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1 **Histamine in diabetes: is it time to reconsider?**

2  
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24 **Abstract**

25 The first studies of histamine and diabetes date back to the 1950s. Since that time the involvement  
26 of histamine in diabetes was related to its well known vasoactive properties and permeability  
27 leakage effects. In particular, the first evidence for a correlation between histamine and diabetes  
28 arose in 1989 when an increase in plasma and leucocyte histamine content was observed. Limited  
29 independent evidence followed in the subsequent two decades, focusing on both histamine  
30 glyceamic control and macro- and microvascular complications of diabetes. However, recent  
31 observations have sparked the question whether it is time to reconsider the functional contribution  
32 of histamine in diabetes. We reveal an interesting upsurge in the field which provides scope for new  
33 insights into the role of histamine in diabetes.

34

35 **Keywords:** histamine, histamine receptor, diabetes, nephropathy, retinopathy, neuropathy

36

37 **Abbreviations:**

38 ADP= action potential duration; AGEs = advanced glycation end-products; BM = basement  
39 membrane; BRB = blood-retinal barrier; CGRP = calcitonin gene related peptide; CKD = chronic  
40 kidney disease; DAO = diamine oxidase; DiO = diet-induced obesity; ESRD = end-stage renal  
41 disease; H<sub>1-4</sub>Rs = histamine H<sub>1-4</sub>Rs; HbA<sub>1c</sub> = glycated hemoglobin; HDC = histidine decarboxylase;  
42 STZ = streptozotocin; TGF- $\beta$  = tissue growth factor- $\beta$ ; TCAs = tricyclic antidepressants; V<sub>max</sub> =  
43 maximum rate of depolarization; VEGF = vascular endothelial growth factor; ZO-1 = zonula  
44 occludent-1

45

## 46 **1 Introduction**

47 Diabetes mellitus can be considered a family of chronic degenerative disorders associated with a  
48 hyperglycemic status caused by either the loss of insulin production due to the destruction of beta  
49 pancreatic cells, decreased insulin sensitivity, or both [1, 2]. In 2014, the global prevalence of 8.3%  
50 has been estimated and by the end of 2030 this value is expected to rise up to 55% [3], resulting in  
51 obvious devastating consequences for healthcare expenditure worldwide. All the antidiabetic drugs  
52 currently available, although effective in reducing the risk of acute complications, such as  
53 hypoglycemia and hyperglycemia [4], are not effective in reversing the progression of this chronic  
54 and degenerative disorder. Indeed, diabetic patients are still at a high risk to develop longstanding  
55 complications including cardiovascular disease, such as coronary artery disease, and microvascular  
56 diseases, including neuropathy, retinopathy and nephropathy. Therefore, a better understanding of  
57 the underlying pathophysiology should contribute to new effective therapeutic approaches. Among  
58 the different mediators proposed to contribute to the pathophysiology of diabetes, histamine  
59 involvement has always been controversial and considered almost marginal. However, several lines  
60 of evidence support the contribution of histamine to the diabetic milieu resulting from the persistent  
61 hyperglycemia. For instance, the advanced glycation end-products (AGEs) have been demonstrated  
62 to activate mast cells whose degranulation may contribute to a vicious cycle, ultimately resulting in  
63 a low-grade inflammation typical of chronic diseases such as diabetes [5]. Therefore, this review  
64 aims to revisit the concept of histamine in the pathophysiology of diabetes and, in particular, its  
65 complications.

## 66 **2 Histamine and glycaemia**

67 Histamine is involved in a wide variety of pathophysiological events mostly related to the  
68 inflammatory response through four receptors, namely H<sub>1-4</sub>Rs. The first studies of histamine and  
69 diabetes date back to the 1950s. Since that time the involvement of histamine in diabetes was

70 related to its well-known vasoactive properties and permeability leakage effects correlated to  
71 microvascular complications. In particular, the first evidence for a correlation between histamine  
72 and diabetes came in 1989 through the work of Gill and colleagues when they reported an increase  
73 in plasma and leucocyte histamine content which was claimed to contribute to the underlying  
74 pathogenesis evoking endothelial permeability [6]. These findings were in keeping with *in vivo*  
75 studies of experimental diabetes suggestive of an increased histaminergic tone in diabetic rodents.  
76 Indeed, histamine was found to be increased in plasma, kidney, brain, lung, heart, pancreas and  
77 intestine [6, 7] of diabetic rats. Independent evidence also suggested a parallel imbalance of the  
78 anabolism and catabolism of this amine with an increased synthesis and a simultaneous decreased  
79 catabolism [8-11]. For instance, a significant drop in intestinal diamine oxidase (DAO) activity [7]  
80 as well as an increase of histidine decarboxylase (HDC) activity in various tissues [12] were  
81 observed, thus providing evidence for a nascent histamine pool. The very recent observation of a  
82 reduced prevalence of hyperglycemia in HDC<sup>-/-</sup> NOD mice (an animal model of spontaneous type 1  
83 diabetes) in comparison with the wild-type counterpart [13] strongly lends weight to this original  
84 hypothesis.

85 More intriguingly, it has been reported that histamine plasma and aortic synthesis [10] in diabetic  
86 rats are reduced when insulin is administered [14], thus strongly supporting the hypothesis for an  
87 interconnection between histamine and glycaemic status. This hypothesis is further strengthened by  
88 the study of Azevedo and colleagues (1990) reporting an increase of pancreatic islet histamine  
89 content in streptozotocin (STZ)-induced diabetes rats [15]. Interestingly, recent data suggest the  
90 involvement of the peripheral H<sub>3</sub>R in the insulin-histamine loop (Supplementary Figure 1). Indeed,  
91 Nakamura and colleagues (2014) provided the first evidence for a potential diabetogenic effect of  
92 the pancreatic H<sub>3</sub>R, through reporting the presence of functional histamine H<sub>3</sub>R in this tissue. In  
93 particular, it has been demonstrated that H<sub>3</sub>R activation in pancreatic beta cells by imetit (PubChem  
94 CID 3692) inhibits the insulin secretion associated with high glucose levels in MIN6 cells [16].  
95 Moreover, the same authors reported H<sub>3</sub>R expression in pancreatic alpha cells, indicating that H<sub>3</sub>R

96 activation may reduce glucagon production by  $\alpha$ TC1.6 cells in a non-hyperglycemic condition [17].  
97 Notably, although the H<sub>3</sub>R has been known to play a critical role in homeostatic regulatory  
98 functions, such as control of food intake and maintenance of body weight [18], its contribution to  
99 diabetes is controversial [18-24] and still far from being fully understood. Indeed, the H<sub>3</sub>R inverse  
100 agonist clobenoprit (PubChem CID 2790) has been demonstrated to increase the hypothalamic  
101 histamine release and reduce the energy intake in normal and leptin-resistant mice with diet-induced  
102 obesity (DiO) [25]. So far, some newly synthesized H<sub>3</sub>R antagonists have been specifically tested  
103 in diabetic animal models demonstrating an effectiveness in reducing non-fasting glucose levels by  
104 potentially blocking the increase of HbA<sub>1c</sub> [26]. More interestingly, the strategy of an H<sub>3</sub>R  
105 antagonism combined with a phenylsulfonyleurea (well-known insulinotropic drugs) moiety has  
106 been explored [27]; although an effective prototype remains elusive. On the contrary, the activation  
107 of H<sub>3</sub>R in mice has been reported to decrease food intake and increase energy expenditure. Chronic  
108 dosing with a H<sub>3</sub>R agonist reduces body weight, fat mass, hyperleptinemia, and hyperinsulinemia in  
109 DiO mice [28]. Conversely, the protean H<sub>3</sub>R agonist proxyfan (PubChem CID 6421522) in mice  
110 improves glucose excursion increasing plasma insulin levels without affecting plasma glucagon  
111 levels [29]. Furthermore, the mildly obese H<sub>3</sub>R-deficient mice also demonstrate leptin and insulin  
112 resistance with impaired glucose tolerance [28]. Notably, the majority of these data were obtained  
113 before the clear demonstration of H<sub>3</sub>R peripheral expression [16, 30-34]. In particular, the  
114 pancreatic localization of the H<sub>3</sub>R raises the question of contradictory effects mediated by  
115 peripheral and central H<sub>3</sub>R.

116 Conflicting data concerning the involvement of H<sub>2</sub>R on glycaemia has also arisen. Its antagonism  
117 was reported to decrease [35], not affect [36, 37] and increase [38, 39] glucose levels. In  
118 comparison, the clinical experience with antipsychotic drugs generated clearer evidence for the  
119 involvement of the central H<sub>1</sub>R in the development of a diabetic phenotype [40]. Consistently, it has  
120 been found that the intra-ventricle or –hypothalamic administration of an H<sub>1</sub>R agonist induces  
121 satiety evoking an anti-obesity effect [41, 42]. Moreover, a strategy based on the contemporary H<sub>1</sub>R

122 agonism and H<sub>3</sub>R antagonism was demonstrated to have the potential to reduce obesity also in  
123 patients with comorbidities such as diabetes [43].

### 124 **3 Histamine and diabetes complications**

125 As mentioned above, despite the effectiveness of the different anti-diabetic strategies in controlling  
126 glycaemic levels, due to the glucose variability, patients are still exposed to a high risk of  
127 developing one or more of the longstanding and serious complications [4]. According to the  
128 definitions by the World Health Organization, the complications can be divided into macrovascular  
129 complications (including coronary artery disease, peripheral arterial disease and stroke) and  
130 microvascular complications (including diabetic nephropathy, neuropathy and retinopathy).  
131 Notably, for each new case of one given complication, a higher probability to display another one  
132 has been clearly documented [44].

133 Interestingly, a higher content of histamine in the anatomical districts involved in the diabetic  
134 longterm complications has been reported in different studies [6, 7]. Independently from the source  
135 of histamine within these districts, due to an activation of mast cells, a recruitment of basophils, an  
136 imbalance in the amine anabolism/catabolism or all three, the increased histaminergic tone is a  
137 common feature of the different complications and deserves to be further clarified. In particular,  
138 based on its vascular actions, histamine has been suggested to be a key triggering stimulus for the  
139 functional microangiopathy in diabetes mellitus, from retinopathy to nephropathy. However, its  
140 complete functional contribution to diabetes microvascular complications is yet to be elucidated.

#### 141 **3.1 Histamine and macrovascular complications**

142 Cardiovascular diseases (CVD) are one of the leading cause of death in diabetics, with an increased  
143 rate of heart disease or stroke from two- to four-fold compared to non-diabetic patients [45].  
144 Notably, histamine has been reported to regulate several cardiovascular and endothelial functions  
145 through concerted actions on both smooth muscle and endothelial cells. These actions result in

146 vasoconstriction or vasodilation based on histamine level, diameter and initial vessel tone, and  
147 relative location within the coronary circulation [46]. Again the first evidence for histamine  
148 involvement in diabetic macrovascular complications comes from the 1980s studies, when the  
149 histamine metabolism in both aortic endothelial and subjacent smooth muscle cells of control and  
150 diabetic rats was studied [47]. Despite such intriguing initial results, the hypothesis suggested was  
151 not further developed, with sparse, indirect and almost contrasting data remaining in the literature.

152 The evidence for a role of histamine stems from mast cell activation during the coronary blood  
153 vessel inflammation underling the atherogenesis process [48, 49], but also from its release from  
154 activated platelets [50]. Indeed, the number of mast cells was found to be increased in the narrow  
155 parts of blood vessels or at the site of plaque rupture in patients suffering from ischemic heart  
156 diseases [51, 52]. Notably, histamine release was demonstrated to significantly increase in coronary  
157 circulation during myocardial ischemia irrespective of the incidence of risk factors such as  
158 hypertension, type 2 diabetes, or dyslipidaemias [53].

159 Among the different receptors, historically the macrovascular effects of histamine seems to be  
160 mostly related to the H<sub>1</sub>R and H<sub>2</sub>R, but no specific studies were designed to investigate the whole  
161 histamine receptor family and only one observation claims the ability of H<sub>3</sub>R to regulate the  
162 coronary vascular response [54]. H<sub>1</sub>R has been reported to mediate the overexpression of the  
163 adhesion molecules [55] and the activation of nitric oxide synthase [55-57] evoked by histamine in  
164 vascular endothelial cells. H<sub>2</sub>R has been demonstrated to cause coronary dilation in both an  
165 endothelium independent [56] and dependent [54] manner.

166 Apart from atherosclerosis, patients with diabetes mellitus also exhibit QT (QTc) interval  
167 prolongation and increased QTc dispersion. Interestingly, HDC<sup>-/-</sup> mice with aging showed a  
168 decrease in maximum rate of depolarization (V<sub>max</sub>) and action potential duration (ADP)<sub>90</sub>  
169 prolongation comparable to those observed in the wild-type counterpart following diabetes  
170 induction by STZ administration [58]. This observation is still far from being conclusive, but it is in



171 keeping with the suggested arrhythmogenic potential of histamine [59, 60]. Although no specific  
172 receptor involvement have been described, histamine has been reported to induce Purkinje-fibers  
173 depolarization drive to ventricular tachycardia [61]. In mastocytosis patients, when a massive mast  
174 cells recruitment and degranulation occur, cardiac arrest has been observed [62]. Moreover, atrial  
175 fibrillation was described consequently to anaphylaxis reaction to venom and pollen  
176 immunotherapy in patients with established hyperhistaminemia [63]. Finally, a recent study  
177 pointing at a connection between histamine and diabetes macrovascular complications concluded  
178 that manipulation of cardiac mast cell function with nedocromil (PubChem CID 50294), a mast cell  
179 stabilizer, is sufficient to attenuate cardiomyopathy stimulated by diabetes [64].

180 Collectively, in the literature, there are not enough data to support any conclusive dissertation on  
181 the role of histamine in the development/maintenance of the macrovascular complication of  
182 diabetes, with the majority of its effects ascribable to its general anti-inflammatory properties.

### 183 **3.2 Histamine and microvascular complications**

184 The vasoactive properties of histamine led to the hypothesis advocating its contribution to the  
185 development and maintenance of diabetes-related microvascular complications. As discussed  
186 above, the role of the amine was investigated in the different end-organ(s).

#### 187 ***3.2.1 Diabetic neuropathy***

188 Diabetic neuropathy is an heterogeneous family of nerve disorders resulting in improper locomotor  
189 and visceral organ dysfunctions at the level of peripheral, central, and visceral sensorimotor and  
190 motor nerves [65]. According to this definition we can recognize peripheral, autonomic, proximal,  
191 or focal neuropathy. Among these different neuropathies the peripheral subtype is the most  
192 common. As a consequence of the peripheral nerve degeneration, triggered by persistent  
193 hyperglycaemia, and according to the affected nerves, diabetes patients suffer from pain, weakness,  
194 and eventual loss of sensation in addition to severe chronic pain syndromes.

195 The wheal response to intradermal application of histamine in diabetic patients have been assessed  
196 since 1930 [66], but its involvement in pain transmission was clearly recognized only by Schwartz  
197 and collaborators in 1991. So far many strands of evidence have pointed to histaminergic  
198 neurotransmission as an important factor in the control of pain [67-70]. Indeed, diabetic patients  
199 have been described to be less responsive to histamine as well as other neurogenic inflammation  
200 mediators such as substance P. In addition, a bidirectional relationship between different  
201 neurotransmitters and histamine exists [71]. The mRNA of H<sub>1</sub>R has been detected in many  
202 substance P positive neurons [72] and histamine has been shown to mediate the release of substance  
203 P and glutamate [73]. Also, the expression of H<sub>1</sub>R and/or H<sub>3</sub>R within calcitonin gene related peptide  
204 (CGRP) positive neurons [72] was determined. CGRP and histamine can establish a vicious circle  
205 inducing one another [70, 74, 75].

206 Although histamine has been reported to modulate nociception through all four types of its receptor,  
207 H<sub>1</sub>R [69, 76-78], H<sub>2</sub>R [76, 78, 79], H<sub>3</sub>R [78, 79] and H<sub>4</sub>R [80-85], in 2014 the H<sub>3</sub>R antagonists were  
208 reported as very promising for neuropathic pain [86]. However, only one study was designed to  
209 evaluate the antinociceptive effect of the H<sub>3</sub>R in a diabetic model. This respective study showed  
210 that the selective agonist immpip (PubChem CID 3035842) reversed formalin-induced  
211 hyperalgesia in both phases of the formalin test [87]. This effect could be associated with both H<sub>3</sub>R  
212 peripheral activation, resulting in a reduction in inflammatory peptides release, and H<sub>3</sub>R central  
213 activation, leading to the inhibition of pain transmission [88-92]. Consistent with this theory,  
214 immpip (PubChem CID 3035842) was found to inhibit mechanical, not thermal sensitivity in rats,  
215 but was shown to affect neither mechanical nor thermal sensitivity in mice [93]. Moreover, the role  
216 of H<sub>3</sub>R receptor in nociception is still controversial, with different antagonists, including  
217 GSK189254 (PubChem CID 9798547), GSK334429 (PubChem CID 11452311) and ABT-239  
218 (PubChem CID 9818903), demonstrated to be effective in reducing the sensitivity to mechanical  
219 stimuli [94] or in relief from surgically- and virally-induced neuropathic pain as well as  
220 inflammatory pain [82, 95, 96], respectively. The discrepancy emerging from the above described

221 literature can be specifically explained by the observation that the H<sub>3</sub>R receptor is expressed both as  
222 an autoreceptor and heteroreceptor which inhibits the release of histamine [97] and other  
223 neurotransmitters, respectively, including acetylcholine, noradrenaline, dopamine and serotonin  
224 [98-102].

225 Notably, histamine has also been shown to play a role in autonomic neuropathy. Indeed, the  
226 deranged autonomic function of the airways in diabetic patients with autonomic neuropathy has  
227 been demonstrated to elicit an exaggerated response to histamine-induced bronchoconstriction  
228 [103]. A direct stimulation of bronchial smooth muscle contraction combined with vagal-mediated  
229 reflexes after stimulation of rapidly adapting irritant receptors and C-fibers has been argued to be  
230 the mechanism underling the histamine-induce bronchoconstriction, while bronchomotor tone is  
231 mainly controlled by the parasympathetic nervous system. Therefore, the exaggerated response to  
232 histamine in diabetic patients could be due to the widespread autonomic damage to the respiratory  
233 parasympathetic and sympathetic pathways (including non-adrenergic non-cholinergic pathways  
234 influencing airway tone) and/or denervation hypersensitivity [104-111]. However, despite the above  
235 observations the role of histamine in autonomic neuropathy is still far from clear.

### 236 ***3.2.2 Diabetic retinopathy***

237 Diabetic retinopathy is still one of the major worldwide cause of blindness. Its development can be  
238 divided into non-proliferative, with microaneurysms, hard exudates, haemorrhages, and venous  
239 abnormalities and proliferative, with neovascularization, pre-retinal or vitreous haemorrhages, and  
240 fibrovascular proliferation [112, 113]. Development of glaucoma, retinal detachment, and vision  
241 loss may also happen at this stage [114].

242 A possible role for histamine in this context was postulated when diabetic retinopathy was mainly  
243 considered a microvascular complication of endothelial dysfunction with capillary basement  
244 membrane (BM) thickening, pericyte and endothelial cell loss, blood-retinal barrier (BRB)  
245 breakdown and leakage, acellular capillaries, and neovascularization [115, 116]. Indeed, most of

246 these vascular effects are consistent with the vasoactive properties of histamine. Antihistamines,  
247 such as diphenhydramine (PubChem CID 3100), astemizole (PubChem CID 2247) and ranitidine  
248 (PubChem CID 3001055), have been shown to reduce the leakage of retinal vessels in diabetic rats  
249 and humans [117, 118], but also to attenuate blood-brain barrier permeability and to ameliorate  
250 cerebral blood flow disturbances [119].

251 In particular, it was reported that histamine specifically affects the zonula occludent (ZO)-1  
252 expression in cultured retinal microvascular endothelial cells [120]. Interestingly, the same authors  
253 described a similar inhibitory effect on ZO-1 expression for both high glucose (20mM) and low  
254 insulin ( $10^{-12}$ M) culturing condition [121]. These data provide a mechanistic interpretation of the  
255 ability of histamine to induce a BRB dysfunction in both experimental diabetes and diabetic  
256 patients [118, 122, 123], suggesting that the increased histaminergic tone consequent to the diabetic  
257 milieu could directly account for the BRB breakdown and leakage vascular, for many years  
258 considered pivotal in the pathogenesis of diabetic retinopathy. These effects can be considered at  
259 least qualitatively equivalent to those observed for the vascular endothelial growth factor (VEGF)  
260 on permeability leakage [124].

261 The possible involvement of histamine in diabetic retinopathy is still plausible, although not deeply  
262 investigated, when, according to the neurodegenerative nature of this disease, the other components  
263 of the retina, such as neurons and glial cells are taken into account. It is currently acknowledged  
264 that cellular, molecular, and functional changes are evidenced in all the retina cellular  
265 compartments [115, 116, 125-127] at an early stage of diabetic retinopathy. Intriguingly, an  
266 increase in histamine synthesis was observed within the retinas of diabetic rats [117, 128]. This was  
267 due to an over-expression of the HDC enzyme in both the retinal neurons and glia [129]. As  
268 mentioned above for plasma, aorta and pancreas, an insulin-histamine loop does exist also within  
269 the retina. The histamine overproduction induced by diabetes was decreased by both the HDC  
270 inhibitor or insulin administration in experimental diabetes [128].

271 Therefore, collectively the data in the literature suggest that histamine could at least participate in  
272 the neural cell contribution to the diabetes-induced vascular leakage.

### 273 **3.2.3 Diabetic nephropathy**

274 Diabetic nephropathy is one of the most important causes of chronic kidney disease (CKD), and  
275 therefore of end-stage renal disease (ESRD) in Western nations. It has been estimated that the risk  
276 of developing CKD is increased by a factor of 12-fold in type 1 diabetes and 6-fold in type 2  
277 diabetes, compared with non-diabetic individuals [130]. About one-third of diabetic patients begin  
278 to show persistently high urinary albumin excretion, thence being at high risk to develop *in primis*  
279 diabetic ESRD, but also cardiovascular diseases and premature mortality, even without progression  
280 to ESRD [131].

281 Intriguingly, the first evidence for a possible role of histamine in the development of diabetic  
282 nephropathy arose from studies performed in STZ diabetic rats in which histamine levels, consistent  
283 with the generalized increase of the amine induced by diabetes, were found to be significantly  
284 increased in the kidney [132, 133]. Again, a greater tissue HDC activity without a concomitant  
285 decrease in histaminase activity could account for this event [133] especially at the glomerular level  
286 which has been identify as the major site of intrarenal histamine synthesis and accumulation [109,  
287 134]. The demonstrated ability of histamine to increase salt and water excretion [135-137], decrease  
288 the ultrafiltration coefficient by reducing the total filtration surface area [137], and increase renin  
289 release [138] led to the hypothesis of a direct involvement of histamine in regulating the renal  
290 microcirculation. For a long period, histamine was claimed to affect the glomerular  
291 microcirculation. However, recent evidence suggest and support the hypothesis of direct effects of  
292 histamine on glomerular integrity and function, far beyond simply modifying the glomerular  
293 hemodynamic microcirculation [139].

294 At the tubular level, the first evidence of a histamine detrimental effect on tubular integrity and  
295 function was already available in the 1960s and 1970s when several reports suggested that mast

296 cells may be involved in kidney diseases, but as mast cells were not easily detected by routine  
297 histochemical staining, they were ignored or forgotten by nephrologists for many years [140]. In the  
298 normal kidney, mast cells are constitutively present at a low number. However, their density  
299 increases in the renal cortical tubulointerstitium, in the periglomerular and perivascular area, but  
300 not in glomeruli, in a variety of human renal diseases including diabetic nephropathy [140-142].  
301 Moreover, mast cells have occasionally been found in the wall of atrophied tubules [142]. In  
302 particular, it has been shown that with disease progression, the number and degranulation status of  
303 mast cells increased, suggesting that histamine released by mast cells into the tubular interstitium  
304 may promote renal inflammation and fibrosis [141, 142]. Indeed, histamine has been reported to  
305 promote fibrosis affecting the tissue growth factor (TGF)- $\beta$ /Smad3/4 axis in the lung [143].

306 In the past several decades, all the renal effects of histamine were ascribed only to H<sub>1</sub>R and H<sub>2</sub>R,  
307 both identified in the glomeruli [12, 132]. Consistent with results obtained in rats [138], it was  
308 found in humans that the H<sub>2</sub>R is the subtype present in glomeruli and involved in the cAMP  
309 accumulation subsequent to the increasing histamine [144]. Moreover, it has been demonstrated that  
310 histamine modulates mesangial cells and glomeruli via H<sub>1</sub>R [145]. In the last few years, convergent  
311 lines of evidence strongly support the conclusion that all four histamine receptors are present and  
312 functional in the human nephron, although with a differential anatomical topology [34]. Notably,  
313 among them, both the H<sub>3</sub>R and the H<sub>4</sub>R have been reported to be profoundly upregulated at the  
314 tubular level in STZ treated rats, which also displayed parallel renal damage (mostly again at the  
315 tubular level) [33, 146]. These latter data led to a new interest in histamine in kidney  
316 (patho)physiology supporting the hypothesis that it could directly and specifically contribute to the  
317 onset/progression of diabetic nephropathy.

#### 318 **4 Conclusion**

319 Is it really the time to reconsider the functional contribution of histamine in diabetes? Indeed,  
320 although still far from conclusive, different elements point to a clear role of histamine in diabetes

321 and diabetic complications etiopathogenesis. The evidence is strong in some cases, sometimes  
 322 independent, but sometimes contradictory; despite this heterogeneity, when viewing the timeline of  
 323 interest for histamine involvement in this disease (Figure 1) it appears phasic with a clear upturn  
 324 and renewal in interest in the last couple of years, thanks to the very recent discovery of a direct  
 325 effect of histamine on glycaemia [13, 16, 17] as well as a profound up-regulation of both H<sub>3</sub>R and  
 326 H<sub>4</sub>R in the diabetic animal kidney [33, 146]. As a whole, the revisit of the literature herein clearly  
 327 shows growing independent lines of evidence for a bidirectional connection between histamine and  
 328 diabetes (Table I).

**Table I. The diabetes-histamine loop: the state of the art**

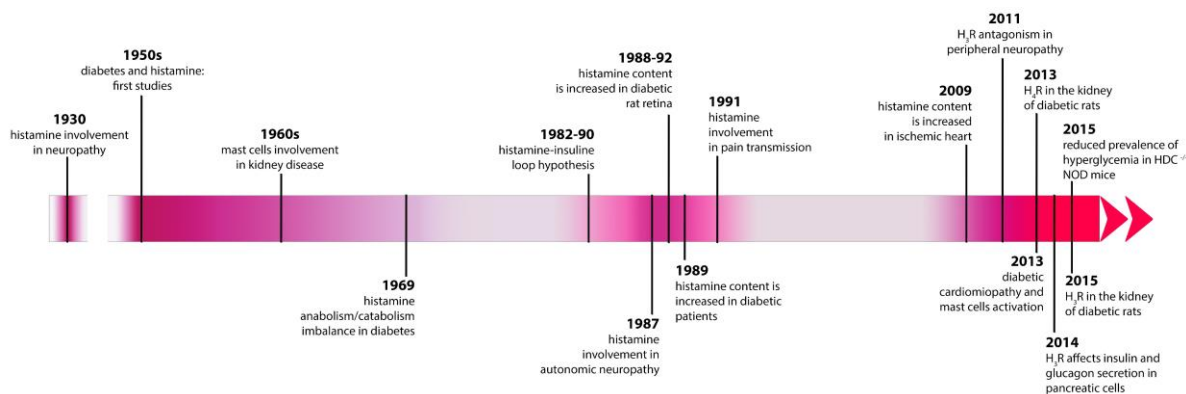
Diabetes complication	Diabetes affects histamine	Histamine influences the progression	Receptor involved			
			H <sub>1</sub> R	H <sub>2</sub> R	H <sub>3</sub> R	H <sub>4</sub> R
<b>macrovascular</b>	↑ HDC and histamine in aortic endothelial and smooth muscle cells	atherogenesis coronary dilation, arrhythmogenic activity (QT-prolongation)	++	++	+	n.d.
<b>microvascular</b>						
<b><u>neuropathy</u></b>						
<i>peripheral neuropathy</i>		pain control, neurogenic inflammation	n.d.	n.d.	+	n.d.
<i>autonomic neuropathy</i>		↑ bronchoconstriction	n.d.	n.d.	n.d.	n.d.
<b><u>retinopathy</u></b>	↑ HDC and histamine	↑ vascular leakage	++			
<b><u>nephropathy</u></b>	↑ HDC, histamine, H <sub>3</sub> R and H <sub>4</sub> R expression	↑ salt and water excretion, ↓ ultrafiltration coefficient, ↑ renin release	+	+	?	?

++ = strongest evidence; + = spare evidence; ? = under investigation/characterization; n.d. = no data

329

330

331 Therefore, a pathophysiological role for this amine cannot be discounted anymore and new studies  
332 specifically aimed to assess its function in the onset and progression of the longstanding diabetes  
333 complications are strictly warranted. The state of the art on histamine in diabetes is recapitulated in  
334 Figure 1.



335

336 **Figure 1. Milestones in the story of histamine and diabetes.** Timeline of major events in the  
337 history of histamine and its link to diabetes and its complications - 1930s to present day. The phasic  
338 interest with the recent upsurge in the last couple of years is depicted.

339

340 As reported in Table I, not all the diabetic complications have been provided with the same level of  
341 compelling evidence. Many blind spots remain regarding the role of histamine in macrovascular  
342 complications where the effect of the amine seems to be mostly related to its general vasoactive  
343 properties rather than to a specific function in diabetes. The discrepancies often observed in the  
344 literature can be mostly ascribed to the different models adopted as well as to the doses, the  
345 administration route and the actual selectivity of the compound used, which could differentially  
346 affect the central and peripheral histaminergic system. More notably, the majority of the evidence  
347 for histamine involvement in the different diabetes complications arises from studies not directly  
348 aimed to assess its role in diabetic disease. This is in particular the case for diabetic peripheral  
349 neuropathy where the studies were designed to assess a general role in nociception and/or



350 neuropathic pain. Other fields, such as retinopathy, have found using new strategies, effective and  
351 specific pharmacological tools that have downgraded the antihistaminergic approach to a supporting  
352 role. However, since many of the investigations were prior to the discovery of the newest histamine  
353 receptor members H<sub>3</sub>R and H<sub>4</sub>R, [147] there is scope for new insights in histamine and diabetes,  
354 and the opportunity to develop new antihistamine drugs to overcome the paucity of effective  
355 therapies.

356

357 **Conflict of interest** none

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362 authors contributed and have approved the submitted version of the paper.

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