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HISTAMINASE AND RELATED AMINE OXIDASES

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I. INTRODUCTION

An enzymatic activity that catalyzes the oxidative deamination of histamine in the tissues of mammals was first described by Best in 1929 (26) and was called histaminase. The subject of histaminase has been thoroughly reviewed in the past (112, 249–252).

Interest in these enzymatic activities has been renewed because of (a) technical progress in the identification of small amounts of metabolites possibly produced by the action of histaminase, (b) the isolation of highly purified enzymes with histaminase activity, (c) the generally increased interest in the processes of oxidative deamination of biogenic amines, and (d) the discovery and introduction into therapy of drugs able to interfere with the metabolic pathways of such amines. Although the best known of such drugs are monoamine oxidase inhibitors, soon the problem arose of their possible interference also with the oxidative pathways of histamine catabolism (143). Information on this subject may be found in the reviews on monoamine oxidases (35, 36, 87, 178).

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The importance of these types of enzymatic activity in mammals depends on the fact that 60 to 80% of the metabolites of histamine in mammals is derived from oxidative deamination, *i.e.*, involves mono- and diamine oxidases (189).

The main purpose of this review is to point out the characteristics that distinguish the histaminases recently identified from other amine oxidases.

II. DEFINITION OF THE MAMMALIAN ENZYME TYPES

The enzymes able to catalyze the oxidative deamination of histamine catalyze the general reaction[2]

$$R\cdot CH_2\cdot NH_2 + O_2 + H_2O \rightarrow R\cdot COH + NH_3 + H_2O_2$$

They are therefore amine:oxygen oxidoreductase (deaminating) enzymes, according to the terminology of the Enzyme Commission. They have been found in many tissues of mammals (see 252) and also in the blood plasma of some animal species (see 252).

Two different terms have been used to indicate these enzymatic activities; one, "histaminase," emphasizes the physiological significance of these enzymes in the metabolism of histamine; the other, "diamine oxidase," was introduced by Zeller (246) on the basis of the fact that pig kidney histaminase acted also on short aliphatic diamines such as 1,4-diaminobutane (putrescine) and 1,5-diaminopentane (cadaverine). The two terms have been used interchangeably although the demonstration of the identity of histaminase with diamine oxidase has not always been achieved. The homogeneity of the histaminases present in different tissues and in different mammalian species is still an unsolved problem because only the histaminases of pig kidney and human placenta have been purified and characterized (118, 120, 167).

Recent studies have shown that histaminase activity is a property of two mammalian enzymes which are closely related chemically, but which differ in their substrate specificity. In the pig both types of enzyme occur (51, 54). One of them is usually obtained from the kidney; the other is present in the blood plasma (54). Both occur also in man, one in the tissues and in the placenta (118), the other in blood plasma (164). The histaminase activity of pig blood plasma is an intrinsic property of the enzyme which acts on benzylamine (benzylamine oxidase) and certain other monoamines, but not on catecholamines (54). The histaminase activity of human blood plasma is like that of pig blood plasma, but also reflects an enzyme that acts on cadaverine and putrescine (diamine oxidase) the level of which increases in pregnancy and probably in other conditions (162; see Sections VII and VIII).

Plasma enzymes of the "benzylamine oxidase" type are widely distributed in mammals (35, 38). They have been recently found also in the blood plasma of rats, rabbits, and cats (176). These oxidases have been named according to their preferential substrate. Two main types of plasma oxidases can be distinguished in different species. The first of these was described as spermine oxidase (106),

[2] The hydrogen peroxide formed in the reaction is generally decomposed by catalase and the aldehyde transformed either to an acid or to an alcohol (212, 213).

TABLE 1

Characteristics that distinguish mammalian histaminases and related oxidases from intracellular monoamine oxidases

Both monoamine oxidases and diamine oxidases are localized in mitochondria and microsomes, but the first are insoluble, the second soluble enzymes (36, 256); a soluble monoamine oxidase has been found in guinea-pig liver (134).

Enzymes	Source of Enzyme	Act upon a Terminal Amino Group				Act upon		Inhibited by		Substrates Preferential	Ref.
		$-CH_2\cdot N\langle^{H}_{H}$	$-CH_2\cdot N\langle^{R}_{H}$	$-CH_2\cdot N\langle^{R}_{R}$	$-CH\cdot N\langle^{H}_{R}$	Histamine	1-Methyl-histamine	Cyanide	Semi-carba-zide[a]		
Amine oxidase Monoamine oxidase Monoamine:oxygen oxidoreductase (deaminating)	Liver and many other tissues[b]	Yes	Yes	Yes	No	No[c]	Yes[c]	No	No	Tyramine	33 36
Histaminase Diamine oxidase Diamine: oxygen oxidoreductase (deaminating)	Pig kidney	Yes	No	No	No[d]	Yes	Yes	Yes	Yes	Cadaverine	120 167 252
	Human placenta	Yes	—	—	—	Yes	—	Yes	Yes	Cadaverine	118
Plasma amine oxidase Amine·oxygen oxidoreductase (deaminating)	Ox plasma	Yes	No	No	No[e]	Yes[f,g]	Yes[f]	Yes	Yes	Spermine	241
	Pig plasma	Yes	No	No	No[e]	Yes	Yes[f]	Yes	Yes	Benzylamine	54
	Human plasma	Yes	—	—	—	Yes	—	Yes	Yes	Benzylamine	162

[a] Other inhibitors = hydroxylamine, aminoguanidine (carbonyl reagents).

[b] Crude preparations; rabbit liver contains an oxidase (mescaline oxidase) which is inhibited by cyanide and semicarbazide (24, 34, 207, 254) and acts on histamine.

[c] The amine oxidases of rabbit and guinea-pig liver act on methylhistamine (147), the amine oxidases of cat and mouse liver act on histamine and methylhistamine (125, 126, 137); the role of monoamine oxidases in the oxidation of methylhistamine is discussed in Section VIII.

[d] References 8, 111.

[e] Unpublished results.

[f] Reference 43.

[g] Poor substrate.

an enzyme with high activity on the two polyamines, spermine and spermidine. The other type has provisionally been called benzylamine oxidase (21) because benzylamine is a good substrate. Only one difference has been found between these two oxidases: benzylamine oxidase is without any significant action on spermine or spermidine, whereas these two amines are preferentially oxidized by spermine oxidase. The latter acts on many amines attacked by benzylamine oxidase, including benzylamine.

It is not known if plasma amine oxidases, other than those of the pig and man, have histaminase activity. The partially purified spermine oxidase of ox plasma shows a very weak histaminase activity although it is chemically very closely related to the pig plasma enzyme (see Section V).

From the distinctive characteristics reported in Table 1 it is clear that plasma amine oxidases are more closely related to intracellular histaminases (diamine oxidases) than to intracellular monoamine oxidases. Like histaminase, the plasma amine oxidases do not act on secondary and tertiary amines, act on both histamine and methylhistamine, and are inhibited by cyanide and carbonyl reagents. Plasma amine oxidases are also closely related to some plant enzymes like the pea seedling oxidase (105) and to some bacterial enzymes (217) in substrate and inhibitor specificity.

The distinction between the group of histaminase and related enzymes, both cellular or in the plasma, and the group of cellular monoamine oxidases is provisional because the characterization of cellular monoamine oxidases is not yet achieved. Some recent studies (87, 174, 195) suggest the existence of more than one monoamine oxidase and confirm the previous observations that the substrate specificity of the monoamine oxidases differs in different tissues (36).

In this review the term "*histaminase related enzymes*" has been introduced to indicate the mammalian plasma enzymes, the higher plant enzymes, and the microbial enzymes that can oxidatively deaminate histamine. The term "histaminase" is attributed only to the intracellular mammalian enzymes.

The literature on some plant and microbial enzymes has been recently reviewed (217). Some of the microbial enzymes do not belong to the group of histaminase related enzymes, as for instance the spermine oxidase of *Serrantia marcescens* (15, 216) and the putrescine oxidase of *Micrococcus rubens* (see Section VI).

Methods for the determination of these enzymatic activities *in vitro* are based either on the measurement of oxygen consumption or on the determination of the products of reaction (see review by Zeller 252 and 4, 161, 167, 179, 219, 258). The validity of the measurement of hydrogen peroxide through the decolorization of indigo carmine has been recently disputed (253).

III. CHARACTERISTICS OF THE MAMMALIAN INTRACELLULAR ENZYMES

A. Purification and chemical properties

Until 1965, the only intracellular mammalian diamine oxidase that had been purified was pig kidney histaminase (120, 167). In 1965 Kapeller-Adler (118) published a preliminary report on the purification of human placental histaminase.

Considerable purification of pig kidney enzyme (200- to 240-fold) was obtained by Tabor (213) in 1951. Higher degrees of purification were successively obtained by applying column chromatography and electrophoresis (13, 211, 223) By chromatography on DEAE-cellulose, Kapeller-Adler and MacFarlane (120) obtained from pig kidney cortex a preparation of histaminase that appeared homogeneous by the criteria of analytical electrophoresis. A similar degree of purity of pig kidney histaminase has been achieved by Mondoví and co-workers (167).

Both groups followed the ratio of rate of oxidation of cadaverine to rate of oxidation of histamine during the purification procedure. There is a striking difference in the results: the purest preparation obtained by Kapeller-Adler and MacFarlane does not act on cadaverine, whereas the purest preparation obtained by Mondoví and co-workers does act on cadaverine and the ratio of cadaverine rate to histamine rate remains pratically constant during the purification procedure. There is also a difference in the specific activity of the purest preparation when histamine is used as substrate. The specific activity of the enzyme purified by Kapeller-Adler and MacFarlane (120) at 37°C is 188×10^{-3} international units, that of the enzyme obtained by Mondoví and co-workers (167) at 38°C is 340×10^{-3} international units. The difference cannot be due to the difference in temperature. It may be that these discrepancies are mainly dependent on the method used for the enzyme assay: the indirect method based on indigo carmine oxidation used by Kapeller-Adler and MacFarlane (120), or the direct method based on oxygen uptake used by Mondoví and co-workers (167). In addition the assays were carried out at different pH and substrate concentrations. Blaschko *et al.* (43) showed that the optimum pH's for cadaverine and histamine oxidation by a pig kidney diamine oxidase preparation are different, pH 6.3 being optimum for histamine whereas the oxidation of cadaverine at this pH is very low. This has been confirmed with purified enzyme (167).

The effect of substrate concentration is also different for the two substrates (167, 168). The activity of pig kidney diamine oxidase with respect to different substrates cannot therefore be compared at any pH and substrate concentration. The results obtained with optimal substrate concentration (167) indicate that pig kidney cortex diamine oxidase and histaminase activities are properties of the same enzyme. This has been confirmed in personal experiments (52) and also by Mondoví and co-workers (167) with an enzyme preparation obtained by the procedure described by Kapeller-Adler and MacFarlane (120).

Highly purified human placental histaminase has been obtained with a technique very similar to that used for the purification of pig kidney histaminase by Kapeller-Adler (118). This enzyme differs significantly from the kidney enzyme. It does not withstand heating at 60°C and it has completely different spectroscopic and spectrofluorimetric properties; its concentrated solutions are pink like those of the plasma enzymes (see Section IV).

Diamine oxidase activity and histaminase activity have been followed during the purification procedure (118). The ratio of rate of oxidation of putrescine to rate of oxidation of cadaverine remained constant through the entire procedure.

The ratio of histamine to cadaverine varied widely at different stages, but the highly purified placental enzyme finally obtained was active on cadaverine, putrescine, and histamine in decreasing order. Therefore both diamine oxidase and histaminase activities seemed to be properties of the same enzyme. It is difficult to understand why, in contrast to the kidney enzyme, the indigo disulphonate method was able to measure the diamine oxidase activity of this enzyme. It is probably necessary to assume that the enzyme itself catalyzes the coupled oxidation reaction of indigo carmine. This effect might be possible if the enzyme were a copper enzyme like the plasma oxidases. Further study is necessary on this point.

Some properties of pig kidney histaminase have been described, such as electrophoretic mobility and stability. The isoelectric point of the enzyme is between pH 5.0 and 5.15 (120). The enzyme is stable in a wide range of temperatures between −20°C to 62°C (120). Pure preparations of pig kidney histaminase show a peak in the region between 400 and 450 mμ; a shoulder is also evident around 320 to 350 mμ which disappears after the addition of histamine to the enzyme solution (120). This behaviour of the spectrum has been considered an indication of the presence of pyridoxal phosphate bound to the enzyme in the form of a Schiff base. Many pyridoxal enzymes show similar spectra (82). The pure pig kidney histaminase obtained by Mondoví and co-workers (166) does not show a spectrum similar to that described by Kapeller-Adler and MacFarlane (120), whereas a peak in the region of 400 to 450 mμ was observed by Mondoví and co-workers (166) with less pure preparations of the enzyme. On the other hand it is not improbable that the absence of this maximum might be an indication of a loss of pyridoxal phosphate during the purification procedure. In agreement with this hypothesis is the fact that the pure enzyme obtained by Mondoví and co-workers (167) is activated by pyridoxal phosphate, while the enzyme obtained by Kapeller-Adler and MacFarlane (120) is activated only after a prolonged dialysis, a condition in which the enzyme may lose pyridoxal phosphate. On the other hand Goryachenkova and co-workers (94) concluded that the peaks around 415, 525, and 575 mμ observed in the spectrum of a partially purified pig kidney histaminase preparation was explained by the presence of an enzymatically inactive contaminating protein.

B. Cofactors

It was first suggested by Zeller and co-workers (257), and experimental evidence has been presented by some workers (114, 209), that histaminase is a flavoprotein. It was also suggested some time ago that histaminase and related oxidases are pyridoxal enzymes (76, 197, 230). This suggestion was based on the fact that many substances known to inhibit pyridoxal enzymes are inhibitors of these oxidases, and on the fact that the diamine oxidase activity of lung and intestinal mucous membrane of rats decreases in vitamin B_6 and B_2 deficiencies. The effect is reversed by the treatment of the animals with these vitamins (92). Recently these observations received further support when Kapeller-Adler and MacFarlane (120) obtained spectrofluorimetric evidence suggesting the presence

of both these substances in their purified kidney histaminase. However, it has not been possible so far to isolate the prosthetic group of this enzyme (94).

In support of the presence of pyridoxal phosphate and flavin adenine dinucleotide (FAD) in pig kidney histaminase (with the limitation caused by the method used for the enzyme assay) is the fact, observed by Kapeller-Adler and MacFarlane, that both these substances can reactivate the enzyme (120). The concentration of pyridoxal phosphate had a sharp optimum (120). No evidence for the presence of FAD has been obtained by Mondovì and co-workers (167) in their purified pig kidney histaminase. These authors have shown instead that the enzyme contains copper (169).

The discrepancies between these findings clearly show that further study is necessary on this point. The presence of copper and pyridoxal phosphate would be in agreement with the nature of the active site of similar oxidases, particularly of the benzylamine oxidase (histaminase) of pig plasma (39, 54). On the other hand it is also possible that FAD is not closely bound to the enzyme and that it might be lost during the purification procedure, as happens for D-amino acid oxidase (74).

The requirement of FAD and an additional electron carrier has been recently shown by Tabor and co-workers (217) for the spermidine oxidase of *Serratia marcescens*. However this enzyme is clearly not related to the enzymes of the copper-pyridoxal group, as, for instance, it acts also on secondary amines.

C. Substrate specificity

Both pig kidney histaminase and human placenta histaminase oxidize cadaverine faster than histamine (118, 167); this is in agreement with previous observation with less pure enzyme preparations (250).

Pig kidney diamine oxidase acts not only on aliphatic diamines (255), but also on aliphatic monoamines such as propylamine (83), although with a lower affinity. For this reason, and because the aliphatic diamines most readily oxidized have an optimum of length (C_5), Zeller (252) suggested that the amine group that is not removed by the enzyme is important in the interaction of the enzyme and the substrate, as if the enzyme had a negatively charged attracting group, which leads to the high affinity of some diamines. In agreement with this hypothesis is the fact that the oxidation of cadaverine and histamine have different pH optima (43, 167). The pH-dependence indicates that these substances are substrate when in dicationic form. Zeller (252) has fully discussed the general structure for aliphatic diamines as substrates of the pig kidney enzyme.

The chemical groups to which the substrates of this enzyme belong are reported in Table 2. From the physiological point of view it is important to point out that the pig kidney enzyme acts on spermine, spermidine, cadaverine, putrescine, taurine, and lysine in addition to histamine and methylhistamine. The relative rate of oxidation of these amines has not been studied with purified enzymes. The ratio of cadaverine oxidase activity to histaminase activity of the highly purified pig kidney enzyme was 2.0 (167).

Methylhistamine is a good substrate of this enzyme, as was first shown by

TABLE 2

Substrates of pig kidney diamine oxidase (histaminase)[a]

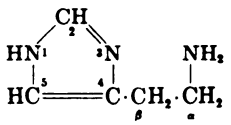
Substrate	References
a) Aliphatic diamines: $NH_2(CH_2)_nNH_2$	44, 246, 255
b) Aliphatic polyamines:	247
spermine $NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$	
spermidine $NH_2(CH_2)_3NH(CH_2)_4NH_2$	
c) N-substitute aliphatic diamines: $NH_2(CH_2)_nNR_1R_2$	255
d) Aliphatic aminoguanidines: $NH_2(CH_2)_nNH \cdot C(=NH)NH_2$	255
when n = 2 to 6	
e) Aliphatic amino alcohol: $CH_2OH(CH_2)_nNH_2$	83, 251
f) Amino acids:	
$\alpha\epsilon$-diamino-n-caproic acid (lysine)	166
g) Imidazole derivatives:	
histamine	120, 167, 255
1-methyl-4-(2′-aminoethyl)-imidazole	
1-methyl-5-(2′-aminoethyl)-imidazole	
2-methyl-4-(2′-aminoethyl)-imidazole	
h) Pyrazole, triazole derivatives:	136, 147, 255
3-(2′-aminoethyl)-pyrazole	
4-(2′-aminoethyl)-pyrazole	
4-(3′-aminoethyl)-pyrazole	
4-(2′-aminoethyl)-1,2,3-triazole	
i) Cyclic derivatives:	20, 64, 65, 68, 77, 78
cystamine	
homocystamine	
j) Amino-polymethylene-trimethyl = ammonium derivatives: $(CH_3)_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3$	255
ω-amino-n-pentyltrimethylammonium bromide	

[a] When the representative substrates of each group are not reported it means that a long series has been studied.

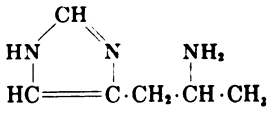
Kapeller-Adler and Iggo (119) and confirmed by others (252). Derivatives of histamine having a methyl in the α-position of the side chain are not substrates of this enzyme (8). Kapeller-Adler and Iggo (119) found that neither the N-methylhistamine nor N-dimethylhistamine are substrates of the pig kidney histaminase, in agreement with the fact that this enzyme attacks only primary amines. The N-acetylhistamine is not attacked either (119). It is also important to point out that histamine, at a concentration higher than 10^{-3} M, inhibits enzymatic activity (167, 168), whereas cadaverine does not inhibit the enzyme up to 17 mM.

D. Reaction mechanism

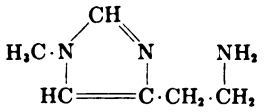
Evidence has been obtained that pig kidney histaminase catalyzes the general reaction reported in Section II. The formation of aldehyde (116), ammonia, and



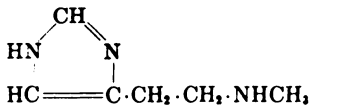
β-(imidazolyl-4-)ethylamine histamine



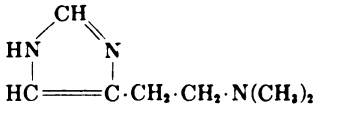
β-(imidazolyl-4-)isopropylamine
α-methylhistamine



β-(1-methylimidazolyl-4-)ethylamine
1-methylhistamine



β-(imidazolyl-4-)methylethylamine
N-methylhistamine



β-(imidazolyl-4-)dimethyl-ethylamine
N-dimethylhistamine

hydrogen peroxide has been shown by direct and indirect methods (reviewed in 214, 249, 252). The possibility that the enzyme contains two negatively charged binding sites has been suggested and discussed by Zeller (252).

In Tables 3 *A* and *B* two reaction mechanisms are suggested for pig kidney histaminase: both have been discussed by Kapeller-Adler and MacFarlane (120). In Table 3 *A*, the amine group of the substrate reacts with the aldehyde group of pyridoxal phosphate to give a Schiff base which undergoes a tautomeric transformation to azomethine; this is followed by hydrolysis. The pyridoxal form of the enzyme is regenerated by FAD. Goryachenkova (91) did not obtain clear evidence for this mechanism of reaction with pig kidney diamine oxidase and pea seedling enzyme.

The mechanism in Table 3 *B* is similar to that proposed by Werle and Pechmann (230) for the action of plant diamine oxidases. The only difference from that shown in Table 3 *A* is the absence of a tautomeric rearrangement of the Schiff base and, consequently, a direct dehydrogenation by FAD of the azomethine bond.

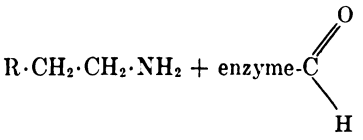
Further studies will be necessary to decide which of the two mechanisms is operating with the pig kidney diamine oxidase and whether FAD is involved in the reaction.

Little is known about hydrogen transfer from the substrate to oxygen, except that oxygen cannot be replaced by other hydrogen acceptors. If flavin is not a part of diamine oxidase, copper might be suspected of participating in the activation of oxygen. Mondoví (165) did not observe any valency change of the copper during enzymatic reaction.

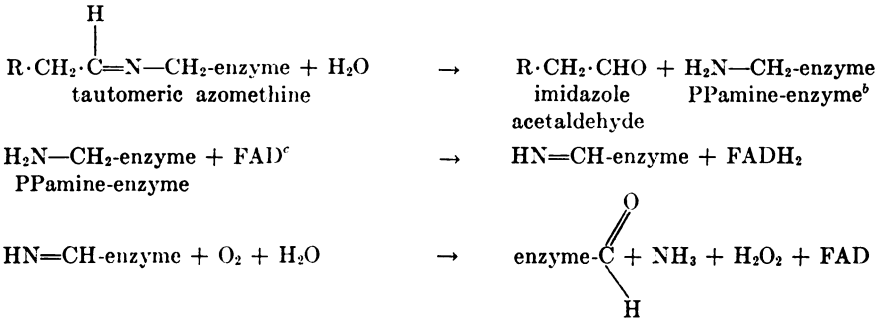
TABLE 3

Proposed reaction mechanisms of pig kidney histaminase
[see Kapeller-Adler and MacFarlane (120)]

A.



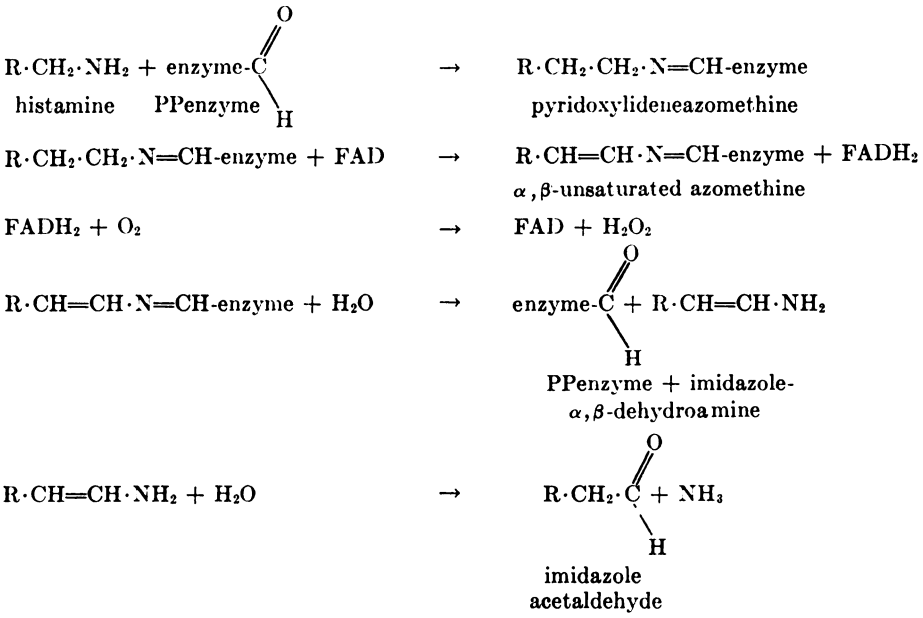
histamine PPenzyme[a] pyridoxylideneazomethine (Schiff base)



tautomeric azomethine imidazole acetaldehyde PPamine-enzyme[b]

PPamine-enzyme

B.



histamine PPenzyme pyridoxylideneazomethine

α,β-unsaturated azomethine

PPenzyme + imidazole-α,β-dehydroamine

imidazole acetaldehyde

[a] PPenzyme = pyridoxal phosphate enzyme.
[b] PPamine - enzyme = pyridoxamine phosphate enzyme.
[c] FAD = flavin adenine dinucleotide.

TABLE 4

Inhibitors of pig kidney diamine oxidase or histaminase

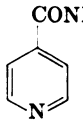
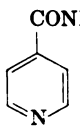
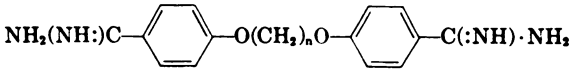
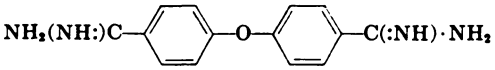
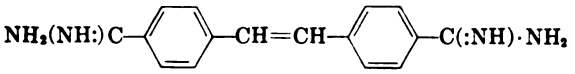
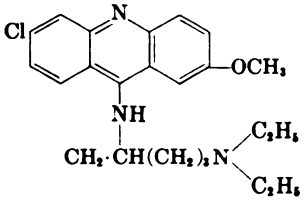
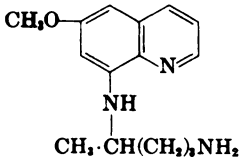
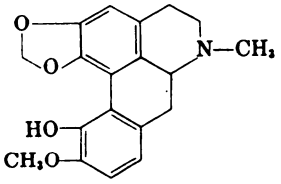
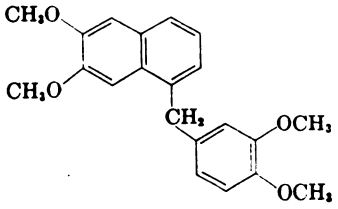
Inhibitors	References
a) Cyanide	248
b) Hydroxylamine: NH_2OH	256
c) Hydrazine derivatives:	
hydrazine: $H_2N \cdot NH_2$	193
d) Hydrazide derivatives:	
isonicotinic acid hydrazide or isoniazid:	
	43
1-isonicotinoyl-2-isopropylhydrazine or iproniazid:	
	43
semicarbazide: $H_2N \cdot CO \cdot NH \cdot NH_2$	247
e) Guanidine derivatives:	
α-aminoguanidine: $H_2N \cdot NCH(:NH) \cdot NH_2$	43
$CH_3(CH_2)_nNHC(:NH) \cdot NH_2$	42, 246
f) Diguanidine derivatives:	
$NH_2(NH:)CHN(CH_2)_nHNC(:NH) \cdot NH_2$	42, 246
g) Straight-chain monoamidines:	
$CH_3 \cdot (CH_2)_n \cdot C(:NH) \cdot NH_2$	42
h) Straight-chain diamidines:	
$NH_2(NH:)C \cdot (CH_2)_n \cdot C(:NH) \cdot NH_2$	42
i) Aromatic diamidines:	
	42
phenamidine:	
	42
stilbamine:	
	42
j) Cysteamine:	
$HS \cdot CH_2 \cdot CH_2 \cdot NH_2$	79
k) Monoisothiourea derivatives:	
$CH_3(CH_2)_nS \cdot C(:NH) \cdot NH_2$	42
l) Diisothiourea derivatives:	
$NH_2(NH:)C \cdot S(CH_2)_nS \cdot C(:NH) \cdot NH_2$	42
m) Straight-chain diamines:	
$H_2N(CH_2)_nNH_2$	44

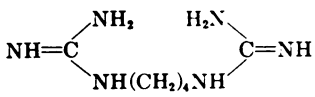
TABLE 4—*Continued*

Inhibitors	References
n) Pyridine derivatives:	
2-(2-aminoethyl)pyridine	252
picolylamine(2-, 3- and 4-aminomethylpyridine)	46
o) Pyrimidine derivatives:	
thiamine or vitamin B_1	42
p) Imidazole derivatives:	
imidazole-acrylcholine	212, 235
imidazole-propionylcholine	212, 235
q) Aminoquinoline derivatives:	
quinacrine  primaquine 	252
r) β-Phenylethylamine derivatives:	
Mescaline or 3,4,5-trimetoxy-β-phenylethylamine	94
s) Bulbocapnine: 	67
t) Papaverine: 	59
u) Dyes	252

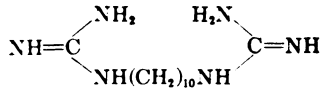
E. Inhibitors

The literature on the inhibitors of histaminase (diamine oxidase) has been recently reviewed (252). The most important chemical groups are listed in Table 4. Hydroxylamine, hydrazine, semicarbazide, and α-aminoguanidine belong to the group of carbonyl-reagents. Long chain diamines are not substrates of pig kidney histaminase, but they show an affinity for the enzyme that results in inhibition (92). The inhibition is competitive.

Guanidine was the first amidine compound that was found to inhibit histaminase (42). Zeller (247) showed that the two diguanidines, arcaine, and Synthalin A were even stronger inhibitors. Both are competitive inhibitors.



arcaine



Synthalin A

It is always in the series of compounds with two amidine groups that the strong inhibitors are found: the monoamidines are less active (42).

The use of drugs interfering in the catabolism of a biogenic amine to change the tissue levels of the amine or to study the metabolic pathways of its catabolism has been extended to histaminase inhibitors (see later in this section and in Section VIII). It is therefore important to point out that few of the substances belonging to the groups listed in Table 4 have the selectivity required for this purpose.

Many of the diamidines cause an increase in blood histamine concentration (21, 151) by releasing histamine from the tissues. Some of the compounds of this group particularly active as inhibitors of histaminase are also highly active as histamine releasers, but there is no general parallelism between histaminase-blocking activity and histamine release.

Monoamidine, diamidine, polyamidine, diguanidine, monoisothiourea, and diisothiourea derivatives are also inhibitors of monoamine oxidases (33). The same has been observed for cysteamine (89), but whereas cysteamine is a short-acting inhibitor of pig kidney histaminase, because it is readily transformed to cystamine, which is a substrate of this enzyme (79), it is a strong and irreversible inhibitor of monoamine oxidases. The inhibition of monoamine oxidases by cysteamine can be avoided by a preincubation of the enzyme with bivalent metal ions like Co^{++}. In the case of histaminase, cysteamine interferes with the enzymatic activity as long as it is present in the reduced state. Its oxidative transformation is not catalyzed by the enzyme (79). The difference in the effect of cysteamine on histaminase and monoamine oxidase further supports the difference in the active sites of these enzymes. In the case of histaminase the formation of a thiazolidine ring with the carbonyl group of pyridoxal phosphate by cysteamine can be suggested (79), whereas in the case of monoamine oxidase an interaction with a metal ion on the active site of the enzyme (96) may take place.

Similar overlap in the inhibition of diamine oxidases and monoamine oxidases

has been observed in the group of hydrazine and hydrazide derivatives. Some hydrazine and hydrazide derivatives are also strong inhibitors of monoamine oxidases. The nonhydrazine or hydrazide inhibitors of monoamine oxidases interfere only to a slight extent with diamine oxidase activities (57, 196).

The fact that hydrazines and hydrazides inhibit mono- and diamine oxidase activities is not an argument for a similarity in the active sites of these enzymes, because the mechanism of action on the two enzymatic activities (95, 96, 107) is different. There are many striking similarities between the inhibition of monoamine oxidases by hydrazine derivatives and their decomposition catalyzed by cupric ion (96). Both processes require oxygen and both are markedly potentiated by cyanide ions. Both can be retarded or suppressed by compounds capable of chelating with or being oxidized by cupric ions (96).

The decrease in the extent of inhibition found when monoamine oxidases and inhibitors are incubated under nitrogen instead of oxygen was first noticed by Davison (76), both for iproniazid and isopropylhydrazine. These and many other observations suggest that the inhibition of monoamine oxidases by hydrazide derivatives results from a copper-catalyzed liberation of free radicals in the neighbourhood of the enzyme's active centre. The metal would necessarily be a part of the enzyme (96). This is not yet proved. On the other hand this mechanism is also in agreement with the prospected mechanism of action of cysteamine (79). Cysteamine suppresses the irreversible inhibition by iproniazid if added before the inhibitor, but it is completely devoid of effect when the inhibition has been already obtained (89).

It has been proposed that the mechanism of action of hydrazine derivatives on diamine oxidases is linked to their carbonyl reagent properties (252). The reversal of the inhibition obtained with pyridoxal phosphate in the case of isoniazid inhibition can be explained by assuming that pyridoxal phosphate removes the inhibitor from the enzyme; but the fact that neither pyridoxal nor pyruvate can reactivate the inhibited enzyme makes probable a difference in the mechanism. The possibility that pyridoxal phosphate is not stably bound to the enzyme has already been discussed; it may be that isoniazid sets free the coenzyme from the apoenzyme, forming a pyridoxal-phosphate hydrazone.

The fact that the inhibition by isoniazid can be reversed by ferricyanide (132) shows that the oxidation of the hydrazine group by ferricyanide inactivates the inhibitors.

Hydrazine derivatives are competitive inhibitors of plasma oxidases (52, 90, 243). The cations of metals added to the isoniazid solutions before its addition to the enzyme prevents the inhibition. Dialysis of the inhibited enzyme against some bivalent metals can reactivate the enzymatic activity (90). This does not allow any definitive conclusion to be drawn on the mechanism of action of these inhibitors, but it shows the similarity in the behaviour of plasma enzymes and diamine oxidases in this respect. The spectrophotometric behaviour of the interaction of hydrazine compounds with pig or ox plasma amine oxidases favours the formation of hydrazone derivative with the carbonyl group of these enzymes (39, 243).

TABLE 5

Comparison of diamine oxidase inhibitors in vivo and in vitro[a]

Inhibitor	ED50[b] μmol/kg (fiducial limits)	I50[c] μM	I50× 100/ ED50
Iproniazid	5.5 (2.8–11.6)	0.07	1.3
Isoniazid	51.7 (19.0–91.7)	0.09	0.18
N′-Isonicotinyl-N′:N″-diisopropyl-hydrazine	19.4 (10.0–66.0)	>10	>52
Isopropylhydrazine	1.0 (0.4–1.3)	0.0008	0.08
N′:N″-diisopropylhydrazine	2.4 (2.0–3.1)	0.025	1.0
N′:N″-diisopropylsemicarbazide	15.2 (8.8–24.5)	>10	>66
Semicarbazide	6.5 (3.5–10.4)	0.00085	0.01
Aminoguanidine	0.07 (0.027–0.12)	0.00007	0.001

[a] From Burkard, W. P., Gey, K. F. and Pletscher, A.: Biochem. pharmacol. **3**: 249–255, 1960.

[b] ED50 = Dose for 50% reduction of female Wistar rats' intestinal diamine oxidase activity tested with cadaverine hydrochloride by manometry 4 hr after intraperitoneal injection of the inhibitor.

[c] I50 = Molar concentration that produces 50% reduction of rat intestinal or pig kidney diamine oxidase activity *in vitro* tested by manometry using cadaverine hydrochloride as substrate.

TABLE 6

Comparison of inhibition of diamine oxidase and monoamine oxidase in cat kidney by various compounds[a]

The effect was measured 16 hr after intraperitoneal administration of the inhibitors. The diamine oxidase activity was measured using putrescine as substrate.

Inhibitor	Diamine Oxidase		Monoamine Oxidase	
	ED50 μmol/Kg	Number of cats	ED50 μmol/Kg	Number of Cats
d,l-Transphenylcyclopropyl-amine	>168 (—)[b]	1	3.6 (1.8–7.0)	11
N-Methyl-N-benzyl-2-propinyl-amine	450 (360–1450)	16	16.4 (14.8–19.0)	20
N′-Pivaloyl-N″-benzylhydra-zine	20.2 (15.1–29.2)	20	2.6 (1.0–5.6)	10
Iproniazid	3.5 (2.5–4.9)	8	6.9 (5.0–9.9)	8
Aminoguanidine	0.4 (0.2–0.6)	12	>560 (—)	2

[a] From Burkard, W. P., Gey, K. F. and Pletscher, A.: Biochem. pharmacol. **11**: 177–182, 1962.

[b] Fiducial limits in parentheses.

It is interesting to point out that there is no parallelism between the potency of diamine oxidase inhibitors *in vivo* and *in vitro*, as is shown in Table 5. The comparison between the effect of some inhibitors on monoamine oxidases and diamine oxidases *in vitro* and *in vivo* is shown in Table 6. The most selective inhibitors of intracellular diamine oxidases (histaminase) are semicarbazide, α-aminoguanidine, and isoniazid, both *in vitro* and *in vivo*. Iproniazid inhibits diamine oxidases and monoamine oxidases. On the other hand one of the most

selective inhibitors of diamine oxidases, α-aminoguanidine, shows another important pharmacological effect: an inhibition of the histamine uptake by tissues (194). Among the antimalarial drugs, quinacrine is also a good inhibitor of N-methyltransferase (I50 = 10^{-5} M); primaquine is without effect on this enzyme (71).

The main studies on diamine oxidases inhibitors are related to crude preparations of these enzymes and need to be confirmed with pure preparations. The sensitivity of highly purified histaminase of pig kidney to carbonyl reagents has been confirmed (120). Purified pig kidney histaminase is also inhibited by a copper chelating substance (169); this indicates that it contains copper.

The potentiation of the pharmacological effects of histamine by histaminase inhibitors was first studied by Schild and co-workers (12, 170). Ten inhibitors were examined, including carbonyl reagents, diamines, guanidines, and imidazole derivatives. Histaminase inhibitors potentiated the response to histamine of the isolated guinea-pig tracheal chain, ileum, and uterus. The effect of histamine on cat blood pressure was not consistently potentiated. The trachea, ileum, and uterus of the guinea-pig contain histaminase and there was a significant correlation between the concentration of inhibitors required to produce enzyme inhibition and pharmacological potentiation. Potentiation by histaminase inhibitors was confined to histamine; no potentiation occurred in the case of choline or acetylcholine, or of histamine analogs that were resistant to histaminase.

In agreement with the previous results, histaminase inhibitors potentiated the effects of histamine injected into the renal artery of cats but were ineffective when the histamine was injected into the femoral artery or vein (146). Similar results were obtained in dogs (142). These observations are in accordance with the evidence that histaminase activity of cats and dogs is high in kidney whereas in other tissues methylation predominates (see Section VIII).

The effect of histamine on isolated guinea-pig ileum is potentiated by the three picolylamine isomers, inhibitors of pig kidney histaminase (46). In this series it was shown that the corresponding N-methyl derivatives, which are without inhibitory effect, were not potentiators of the response of the ileum to histamine (46).

Mescaline potentiates the hypotensive effect of histamine in rats anaesthetized with ethyl-urethane and also potentiates the contractile effect of histamine on guinea-pig ileum (60). Papaverine and bulbocapnine potentiate the effect of histamine on the permeability of the capillary vessels of guinea-pigs: moreover papaverine when injected with histamine or histidine develops a catatonic state in mice (59). It has been suggested that this effect is mediated through an inhibition of histamine metabolism (59).

It has been shown that aminoguanidine potentiates the effect of histamine on gastric secretion and also the effect of those histamine analogs that are substrates of diamine oxidase (108).

The potentiation by imidazole acrylylcholine and imidazole propionylcholine on the effect of histamine on smooth muscle (guinea-pig ileum, lung, and trachea) is accounted for by the diamine oxidase inhibition caused by these substances

(212). The same compounds (and aminoguanidine) do not potentiate the hypotensive action of intravenous histamine in dogs or the vasodilator action of intra-arterial histamine (235).

IV. PLASMA BENZYLAMINE OXIDASE

A. Purification and chemical properties

Pig plasma benzylamine oxidase was purified in 1963 (51, 54). The purification procedure included several precipitations with ammonium sulphate and separation by column chromatography. The crystalline enzyme appeared homogeneous when studied by starch gel electrophoresis and by ultracentrifugation.

The amines used to test the purification procedure and found to be oxidized were benzylamine, mescaline, histamine, and 4-picolylamine. These experiments conclusively established that the histaminase activity of pig plasma is an intrinsic property of the enzyme that acts on benzylamine and other monoamines. The enzyme does not act on short aliphatic diamines like putrescine and cadaverine, and in this respect it clearly differs from pig kidney histaminase.

Human plasma benzylamine oxidase has been purified recently (162). The specific activity of the highest purified preparation in international units at 25°C is about 6×10^{-3}, *i.e.*, $\frac{1}{30}$ of the specific activity of the crystalline pig plasma oxidase, when benzylamine is substrate.

The pig plasma benzylamine oxidase is a protein with a molecular weight of 196000 (54), and is stable at 0 to 4°C under ammonium sulphate in the dark for months (39, 54). The spectrum shows a maximum at 280 mμ and a shoulder at 480 mμ. The enzyme contains 4 moles of phosphorus per mole (39), 15.12% of nitrogen and 3 to 4 atoms of copper per mole (39).

Both enzymes, pig plasma and human plasma benzylamine oxidases, catalyze the same general reaction as pig kidney histaminase (54, 162). The enzymes show higher activity at alkaline pH (54, 162).

B. Cofactors

Evidence has been obtained that pig plasma benzylamine oxidase contains a stably bound pyridoxal phosphate in the proportion of 4 moles of coenzyme per mole of enzyme (39). It is also a copper protein (54). To judge from sensitivity to the inhibitors both copper and pyridoxal phosphate are essential for the enzymatic reaction (39).

C. Substrate specificity

The substrate specificity of pig plasma benzylamine oxidase has been extensively studied by Blaschko *et al.* (43) with crude preparations of this enzyme. The most interesting substrates have been also tested with the crystalline enzyme (52, 54). The substrate specificity of this enzyme is in Table 7. The enzyme does not act on catecholamines, while a little oxidation of 5-hydroxytryptamine has been obtained with the crystalline enzyme (52), but the oxidation of this substance by the pig plasma is mainly due to caeruloplasmin (47).

The best substrate of human plasma oxidase is benzylamine, and the oxidation

TABLE 7

Substrate specificity of pig plasma benzylamine oxidase (histaminase)[a]

Substrate Tested		Ref.	µl O_2/30 min[b]	Substrate Tested		Ref.	µl O_2/30 min[b]
Methylamine	+[c]	35		Pyridoxamine	0	52	
Isoamylamine	+	43	15	Hordenine	0	43	0
Benzylamine	+	43, 54	47	8-(4-Amino-1-methylbutyl-amino)-6-methoxyquinoline (primaquine)	+	43	12
β-Phenylethylamine	+	43	8				
β-Phenylethanolamine	0	43	0				
γ-Phenylpropylamine	+	35		ω-Amino-n-heptanoic acid	±	45	
4-Aminophenylethylamine	+	35		ω-Amino-n-octanoic acid	±	45	
Tyramine	+	43, 52	29	ω-Amino-n-hendecanoic acid	+	45	
Tryptamine	+	43, 52	15				
5-Hydroxytryptamine	±	43, 52	4	Ethylenediamine	0	43	3
Mescaline	+	43, 54	52	Propylenediamine	0	43, 52	2
4-O-Methyldopamine	+	35		Butylen ediamine (putrescine)	0	43	0
3-O-Methyldopamine	+	35					
Histamine	+	43, 54	15	Pentamethylenediamine (cadaverine)	0	43	0
1-Methylhistamine	+	34					
2-Picolylamine	+	41		Hexamethylenediamine	0	43	2
3-Picolylamine	+	41		Heptamethylenediamine	±	43	8
4-Picolylamine	+	41		Decamethylenediamine	+	43	18
Lysine or αε-diamino-n-caproic acid	0	52		Dodecamethylenediamine	+	43	13
				o-, *m*-Xylylenediamine	+	41	
Taurine	0	52		*p*-Xylylenediamine	0	41	
Cystamine	+	43	12	Spermine	0	52	0
Homocystamine	+	43	18.5	Spermidine	0	52	0
Aminoacetone	0	53		Agmatine or 1-amino-4-guanidobutane	0	43	0
δ-Aminolaevulenic acid	0	53					
DL-ε-Aminocaproic acid	0	43	0	ω-Amino-n-dodecanol	+	37	

[a] From Blaschko and co-workers (43).

[b] Pure enzyme, references 52, 54.

[c] + = Good substrate, ± = poor substrate, 0 = not oxidized.

of histamine is very slight. Interesting from the physiological point of view is the oxidation of tyramine, tryptamine, and dopamine.

D. Reaction mechanism

In agreement with the fact that pig plasma benzylamine oxidase behaves like a monoamine oxidase, although it acts on histamine, is the observation that the relative rate of oxidation of histamine increases with increasing pH or as the concentration of the monocationic form of this amine increases, whereas the opposite happens with the pig kidney histaminase (43, 52, 163).

It is possible to formulate the hypothesis that in plasma amine oxidases there is a "hydrophobic binding site" near the active centre. This hypothesis is based on the fact that these enzymes act on the nonprotonated form of the substrate and that a charged group in proximity of the amine group has a strong disturbing effect.

Direct evidence for the formation of a Schiff base between enzyme and substrate in the first step of reaction has been obtained with pig plasma enzyme and C^{14}-histamine (52). It has been found that in anaerobic conditions the enzyme binds 3 moles of histamine per mole of protein, forming an imine bond (Schiff base) between the aldehyde group of pyridoxal and the amine group of histamine. The borohydride-reduced Schiff base, pyridoxyl-histamine-5′-phosphate, has been isolated by acid hydrolysis and identified by paper chromatography and by fluorescence properties (52). Changes of the absorption spectrum in anaerobic conditions after addition of substrate have been observed with pig plasma enzyme (54). The probable mechanism of reaction of pig plasma enzyme can be considered analogous to that of the upper part of Table 3 *A*. The role of copper is still unknown.

TABLE 8

Inhibition of pig plasma benzylamine oxidase (from 39, 52)

The inhibitors were added with the phosphate buffer, pH 7.4, 0.06 M, and incubated with the enzyme for 15 min before the substrate was added. The spectrophotometric method (54) at a temperature of 37°C was used in these experiments except with cycloserine, which was studied manometrically.

Inhibitor	Concentration M	Inhibition %
Sodium cyanide	10^{-3}	100
	10^{-4}	32
Hydroxylamine	10^{-6}	60
Phenylhydrazine	10^{-6}	52
	10^{-7}	20
Iproniazid	10^{-4}	86
Semicarbazide	5×10^{-5}	100
	10^{-5}	70
	5×10^{-6}	50
α-Aminoguanidine	2×10^{-2}	100
	8×10^{-3}	50
4-Amino-3-isoxazolidone (cycloserine)	10^{-3}	75
	5×10^{-4}	50
Thioglicollate	10^{-3}	6
p-Chloromercuribenzoate	10^{-3}	100
	10^{-4}	54
Diaminoethanetetraacetic acid (EDTA)	10^{-3}	14
2,2-Dipyridyl	2×10^{-4}	9
	10^{-4}	0
o-Phenanthroline	5×10^{-5}	14
2,9-Dimethyl-1, 10-phenanthroline or neocuproine	10^{-4}	14
	5×10^{-5}	12
Bis-cyclohexanone-oxalyldihydrazone or cuprizon	10^{-4}	100
	5×10^{-5}	42
	10^{-5}	16
Sodium diethyldithiocarbamate	10^{-4}	100
	10^{-5}	28

E. Inhibitors

Plasma benzylamine oxidases are sensitive to carbonyl reagents and to chelating agents (39, 163); they are also inhibited by cyanide, a feature that clearly distinguishes these enzymes from intracellular monoamine oxidases. Human plasma oxidase differs from pig plasma oxidase in its sensitivity to chelating agents, but the fact that it is inhibited by cuprizone allows one to suspect the presence of copper, as in pig plasma enzyme. The different sensitivity to chelating agents between these two enzymes may depend on a difference in the affinity of copper for protein, and in the steric accessibility to the chelating agent (84) Diethyldithiocarbamate can remove copper from pig benzylamine oxidase. The copper-free enzyme is inactive, but the activity can be regenerated by dialysis against cupric sulphate (52). The inhibitors of pig plasma oxidase are reported in Table 8. Further studies are necessary to find out the physiological significance of plasma oxidases, and for this the discovery of selective inhibitors would be of great help.

V. PLASMA SPERMINE OXIDASE

It has been suggested that the plasma oxidases of different species and with different substrate specificities belong to the same family of enzymes (35). In agreement with this hypothesis is the finding that the spermine oxidase of ox plasma isolated and crystallized by Yamada and Yasunobu (241) resembles pig plasma benzylamine oxidase in its chemical properties, although it clearly differs in the substrate specificity (219). Strong evidence has been reported for the presence of copper and pyridoxal-phosphate in the prosthetic group of this enzyme (239, 241–245), although the pyridoxal-phosphate has not been isolated and identified as it has in the case of pig plasma oxidase.

Like pig plasma oxidase, ox plasma spermine oxidase acts also on benzylamine but does not show any appreciable histaminase activity. This enzyme represents the only mammalian spermine oxidase that has been isolated. It is not improbable that the spermine oxidase of other species will differ only in the enzyme protein, and that will determine differences in the substrate specificity. The configuration and some other properties of apoenzyme may be responsible for the diversity observed in the pattern of substrate specificity among the benzylamine oxidases of different species, as well as between benzylamine oxidases and spermine oxidases.

VI. PLANT AND MICROBIAL ENZYMES

Enzymatic activities able to catalyze the oxidative deamination of diamines and polyamines and also of histamine are widely distributed among higher plants and microorganisms. Two groups can be distinguished: one represents the oxidases dependent on FAD, the other the oxidases that show many chemical similarities to mammalian histaminases. To the first group belong the spermine oxidase of *Serratia marcescens* and the putrescine oxidase of *Micrococcus rubens* (15, 216, 237, 240), to the second the pea seedling oxidase and some fungal amine oxidases that have been recently studied.

Pea seedling amine oxidase is a copper protein containing 0.087% of copper (104, 105, 152) and having a molecular weight of 96000 (104). The absorption spectrum of this enzyme is very similar to that of mammalian plasma enzymes; it shows a shoulder around 500 mμ. Although the enzyme is inhibited by carbonyl reagents (152), no experimental evidence has been published on the presence of pyridoxal phosphate. The purified and crystalline amine oxidase of *Aspergillus niger* shows an absorption spectrum similar to that of pea seedling oxidase and mammalian plasma enzymes (238) and is inhibited by chelating agents and carbonyl reagents, but no studies on the nature of its prostethic group have so far been published. The amine oxidases of *Aspergillus niger*, *Penicillum chrysogenum*, *Monascus anca*, and *Fusarium bulbigenum* catalyze the oxidative deamination of histamine although their best substrate is a monoamine (butylamine). Only the amine oxidase of *Monascus anca* does not act on diamines and polyamines (236). Pea seedling oxidase shows a weak histaminase activity but easily acts on aliphatic diamines and also on spermine and spermidine (105).

The behaviour pattern of the substrate specificity of these oxidases shows that in living organisms many amine oxidases can exist able to act either on histamine or on short aliphatic diamines, or on both, but the two activities are not necessarily linked to the same enzyme.

VII. FACTORS AFFECTING ENZYME ACTIVITY IN PLASMA AND TISSUES

A. Age

The influence of age on the level of histaminase in tissues has been already reported by Tabor (214). The enzymatic activity increases with age. Recently Waton (227) could not observe any difference in the inactivation of histamine by the tissues of foetuses or adult cats. It has been clearly shown that the plasma amine oxidases in pigs and goats are absent at birth and develop during the 20 to 30 days after birth (38).

B. Deficiency of dietary copper or vitamins

In pyridoxine deficiency histaminase activity is decreased in the skin, intestine and lung of rats. Some restoration is achieved by adding pyridoxal phosphate (197) to the tissue homogenates. Goryachenkova (93) has confirmed this result, adding the observation that in FAD deficiency the enzyme decreased to 45 to 50% in rat tissues and it was restored by addition of FAD *in vitro*. In combined B_6 and B_2 deficiency the decrease of enzymatic activity was higher in lung and intestine and it was restored by adding both pyridoxal phosphate and FAD *in vitro*. The influence of B_6 deficiency on intestinal histaminase activity and the activating effect of the combined addition of pyridoxal phosphate and FAD have been recently confirmed in rats (2).

The effect of pyridoxine deficiency on the level of plasma oxidases has not been investigated, whereas it has been shown that in copper deficiency pig plasma does not have any benzylamine oxidase activity. The enzymatic activity is restored by copper therapy (40).

C. Adrenal glands

A lower level of histaminase activity has been observed in various tissues of adrenalectomized animals: rats (121, 220), cats (100), and guinea-pigs (110). The decrease observed in kidney and intestinal mucous membrane of cats was associated with the release of the enzyme into the thoracic duct lymph (62). An increase in the histamine content of tissues (17, 85, 103, 153, 220) and in the sensitivity to histamine (13, 22, 186) has also been described. In contrast to the decrease of the histaminase activity of tissues, the study of the catabolism of injected C^{14}-histamine in adrenalectomized rats failed to reveal any variation in the urinary excretion of imidazole acetic acid, although there was less excretion of free histamine than in previous observations in the rat (28, 29) and in man (80). Obviously the discrepancy between the results *in vitro* and those *in vivo* may be dependent on factors other than the histaminase activity of tissues.

D. Thyroid gland

The thyroid hormone increases histidine decarboxylase activity and the urinary excretion of histamine (30, 135, 204). It has been discussed whether this is a direct effect or one that is mediated through the adrenal gland (204). A direct experimental evidence on the effect of thyroid function on the histaminase activity of tissues has not been described. Spencer and West (205) observed a decrease of intestinal histaminase activity in mice after treatment with thyroxine.

E. Sex glands

Although it is well known that sex hormones influence histamine levels in the tissues (14, 31, 133, 154, 173) as well as the methylation of histamine (23), there are no studies concerning histaminase. In 1956 Kapeller-Adler (115) reported that sex hormones have a direct effect on histaminase by enhancing histaminase activity *in vitro*. Because the assay was based on the indigo carmine method, these results need to be confirmed by other methods. A direct antihistaminic effect of testosterone on guinea-pig ileum and an enhancing effect of oestradiol on the effect of histamine on guinea-pig ileum have been observed (222).

F. Pregnancy

A marked rise in diamine oxidase level in the blood plasma of pregnant women has been reported by numerous investigators (see Tabor, 214). Recently Kobayashi (127) has developed a specific and sensitive method for the estimation of diamine oxidase activity, based on the oxidative deamination of C^{14}-putrescine. With this method earlier findings on plasma histaminase activity during pregnancy have been confirmed (27, 202). The activity of the enzyme increases after 5 to 6 weeks of pregnancy and rapidly reaches a value 400 to 1000 times normal, at which it remains until parturition. After parturition it returns to normal values (1.5 to 3.4 units, when 1 unit = 0.01 μg of putrescine metabolized in 2 hr at 37°C) (202). Similar results have been recently obtained with the microvolumetric method of Kapeller-Adler by Maslinski *et al.* (159). The level of "benzylamine oxidase" activity does not change during pregnancy (161).

The placenta has a very high diamine oxidase content, and this has been considered as the source of plasma diamine oxidase in pregnancy (208). Placental diamine oxidase has been exhaustively studied by Swanberg (208), who showed that the oxidase of the human placenta was concentrated in the maternal decidua.

The marked increase in blood histaminase activity during pregnancy has not been observed in all species of laboratory animals: high levels have been found in rats (28) and guinea-pigs (158), but not in cats (61). Those animals in which the placenta had a substantial maternal component had high histaminase levels.

That the foetus was not essential for the production of the placental enzyme was shown by the high levels of histaminase produced in experimental deciduoma in the nonpregnant uterus of rabbits, as well as the high level found in pseudopregnancy (208). High levels could be produced in the endometrium of progesterone-treated rabbits (208).

An increase in histamine-forming capacity has been observed during pregnancy in rats, mice, and guinea-pigs; it was reflected also in an increased urinary excretion of histamine (111, 184). The embryonic tissues largely participates in this histamine forming capacity (160).

The metabolism of injected C^{14}-histamine in human pregnancy has been studied by Schayer (189) and Lindberg *et al.* (138–141). In pregnant women imidazole acetic acid was the predominant metabolite, while in nonpregnant women (138) it was methylimidazole acetic acid. During a continuous infusion of histamine, blood samples were taken: the C^{14}-histamine level was about 50% lower in pregnant than in nonpregnant women (138). Lindberg and co-workers concluded that the major route of histamine metabolism in the placenta and myometrium of pregnant women is oxidative deamination, and in the myometrium of nonpregnant women, it is methylation by N-methyltransferase. They showed also that the human foetus possesses mechanism for formation and degradation of histamine; the main route of degradation is methylation (140, 141).

G. Diseases

Variations of the level of histaminase activity have been described in several diseases. For example, an increase of the histaminase activity of blood serum has been reported in some tumors, such as bronchial carcinoma (63, 206) and endometrial carcinoma (48); a decrease in plasma histaminase activity in pre-eclamptic toxemia (113); a decrease in plasma histaminase activity in some diseases of the oral cavity (9); a decrease in histaminase activity, deduced by the analysis of the urinary metabolites, in diseases involving the diencephalon (224).

In schizophrenia an altered metabolism of an injected dose of C^{14}-histamine has been reported (129). The analysis of the metabolites excreted in the urine showed a decrease of imidazole acetic acid and methylimidazole acetic acid and an increase in methylhistamine and conjugated histamine. This seems an indication of decreased histaminase activity, yet the serum of schizophrenic patients has a higher histaminase activity than the serum of normal men (25). Further studies are therefore necessary on this point.

In experimental atherosclerosis in rabbits serum histaminase activity is decreased (16).

An alteration in histamine metabolism has been observed in allergy: in asthma an absence of methylimidazole acetic acid has been found in urine (123). The behaviour of blood histaminase activity during anaphylaxis needs particular mention. An increase in the level of blood histaminase activity has been observed in different animal species immediately after anaphylactic shock (23, 149, 150). This increase is dependent on a release of this enzyme by the tissues. Cedrangolo *et al.* (66) observed a decrease of histaminase activity in different organs of the rabbit and guinea-pig after shock. The site of histaminase release in rats seems to be the intestinal tract, probably the small intestine, as has been shown in experiments in which blood vessels were ligated (149). In the guinea-pig, the liver seems the most important source of enzyme and its release seems mediated through the concomitant release of heparin (86, 191, 192). Heparin has in fact the ability to release liver histaminase, as has been shown in experiments on perfused guinea-pig liver (86).

If it could be confirmed in man, this might explain the favourable effects of heparin treatment in some allergic reactions (75). In our laboratory, in two cases of anaphylactic shock after the injection of penicillin an increase of the histaminase activity of blood was observed (98).

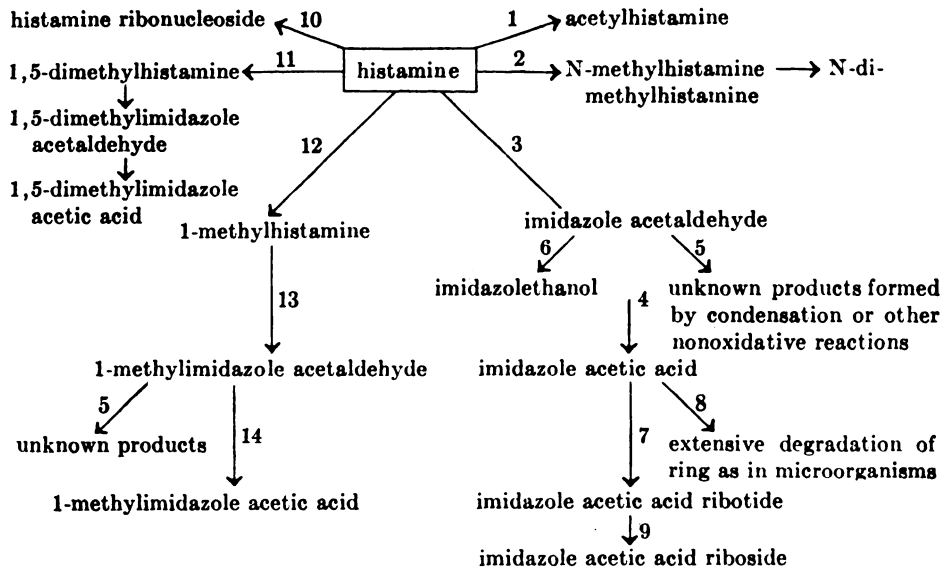
VIII. BIOLOGICAL SIGNIFICANCE OF THE ENZYMES

The position of histaminase in the metabolism of histamine is shown in Table 9.

The analysis of urinary metabolites in animals given small doses of C^{14}-histamine labelled in the imidazole ring have shown that histaminase and N-methyltransferase are responsible for the major part of exogenous histamine metabolism in various species (189). The relative importance of these pathways is different in the different species (189, 190). The oxidative products of histamine catabolism, imidazole acetic acid and methylimidazole acetic acid, represent the largest amount of the urinary metabolites (60–80%) in the rat, mouse, rabbit, guinea-pig, cat, and dog, and in man (189, 190). The ratio of imidazole acetic acid (free and conjugated) to methylimidazole acetic acid is high in the rat, lower in the mouse, rabbit, and guinea-pig, and very low in the cat and dog and in man (189).

The position of histaminase in the metabolism of methylhistamine *in vivo* is still uncertain (117). Although histaminase acts on methylhistamine *in vitro* (117), some experimental evidence shows a predominant role of an enzyme system insensitive to aminoguanidine in the oxidation of methylhistamine *in vivo* (28, 152, 185, 199). This enzyme system is sensitive to iproniazid, an inhibitor of mono- and diamine oxidase (see Section III E). On this experimental basis it is impossible to decide whether this enzyme system is identical with the monoamine oxidases that acts on catecholamines and indolamines, or if it represents a further group of oxidases. Mouse and cat liver contains an enzyme system that resembles monoamine oxidases in its sensitivity to inhibitors, although it shows both mono- and diamine oxidase activity (see Section II; 125–127), and therefore clearly differs from monoamine oxidases. Considerable oxidation of methylhistamine by

TABLE 9
Histamine metabolism



1 = A minor pathway in mammals, important in bacteria (189, 214).
2 = Kapeller-Adler and Iggo (119) found these metabolites in human urine; it is not known whether this reaction can be carried out in mammalians or whether bacteria are responsible.
3 = Catalyzed by histaminase.
4 = Can be catalyzed *in vitro* by xanthine oxidase or aldehyde oxidase (213, 214).
5 = Not proved.
6 = Occurs in man and in the rat (172).
7 = Occurs *in vitro*; catalyzed by an enzyme of rabbit liver (73).
8 = Not proved to occur in mammals; occurs in microorganisms (214).
9 = Probably formed from ribotide; found in rat and mouse tissues (181, 182, 200, 201).
10 = Probably formed by degradation of histamine adenine dinucleotide (6, 7, 171).
11 = Occurs only when large quantities of histamine are given (189).
12 = Catalyzed by N-methyltransferase (50), a major pathway of histamine in several animal species (189).
13 = Catalyzed either by monoamine oxidases or by histaminase (190).
14 = 1-Methylimidazole acetic acid has been identified in human urine and shown to be a normal metabolite of endogenous histamine (123, 221).
Further data can be found in the references 148, 190, 215.

a crude preparation of rabbit and guinea-pig liver monoamine oxidases occurs (147); but this, together with the experiments in which a competition was observed between methylhistamine and *p*-hydroxy-α-(methylaminomethyl)benzyl alcohol (Sympathol), did not conclusively exclude the possibility that the enzyme responsible for the oxidation of methylhistamine might not be identical with monoamine oxidases.

In the catabolism of exogenous histamine deduced from the analysis of urinary

metabolites, the relative importance of the first two alternative pathways, oxidation by histaminase and methylation by N-methyltransferase does not necessarily reflect the metabolism of endogenous histamine. Injected C^{14}-histamine is unequally distributed among the tissues (181, 182, 187, 188, 200, 201). From the data concerning distribution it is possible to deduce that the largest contribution to the urinary histamine metabolites comes from the kidney after intravenous injection. This has been proved in man (102) and the dog (144, 145). The intestine and liver predominate in the metabolism of histamine taken by mouth. In mice fed histamine, the compound is excreted mainly as free or conjugated imidazole acetic acid; histamine injected subcutaneously is excreted mainly as methylhistamine (32%) and as free and conjugated imidazole acetic acid (21%) (189). High doses of exogenous histamine are catabolized mainly by histaminase in mice (122) and in rats (31).

The distribution of histaminase and histamine-N-methyltransferase activities in the tissues and blood plasma of some mammals is reported in Table 10. The peculiar high concentration of histaminase in tissues with a high blood supply suggests a role of this enzyme in the catabolism of the histamine carried by the blood to the tissues.

An interesting aspect of the distribution of histaminase is its generally high level in the intestinal mucosa (55, 226) and its absence in the brain (58, 109, 232) of some species, such as rabbit, guinea-pig (58, 72), and cat (109)[3]. The absence of histaminase in the brain would be in agreement with the relative impermeability of this tissue to histamine (3, 101, 182). The high histaminase activity in the small intestine and liver might be a limitation to the intestinal absorption of histamine. For instance in sheep, where the rumen has a high amount of histamine, the liver has an important function in the protection of the animals from the histamine that is absorbed by the alimentary tract (198). The toxicity of histamine is lower when given by mouth than when injected (49).

The high histaminase activity of placenta is also in agreement with the fact that histaminase is present in tissues with high blood supply. It has been recently shown that little C^{14}-histamine passes unchanged through the placental barrier in pregnant women (140). The high histaminase activity of placenta and blood could protect the mother from histamine produced in the foetal tissues (141) or released by oestrogenic disruption of uterine mast cells (211). In confirmation of this it has been shown that the highest specific activity of blood histamine after injection of C^{14}-histamine into pregnant women is about 50% lower than in nonpregnant women (138).

All these facts support the hypothesis that the metabolic pathway catalyzed by histaminase has the role of limiting the biological effects of exogenous histamine or of the endogenous histamine escaping in the circulation when it is released in a large amount. The pathway catalyzed by N-methyltransferase seems more specialized in the regulation of the levels of endogenously formed histamine

[3] In the brain of rats and mice, Cotzias and Dole (72) found some histaminase activity, whereas Burkard and co-workers (58) could not find any diamine oxidase activity, using C^{14}-putrescine as substrate.

TABLE 10

Distribution of histaminase (DAO) and of histamine-N-methyltransferase (NMT) activities in tissues and blood plasma of some mammals

Results obtained *in vitro*. The values of NMT are expressed as percentage of activity relative to guinea-pig brain (from 50). The values of DAO (225, 226) are expressed as micrograms of histamine destroyed per gram of wet tissue at 37 to 38°C. The values of DAO (72) are expressed as micromoles of NH_3 produced in 24 hr per gram of wet tissue at 10°C.

Species	Intestine		Liver		Spleen		Lung		Heart		Brain		Blood plasma		Placenta		Kidney		Ref.
	DAO	NMT	DAO	NMT	DAO	NMT	DAO	NMT	DAO	NMT	DAO	NMT	DAO	NMT	DAO	NMT	DAO	NMT	
Rat	100	29	1.1	0	—	0	3.8	0	—	tr.	0[a]	22	+[b]	—	+[c]	—	0.2	46	225
	3		0.3		0		8.25		2.52		0.72						0.93		72
Mouse	3.06	—	0.82	47	0.74	50	1.17	69	0.73	36	0.18	62	—	—	—	—	1.30	73	72
Rabbit	169	13	1.1	62	—	29	3.8	40	—	32	0[a]	62	+[c]	—	+[d]	—	31	55	225
	3.35		6.53		1.34		21.2		2.52								4.8		72
Guinea-pig	0–15	74	5.8	21	—	78	1.8[n]	85	—	50	0[a]	100	+[e]	—	—	—	31	63	225
	1.54		1.88		0.44		0.6		1.3		0						0.73		72
Cat	36–70	tr.	0–1	56	—	56	3–4	64	—	49	tr.[f]	+[f]	0[c]	—	0[g]	—	170	tr.	226
Dog	537	—	6.9	—	—	—	0.75	—	—	—	—	—	0[c]	—	0[c]	—	529	+[o]	225
Pig	286	—	14.8	—	—	—	9.3	—	—	—	—	—	9.9[h]	—	0[c]	—	457	—	225
Man	14–35	—	0–1.5	—	—	—	0.1[i]	—	—	—	0.1[j]	—	0.006[c]	0[m]	50–180[i]	+[m]	20–21	+[l]	226
													0.0003[k]						

+ = Present; — = not determined.

[a] = Reference (58).

[b] = Reference (128).

[c] = References (5, 11).

[d] = Reference (208).

[e] = Reference (158).

[f] = References (232, 233).

[g] = Reference (227).

[h] = Plasma activity = histamine μmol/ml/h at 37°C; the histaminase activity of normal pig plasma is dependent by the presence of benzylamine oxidase (54), we do not know if in pregnancy another enzyme is present with diamine oxidase activity.

[i] = Reference (148); lung activity = histamine hydrochloride μg/g/3 hr; placenta activity = μg/g/h; plasma activity = histamine base μg/ml/h.

[j] = Reference (148) histamine μmol/g/h.

[k] = Plasma activity = histamine μmol/ml/h substained by "benzylamine oxidase" (from 162).

[l] = Shown to be present by experiments *in vivo* (102).

[m] = Reference (148).

[n] = Reference (18).

[o] = Shown to be present by experiments *in vivo* (144, 145).

or of histamine already present in the tissues and released by the stores in a small amount. This may depend on the fact that N-methyltransferase requires S-adenosylmethionine; its activity may be limited by the availability of this substance.

Strong experimental evidence suggests the role of histamine as a chemostimulator of gastric secretion (69). Rat stomach contains histaminase (130), but the gastric mucous of dogs does not contain histaminase activity (131). N-Methyltransferase is present in the stomach of guinea-pigs, cats, rabbits, and mice (50). Histaminase activity therefore does not seem to be the factor that limits the biological response of the stomach mucosa to the released endogenous histamine. On the other hand the treatment of animals with aminoguanidine results in an increased gastric secretion (108). This might reflect an increase in the blood level of histamine which is presumed to occur, considering the increased urinary excretion of this amine after treatment with aminoguanidine (108).

It would be interesting to know the nature of the urinary catabolites of endogenous histamine. The urinary catabolites of histamine released during anaphylaxis might give an idea of the role taken by histaminase in this process, *i.e.*, in the catabolism of the high levels of histamine released by disruption of mast cells. However, only the increase in the urinary excretion of free histamine has been followed during anaphylaxis (234).

On the basis of the change measured in the methylhistamine-to-histamine ratio found in the urine of women in different hormonal conditions, it has been suggested that the histamine released by a relatively low oestrogenic response is catabolized in the normal manner to methylhistamine. When the oestrogenic response is increased still further, a greater proportion of the released histamine is catabolized by histaminase, and this results in a diminished histamine excretion but unchanged methylhistamine excretion (97). Because oestrogens disrupt mast cells in both endometrium and myometrium in human beings, the same could happen in anaphylaxis. The tests of what has been stated here must await the measurement of the endogenously formed catabolites of histamine.

The significance of histaminase in the limitation of the biological response to histamine is also clearly shown by the studies concerning the potentiation of the pharmacological effects of histamine by histaminase inhibitors (see Section III E).

It can be suggested that the level of histaminase in the tissues might be adaptively increased by the substrate like that of similar oxidases elsewhere (35, 38). For example, in rats fed a diet containing 1% of phthalylsulphathiazole, intestinal histaminase activity decreased by about 30% in 43 days; this effect was dependent on the lower intestinal bacterial formation and uptake of histamine (2). The increased histaminase activity of a pregnant uterus might also be the expression of an adaptive increase induced by a strong oestrogenic response releasing a large amount of histamine by disrupting mast cells. The fact that enzymatic activity increases with age (see Section VIII A) could be the expression of a similar adaptive mechanism independent of the increased intestinal formation and absorption of histamine. This behaviour is similar to that observed with the plasma oxidases (38). Against an adaptive increase of level of histaminase

induced by substrate is the fact that the level of this enzymatic activity does not increase in animals adapted to histamine (guinea-pigs, 10, 156, 157; rats, 183; and dogs, 27), although they show a higher resistance to histamine.

The identity of histaminase with diamine oxidase has not been proved in all tissues. Therefore we do not know if these enzymatic activities may have a role also in the metabolism of other amines present in mammalian tissues, such as diamines and polyamines and also taurine and lysine, which are substrates of pig kidney diamine oxidase. Although the physiological significance of diamines and polyamines in mammalian tissues is not clear (see 217), at least these amines could competitively interfere with the oxidative deamination of histamine. It is also unknown if histaminase has a role in the transformation of taurine to isethionic acid *in vivo* (229), and this could have an important physiological significance because the proposed role of this substance in the ionic exchange of excitable tissues (180, 228, 229). Another unsolved aspect is the position of histaminase in the oxidative deamination of lysine *in vivo*. Recently an interesting hypothesis has been formulated that a copper-enzyme might be the catalyzer of desmosine and isodesmosine synthesis by the oxidation of the ϵ-amino group of lysine (174). This suggestion is based on the fact that desmosine and isodesmosine are decreased in elastic tissues from copper-deficient animals and that β-aminopropionitrile, which is an inhibitor of copper-containing enzymes, causes a syndrome analogous to that of copper deficiency in pigs (174). Aortas from copper-deficient animals contain less elastin and an abnormal high concentration of lysine (174). Direct evidence of the role of a copper-enzyme like histaminase or plasma oxidases has not yet been investigated. If this could be proved another aspect of the physiological significance of these oxidases might become apparent.

It is clear that human plasma oxidase does not show so exclusive an affinity towards histamine that this substance can be considered its main physiological substrate. Although pig plasma oxidase accounts for the high histaminase activity of pig plasma (see Table 11), the affinity of this enzyme for histamine is $\frac{1}{10}$ of that of pig kidney histaminase. Therefore the position of plasma oxidases in respect to cellular histaminase is similar to that of plasma cholinesterase in respect to cellular acetylcholinesterase.

The possibility that plasma amine oxidases chiefly act on amines taken up from the lumen of the gastrointestinal tract has been discussed by Blaschko (35). This does not necessarily mean that they have a detoxicating function. Spermine oxidase has been considered a catalyst for removal of excess of spermine (35) This would account for its presence in herbivorous animals with a large absorbing surface in the stomach (ruminants, Tylopoda or camels, and the hippopotamus) and in Hyracoidea with their many caeca (35). The amine on which benzylamine oxidase could act is not yet known, although some benzylamine derivatives have been found in human urines (124) and in some vegetables eaten by man (177). The possibility that plasma oxidases may represent adaptative enzymes is tempting, but it has not been proved.

Blaschko (35) suggested that benzylamine oxidase, spermine oxidase, histaminase, and mescaline oxidase, as well as plant and microbial enzymes might

represent members of the same family in evolution. Histamine-N-methyltransferase seems a more specialized enzyme, and in fact it is present only in vertebrates (99).

It is interesting to point out that plasma oxidases can have a significance in the metabolism of many drugs such as mescaline.

From what is known of the distribution of histaminase and related oxidases it seems clear that it would be wrong to consider this group of oxidases only from the standpoint of their role in the biological inactivation of histamine. There is every reason to believe that these enzymes will be found to have a much wider physiological significance and that histaminase activity is the expression of only one aspect.

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