Aortic Endothelial and Smooth Muscle Histamine Metabolism in Experimental Diabetes

Alicia Orlidge and Theodore M. Hollis

We studied histamine metabolism, i.e., histidine decarboxylase (HD)-mediated synthesis and histaminase-mediated catabolism, in relation to intracellular histamine content in both aortic endothelial and subjacent smooth muscle cells of control and diabetic rats. Diabetes was induced by a single jugular vein injection of streptozotocin (55 mg/kg in acidified saline, pH 4.5), and animals were held for either 2 or 4 weeks following overt manifestation of diabetes. An additional 4-week diabetic group received insulin (Iletin NPH, 10 U per 24 hour) during the last week. With respect to control values, the histamine content of aortic endothelial cells increased 138%, HD activity increased 250%, and histaminase activity decreased 50% over the 4-week period. In subjacent smooth muscle cells, the histamine content increased in excess of 150%, HD activity increased more than 300%, and histaminase activity decreased in excess of 30%. Insulin treatment for the last week resulted in complete reversal of all these changes. These results support the concept that a large vessel response similar to the microcirculatory prolonged phase of inflammation occurs in experimental diabetes, a change similar to that occurring in experimental atherosclerosis. They also indicate that both synthetic and catabolic changes occur in histamine metabolism under these conditions, changes that alter arterial wall histamine pools, and suggest that insulin administration under conditions of experimental diabetes may modulate aortic histamine metabolism and the resultant intraaortic histamine pools.

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which are intimately associated with altered wall permeability or intravascular accumulation of macromolecules, such as low density lipoprotein (LDL), could be extremely important in determining the atherogenic potential of diabetes.

The present study is concerned with the characterization of aortic endothelial and smooth muscle histamine metabolism and intracellular histamine content under normal conditions as well as in experimental diabetes. The rationale for undertaking these studies comes from previous work we have performed which indicates that, under a variety of atherogenic conditions, aortic histamine synthesis is increased, that this increase is in many cases intimately associated with an increase in arterial transmural uptake of circulating albumins, and that partial inhibition of aortic histamine synthesis under conditions of dietary-induced hyperlipidemia reduces both increases in aortic albumin uptake as well as the severity of atherosclerosis.

Methods

Experimental Protocol

Male Wistar rats having initial body weights of 180 to 220 g (8 to 10 weeks old) were used in these studies. Diabetes was induced by a single jugular vein injection of streptozotocin (Sigma Chemical Company, St. Louis, Missouri) at a dose of 55 mg/kg in 0.5 ml of 0.9% saline containing 0.02 M sodium citrate (pH 4.5). Control animals received acidified, citrated saline only. Animals were housed in metabolic cages for daily monitoring of food and water intake and urine output. Urinary glucose was monitored using glucose oxidase method as adapted for a Yellow Spring glucose autoanalyzer on blood obtained from tail clipping. Animals were held for 2 or 4 weeks following overt manifestation of diabetes, e.g., hyperglycemia, glycosuria; in the 4-week group, additional rats were given 10 units of insulin (lletin NPH, Eli Lilly and Company, Indianapolis, Indiana) subcutaneously in the late afternoon daily during the fourth week. Animals were killed by decapitation, the thoracic aorta excised, and endothelial cells removed as described by Gospodarowicz et al. Verification of isolated cell types (endothelial and smooth muscle) involved both transmission electron microscopy of fresh isolates and phase contrast microscopy of primary cell cultures established from these cell isolates (see below).

Each cell type (endothelial or smooth muscle) from each aorta was placed in a separate test tube containing 2 ml of ice-cold phosphate-buffered saline (0.01 M, pH 7.0) containing 0.1% Triton X-100 and homogenized using a ground glass pestle. Then 1 ml of this homogenate was subjected to Sephadex G-25 filtration (Pharmacia Fine Chemicals, Piscataway, New Jersey) for removal of endogenous substrates (such as histamine, histidine, and S-adenosylmethionine) which might influence specific enzymatic reactions of the assay. The collected protein fraction was stored in liquid N2 for subsequent determination of histidine decarboxylase (EC 4.1.1.22) and histaminase (EC 1.4.3.6) activities. Histamine content was determined from boiled tissue homogenates to prevent in vitro catabolism. All measurements were performed at least in triplicate.

Biochemical Procedures

Tissue histamine content and histidine decarboxylase (HD) activity were determined by modification of the double isotopic microassay of Taylor and Snyder. This assay uses imidazole-N-methyltransferase (HMT) prepared from guinea pig brain as described by Shore. With [14C]-S-adenosylmethionine ([14C]-SAM, 58.4 Ci/mM, New England Nuclear, Boston, Massachusetts) used as the methyl donor, guinea pig brain HMT methylates sample histamine, thereby forming 1-methyl-(-)-imidazole [14C]-methylhistamine. Trace amounts of [3H] histamine (6.1 mCi/mM, 0.64 pCi/nM, New England Nuclear, Boston, Massachusetts) were added to correct for varying degrees of methylation among samples. With use of a standard curve of known amounts of histamine, constructed at the time of each individual assay, the ratio of [14C]-dpm/[3H]-dpm gives the amount of histamine present per sample. Specific details of these assays have been described previously.

For determination of cell histaminase activity, triplicate assays were performed with the method of Kuper and Roscoe. This assay was performed on supernatant not subjected to Sephadex filtration, with the incubation medium containing 0.2 ml of cell homogenate, 0.4 ml of 0.25 M phosphate buffered saline (PBS, pH 7.5), 0.1 ml of [14C] histamine dihydrochloride (labeled in the two positions on the imidazole ring; 0.25 mCi, 0.91 mCi/μM, Amersham Corporation, Arlington Heights, Illinois), and 1.9 ml of distilled water. Blanks were prepared using boiled homogenate with a 90-minute incubation period. Results were standardized on the basis of protein.

Cell Type Verification

Verification of cell types used for biochemical evaluations involved both ultrastructural examination of cell isolates and phase contrast examina-
tion of primary cultures established from these isolates.

For ultrastructural examination, cells were removed as described above and collected in cold PBS (4°C, pH 7.35). Cold glutaraldehyde was added to make a final concentration of 2.5%. After incubation for 1 hour (4°C), suspensions were centrifuged (10,000 g, 5 min, 25°C), and the cell pellet was resuspended in 0.3 ml of agar (45°C). This was then allowed to harden on a glass coverslip. Square blocks (1 mm²) were then cut and postfixed with 1% osmium tetroxide in PBS (pH 7.4) overnight, washed in PBS, and stained for 2 hours in 0.1 M sodium acetate-buffered uranyl acetate. Cells were dehydrated at 20-minute intervals in a graded series of ethanol and infiltrated with Spurr's epoxy resin. Following a 12-hour incubation period at 80°C, thin sections (silver to gray) were cut on a Sorval-Porter-Blum MT-2 ultramicrotome with glass knives, captured on a 300-mesh grid, and stained for 20 minutes with 3% uranylacetate in 15% methanol, followed by a 2-minute staining with 0.2% lead citrate. Photomicrographs were taken with a Hitachi 11 E transmission electron microscope.

Primary cultures were established using standard tissue culture techniques. For endothelial cells, isolates were removed using sterile swabs and collected in Minimum Essential Medium with Earles salts (MEM, Flow Laboratories, Inc., McLean, Virginia) containing 10% fetal bovine serum (FBS, Sterile Systems, Logan, Utah). They were plated onto sterile collagen-coated coverslips (1 mg/ml, Ethicon Corp., Sommerville, New Jersey), and held in culture for 5 to 10 days (37°C, 5% CO₂) or until apparently confluent. Refeeding occurred every 48 hours. Smooth muscle strips were cut into 1 mm² pieces, and explant cultures were established in MEM-10% FBS as before. Both were then viewed using phase contrast microscopy and photographed using a Nikon inverted phase microscope.

### Results

#### Characteristics of Animal Groups

Final body weights, serum glucose concentration, and other parameters used to monitor the diabetic state for each animal group are given in Table 1. It is apparent that animals receiving streptozotocin exhibited a reduced rate of weight gain, hyperglycemia, increased water intake, and urine output. All differences between the diabetic groups and control animals were significant (p < 0.001). Insulin treatment during the 4th week eliminated all apparent diabetic symptoms except the reduced weight gain.

#### Ultrastructural Findings

Photomicrographs of cell isolates and resulting primary cultures from a control animal are shown in Figures 1 and 2. Figure 1 shows electron photomicrographs of cells obtained by aortic luminal surface scrapings (A) and by removal of subjacent medial layers (B). Figure 2 shows phase contrast photomicrographs of primary cultures of these cell isolates. Ultrastructural features of the luminal cells were characteristically endothelial, with numerous endocytic vesicles, a prominent ovoid nu-

### Table 1. Characteristics of Animal Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Final body weight (g)</th>
<th>Serum glucose (mg/dl)</th>
<th>Urine volume (ml/48 hrs)</th>
<th>Urine glucose</th>
<th>H₂O intake (ml/48 hrs)</th>
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</thead>
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<tr>
<td>Control</td>
<td>20</td>
<td>362 ± 3</td>
<td>128 ± 14</td>
<td>48 ± 3</td>
<td>negative</td>
<td>99 ± 9</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic (2 wks)</td>
<td>10</td>
<td>238 ± 10†</td>
<td>394 ± 28</td>
<td>342 ± 9†</td>
<td>dark*</td>
<td>520 ± 16</td>
</tr>
<tr>
<td>Diabetic (4 wks)</td>
<td>10</td>
<td>243 ± 9†</td>
<td>414 ± 76†</td>
<td>325 ± 8†</td>
<td>dark</td>
<td>509 ± 11</td>
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<tr>
<td>Diabetic (3+ wks)</td>
<td>10</td>
<td>240 ± 3†</td>
<td>85 ± 19</td>
<td>67 ± 5</td>
<td>negative</td>
<td>71 ± 6</td>
</tr>
</tbody>
</table>

All values represent means ± mean standard errors. Diabetes was induced by a single jugular vein injection of streptozotocin (55 mg/kg) in acidified citrated saline (pH 4.5).

*dark = Ames Clinistix color denoting urinary glucose concentration > 150 mg/dl.
†Significant difference from control (p < 0.001), determined by variance analysis followed by Duncan's multiple range test.
Figure 1. Transmission electron photomicrographs of endothelial and smooth muscle cells isolated from rat aorta. A. Transmission electron photomicrograph of a fresh isolate of endothelial cells; the internal marker equals 0.5 μm. B. Transmission electron photomicrograph of an isolate of smooth muscle cells from the same aorta as in A; internal marker equals 1 μm.
Figure 2. Phase contrast photomicrographs of primary cultures derived from endothelial and smooth muscle cells isolated from rat aorta. A. Phase contrast photomicrograph of a fresh isolate of endothelial cells; internal marker represents 0.5 μm. B. Phase contrast photomicrograph of an isolate of smooth muscle cells from the same aorta; internal marker equals 20 μm.
Table 2. Aortic Histamine Metabolism in Endothelial and Subjacent Smooth Muscle Cells After 2 Weeks of Diabetes

<table>
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<th>Control</th>
<th>Diabetic</th>
<th>Control</th>
<th>Diabetic</th>
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<th>Diabetic</th>
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</tr>
<tr>
<td>EC</td>
<td>2.66</td>
<td>5.04</td>
<td>0.74</td>
<td>8.59</td>
<td>0.476</td>
<td>0.280</td>
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<td>SMC</td>
<td>2.72</td>
<td>4.26</td>
<td>5.85</td>
<td>9.19</td>
<td>0.550</td>
<td>0.197</td>
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<tr>
<td></td>
<td>2.69</td>
<td>2.85</td>
<td>5.04</td>
<td>8.18</td>
<td>0.398</td>
<td>0.100</td>
</tr>
<tr>
<td></td>
<td>2.69</td>
<td>2.85</td>
<td>5.04</td>
<td>8.18</td>
<td>0.472</td>
<td>0.229</td>
</tr>
<tr>
<td></td>
<td>2.69</td>
<td>2.85</td>
<td>5.04</td>
<td>8.18</td>
<td>0.472</td>
<td>0.229</td>
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<td>2.42</td>
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<td>2.97</td>
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<td>7.57</td>
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<td>HD Activity (nmole/hr/mg)*</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>EC</td>
<td>0.476</td>
<td>0.550</td>
<td>0.398</td>
<td>0.472</td>
<td>0.472</td>
<td>0.610</td>
</tr>
<tr>
<td>SMC</td>
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<td>0.197</td>
<td>0.100</td>
<td>0.229</td>
<td>0.610</td>
<td>0.568</td>
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<td>0.100</td>
<td>0.229</td>
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<td>0.100</td>
<td>0.229</td>
<td>0.610</td>
<td>0.568</td>
</tr>
<tr>
<td>Histaminase (dpm/mg)*</td>
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<tr>
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<td>792.0</td>
<td>911.7</td>
<td>721.1</td>
<td>767.9</td>
<td>683.3</td>
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<td></td>
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<td>721.1</td>
<td>767.9</td>
<td>683.3</td>
</tr>
</tbody>
</table>

EC = endothelial cells; SMC = smooth muscle cells; HD = histidine decarboxylase. Diabetes induced by administration of streptozotocin (55 mg/kg, i.v.).

*Activity standardized on the basis of mg cell protein.

†Difference from control EC significant (p < 0.005); determined by variance analysis followed by Duncan's multiple range test.

The histamine content, HD, and histaminase activities of aortic endothelial and subjacent smooth muscle cells from both control and 2-week diabetic rats are given in table 2; data for the 4-week groups are summarized in figure 3. With respect to the 2-week experiments, data indicated that under control conditions the histamine content of smooth muscle cells was 52% higher (p < 0.005) than that of the overlying endothelial cells. Interesting, however, was the finding that endothelial HD and histaminase activities were both more than twice that of smooth muscle cells, i.e., control endothelial cells had a lower histamine content but higher rates of synthesis and catabolism than did their subjacent smooth muscle cells. These differences were likewise highly significant (p < 0.005).

Figure 3. Aortic histamine metabolism in endothelial and subjacent smooth muscle cells after 4 weeks of diabetes with and without insulin treatment. Diabetes was induced by i.v. administration of streptozotocin (55 mg/kg) in acidified citrated saline (pH 4.5). Diabetic period was 4 weeks. Insulin (10 U, lletin NPH) was given daily for the last 7 days to the diabetic-insulin group only. Each group contained 10 rats (n = 10). EC = endothelial cells; SMC = smooth muscle cells; HD = histidine decarboxylase activity.
Changes Occurring in Experimental Diabetes

These data also show that, under conditions of experimental diabetes, striking and highly significant (p < 0.005) alterations occurred in both aortic endothelial and smooth muscle histamine metabolism over this 2-week period. Specifically, in endothelial cells the intracellular histamine content was elevated 52%, HD activity was increased by 226%, with histaminase activity reduced 50%. In smooth muscle cells from these same aortas, the histamine content showed a 119% increase, HD activity a 385% increase, and histaminase activity a 46% decrease.

Over the 4-week period of streptozotocin-induced diabetes, changes in histamine content and HD activity became significantly more pronounced. In endothelial cells, histamine content was increased over control values by 150%, with HD activity increased by 260%. In smooth muscle, histamine showed a 165% increase over control values, with HD activity increasing 300%. For both cell types, these differences between 2- and 4-week treatment groups were highly significant (p < 0.005). However, with insulin treatment for the last 7-day period, it was apparent that a complete reversal in all measured parameters occurred, since under this condition no significant difference existed in either endothelial or smooth muscle histamine content and histaminase activity with respect to corresponding control values. In the case of HD activity, in both cell types this activity was significantly lower (p < 0.05) than that of the control cells.

Statistical Analyses

A series of multiple regression analyses were undertaken to determine which metabolic parameter best predicts the observed intracellular histamine content. In the control endothelial cells, interactions of HD-mediated synthesis and histaminase-mediated catabolism yielded an \( r^2 \) of 0.81 (p < 0.001) and was described by the equation

\[
y = 0.203 + 4.93x_1 + 0.001x_2, \quad \text{where } x_1 \text{ and } x_2 \text{ represent HD and histaminase activities, respectively.}
\]

The strongest single predictor of the histamine content in this cell type was the HD activity (\( r^2 = 0.79, p < 0.001; y = 0.025 + 4.81x \)). Both the 2- and 4-week diabetic endothelial cells exhibited similar relationships, with 94% of the histamine content accounted for by combined histamine synthesis and catabolism. The equation was

\[
y = 14.4 + 1.13x_1 - 0.012x_2 \quad \text{(r}^2 = 0.94, p < 0.001\), where \( x_1 \) and \( x_2 \) are again respective activities of HD and histaminase. Similarly, in this diabetic state the strongest single predictor of histamine content was again HD-mediated synthesis (\( y = -3.13 + 5.31x, r^2 = 0.91, p < 0.005\)).

With respect to smooth muscle, under control conditions the multiple regression equation was

\[
y = 2.21 + 10.7x_1 - 0.007x_2 \quad \text{(r}^2 = 0.61, p < 0.025\) for these same parameters. In this case, histaminase activity was the strongest single predictor (\( y = 9.99 - 0.0096x, r^2 = 0.71, p < 0.005\)). Interestingly, in smooth muscle cells from the 2- and 4-week diabetic groups, combined HD and histaminase activities statistically accounted for more than 90% of the total intracellular histamine. With insulin treatment, 92% of the smooth muscle histamine was statistically accounted for by histaminase activity alone (\( y = 7.57 - 0.008x, r^2 = 0.92, p < 0.001\)).

Discussion

Kahlson and Rosengren\(^{28}\) and Levine and Noll\(^{29}\) have described three metabolic pools of histamine present in mammalian tissues. Of these, two have slow turnover rates and consist of inactive, bound histamine. One of these slow turnover or inactive pools is associated with mast cells and is readily depleted by Compound 48/80; the other is not fully characterized and its depletion has not yet been achieved. Both, however, are associated with low HD activities. The third pool, nascent or inducible histamine, consists of unbound, HD-dependent active histamine. Its magnitude is determined by the balance between histamine synthesis and catabolism, and is readily depleted by the inhibition of HD. This pool has been implicated in the regulation of microcirculatory flow,\(^{30,31}\) and aortic transmural permeability and macromolecule accumulation under conditions of vascular injury (see ref. 14 for summary of references). In the rabbit aorta, Foldes et al.\(^{32}\) have shown that 37% of arterial histamine is present in this pool; in dogs, Owens and Hollis\(^{19}\) have found that the magnitude of the nascent pool varies depending on aortic location, i.e., regions exposed to locally disturbed flow and that take up Evans blue dye have significantly higher nascent histamine than do adjacent, white aortic regions.

In our present study, under normal conditions endothelial cells have an HD activity that is almost twice that of the underlying smooth muscle cells and a histaminase activity that is essentially double that of these same smooth muscle cells; however, the smooth muscle histamine content is 58% higher than these endothelial cells. By regression analyses, results indicate that more than 80% of the endothelial histamine content can be accounted for on the basis of combined interactions of HD and histaminase activities, while in smooth muscle the most significant predictor is the rate of histamine catabolism. From these findings, we conclude that a major component of endothelial histamine appears to be contained within the nascent histamine pool, while in smooth muscle under normal conditions the nascent histamine pool
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is relatively small; in the latter case, the majority of intracellular histamine must be derived from some other source. Undoubtedly, for both endothelial and smooth muscle cells one such source is plasma, since Foldes et al. have shown incubated aortic strips accumulate histamine against a histamine concentration gradient. For smooth muscle, we speculate that an additional and significant source may be endothelial-derived, for while enzymatic activities of endothelial cells indicate that they have a relatively rapid histamine turnover, it is also possible that there may be significant histamine diffusion from both endothelium to blood and from endothelium to the underlying smooth muscle. If this is the case, these results would indicate that under normal conditions vascular smooth muscle could act as an intracellular histamine sink.

In the diabetic state, results of this study indicate that marked alterations occur in histamine content and histamine metabolism of both endothelial and underlying smooth muscle cells. For endothelial cells, HD activity increases during the 4-week period by over 260%, while histaminase activity is reduced by essentially 50%. The intracellular histamine content is increased by up to 150% over control values. For smooth muscle cells there is, over this period, a striking 300% increase in HD activity and up to 40% reduction in histaminase activity. Histamine in these cells increases in excess of 165% over control values. Significantly, insulin treatment for a 1-week duration produces complete reversal in all of these parameters. From the statistical data it is thus apparent that under these diabetic conditions there occurs a large increase in the HD-dependent histamine pool of both cell types, with the largest increase occurring in smooth muscle. Indeed, in these cells from diabetic animals, combined histamine synthesis and catabolism can account for 90% of the intracellular histamine present. That these marked alterations in histamine metabolism are completely reversed in the insulin-treated group is strong evidence that insulin treatment in some way modulates histamine metabolism and the resultant nascent histamine pool in the aorta, and that in this respect the aorta may be considered an insulin-sensitive organ, at least in experimental diabetes.

As previously noted, increases in aortic and aortic endothelial histamine synthesis occur under conditions of experimental hypertension following exposure of the aorta to elevated shear stresses and in dietary-induced hypercholesterolemia (see ref. 14 for a summary of references). All of these constitute known atherogenic risk factors. In the case of hypercholesterolemia, the increase in histamine synthesis is transient, restricted to the endothelium, and is intimately associated with transient increases in aortic transmural uptake of circulating albumin. In this case, partial inhibition of aortic HD resulted in a 51% decrease in aortic albumin uptake and a 63% decrease in atherosclerotic lesion severity. Thus, under at least experimental dietary hypercholesteremia, the endothelial nascent histamine pool influences aortic uptake or accumulation of circulating macromolecules. From the present study, it is apparent that histamine synthesis is likewise increased in streptozotocin-induced diabetes, but with the following important differences: 1) changes in histamine metabolism occur in both endothelial and smooth muscle cells; 2) they are of considerably greater magnitude than those observed in dietary-induced hypercholesteremia; 3) these changes are exacerbated over time rather than transient.

Obviously, additional studies must be completed before definitive statements can be made regarding the true significance of the data of the present study. However, with previous work showing correlations between local vessel wall histamine synthesis and wall albumin accumulation under a variety of atherogenic conditions, including experimental diabetes mellitus, as well as with other data clearly demonstrating reduced capacity of the diabetic aortic smooth muscle to catabolize internalized LDL, we believe that the increased nascent histamine pool is at least one mechanism having potential for increasing the rate of presentation of this substrate to underlying wall components. If so, then altered arterial wall histamine metabolism resulting in an increased nascent histamine pool may represent an important link with respect to the atherogenicity of diabetes mellitus.

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