

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Histamine in diabetes: Is it time to reconsider?

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1611493> since 2021-04-19T12:38:36Z

Published version:

DOI:10.1016/j.phrs.2016.06.021

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 Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in PHARMACOLOGICAL RESEARCH, 111, 2016, 10.1016/j.phrs.2016.06.021.

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

- (1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.
- (2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.
- (3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>), 10.1016/j.phrs.2016.06.021

The publisher's version is available at:

<http://linkinghub.elsevier.com/retrieve/pii/S1043661816305953>

When citing, please refer to the published version.

Link to this full text:

<http://hdl.handle.net/2318/1611493>

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

2
3 *Alessandro Pini^a, Ilona Obara^b, Emma Battell^c, Paul L Chazot^c, Arianna Carolina Rosa^{c,d}*

4
5
6 *^aDepartment of Clinical and Experimental Medicine, University of Florence, Viale Pieraccini 6 -*
7 *50139, Florence, Italy, apini@unifl.it; ^bSchool of Medicine, Pharmacy and Health, Durham*
8 *University, Stockton-on-Tees TS17 6BH, United Kingdom, ilona.obara@durham.ac.uk; ^cSchool of*
9 *Biological and Biomedical Science, Durham University, Durham DH13LE, UK,*
10 *emma.battell@durham.ac.uk and paul.chazot@durham.ac.uk; ^dDepartment of Scienza e*
11 *Tecnologia del Farmaco, University of Turin, Via P. Giuria 9 - 10125, Turin, Italy, acrosa@unito.it*

12
13
14
15

16 **Corresponding author:**

17 Alessandro Pini,
18 Department of Clinical and Experimental Medicine, University of Florence,
19 Viale Pieraccini 6 - 50139, Florence, Italy
20 Phone: +390552758155
21 e-mail: apini@unifi.it

22

23 **Abstract**

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

33

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

35

36 **Abbreviations:**

37 ADP= action potential duration; AGEs = advanced glycation end-products; BM = basement
38 membrane; BRB = blood-retinal barrier; CGRP = calcitonin gene related peptide; CKD = chronic
39 kidney disease; DAO = diamine oxidase; DiO = diet-induced obesity; ESRD = end-stage renal
40 disease; H₁₋₄Rs = histamine H₁₋₄Rs; HbA₁ = glycated hemoglobin; HDC = histidine decarboxylase;
41 STZ = streptozotocin; TGF- β = tissue growth factor- β ; TCAs = tricyclic antidepressants; V_{max} =
42 maximum rate of depolarization; VEGF = vascular endothelial growth factor; ZO-1 = zonula
43 occludent-1

44 **1 Introduction**

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

64 **2 Histamine and glycaemia**

65 Histamine is involved in a wide variety of pathophysiological events mostly related to the
66 inflammatory response through four receptors, namely H₁₋₄Rs. The first studies of histamine and
67 diabetes date back to the 1950s. Since that time the involvement of histamine in diabetes was
68 related to its well-known vasoactive properties and permeability leakage effects correlated to

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

83 More intriguingly, it has been reported that histamine plasma and aortic synthesis [10] in diabetic
84 rats are reduced when insulin is administered [14], thus strongly supporting the hypothesis for an
85 interconnection between histamine and glycaemic status. This hypothesis is further strengthened by
86 the study of Azevedo and colleagues (1990) reporting an increase of pancreatic islet histamine
87 content in streptozotocin (STZ)-induced diabetes rats [15]. Interestingly, recent data suggest the
88 involvement of the peripheral H₃R in the insulin-histamine loop (Supplementary Figure 1). Indeed,
89 Nakamura and colleagues (2014) provided the first evidence for a potential diabetogenic effect of
90 the pancreatic H₃R, through reporting the presence of functional histamine H₃R in this tissue. In
91 particular, it has been demonstrated that H₃R activation in pancreatic beta cells by imetit (PubChem
92 CID 3692) inhibits the insulin secretion associated with high glucose levels in MIN6 cells [16].
93 Moreover, the same authors reported H₃R expression in pancreatic alpha cells, indicating that H₃R
94 activation may reduce glucagon production by α TC1.6 cells in a non-hyperglycemic condition [17].

95 Notably, although the H₃R has been known to play a critical role in homeostatic regulatory
96 functions, such as control of food intake and maintenance of body weight [18], its contribution to
97 diabetes is controversial [18-24] and still far from being fully understood. Indeed, the H₃R inverse
98 agonist clobenoprit (PubChem CID 2790) has been demonstrated to increase the hypothalamic
99 histamine release and reduce the energy intake in normal and leptin-resistant mice with diet-induced
100 obesity (DiO) [25]. So far, some newly synthesized H₃R antagonists have been specifically tested
101 in diabetic animal models demonstrating an effectiveness in reducing non-fasting glucose levels by
102 potentially blocking the increase of HbA_{1c} [26]. More interestingly, the strategy of an H₃R
103 antagonism combined with a phenylsulfonyleurea (well-known insulinotropic drugs) moiety has
104 been explored [27]; although an effective prototype remains elusive. On the contrary, the activation
105 of H₃R in mice has been reported to decrease food intake and increase energy expenditure. Chronic
106 dosing with a H₃R agonist reduces body weight, fat mass, hyperleptinemia, and hyperinsulinemia in
107 DiO mice [28]. Conversely, the protean H₃R agonist proxyfan (PubChem CID 6421522) in mice
108 improves glucose excursion increasing plasma insulin levels without affecting plasma glucagon
109 levels [29]. Furthermore, the mildly obese H₃R-deficient mice also demonstrate leptin and insulin
110 resistance with impaired glucose tolerance [28]. Notably, the majority of these data were obtained
111 before the clear demonstration of H₃R peripheral expression [16, 30-34]. In particular, the
112 pancreatic localization of the H₃R raises the question of contradictory effects mediated by
113 peripheral and central H₃R.

114 Conflicting data concerning the involvement of H₂R on glycaemia has also arisen. Its antagonism
115 was reported to decrease [35], not affect [36, 37] and increase [38, 39] glucose levels. In
116 comparison, the clinical experience with antipsychotic drugs generated clearer evidence for the
117 involvement of the central H₁R in the development of a diabetic phenotype [40]. Consistently, it has
118 been found that the intra-ventricle or –hypothalamic administration of an H₁R agonist induces
119 satiety evoking an anti-obesity effect [41, 42]. Moreover, a strategy based on the contemporary H₁R

120 agonism and H₃R antagonism was demonstrated to have the potential to reduce obesity also in
121 patients with comorbidities such as diabetes [43].

122 **3 Histamine and diabetes complications**

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

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

139 **3.1 Histamine and macrovascular complications**

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

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

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

157 Among the different receptors, historically the macrovascular effects of histamine seems to be
158 mostly related to the H₁R and H₂R, but no specific studies were designed to investigate the whole
159 histamine receptor family and only one observation claims the ability of H₃R to regulate the
160 coronary vascular response [54]. H₁R has been reported to mediate the overexpression of the
161 adhesion molecules [55] and the activation of nitric oxide synthase [55-57] evoked by histamine in
162 vascular endothelial cells. H₂R has been demonstrated to cause coronary dilation in both an
163 endothelium independent [56] and dependent [54] manner.

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

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

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

181 **3.2 Histamine and microvascular complications**

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

185 ***3.2.1 Diabetic neuropathy***

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

193 The wheal response to intradermal application of histamine in diabetic patients have been assessed
194 since 1930 [66], but its involvement in pain transmission was clearly recognized only by Schwartz
195 and collaborators in 1991. So far many strands of evidence have pointed to histaminergic
196 neurotransmission as an important factor in the control of pain [67-70]. Indeed, diabetic patients
197 have been described to be less responsive to histamine as well as other neurogenic inflammation
198 mediators such as substance P. In addition, a bidirectional relationship between different
199 neurotransmitters and histamine exists [71]. The mRNA of H₁R has been detected in many
200 substance P positive neurons [72] and histamine has been shown to mediate the release of substance
201 P and glutamate [73]. Also, the expression of H₁R and/or H₃R within calcitonin gene related peptide
202 (CGRP) positive neurons [72] was determined. CGRP and histamine can establish a vicious circle
203 inducing one another [70, 74, 75].

204 Although histamine has been reported to modulate nociception through all four types of its receptor,
205 H₁R [69, 76-78], H₂R [76, 78, 79], H₃R [78, 79] and H₄R [80-85], in 2014 the H₃R antagonists were
206 reported as very promising for neuropathic pain [86]. However, only one study was designed to
207 evaluate the antinociceptive effect of the H₃R in a diabetic model. This respective study showed
208 that the selective agonist immpip (PubChem CID 3035842) reversed formalin-induced
209 hyperalgesia in both phases of the formalin test [87]. This effect could be associated with both H₃R
210 peripheral activation, resulting in a reduction in inflammatory peptides release, and H₃R central
211 activation, leading to the inhibition of pain transmission [88-92]. Consistent with this theory,
212 immpip (PubChem CID 3035842) was found to inhibit mechanical, not thermal sensitivity in rats,
213 but was shown to affect neither mechanical nor thermal sensitivity in mice [93]. Moreover, the role
214 of H₃R receptor in nociception is still controversial, with different antagonists, including
215 GSK189254 (PubChem CID 9798547), GSK334429 (PubChem CID 11452311) and ABT-239
216 (PubChem CID 9818903), demonstrated to be effective in reducing the sensitivity to mechanical
217 stimuli [94] or in relief from surgically- and virally-induced neuropathic pain as well as
218 inflammatory pain [82, 95, 96], respectively. The discrepancy emerging from the above described

219 literature can be specifically explained by the observation that the H₃R receptor is expressed both as
220 an autoreceptor and heteroreceptor which inhibits the release of histamine [97] and other
221 neurotransmitters, respectively, including acetylcholine, noradrenaline, dopamine and serotonin
222 [98-102].

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

234 ***3.2.2 Diabetic retinopathy***

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

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

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

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

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

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

271 **3.2.3 Diabetic nephropathy**

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

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

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

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

304 In the past several decades, all the renal effects of histamine were ascribed only to H₁R and H₂R,
305 both identified in the glomeruli [12, 132]. Consistent with results obtained in rats [138], it was
306 found in humans that the H₂R is the subtype present in glomeruli and involved in the cAMP
307 accumulation subsequent to the increasing histamine [144]. Moreover, it has been demonstrated that
308 histamine modulates mesangial cells and glomeruli via H₁R [145]. In the last few years, convergent
309 lines of evidence strongly support the conclusion that all four histamine receptors are present and
310 functional in the human nephron, although with a differential anatomical topology [34]. Notably,
311 among them, both the H₃R and the H₄R have been reported to be profoundly upregulated at the
312 tubular level in STZ treated rats, which also displayed parallel renal damage (mostly again at the
313 tubular level) [33, 146]. These latter data led to a new interest in histamine in kidney
314 (patho)physiology supporting the hypothesis that it could directly and specifically contribute to the
315 onset/progression of diabetic nephropathy.

316 **4 Conclusion**

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

319 and diabetic complications etiopathogenesis. The evidence is strong in some cases, sometimes
 320 independent, but sometimes contradictory; despite this heterogeneity, when viewing the timeline of
 321 interest for histamine involvement in this disease (Figure 1) it appears phasic with a clear upturn
 322 and renewal in interest in the last couple of years, thanks to the very recent discovery of a direct
 323 effect of histamine on glycaemia [13, 16, 17] as well as a profound up-regulation of both H₃R and
 324 H₄R in the diabetic animal kidney [33, 146]. As a whole, the revisit of the literature herein clearly
 325 shows growing independent lines of evidence for a bidirectional connection between histamine and
 326 diabetes (Table I).

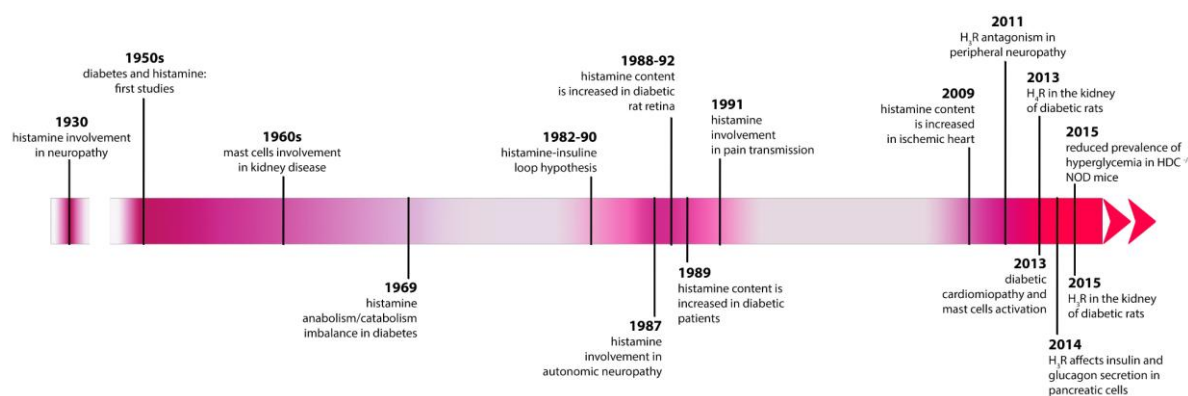
Table I. The diabetes-histamine loop: the state of the art

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

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

327

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



332

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

336

337 As reported in Table I, not all the diabetic complications have been provided with the same level of
 338 compelling evidence. Many blind spots remain regarding the role of histamine in macrovascular
 339 complications where the effect of the amine seems to be mostly related to its general vasoactive
 340 properties rather than to a specific function in diabetes. The discrepancies often observed in the
 341 literature can be mostly ascribed to the different models adopted as well as to the doses, the
 342 administration route and the actual selectivity of the compound used, which could differentially
 343 affect the central and peripheral histaminergic system. More notably, the majority of the evidence
 344 for histamine involvement in the different diabetes complications arises from studies not directly
 345 aimed to assess its role in diabetic disease. This is in particular the case for diabetic peripheral
 346 neuropathy where the studies were designed to assess a general role in nociception and/or
 347 neuropathic pain. Other fields, such as retinopathy, have found using new strategies, effective and
 348 specific pharmacological tools that have downgraded the antihistaminergic approach to a supporting
 349 role. However, since many of the investigations were prior to the discovery of the newest histamine
 350 receptor members H₃R and H₄R, [147] there is scope for new insights in histamine and diabetes,
 351 and the opportunity to develop new antihistamine drugs to overcome the paucity of effective
 352 therapies.

353

354 **Conflict of interest** none

355 **Acknowledgements** This work was funded by the University of Turin (ex60% 2014), World Wide
356 Style Project (WWS; University of Turin/Fondazione CRT) and University of Florence (ex60%
357 2014). ACR and AP designed the study; AP, EB and IO conducted the literature search and
358 analysis; ACR, AP, IO and PLC wrote or contributed to the writing of the manuscript. All co-
359 authors contributed and have approved the submitted version of the paper.

360 **References**

361

362 [1] K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its
363 complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO
364 consultation, *Diabetic medicine : a journal of the British Diabetic Association* 15(7) (1998) 539-53.

365 [2] A. American Diabetes, Diagnosis and classification of diabetes mellitus, *Diabetes care* 33 Suppl
366 1 (2010) S62-9.

367 [3] J.E. Shaw, R.A. Sicree, P.Z. Zimmet, IDF Diabetes atlas - Key findings 2014, *Res Clin Pract* 87
368 (2014) 4-14.

369 [4] D. Murphy, Acute complications of diabetes mellitus, *Nurse practitioner forum* 9(2) (1998) 69-
370 73.

371 [5] E. Sick, S. Brehin, P. Andre, G. Coupin, Y. Landry, K. Takeda, J.P. Gies, Advanced glycation
372 end products (AGEs) activate mast cells, *British journal of pharmacology* 161(2) (2010) 442-55.

373 [6] D.S. Gill, M.A. Barradas, V.A. Fonseca, P. Dandona, Plasma histamine concentrations are
374 elevated in patients with diabetes mellitus and peripheral vascular disease, *Metabolism: clinical and*
375 *experimental* 38(3) (1989) 243-7.

376 [7] W.A. Fogel, C. Chmielecki, M. Gralek, C. Maslinski, Histamine metabolism in diabetic rats,
377 *Agents and actions* 30(1-2) (1990) 243-6.

378 [8] G. Kahlson, E. Rosengren, R. Thunberg, Accelerated mobilization and formation of histamine in
379 the gastric mucosa evoked by vagal excitation, *The Journal of physiology* 190(3) (1967) 455-63.

380 [9] R.J. Levine, W.W. Noll, Histidine decarboxylase and its inhibition, *Annals of the New York*
381 *Academy of Sciences* 166(1) (1969) 246-56.

382 [10] A. Orlidge, T.M. Hollis, Aortic endothelial and smooth muscle histamine metabolism in
383 experimental diabetes, *Arteriosclerosis* 2(2) (1982) 142-50.

384 [11] T.M. Hollis, S.G. Gallik, A. Orlidge, J.C. Yost, Aortic endothelial and smooth muscle
385 histamine metabolism. Relationship to aortic ¹²⁵I-albumin accumulation in experimental diabetes,
386 *Arteriosclerosis* 3(6) (1983) 599-606.

387 [12] D.S. Gill, C.S. Thompson, P. Dandona, Histamine synthesis and catabolism in various tissues
388 in diabetic rats, *Metabolism: clinical and experimental* 39(8) (1990) 815-8.

389 [13] M. Alkan, F. Machavoine, R. Rignault, J. Dam, M. Dy, N. Thieblemont, Histidine
390 Decarboxylase Deficiency Prevents Autoimmune Diabetes in NOD Mice, *Journal of diabetes*
391 *research* 2015 (2015) 965056.

392 [14] T.M. Hollis, J.A. Kern, N.A. Enea, A.J. Cosgarea, Changes in plasma histamine concentration
393 in the streptozotocin-diabetic rat, *Experimental and molecular pathology* 43(1) (1985) 90-6.

394 [15] M.S. Azevedo, I.J. Silva, J.F. Raposo, I.F. Neto, J.G. Falcao, C.F. Manso, Early increase in
395 histamine concentration in the islets of Langerhans isolated from rats made diabetic with
396 streptozotocin, *Diabetes research and clinical practice* 10(1) (1990) 59-63.

397 [16] T. Nakamura, T. Yoshikawa, N. Noguchi, A. Sugawara, A. Kasajima, H. Sasano, K. Yanai,
398 The expression and function of histamine H₃ receptors in pancreatic beta cells, *British journal of*
399 *pharmacology* 171(1) (2014) 171-85.

400 [17] T. Nakamura, T. Yoshikawa, F. Naganuma, A. Mohsen, T. Iida, Y. Miura, A. Sugawara, K.
401 Yanai, Role of histamine H₃ receptor in glucagon-secreting alphaTC1.6 cells, *FEBS open bio* 5
402 (2015) 36-41.

- 403 [18] A.A. Hancock, M.E. Brune, Assessment of pharmacology and potential anti-obesity properties
404 of H3 receptor antagonists/inverse agonists, *Expert opinion on investigational drugs* 14(3) (2005)
405 223-41.
- 406 [19] K. Ookuma, T. Sakata, K. Fukagawa, H. Yoshimatsu, M. Kurokawa, H. Machidori, K.
407 Fujimoto, Neuronal histamine in the hypothalamus suppresses food intake in rats, *Brain research*
408 628(1-2) (1993) 235-42.
- 409 [20] H. Yoshimatsu, H. Machidori, T. Doi, M. Kurokawa, K. Ookuma, M. Kang, K. Fujimoto, T.
410 Sakata, Abnormalities in obese Zuckers: defective control of histaminergic functions, *Physiology &*
411 *behavior* 54(3) (1993) 487-91.
- 412 [21] A. Lecklin, P. Etu-Seppala, H. Stark, L. Tuomisto, Effects of intracerebroventricularly infused
413 histamine and selective H1, H2 and H3 agonists on food and water intake and urine flow in Wistar
414 rats, *Brain research* 793(1-2) (1998) 279-88.
- 415 [22] A. Mollet, T.A. Lutz, S. Meier, T. Riediger, P.A. Rushing, E. Scharrer, Histamine H1 receptors
416 mediate the anorectic action of the pancreatic hormone amylin, *American journal of physiology.*
417 *Regulatory, integrative and comparative physiology* 281(5) (2001) R1442-8.
- 418 [23] K. Tsuda, H. Yoshimatsu, A. Nijjima, S. Chiba, T. Okeda, T. Sakata, Hypothalamic histamine
419 neurons activate lipolysis in rat adipose tissue, *Experimental biology and medicine* 227(3) (2002)
420 208-13.
- 421 [24] D.K. Sindelar, M.L. Shepperd, R.T. Pickard, J. Alexander-Chacko, M.J. Dill, J.W. Cramer,
422 D.P. Smith, R. Gadski, Central H3R activation by thioperamide does not affect energy balance,
423 *Pharmacology, biochemistry, and behavior* 78(2) (2004) 275-83.
- 424 [25] T. Ishizuka, K. Hatano, T. Murotani, A. Yamatodani, Comparison of the effect of an H(3)-
425 inverse agonist on energy intake and hypothalamic histamine release in normal mice and leptin
426 resistant mice with high fat diet-induced obesity, *Behavioural brain research* 188(2) (2008) 250-4.
- 427 [26] D.I.G. Replication, C. Meta-analysis, C. Asian Genetic Epidemiology Network Type 2
428 Diabetes, C. South Asian Type 2 Diabetes, C. Mexican American Type 2 Diabetes, C. Type 2

429 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples, A.
430 Mahajan, M.J. Go, W. Zhang, J.E. Below, K.J. Gaulton, T. Ferreira, M. Horikoshi, A.D. Johnson,
431 M.C. Ng, I. Prokopenko, D. Saleheen, X. Wang, E. Zeggini, G.R. Abecasis, L.S. Adair, P.
432 Almgren, M. Atalay, T. Aung, D. Baldassarre, B. Balkau, Y. Bao, A.H. Barnett, I. Barroso, A.
433 Basit, L.F. Been, J. Beilby, G.I. Bell, R. Benediktsson, R.N. Bergman, B.O. Boehm, E. Boerwinkle,
434 L.L. Bonnycastle, N. Burtt, Q. Cai, H. Campbell, J. Carey, S. Cauchi, M. Caulfield, J.C. Chan, L.C.
435 Chang, T.J. Chang, Y.C. Chang, G. Charpentier, C.H. Chen, H. Chen, Y.T. Chen, K.S. Chia, M.
436 Chidambaram, P.S. Chines, N.H. Cho, Y.M. Cho, L.M. Chuang, F.S. Collins, M.C. Cornelis, D.J.
437 Couper, A.T. Crenshaw, R.M. van Dam, J. Danesh, D. Das, U. de Faire, G. Dedoussis, P. Deloukas,
438 A.S. Dimas, C. Dina, A.S. Doney, P.J. Donnelly, M. Dorkhan, C. van Duijn, J. Dupuis, S. Edkins,
439 P. Elliott, V. Emilsson, R. Erbel, J.G. Eriksson, J. Escobedo, T. Esko, E. Eury, J.C. Florez, P.
440 Fontanillas, N.G. Forouhi, T. Forsen, C. Fox, R.M. Fraser, T.M. Frayling, P. Froguel, P. Frossard,
441 Y. Gao, K. Gertow, C. Gieger, B. Gigante, H. Grallert, G.B. Grant, L.C. Grrop, C.J. Groves, E.
442 Grundberg, C. Guiducci, A. Hamsten, B.G. Han, K. Hara, N. Hassanali, A.T. Hattersley, C.
443 Hayward, A.K. Hedman, C. Herder, A. Hofman, O.L. Holmen, K. Hovingh, A.B. Hreidarsson, C.
444 Hu, F.B. Hu, J. Hui, S.E. Humphries, S.E. Hunt, D.J. Hunter, K. Hveem, Z.I. Hydrie, H. Ikegami,
445 T. Illig, E. Ingelsson, M. Islam, B. Isomaa, A.U. Jackson, T. Jafar, A. James, W. Jia, K.H. Jockel,
446 A. Jonsson, J.B. Jowett, T. Kadowaki, H.M. Kang, S. Kanoni, W.H. Kao, S. Kathiresan, N. Kato, P.
447 Katulanda, K.M. Keinanen-Kiukkaanniemi, A.M. Kelly, H. Khan, K.T. Khaw, C.C. Khor, H.L. Kim,
448 S. Kim, Y.J. Kim, L. Kinnunen, N. Klopp, A. Kong, E. Korpi-Hyovalti, S. Kowlessur, P. Kraft, J.
449 Kravic, M.M. Kristensen, S. Krithika, A. Kumar, J. Kumate, J. Kuusisto, S.H. Kwak, M. Laakso, V.
450 Lagou, T.A. Lakka, C. Langenberg, C. Langford, R. Lawrence, K. Leander, J.M. Lee, N.R. Lee, M.
451 Li, X. Li, Y. Li, J. Liang, S. Liju, W.Y. Lim, L. Lind, C.M. Lindgren, E. Lindholm, C.T. Liu, J.J.
452 Liu, S. Lobbens, J. Long, R.J. Loos, W. Lu, J. Luan, V. Lyssenko, R.C. Ma, S. Maeda, R. Magi, S.
453 Mannisto, D.R. Matthews, J.B. Meigs, O. Melander, A. Metspalu, J. Meyer, G. Mirza, E. Mihailov,
454 S. Moebus, V. Mohan, K.L. Mohlke, A.D. Morris, T.W. Muhleisen, M. Muller-Nurasyid, B. Musk,

455 J. Nakamura, E. Nakashima, P. Navarro, P.K. Ng, A.C. Nica, P.M. Nilsson, I. Njolstad, M.M.
456 Nothen, K. Ohnaka, T.H. Ong, K.R. Owen, C.N. Palmer, J.S. Pankow, K.S. Park, M. Parkin, S.
457 Pechlivanis, N.L. Pedersen, L. Peltonen, J.R. Perry, A. Peters, J.M. Pinidiyapathirage, C.G. Platou,
458 S. Potter, J.F. Price, L. Qi, V. Radha, L. Rallidis, A. Rasheed, W. Rathman, R. Rauramaa, S.
459 Raychaudhuri, N.W. Rayner, S.D. Rees, E. Rehnberg, S. Ripatti, N. Robertson, M. Roden, E.J.
460 Rossin, I. Rudan, D. Rybin, T.E. Saaristo, V. Salomaa, J. Saltevo, M. Samuel, D.K. Sanghera, J.
461 Saramies, J. Scott, L.J. Scott, R.A. Scott, A.V. Segre, J. Sehmi, B. Sennblad, N. Shah, S. Shah, A.S.
462 Shera, X.O. Shu, A.R. Shuldiner, G. Sigurdsson, E. Sijbrands, A. Silveira, X. Sim, S.
463 Sivapalaratnam, K.S. Small, W.Y. So, A. Stancakova, K. Stefansson, G. Steinbach, V.
464 Steinhorsdottir, K. Stirrups, R.J. Strawbridge, H.M. Stringham, Q. Sun, C. Suo, A.C. Syvanen, R.
465 Takayanagi, F. Takeuchi, W.T. Tay, T.M. Teslovich, B. Thorand, G. Thorleifsson, U.
466 Thorsteinsdottir, E. Tikkanen, J. Trakalo, E. Tremoli, M.D. Trip, F.J. Tsai, T. Tuomi, J.
467 Tuomilehto, A.G. Uitterlinden, A. Valladares-Salgado, S. Vedantam, F. Veglia, B.F. Voight, C.
468 Wang, N.J. Wareham, R. Wennauer, A.R. Wickremasinghe, T. Wilsgaard, J.F. Wilson, S.
469 Wiltshire, W. Winckler, T.Y. Wong, A.R. Wood, J.Y. Wu, Y. Wu, K. Yamamoto, T. Yamauchi, M.
470 Yang, L. Yengo, M. Yokota, R. Young, D. Zabaneh, F. Zhang, R. Zhang, W. Zheng, P.Z. Zimmet,
471 D. Altshuler, D.W. Bowden, Y.S. Cho, N.J. Cox, M. Cruz, C.L. Hanis, J. Kooner, J.Y. Lee, M.
472 Seielstad, Y.Y. Teo, M. Boehnke, E.J. Parra, J.C. Chambers, E.S. Tai, M.I. McCarthy, A.P. Morris,
473 Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2
474 diabetes susceptibility, *Nature genetics* 46(3) (2014) 234-44.
475 [27] J. Ceras, N. Cirauqui, S. Perez-Silanes, I. Aldana, A. Monge, S. Galiano, Novel sulfonylurea
476 derivatives as H3 receptor antagonists. Preliminary SAR studies, *European journal of medicinal*
477 *chemistry* 52 (2012) 1-13.
478 [28] R. Yoshimoto, Y. Miyamoto, K. Shimamura, A. Ishihara, K. Takahashi, H. Kotani, A.S. Chen,
479 H.Y. Chen, D.J. Macneil, A. Kanatani, S. Tokita, Therapeutic potential of histamine H3 receptor

480 agonist for the treatment of obesity and diabetes mellitus, *Proceedings of the National Academy of*
481 *Sciences of the United States of America* 103(37) (2006) 13866-71.

482 [29] M.B. Henry, S. Zheng, C. Duan, B. Patel, G. Vassileva, C. Sondey, J. Lachowicz, J.J. Hwa,
483 Antidiabetic properties of the histamine H3 receptor protean agonist proxyfan, *Endocrinology*
484 152(3) (2011) 828-35.

485 [30] T. Muller, D. Myrtek, H. Bayer, S. Sorichter, K. Schneider, G. Zissel, J. Norgauer, M. Idzko,
486 Functional characterization of histamine receptor subtypes in a human bronchial epithelial cell line,
487 *International journal of molecular medicine* 18(5) (2006) 925-31.

488 [31] H. Francis, A. Franchitto, Y. Ueno, S. Glaser, S. DeMorrow, J. Venter, E. Gaudio, D. Alvaro,
489 G. Fava, M. Marzioni, B. Vaculin, G. Alpini, H3 histamine receptor agonist inhibits biliary growth
490 of BDL rats by downregulation of the cAMP-dependent PKA/ERK1/2/ELK-1 pathway, *Laboratory*
491 *investigation; a journal of technical methods and pathology* 87(5) (2007) 473-87.

492 [32] G. Morini, G. Becchi, F.C. Shenton, P.L. Chazot, D. Grandi, Histamine H3 and H4 receptors
493 are expressed on distinct endocrine cell types in the rat fundic mucosa, *Inflammation research : official journal of the European Histamine Research Society ... [et al.]* 57 Suppl 1 (2008) S57-8.

495 [33] A. Pini, P.L. Chazot, E. Veglia, A. Moggio, A.C. Rosa, H3 receptor renal expression in normal
496 and diabetic rats, *Inflammation research : official journal of the European Histamine Research*
497 *Society ... [et al.]* 64(5) (2015) 271-3.

498 [34] E. Veglia, C. Grange, A. Pini, A. Moggio, C. Lanzi, G. Camussi, P.L. Chazot, A.C. Rosa,
499 Histamine receptor expression in human renal tubules: a comparative pharmacological evaluation,
500 *Inflammation research : official journal of the European Histamine Research Society ... [et al.]*
501 64(3-4) (2015) 261-70.

502 [35] W.A. Stubbs, G. Delitala, G.M. Besser, C.R. Edwards, S. Labrooy, R. Taylor, J.J. Misiewicz,
503 K.G. Alberti, The endocrine and metabolic effects of cimetidine, *Clinical endocrinology* 18(2)
504 (1983) 167-78.

505 [36] A.J. Clark, R.W. Bilous, H. Keen, Ranitidine in insulin-dependent diabetes, *Lancet* 2(8303)
506 (1982) 883-4.

507 [37] J. Feely, W.C. Collins, M. Cullen, A.H. el Debani, R.S. MacWalter, N.R. Peden, I.H.
508 Stevenson, Potentiation of the hypoglycaemic response to glipizide in diabetic patients by histamine
509 H₂-receptor antagonists, *British journal of clinical pharmacology* 35(3) (1993) 321-3.

510 [38] D.B. Jefferys, J.A. Vale, Effect of cimetidine on glucose handling, *Lancet* 1(8060) (1978) 383.

511 [39] R.T. Kubacka, E.J. Antal, R.P. Juhl, The paradoxical effect of cimetidine and ranitidine on
512 glibenclamide pharmacokinetics and pharmacodynamics, *British journal of clinical pharmacology*
513 23(6) (1987) 743-51.

514 [40] F. Montastruc, A. Palmaro, H. Bagheri, L. Schmitt, J.L. Montastruc, M. Lapeyre-Mestre, Role
515 of serotonin 5-HT_{2C} and histamine H₁ receptors in antipsychotic-induced diabetes: A
516 pharmacoepidemiological-pharmacodynamic study in VigiBase, *European*
517 *neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*
518 25(10) (2015) 1556-65.

519 [41] T. Masaki, S. Chiba, T. Yasuda, H. Noguchi, T. Kakuma, T. Watanabe, T. Sakata, H.
520 Yoshimatsu, Involvement of hypothalamic histamine H₁ receptor in the regulation of feeding
521 rhythm and obesity, *Diabetes* 53(9) (2004) 2250-60.

522 [42] T. Yasuda, T. Masaki, T. Sakata, H. Yoshimatsu, Hypothalamic neuronal histamine regulates
523 sympathetic nerve activity and expression of uncoupling protein 1 mRNA in brown adipose tissue
524 in rats, *Neuroscience* 125(3) (2004) 535-40.

525 [43] G. Provensi, P. Blandina, M.B. Passani, The histaminergic system as a target for the prevention
526 of obesity and metabolic syndrome, *Neuropharmacology* (2015).

527 [44] M. Marre, Genetics and the prediction of complications in type 1 diabetes, *Diabetes care* 22
528 Suppl 2 (1999) B53-8.

529 [45] B. Stratmann, D. Tschoepe, Heart in diabetes: not only a macrovascular disease, *Diabetes care*
530 34 Suppl 2 (2011) S138-44.

531 [46] J. Van de Voorde, V. Brochez, B. Vanheel, Heterogenous effects of histamine on isolated rat
532 coronary arteries, *European journal of pharmacology* 271(1) (1994) 17-23.

533 [47] W. Liao, M. Rudling, B. Angelin, Novel effects of histamine on lipoprotein metabolism:
534 suppression of hepatic low density lipoprotein receptor expression and reduction of plasma high
535 density lipoprotein cholesterol in the rat, *Endocrinology* 138(5) (1997) 1863-70.

536 [48] P.T. Kovanen, M. Kaartinen, T. Paavonen, Infiltrates of activated mast cells at the site of
537 coronary atheromatous erosion or rupture in myocardial infarction, *Circulation* 92(5) (1995) 1084-
538 8.

539 [49] K.A. Lindstedt, M.I. Mayranpaa, P.T. Kovanen, Mast cells in vulnerable atherosclerotic
540 plaques--a view to a kill, *Journal of cellular and molecular medicine* 11(4) (2007) 739-58.

541 [50] P.F. Mannaioni, M.G. Di Bello, E. Masini, Platelets and inflammation: role of platelet-derived
542 growth factor, adhesion molecules and histamine, *Inflammation research : official journal of the*
543 *European Histamine Research Society ... [et al.]* 46(1) (1997) 4-18.

544 [51] M. Huang, X. Pang, R. Letourneau, W. Boucher, T.C. Theoharides, Acute stress induces
545 cardiac mast cell activation and histamine release, effects that are increased in Apolipoprotein E
546 knockout mice, *Cardiovascular research* 55(1) (2002) 150-60.

547 [52] J. Steffel, M. Hermann, H. Greutert, S. Gay, T.F. Luscher, F. Ruschitzka, F.C. Tanner,
548 Celecoxib decreases endothelial tissue factor expression through inhibition of c-Jun terminal NH2
549 kinase phosphorylation, *Circulation* 111(13) (2005) 1685-9.

550 [53] V. Zdravkovic, S. Pantovic, G. Rosic, A. Tomic-Lucic, N. Zdravkovic, M. Colic, Z.
551 Obradovic, M. Rosic, Histamine blood concentration in ischemic heart disease patients, *Journal of*
552 *biomedicine & biotechnology* 2011 (2011) 315709.

553 [54] S. Pierpaoli, C. Marzocca, M.G. Bello, W. Schunack, P.F. Mannaioni, E. Masini,
554 Histaminergic receptors modulate the coronary vascular response in isolated guinea pig hearts. Role
555 of nitric oxide, *Inflammation research : official journal of the European Histamine Research Society*
556 *... [et al.]* 52(9) (2003) 390-6.

557 [55] H. Li, C. Burkhardt, U.R. Heinrich, I. Brausch, N. Xia, U. Forstermann, Histamine upregulates
558 gene expression of endothelial nitric oxide synthase in human vascular endothelial cells, *Circulation*
559 107(18) (2003) 2348-54.

560 [56] N. Toda, Mechanism of histamine actions in human coronary arteries, *Circulation research*
561 61(2) (1987) 280-6.

562 [57] F. Lantoin, L. Iouzalén, M.A. Devynck, E. Millanvoeye-Van Brussel, M. David-Duflho, Nitric
563 oxide production in human endothelial cells stimulated by histamine requires Ca²⁺ influx, *The*
564 *Biochemical journal* 330 (Pt 2) (1998) 695-9.

565 [58] A. Szebeni, A. Falus, V. Kecskemeti, Electrophysiological characteristics of heart ventricular
566 papillary muscles in diabetic histidine decarboxylase knockout and wild-type mice, *Journal of*
567 *interventional cardiac electrophysiology : an international journal of arrhythmias and pacing* 26(3)
568 (2009) 155-8.

569 [59] C. Lengyel, L. Virag, T. Biro, N. Jost, J. Magyar, P. Biliczki, E. Kocsis, R. Skoumal, P.P.
570 Nanasi, M. Toth, V. Kecskemeti, J.G. Papp, A. Varro, Diabetes mellitus attenuates the
571 repolarization reserve in mammalian heart, *Cardiovascular research* 73(3) (2007) 512-20.

572 [60] C. Marionneau, F. Aimond, S. Brunet, N. Niwa, B. Finck, D.P. Kelly, J.M. Nerbonne,
573 PPAR α -mediated remodeling of repolarizing voltage-gated K⁺ (K_v) channels in a mouse model
574 of metabolic cardiomyopathy, *Journal of molecular and cellular cardiology* 44(6) (2008) 1002-15.

575 [61] F.J. Quintana, E. Buzas, Z. Prohaszka, A. Biro, J. Kocsis, G. Fust, A. Falus, I.R. Cohen,
576 Knock-out of the histidine decarboxylase gene modifies the repertoire of natural autoantibodies,
577 *Journal of autoimmunity* 22(4) (2004) 297-305.

578 [62] H. Xu, W. Guo, J.M. Nerbonne, Four kinetically distinct depolarization-activated K⁺ currents
579 in adult mouse ventricular myocytes, *The Journal of general physiology* 113(5) (1999) 661-78.

580 [63] D.M. Barry, H. Xu, R.B. Schuessler, J.M. Nerbonne, Functional knockout of the transient
581 outward current, long-QT syndrome, and cardiac remodeling in mice expressing a dominant-
582 negative K_v4 α subunit, *Circulation research* 83(5) (1998) 560-7.

583 [64] Z.G. Huang, Q. Jin, M. Fan, X.L. Cong, S.F. Han, H. Gao, Y. Shan, Myocardial remodeling in
584 diabetic cardiomyopathy associated with cardiac mast cell activation, *PloS one* 8(3) (2013) e60827.

585 [65] S. Tesfaye, A.J. Boulton, P.J. Dyck, R. Freeman, M. Horowitz, P. Kempler, G. Lauria, R.A.
586 Malik, V. Spallone, A. Vinik, L. Bernardi, P. Valensi, G. Toronto Diabetic Neuropathy Expert,
587 Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and
588 treatments, *Diabetes care* 33(10) (2010) 2285-93.

589 [66] N. Aronin, S.E. Leeman, R.S. Clements, Jr., Diminished flare response in neuropathic diabetic
590 patients. Comparison of effects of substance P, histamine, and capsaicin, *Diabetes* 36(10) (1987)
591 1139-43.

592 [67] J.C. Schwartz, [Third histamine receptor: new therapeutic prospects], *La Revue du praticien*
593 41(5) (1991) 443-6.

594 [68] K. Onodera, A. Yamatodani, T. Watanabe, H. Wada, Neuropharmacology of the histaminergic
595 neuron system in the brain and its relationship with behavioral disorders, *Progress in neurobiology*
596 42(6) (1994) 685-702.

597 [69] J.I. Mobarakeh, S. Sakurada, S. Katsuyama, M. Kutsuwa, A. Kuramasu, Z.Y. Lin, T.
598 Watanabe, Y. Hashimoto, T. Watanabe, K. Yanai, Role of histamine H(1) receptor in pain
599 perception: a study of the receptor gene knockout mice, *European journal of pharmacology* 391(1-
600 2) (2000) 81-9.

601 [70] J.I. Mobarakeh, K. Takahashi, S. Sakurada, A. Kuramasu, K. Yanai, Enhanced antinociceptive
602 effects of morphine in histamine H2 receptor gene knockout mice, *Neuropharmacology* 51(3)
603 (2006) 612-22.

604 [71] A.C. Rosa, R. Fantozzi, The role of histamine in neurogenic inflammation, *British journal of*
605 *pharmacology* 170(1) (2013) 38-45.

606 [72] H. Kashiba, H. Fukui, Y. Morikawa, E. Senba, Gene expression of histamine H1 receptor in
607 guinea pig primary sensory neurons: a relationship between H1 receptor mRNA-expressing neurons
608 and peptidergic neurons, *Brain research. Molecular brain research* 66(1-2) (1999) 24-34.

609 [73] W. Riedel, G. Neeck, Nociception, pain, and antinociception: current concepts, *Zeitschrift fur*
610 *Rheumatologie* 60(6) (2001) 404-15.

611 [74] E. Tani, T. Ishikawa, Histamine acts directly on calcitonin gene-related peptide- and substance
612 P-containing trigeminal ganglion neurons as assessed by calcium influx and immunocytochemistry,
613 *Auris, nasus, larynx* 17(4) (1990) 267-74.

614 [75] I. Bileviciute, T. Lundeberg, A. Ekblom, E. Theodorsson, The effect of a single intraperitoneal
615 dose of hrIL-1 alpha on substance P-, neurokinin A-, calcitonin gene-related peptide- and
616 neuropeptide Y-like immunoreactivity in cerebrospinal fluid, plasma and knee joint synovial fluid
617 in the rat, *Regulatory peptides* 53(1) (1994) 71-6.

618 [76] A.O. Oluyomi, S.L. Hart, Involvement of histamine in naloxone-resistant and naloxone-
619 sensitive models of swim stress-induced antinociception in the mouse, *Neuropharmacology* 30(9)
620 (1991) 1021-7.

621 [77] P. Malmberg-Aiello, C. Lamberti, A. Ipponi, A. Bartolini, W. Schunack, Evidence for
622 hypernociception induction following histamine H1 receptor activation in rodents, *Life sciences*
623 63(6) (1998) 463-76.

624 [78] D. Farzin, L. Asghari, M. Nowrouzi, Rodent antinociception following acute treatment with
625 different histamine receptor agonists and antagonists, *Pharmacology, biochemistry, and behavior*
626 72(3) (2002) 751-60.

627 [79] C. Lamberti, A. Bartolini, C. Ghelardini, P. Malmberg-Aiello, Investigation into the role of
628 histamine receptors in rodent antinociception, *Pharmacology, biochemistry, and behavior* 53(3)
629 (1996) 567-74.

630 [80] G. Coruzzi, M. Adami, E. Guaita, I.J. de Esch, R. Leurs, Antiinflammatory and antinociceptive
631 effects of the selective histamine H4-receptor antagonists JNJ7777120 and VUF6002 in a rat model
632 of carrageenan-induced acute inflammation, *European journal of pharmacology* 563(1-3) (2007)
633 240-4.

634 [81] F.M. Smith, H. Haskelberg, D.J. Tracey, G. Moalem-Taylor, Role of histamine H3 and H4
635 receptors in mechanical hyperalgesia following peripheral nerve injury, *Neuroimmunomodulation*
636 14(6) (2007) 317-25.

637 [82] G.C. Hsieh, P. Honore, M. Pai, E.J. Wensink, P. Chandran, A.K. Salyers, J.M. Wetter, C.
638 Zhao, H. Liu, M.W. Decker, T.A. Esbenshade, M.D. Cowart, J.D. Brioni, Antinociceptive effects of
639 histamine H3 receptor antagonist in the preclinical models of pain in rats and the involvement of
640 central noradrenergic systems, *Brain research* 1354 (2010) 74-84.

641 [83] N. Shin, M. Covington, D. Bian, J. Zhuo, K. Bowman, Y. Li, M. Soloviev, D.Q. Qian, P.
642 Feldman, L. Leffet, X. He, K. He Wang, K. Krug, D. Bell, P. Czerniak, Z. Hu, H. Zhao, J. Zhang,
643 S. Yeleswaram, W. Yao, R. Newton, P. Scherle, INCB38579, a novel and potent histamine H(4)
644 receptor small molecule antagonist with anti-inflammatory pain and anti-pruritic functions,
645 *European journal of pharmacology* 675(1-3) (2012) 47-56.

646 [84] N. Galeotti, M.D. Sanna, C. Ghelardini, Pleiotropic effect of histamine H4 receptor modulation
647 in the central nervous system, *Neuropharmacology* 71 (2013) 141-7.

648 [85] M.D. Sanna, H. Stark, L. Lucarini, C. Ghelardini, E. Masini, N. Galeotti, Histamine H4
649 receptor activation alleviates neuropathic pain through differential regulation of ERK, JNK, and
650 P38 MAPK phosphorylation, *Pain* 156(12) (2015) 2492-504.

651 [86] I. Gilron, A.H. Dickenson, Emerging drugs for neuropathic pain, *Expert opinion on emerging*
652 *drugs* 19(3) (2014) 329-41.

653 [87] P. Hasanein, Effects of histamine H3 receptors on chemical hyperalgesia in diabetic rats,
654 *Neuropharmacology* 60(6) (2011) 886-91.

655 [88] A. Delaunois, P. Gustin, M. Garbarg, M. Ansay, Modulation of acetylcholine, capsaicin and
656 substance P effects by histamine H3 receptors in isolated perfused rabbit lungs, *European journal of*
657 *pharmacology* 277(2-3) (1995) 243-50.

658 [89] T. Ohkubo, M. Shibata, ATP-sensitive K⁺ channels mediate regulation of substance P release
659 via the prejunctional histamine H3 receptor, *European journal of pharmacology* 277(1) (1995) 45-9.

660 [90] M. Imamura, H.M. Lander, R. Levi, Activation of histamine H₃-receptors inhibits carrier-
661 mediated norepinephrine release during protracted myocardial ischemia. Comparison with
662 adenosine A₁-receptors and alpha₂-adrenoceptors, *Circulation research* 78(3) (1996) 475-81.

663 [91] A. Nemmar, A. Delaunois, J.F. Beckers, J. Sulon, S. Bloden, P. Gustin, Modulatory effect of
664 imetit, a histamine H₃ receptor agonist, on C-fibers, cholinergic fibers and mast cells in rabbit lungs
665 in vitro, *European journal of pharmacology* 371(1) (1999) 23-30.

666 [92] K.E. Cannon, R. Leurs, L.B. Hough, Activation of peripheral and spinal histamine H₃
667 receptors inhibits formalin-induced inflammation and nociception, respectively, *Pharmacology,*
668 *biochemistry, and behavior* 88(1) (2007) 122-9.

669 [93] K.E. Cannon, J.W. Nalwalk, R. Stadel, P. Ge, D. Lawson, I. Silos-Santiago, L.B. Hough,
670 Activation of spinal histamine H₃ receptors inhibits mechanical nociception, *European journal of*
671 *pharmacology* 470(3) (2003) 139-47.

672 [94] S. McGaraughty, K.L. Chu, M.D. Cowart, J.D. Brioni, Antagonism of supraspinal histamine
673 H₃ receptors modulates spinal neuronal activity in neuropathic rats, *The Journal of pharmacology*
674 *and experimental therapeutics* 343(1) (2012) 13-20.

675 [95] A.D. Medhurst, A.R. Atkins, I.J. Beresford, K. Brackenborough, M.A. Briggs, A.R. Calver, J.
676 Cilia, J.E. Cluderay, B. Crook, J.B. Davis, R.K. Davis, R.P. Davis, L.A. Dawson, A.G. Foley, J.
677 Gartlon, M.I. Gonzalez, T. Heslop, W.D. Hirst, C. Jennings, D.N. Jones, L.P. Lacroix, A. Martyn,
678 S. Ociepka, A. Ray, C.M. Regan, J.C. Roberts, J. Schogger, E. Southam, T.O. Stean, B.K. Trail, N.
679 Upton, G. Wadsworth, J.A. Wald, T. White, J. Witherington, M.L. Woolley, A. Worby, D.M.
680 Wilson, GSK189254, a novel H₃ receptor antagonist that binds to histamine H₃ receptors in
681 Alzheimer's disease brain and improves cognitive performance in preclinical models, *The Journal*
682 *of pharmacology and experimental therapeutics* 321(3) (2007) 1032-45.

683 [96] S.J. Medhurst, S.D. Collins, A. Billinton, S. Bingham, R.G. Dalziel, A. Brass, J.C. Roberts,
684 A.D. Medhurst, I.P. Chessell, Novel histamine H₃ receptor antagonists GSK189254 and

685 GSK334429 are efficacious in surgically-induced and virally-induced rat models of neuropathic
686 pain, *Pain* 138(1) (2008) 61-9.

687 [97] J.M. Arrang, M. Garbarg, J.C. Schwartz, Auto-inhibition of brain histamine release mediated
688 by a novel class (H3) of histamine receptor, *Nature* 302(5911) (1983) 832-7.

689 [98] J.M. Arrang, B. Devaux, J.P. Chodkiewicz, J.C. Schwartz, H3-receptors control histamine
690 release in human brain, *Journal of neurochemistry* 51(1) (1988) 105-8.

691 [99] E. Schlicker, B. Malinowska, M. Kathmann, M. Gothert, Modulation of neurotransmitter
692 release via histamine H3 heteroreceptors, *Fundamental & clinical pharmacology* 8(2) (1994) 128-
693 37.

694 [100] P. Blandina, M. Giorgetti, L. Bartolini, M. Cecchi, H. Timmerman, R. Leurs, G. Pepeu, M.G.
695 Giovannini, Inhibition of cortical acetylcholine release and cognitive performance by histamine H3
696 receptor activation in rats, *British journal of pharmacology* 119(8) (1996) 1656-64.

697 [101] R.E. Brown, D.R. Stevens, H.L. Haas, The physiology of brain histamine, *Progress in*
698 *neurobiology* 63(6) (2001) 637-72.

699 [102] G.B. Fox, T.A. Esbenshade, J.B. Pan, R.J. Radek, K.M. Krueger, B.B. Yao, K.E. Browman,
700 M.J. Buckley, M.E. Ballard, V.A. Komater, H. Miner, M. Zhang, R. Faghieh, L.E. Rueter, R.S.
701 Bitner, K.U. Drescher, J. Wetter, K. Marsh, M. Lemaire, R.D. Porsolt, Y.L. Bennani, J.P. Sullivan,
702 M.D. Cowart, M.W. Decker, A.A. Hancock, Pharmacological properties of ABT-239 [4-(2-{2-
703 [(2R)-2-Methylpyrrolidinyl]ethyl}-benzofuran-5-yl)benzotrile]: II. Neurophysiological
704 characterization and broad preclinical efficacy in cognition and schizophrenia of a potent and
705 selective histamine H3 receptor antagonist, *The Journal of pharmacology and experimental*
706 *therapeutics* 313(1) (2005) 176-90.

707 [103] G.B. Rhind, G.A. Gould, D.J. Ewing, B.F. Clarke, N.J. Douglas, Increased bronchial
708 reactivity to histamine in diabetic autonomic neuropathy, *Clinical science* 73(4) (1987) 401-5.

709 [104] U. Trendelenburg, Supersensitivity and subsensitivity to sympathomimetic amines,
710 *Pharmacological reviews* 15 (1963) 225-76.

711 [105] S.R. Sampson, E.H. Vidruk, Properties of 'irritant' receptors in canine lung, *Respiration*
712 *physiology* 25(1) (1975) 9-22.

713 [106] C.G. Irvin, J.A. Dempsey, Role of H1 and H2 receptors in increased small airways resistance
714 in the dog, *Respiration physiology* 35(2) (1978) 161-76.

715 [107] J.A. Nadel, B. Davis, Parasympathetic and sympathetic regulation of secretion from
716 submucosal glands in airways, *Federation proceedings* 39(13) (1980) 3075-9.

717 [108] R.J. Polinsky, I.J. Kopin, M.H. Ebert, V. Weise, Pharmacologic distinction of different
718 orthostatic hypotension syndromes, *Neurology* 31(1) (1981) 1-7.

719 [109] H.E. Abboud, S.L. Ou, J.A. Velosa, S.V. Shah, T.P. Dousa, Dynamics of renal histamine in
720 normal rat kidney and in nephrosis induced by aminonucleoside of puromycin, *The Journal of*
721 *clinical investigation* 69(2) (1982) 327-36.

722 [110] S.L. Levin, The syndrome of isolated disturbance of the tympanic nerve, *Archives of*
723 *neurology* 40(2) (1983) 106-8.

724 [111] J.C. Coleridge, H.M. Coleridge, Afferent vagal C fibre innervation of the lungs and airways
725 and its functional significance, *Reviews of physiology, biochemistry and pharmacology* 99 (1984)
726 1-110.

727 [112] C.M. Lai, S.A. Dunlop, L.A. May, M. Gorbatov, M. Brankov, W.Y. Shen, N. Binz, Y.K. Lai,
728 C.E. Graham, C.J. Barry, I.J. Constable, L.D. Beazley, E.P. Rakoczy, Generation of transgenic mice
729 with mild and severe retinal neovascularisation, *The British journal of ophthalmology* 89(7) (2005)
730 911-6.

731 [113] N. Cheung, P. Mitchell, T.Y. Wong, Diabetic retinopathy, *Lancet* 376(9735) (2010) 124-36.

732 [114] X. Cai, J.F. McGinnis, Diabetic Retinopathy: Animal Models, Therapies, and Perspectives,
733 *Journal of diabetes research* 2016 (2016) 3789217.

734 [115] A.J. Barber, E. Lieth, S.A. Khin, D.A. Antonetti, A.G. Buchanan, T.W. Gardner, Neural
735 apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin,
736 *The Journal of clinical investigation* 102(4) (1998) 783-91.

737 [116] A.M. Abu-El-Asrar, L. Dralands, L. Missotten, I.A. Al-Jadaan, K. Geboes, Expression of
738 apoptosis markers in the retinas of human subjects with diabetes, *Investigative ophthalmology &*
739 *visual science* 45(8) (2004) 2760-6.

740 [117] T.M. Hollis, H.W. Sill, C. Butler, M.J. Campos, T.W. Gardner, Astemizole reduces blood-
741 retinal barrier leakage in experimental diabetes, *Journal of diabetes and its complications* 6(4)
742 (1992) 230-5.

743 [118] T.W. Gardner, A.W. Eller, T.R. Friberg, J.A. D'Antonio, T.M. Hollis, Antihistamines reduce
744 blood-retinal barrier permeability in type I (insulin-dependent) diabetic patients with
745 nonproliferative retinopathy. A pilot study, *Retina* 15(2) (1995) 134-40.

746 [119] R. Patnaik, S. Mohanty, H.S. Sharma, Blockade of histamine H2 receptors attenuate blood-
747 brain barrier permeability, cerebral blood flow disturbances, edema formation and cell reactions
748 following hyperthermic brain injury in the rat, *Acta neurochirurgica. Supplement* 76 (2000) 535-9.

749 [120] T.W. Gardner, T. Leshner, S. Khin, C. Vu, A.J. Barber, W.A. Brennan, Jr., Histamine reduces
750 ZO-1 tight-junction protein expression in cultured retinal microvascular endothelial cells, *The*
751 *Biochemical journal* 320 (Pt 3) (1996) 717-21.

752 [121] T.W. Gardner, Histamine, ZO-1 and increased blood-retinal barrier permeability in diabetic
753 retinopathy, *Transactions of the American Ophthalmological Society* 93 (1995) 583-621.

754 [122] T.M. Hollis, T.W. Gardner, G.J. Vergis, B.J. Kirbo, C. Butler, R.O. Dull, M.J. Campos, N.A.
755 Enea, Antihistamines reverse blood-ocular barrier breakdown in experimental diabetes, *The Journal*
756 *of diabetic complications* 2(1) (1988) 47-9.

757 [123] N.A. Enea, T.M. Hollis, J.A. Kern, T.W. Gardner, Histamine H1 receptors mediate increased
758 blood-retinal barrier permeability in experimental diabetes, *Archives of ophthalmology* 107(2)
759 (1989) 270-4.

760 [124] E.C. Leal, A.R. Santiago, A.F. Ambrosio, Old and new drug targets in diabetic retinopathy:
761 from biochemical changes to inflammation and neurodegeneration, *Current drug targets. CNS and*
762 *neurological disorders* 4(4) (2005) 421-34.

763 [125] J.S. Ng, M.A. Bearse, Jr., M.E. Schneck, S. Barez, A.J. Adams, Local diabetic retinopathy
764 prediction by multifocal ERG delays over 3 years, *Investigative ophthalmology & visual science*
765 49(4) (2008) 1622-8.

766 [126] M.S. Ola, A.S. Alhomida, Neurodegeneration in diabetic retina and its potential drug targets,
767 *Current neuropharmacology* 12(4) (2014) 380-6.

768 [127] A.J. Barber, Diabetic retinopathy: recent advances towards understanding neurodegeneration
769 and vision loss, *Science China. Life sciences* 58(6) (2015) 541-9.

770 [128] W.J. Carroll, T.M. Hollis, T.W. Gardner, Retinal histamine synthesis is increased in
771 experimental diabetes, *Investigative ophthalmology & visual science* 29(8) (1988) 1201-4.

772 [129] M.J. Gastinger, A.J. Barber, S.A. Khin, C.S. McRill, T.W. Gardner, D.W. Marshak,
773 Abnormal centrifugal axons in streptozotocin-diabetic rat retinas, *Investigative ophthalmology &*
774 *visual science* 42(11) (2001) 2679-85.

775 [130] H. Gallagher, R.J. Suckling, Diabetic nephropathy - where are we on the journey from
776 pathophysiology to treatment?, *Diabetes, obesity & metabolism* (2016).

777 [131] A.T. Reutens, R.C. Atkins, Epidemiology of diabetic nephropathy, *Contributions to*
778 *nephrology* 170 (2011) 1-7.

779 [132] R.A. Markle, T.M. Hollis, A.J. Cosgarea, Renal histamine increases in the streptozotocin-
780 diabetic rat, *Experimental and molecular pathology* 44(1) (1986) 21-8.

781 [133] M. Gill, S.N. Sanyal, M.L. Sareen, Effect of histamine H₂-receptor antagonist, ranitidine on
782 renal brush border and basolateral membranes, *Research in experimental medicine. Zeitschrift fur*
783 *die gesamte experimentelle Medizin einschliesslich experimenteller Chirurgie* 190(5) (1990) 345-
784 56.

785 [134] T.K. Morgan, K. Montgomery, V. Mason, R.B. West, L. Wang, M. van de Rijn, J.P. Higgins,
786 Upregulation of histidine decarboxylase expression in superficial cortical nephrons during
787 pregnancy in mice and women, *Kidney international* 70(2) (2006) 306-14.

788 [135] R.J. Sinclair, R.D. Bell, M.J. Keyl, Effects of prostaglandin E2 (PGE2) and histamine on
789 renal fluid dynamics, *The American journal of physiology* 227(5) (1974) 1062-6.

790 [136] R.O. Banks, J.D. Fondacaro, M.M. Schwaiger, E.D. Jacobson, Renal histamine H1 and H2
791 receptors: characterization and functional significance, *The American journal of physiology* 235(6)
792 (1978) F570-5.

793 [137] I. Ichikawa, B.M. Brenner, Mechanisms of action of histamine and histamine antagonists on
794 the glomerular microcirculation in the rat, *Circulation research* 45(6) (1979) 737-45.

795 [138] U. Schwertschlag, E. Hackenthal, Histamine stimulates renin release from the isolated
796 perfused rat kidney, *Naunyn-Schmiedeberg's archives of pharmacology* 319(3) (1982) 239-42.

797 [139] E. Veglia, A. Moggio, A. Pini, C. Grange, P.L. Chazot, A.C. Rosa, Histamine Reduces ZO-1
798 Tight-Junction Protein Expression in Human Immortalized Podocytes, in: B.P. Society (Ed.)
799 *Pharmacology 2014*, London, 2014.

800 [140] Y. Li, F.Y. Liu, Y.M. Peng, J. Li, J. Chen, Mast cell, a promising therapeutic target in
801 tubulointerstitial fibrosis, *Medical hypotheses* 69(1) (2007) 99-103.

802 [141] B.M. Ruger, Q. Hasan, N.S. Greenhill, P.F. Davis, P.R. Dunbar, T.J. Neale, Mast cells and
803 type VIII collagen in human diabetic nephropathy, *Diabetologia* 39(10) (1996) 1215-22.

804 [142] J.M. Zheng, G.H. Yao, Z. Cheng, R. Wang, Z.H. Liu, Pathogenic role of mast cells in the
805 development of diabetic nephropathy: a study of patients at different stages of the disease,
806 *Diabetologia* 55(3) (2012) 801-11.

807 [143] A.C. Rosa, A. Pini, L. Lucarini, C. Lanzi, E. Veglia, R.L. Thurmond, H. Stark, E. Masini,
808 Prevention of bleomycin-induced lung inflammation and fibrosis in mice by naproxen and
809 JNJ7777120 treatment, *The Journal of pharmacology and experimental therapeutics* 351(2) (2014)
810 308-16.

811 [144] J.R. Sedor, H.E. Abboud, Actions and metabolism of histamine in glomeruli and tubules of
812 the human kidney, *Kidney international* 26(2) (1984) 144-52.

813 [145] J.R. Sedor, H.E. Abboud, Histamine modulates contraction and cyclic nucleotides in cultured
814 rat mesangial cells. Differential effects mediated by histamine H1 and H2 receptors, *The Journal of*
815 *clinical investigation* 75(5) (1985) 1679-89.

816 [146] A.C. Rosa, C. Grange, A. Pini, M.A. Katebe, E. Benetti, M. Collino, G. Miglio, D. Bani, G.
817 Camussi, P.L. Chazot, R. Fantozzi, Overexpression of histamine H(4) receptors in the kidney of
818 diabetic rat, *Inflammation research : official journal of the European Histamine Research Society ...*
819 [et al.] 62(4) (2013) 357-65.

820 [147] P. Panula, P.L. Chazot, M. Cowart, R. Gutzmer, R. Leurs, W.L. Liu, H. Stark, R.L.
821 Thurmond, H.L. Haas, *International Union of Basic and Clinical Pharmacology. XCVIII. Histamine*
822 *Receptors, Pharmacological reviews* 67(3) (2015) 601-55.

Figure(s)
[Click here to download high resolution image](#)

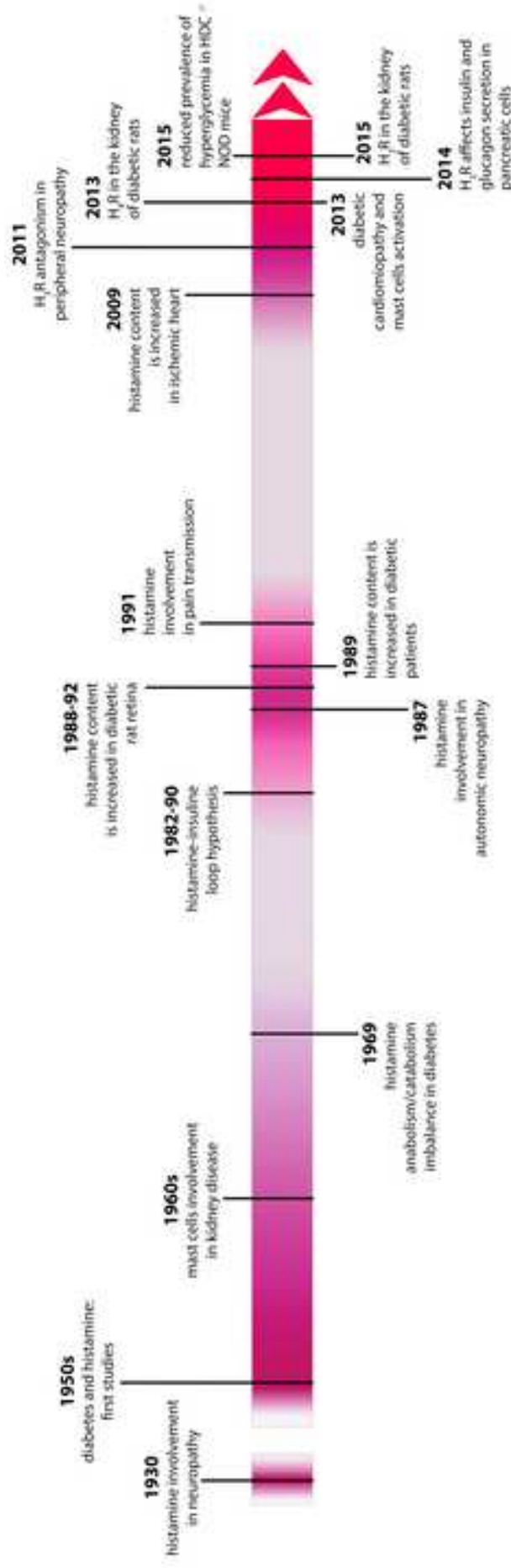
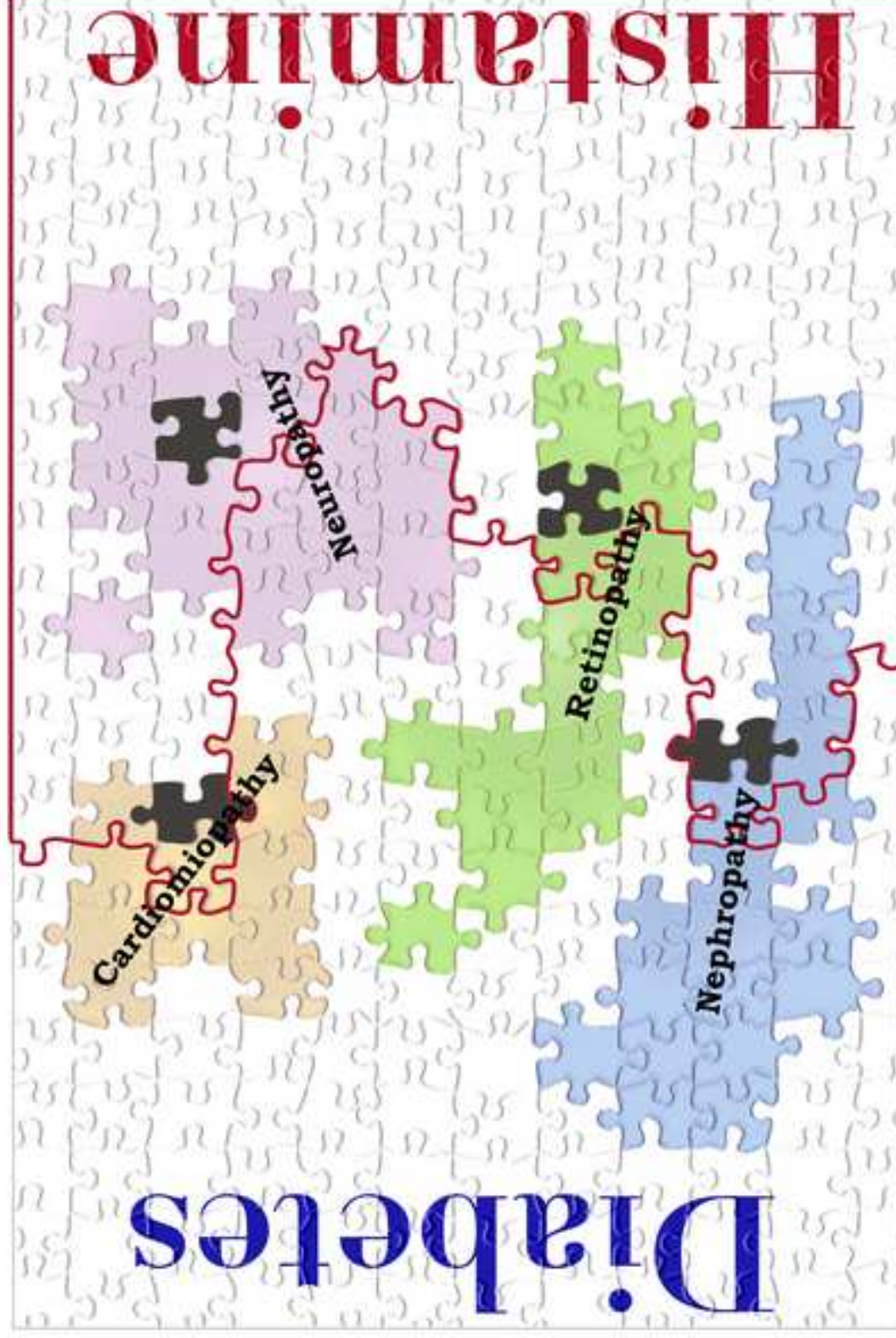
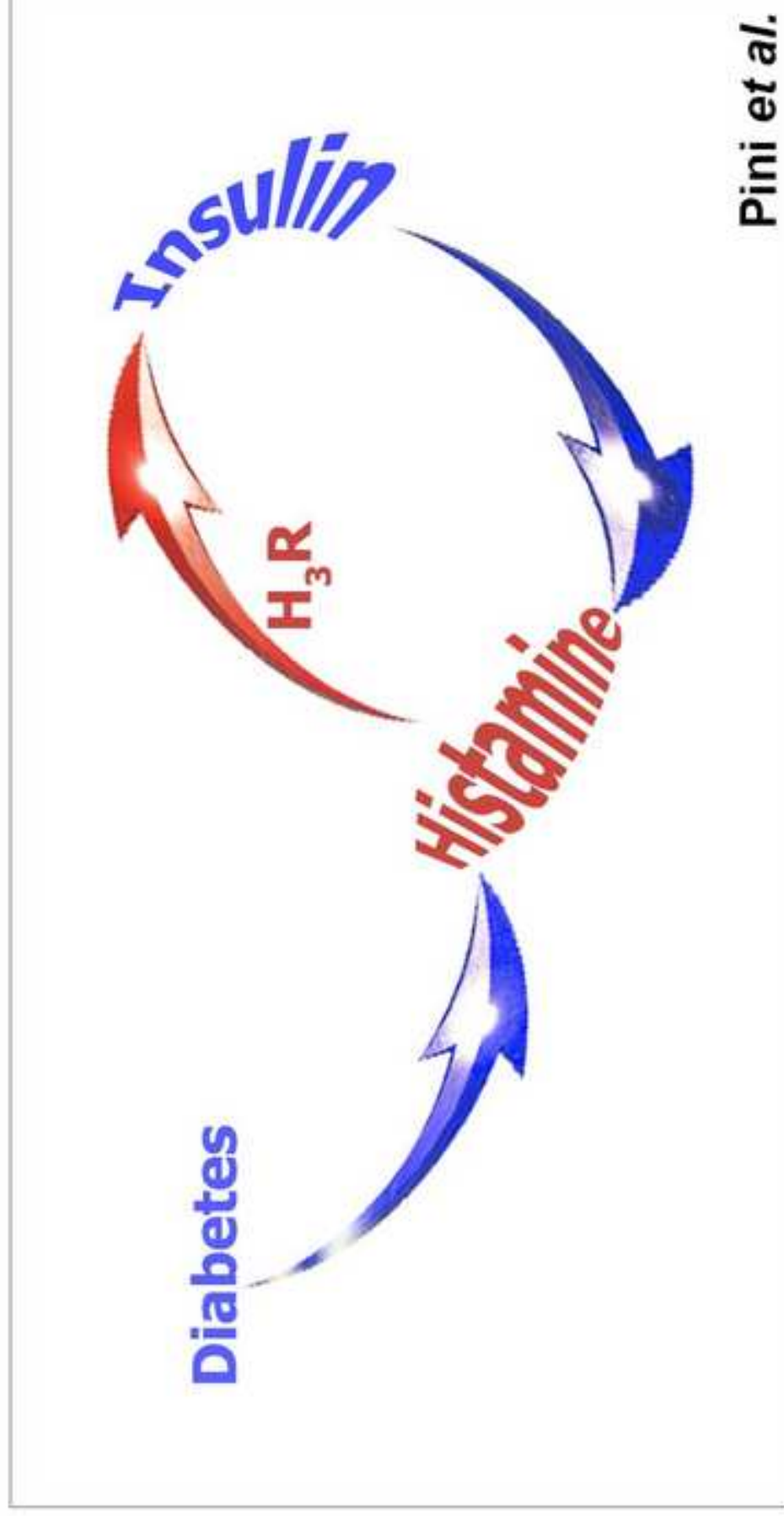


Table I. The diabetes-histamine loop: the state of the art						
Diabetes complication	Diabetes affects histamine	Histamine influences the progression	Receptor involved			
macrovascular	<p>↑ HDC and histamine in aortic endothelial and smooth muscle cells</p>	<p>atherogenesis coronary dilation, arrhythmogenic activity (QT-prolongation)</p>	H ₁ R ++	H ₂ R ++	H ₃ R +	H ₄ R n.d.
microvascular						
neuropathy						
<i>peripheral neuropathy</i>		<p>pain control, neurogenic inflammation</p>	n.d.	n.d.	+	n.d.
<i>autonomic neuropathy</i>		<p>↑ bronchoconstriction</p>	n.d.	n.d.	n.d.	n.d.
retinopathy	<p>↑ HDC and histamine</p>	<p>↑ vascular leakage</p>	++			
nephropathy	<p>↑ HDC, histamine, H₃R and H₄R expression</p>	<p>↑ salt and water excretion, ↓ ultrafiltration coefficient, ↑ renin release</p>	+	+	?	?

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





Pini et al.

Supplementary Figure 1. The insulin-histamine loop in pancreas.

Insulin administration decreases the histamine overproduction induced by diabetes *viceversa* histamine, through H₃R, inhibits insulin secretion from β-cells

This statement is signed by all the authors to indicate agreement that the above information is true and correct (a photocopy of this form may be used if there are more than 10 authors):

Author's name (typed)

Author's signature

Date

Alessandro Pini



5 maggio 2016

Ilona Obara



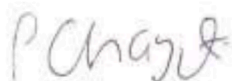
5 maggio 2016

Emma Battel



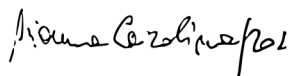
5 maggio 2016

Paul L Chazot



5 maggio 2016

Arianna Carolina Rosa



5 maggio 2016
