conclusion, we report the identification of all four histamine receptors in human renal tubules, althoug with a different distribution along the nephron. In particular, the presence of H_4R has been demonstrated on proximal tubular epithelial cells and H_3R on the collecting ducts. Together with the demonstration of their up-regulation in diabetic rats, these data suggest a possible role of histamine in renal (patho)physiology, where the amine has been reported to regulate the renal microcirculation, to increase salt and water excretion, to decrease the ultrafiltration coefficient, and increase renin release.

Rosa et al. (2013). *Inflamm Res*. 62, 357-365.
Markle et al. (1986). *Exp Mol Pathol*. 44:21–8.