Histamine in diabetes: Is it time to reconsider?

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Abstract

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

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

Abbreviations:

ADP= action potential duration; AGEs = advanced glycation end-products; BM = basement membrane; BRB = blood-retinal barrier; CGRP = calcitonin gene related peptide; CKD = chronic kidney disease; DAO = diamine oxidase; DiO = diet-induced obesity; ESRD = end-stage renal disease; $H_{1\text{-}4}$Rs = histamine $H_{1\text{-}4}$Rs; HbA_1 = glycated hemoglobin; HDC = histidine decarboxylase; STZ = streptozotocin; TGF- β = tissue growth factor-β; TCAs = tricyclic antidepressants; V_{max} = maximum rate of depolarization; VEGF = vascular endothelial growth factor; ZO-1 = zonula occludent-1

1 Introduction

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

2 Histamine and glycaemia

Histamine is involved in a wide variety of pathophysiological events mostly related to the inflammatory response through four receptors, namely $H_{1\text{-}4}$Rs. The first studies of histamine and diabetes date back to the 1950s. Since that time the involvement of histamine in diabetes was related to its well-known vasoactive properties and permeability leakage effects correlated to

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

More intriguingly, it has been reported that histamine plasma and aortic synthesis [10] in diabetic rats are reduced when insulin is administrated [14], thus strongly supporting the hypothesis for an interconnection between histamine and glycaemic status. This hypothesis is further strengthened by the study of Azevedo and colleagues (1990) reporting an increase of pancreatic islet histamine content in streptozotocin (STZ)-induced diabetes rats [15]. Interestingly, recent data suggest the involvement of the peripheral H_3R in the insulin-histamine loop (Supplementary Figure 1). Indeed, Nakamura and colleagues (2014) provided the first evidence for a potential diabetogenic effect of the pancreatic H_3R, through reporting the presence of functional histamine H_3R in this tissue. In particular, it has been demonstrated that H_3R activation in pancreatic beta cells by imetit (PubChem CID 3692) inhibits the insulin secretion associated with high glucose levels in MIN6 cells [16]. Moreover, the same authors reported H_3R expression in pancreatic alpha cells, indicating that H_3R activation may reduce glucagon production by αTC1.6 cells in a non-hyperglycemic condition [17].

Notably, although the H_3R has been known to play a critical role in homeostatic regulatory functions, such as control of food intake and maintenance of body weight [18], its contribution to diabetes is controversial [18-24] and still far from being fully understood. Indeed, the H_3R inverse agonist clobenoprit (PubChem CID 2790) has been demonstrated to increase the hypothalamic histamine release and reduce the energy intake in normal and leptin-resistant mice with diet-induced obesity (DiO) [25]. So far, some newly synthesized H_3R antagonists have been specifically tested in diabetic animal models demonstrating an effectiveness in reducing non-fasting glucose levels by potentially blocking the increase of HbA_1 [26]. More interestingly, the strategy of an H_3R antagonism combined with a phenylsulfonylurea (well-known insulinotropic drugs) moiety has been explored [27]; although an effective prototype remains elusive. On the contrary, the activation of H_3Rs in mice has been reported to decrease food intake and increase energy expenditure. Chronic dosing with a H_3R agonist reduces body weight, fat mass, hyperleptinemia, and hyperinsulinemia in DiO mice [28]. Conversely, the protean H_3R agonist proxyfan (PubChem CID 6421522) in mice improves glucose excursion increasing plasma insulin levels without affecting plasma glucagon levels [29]. Furthermore, the mildly obese H_3R-deficient mice also demonstrate leptin and insulin resistance with impaired glucose tolerance [28]. Notably, the majority of these data were obtained before the clear demonstration of H_3R peripheral expression [16, 30-34]. In particular, the pancreatic localization of the H_3R raises the question of contradictory effects mediated by peripheral and central H_3R.

Conflicting data concerning the involvement of H_2R on glycaemia has also arisen. Its antagonism was reported to decrease [35], not affect [36, 37] and increase [38, 39] glucose levels. In comparison, the clinical experience with antipsychotic drugs generated clearer evidence for the involvement of the central H_1R in the development of a diabetic phenotype [40]. Consistently, it has been found that the intra-ventricle or –hypothalamic administration of an H_1R agonist induces satiety evoking an anti-obesity effect [41, 42]. Moreover, a strategy based on the contemporary H_1R

agonism and H_3R antagonism was demonstrated to have the potential to reduce obesity also in patients with comorbidities such as diabetes [43].

3 Histamine and diabetes complications

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

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

3.1 Histamine and macrovascular complications

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

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

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

Among the different receptors, historically the macrovascular effects of histamine seems to be mostly related to the H_1R and H_2R, but no specific studies were designed to investigate the whole histamine receptor family and only one observation claims the ability of H_3R to regulate the coronary vascular response [54]. H_1R has been reported to mediate the overexpression of the adhesion molecules [55] and the activation of nitric oxide synthase [55-57] evoked by histamine in vascular endothelial cells. H_2R has been demonstrated to cause coronary dilation in both an endothelium independent [56] and dependent [54] manner.

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

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

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

3.2 Histamine and microvascular complications

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

3.2.1 Diabetic neuropathy

Diabetic neuropathy is an heterogeneous family of nerve disorders resulting in improper locomotor and visceral organ dysfunctions at the level of peripheral, central, and visceral sensorimotor and motor nerves [65]. According to this definition we can recognize peripheral, autonomic, proximal, or focal neuropathy. Among these different neuropathies the peripheral subtype is the most common. As a consequence of the peripheral nerve degeneration, triggered by persistent hyperglycaemia, and according to the affected nerves, diabetes patients suffer from pain, weakness, 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 H_1R 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 H_1R and/or H_3R 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 H_1R [69, 76-78], H_2R [76, 78, 79], H_3R [78, 79] and H_4R [80-85], in 2014 the H_3R 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 H_3R in a diabetic model. This respective study showed
208 that the selective agonist immepip (PubChem CID 3035842) reversed formalin-induced
209 hyperalgesia in both phases of the formalin test [87]. This effect could be associated with both H_3R
210 peripheral activation, resulting in a reduction in inflammatory peptides release, and H_3R central
211 activation, leading to the inhibition of pain transmission [88-92]. Consistent with this theory,
212 immepip (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 H_3R 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 H_3R 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 underling the histamine-induce 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

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

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

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

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

3.2.3 Diabetic nephropathy

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

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

At the tubular level, the first evidence of a histamine detrimental effect on tubular integrity and 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 tubulointeirstizium, 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 H_1R and H_2R,
305 both identified in the glomeruli [12, 132]. Consistent with results obtained in rats [138], it was
306 found in humans that the H_2R 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 H_1R [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 H_3R and the H_4R 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

and diabetic complications etiopathogenesis. The evidence is strong in some cases, sometimes independent, but sometimes contradictory; despite this heterogeniety, when viewing the timeline of interest for histamine involvement in this disease (Figure 1) it appears phasic with a clear upturn and renewal in interest in the last couple of years, thanks to the very recent discovery of a direct effect of histamine on glycaemia [13, 16, 17] as well as a profound up-regulation of both H_3R and H_4R in the diabetic animal kidney [33, 146]. As a whole, the revisit of the literature herein clearly shows growing independent lines of evidence for a bidirectional connection between histamine and 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_1R	**H_2R**	**H_3R**	**H_4R**
macrovascular	↑ HDC and histamine in aortic endothelial and smooth muscle cells	atherogenesis coronary dilation, arithomogenic activity (QT-prolongation)	**++**	**++**	**+**	**n.d.**
microvascular						
neuropathy						
peripheral neuropathy		pain control, neurogenic inflammation	**n.d.**	**n.d.**	**+**	**n.d.**
autonomic neuropathy		↑ bronchoconstriction	**n.d.**	**n.d.**	**n.d.**	**n.d.**
retinopathy	↑ HDC and histamine	↑ vascular leackage	**++**			
nephropathy	↑ HDC, histamine, H_3R and H_4R expression	↑ salt and water excretion, ↓ultrafiltration coefficient, ↑ renin release	**+**	**+**	**?**	**?**

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

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

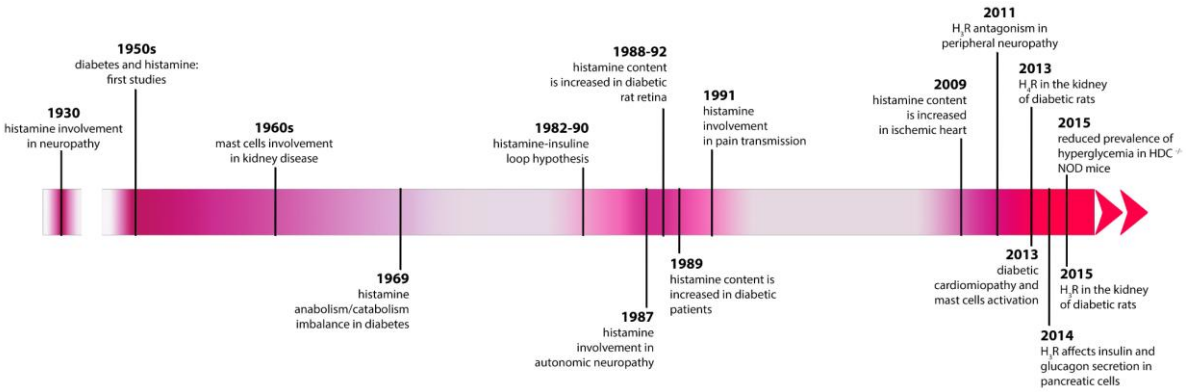

Figure 1. Milestones in the story of histamine and diabetes. Timeline of major events in the history of histamine and its link to diabetes and its complications - 1930s to present day. The phasic interest with the recent upsurge in the last couple of years is depicted.

As reported in Table I, not all the diabetic complications have been provided with the same level of compelling evidence. Many blind spots remain regarding the role of histamine in macrovascular complications where the effect of the amine seems to be mostly related to its general vasoactive properties rather than to a specific function in diabetes. The discrepancies often observed in the literature can be mostly ascribed to the different models adopted as well as to the doses, the administration route and the actual selectivity of the compound used, which could differentially affect the central and peripheral histaminergic system. More notably, the majority of the evidence for histamine involvement in the different diabetes complications arises from studies not directly aimed to assess its role in diabetic disease. This is in particular the case for diabetic peripheral neuropathy where the studies were designed to assess a general role in nociception and/or neuropathic pain. Other fields, such as retinopathy, have found using new strategies, effective and specific pharmacological tools that have downgraded the antihistaminergic approach to a supporting role. However, since many of the investigations were prior to the discovery of the newest histamine receptor members H_3R and H_4R, [147] there is scope for new insights in histamine and diabetes, and the opportunity to develop new antihistamine drugs to overcome the paucity of effective therapies.

Conflict of interest none

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Figure(s)

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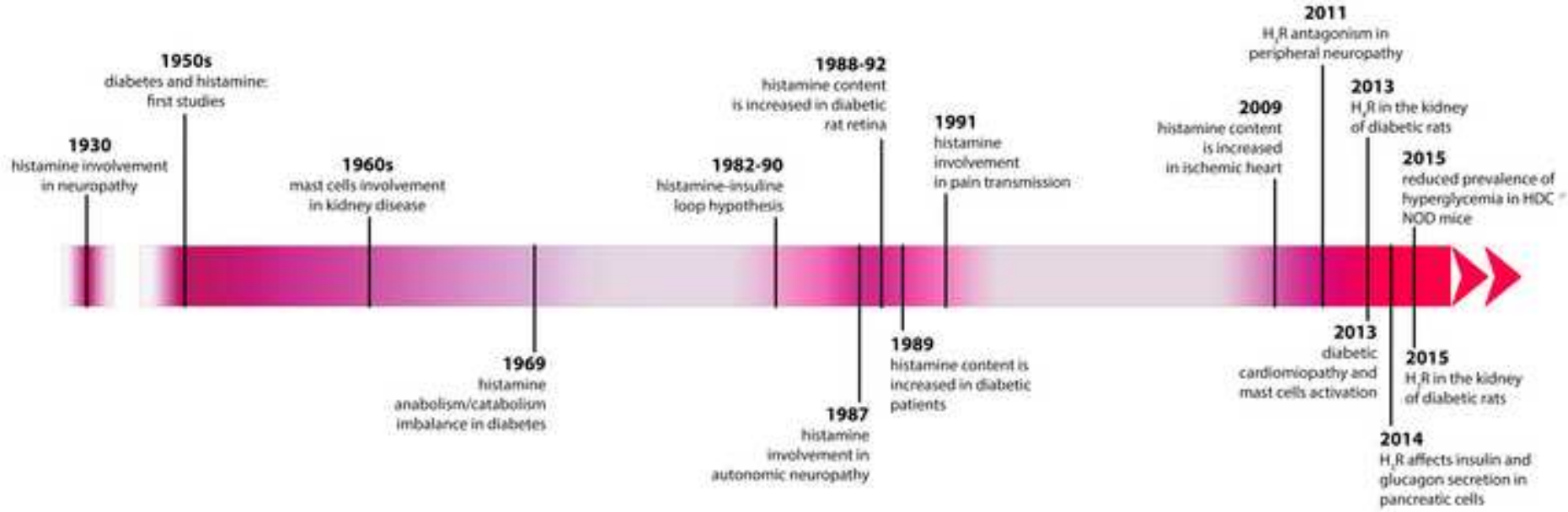

Table(s)

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

Diabetes complication	Diabetes affects histamine	Histamine influences the progression	Receptor involved			
			H_1R	**H_2R**	**H_3R**	**H_4R**
macrovascular	↑ HDC and histamine in aortic endothelial and smooth muscle cells	atherogenesis coronary dilation, arithomogenic activity (QT-prolongation)	**++**	**++**	**+**	**n.d.**
microvascular						
neuropathy						
peripheral neuropathy		pain control, neurogenic inflammation	**n.d.**	**n.d.**	**+**	**n.d.**
autonomic neuropathy		↑ bronchoconstriction	**n.d.**	**n.d.**	**n.d.**	**n.d.**
retinopathy	↑ HDC and histamine	↑ vascular leackage	**++**			
nephropathy	↑ HDC, histamine, H_3R and H_4R expression	↑ salt and water excretion, ↓ultrafiltration coefficient, ↑ renin release	**+**	**+**	**?**	**?**

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

*Graphical Abstract

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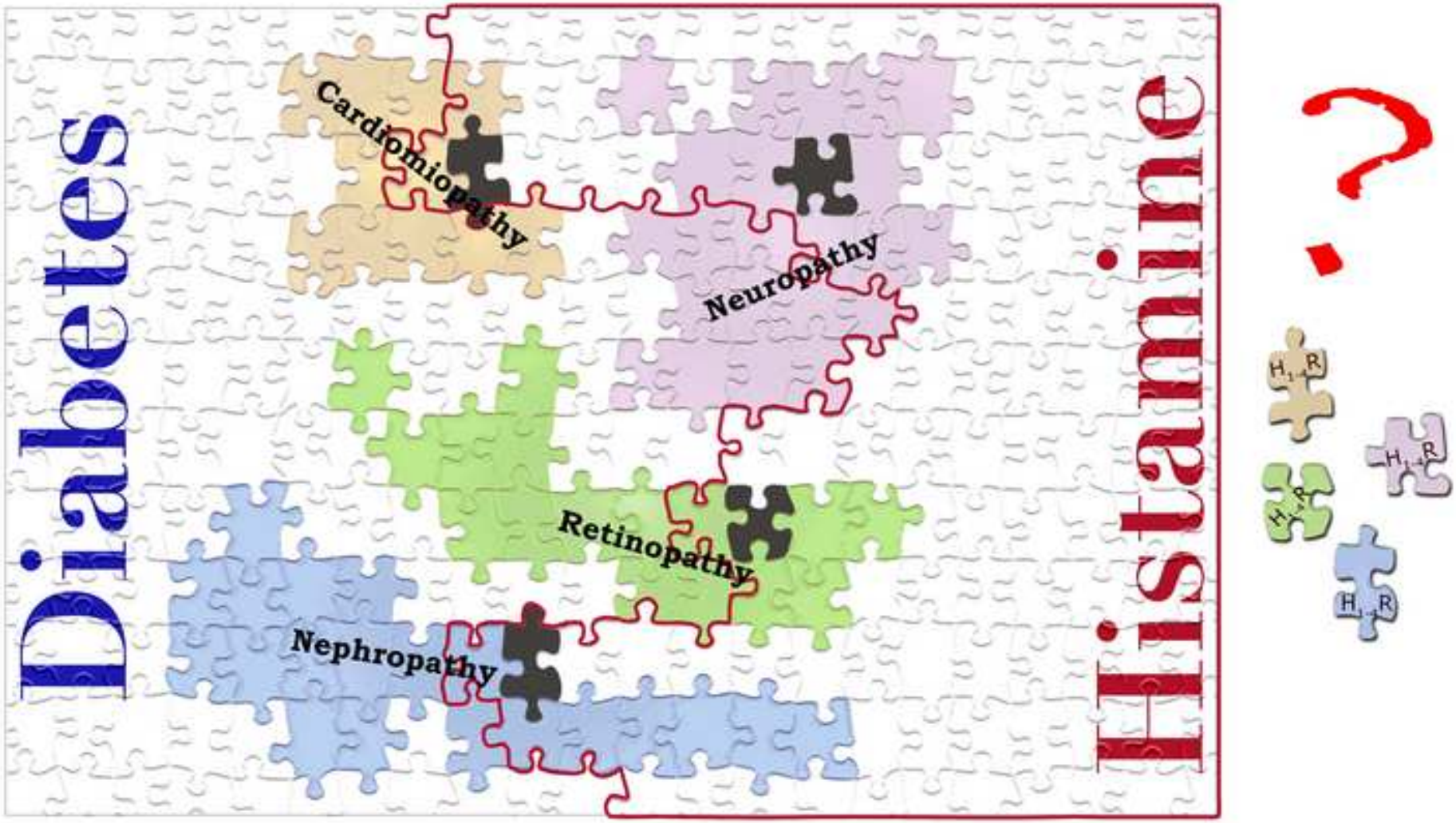

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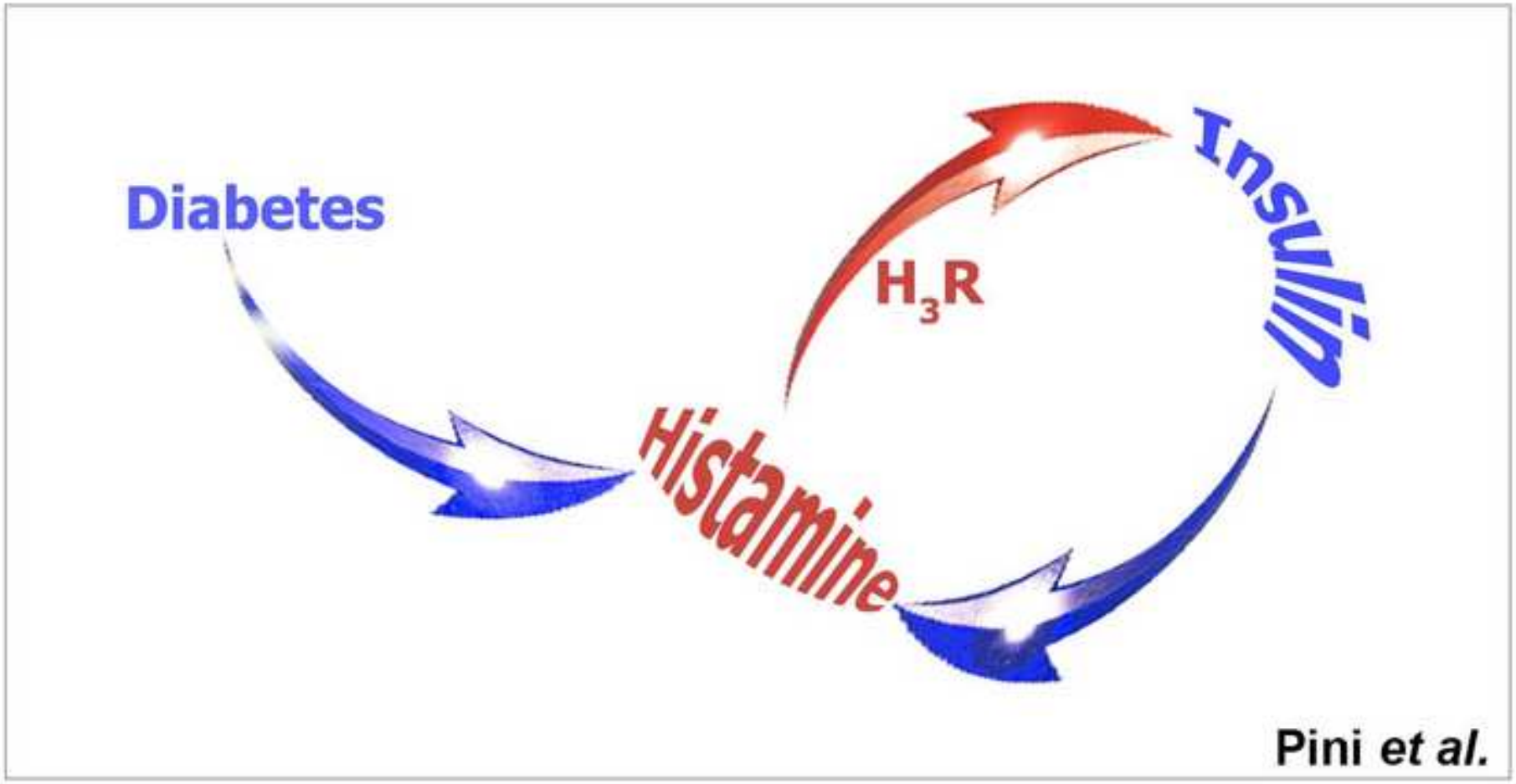

Supplementary Figure 1. The insulin-histamine loop in pancreas. Insulin administration decreases the histamine overproduction induced by diabetes *viceversa* histamine, throught H_3R, inhibits insulin secretion from ß-cells

*Conflict Of Interest

Conflicts of Interest Statement

Manuscript title: Histamine in diabetes: is it time to reconsider?

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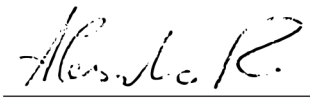
Alessandro Pini		5 maggio 2016
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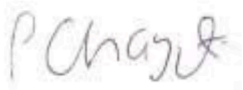
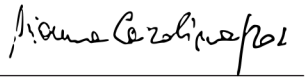
Paul L Chazot		5 maggio 2016
Arianna Carolina Rosa		5 maggio 2016