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Some Histamine-related Compounds Interacting with the Benzylamine-oxidizing Activity of Rat White Adipocytes

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Abstract

In rat white adipocytes histamine is oxidized by a semicarbazide-sensitive amine oxidase which has benzylamine or preferential substrate (Bz-SSAO). To determine whether Bz-SSAO could control the extracellular levels of histamine and other histamine-related compounds active in lipid mobilization, a series of histaminergic compounds was screened as possible substrates or inhibitors of Bz-SSAO activity.

Histaminergic compounds with imidazolo or thiazolo groups are oxidized by rat white-adipocyte Bz-SSAO whereas *S*-isothiourea derivatives, with two- or three-carbon-atom alkyl chains between the isothiourea and the *N,N*-dimethyl residue are, instead, inhibitors of the enzyme. Amtamine has been identified as a selective, high affinity substrate for rat white adipocyte Bz-SSAO. This enzymatic degradation might represent a catabolic pathway for the drug.

These results show that the histaminase property of the rat white-adipocyte enzyme Bz-SSAO also extends to other histamine derivatives active at histamine receptors.

The presence of a benzylamine oxidising activity (Bz-SSAO), which belongs to the class of the semicarbazide-sensitive amine oxidases (EC 1.4.3.6.) has been described in white adipocytes of rat (Raimondi et al. 1991) and of other animal species (Raimondi et al 1992). This enzyme has been characterized in terms of subcellular localization, occurrence in differentiating precursor cells (Raimondi et al 1990), substrate rank of affinity and inhibitor profile. In addition, it shares with other Bz-SSAO (Buffoni et al 1994) and with soluble pig plasma benzylamine oxidase activity (Buffoni 1966) the ability to oxidize histamine.

Histamine is present in the mast-cell population of rat white-adipose tissue (Raimondi et al 1992) and is also taken up by adipocytes (Conforti et al 1994) where it induced weak lipolytic activity (Raimondi et al 1993). Histamine uptake is influenced by histaminergic compounds whereas lipolysis seems to be modulated by Bz-SSAO activity. That lipolysis was modulated by Bz-SSAO activity was considered important in the understanding of the role of Bz-SSAO in rat adipocytes, cells in which the classic diamine oxidase activity (DAO) is absent. In this respect the fact that histamine oxidation in rat white adipocytes occurs as a result of typical Bz-SSAO activity was confirmed (Raimondi et al 1995b) by the inhibition of amine oxidation by B24 (Bertini et al 1988) and MDL 72274 (Lyles et al 1987). The membrane-bound Bz-SSAO activity of rat white adipocytes could thus control extracellular histamine concentrations.

It is, therefore, possible that this kind of enzymatic degradation is extended to other histamine-related compounds active on lipid mobilization or histamine uptake.

To investigate this a series of histaminergic compounds was screened as possible substrates or inhibitors of the Bz-SSAO activity of these cells. We believed it to be important to define the extent of enzyme participation in the metabolism of histamine derivatives to determine the role of the enzyme in the pharmacological activity of the drugs tested.

We also wished to establish whether the histaminase property of rat white adipocyte Bz-SSAO extended to other histamine derivatives. The compounds screened as possible substrates were aromatic amines and some isothiourea derivatives lacking the aromatic ring.

It is already known that many histaminergic compounds interact with the enzymatic pathways involved in histamine synthesis or metabolism (Taylor & Snyder 1972; Shaff & Beaven 1977). We were now interested in verifying the same kind of interaction with the histaminase activity of rat white adipocytes.

In view of growing evidence suggesting new pharmacological uses of isothiourea derivatives, our data could contribute information on the interactions of these chemical structures with other enzymatic pathways. In particular, we have verified the structure–activity relationship which makes a histamine derivative a substrate or an inhibitor of the only enzyme which deaminates histamine in rat white adipocytes.

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Materials and Methods

Collagenase type II, pargyline hydrochloride, *S*-methylisothiourea hemisulphate, thiourea, *N*-methylthiourea histamine dihydrochloride, and pig kidney diamine oxidase were obtained from Sigma (St Louis, MO). Bovine serum albumin was from Boehringer (Mannheim, Germany) and homovanillic acid was from Merck (Darmstadt, Germany). [^{14}C]Hydroxytryptamine (56 mCi mmol^{-1}) and 2-phenyl-1-[^{14}C]ethylamine hydrochloride (50 mCi mmol^{-1}) were from Amersham (UK) and ICN Pharmaceuticals (Irvine, CA), respectively. Dimaprit, nor-dimaprit, homo-dimaprit and amtamine were kindly donated by Professor Timmerman, Leiden University, Amsterdam, The Netherlands.

Preparation of isolated white adipocytes

The epididymal portion of rat white adipose tissue (0·8–1·5 g of tissue) was collected from mature male Wistar rats, 200–350 g, from Morini breeding colonies (S. Polo D'Elsa, Italy) housed under controlled conditions of light and temperature. The tissue was weighed, rinsed in saline solution, minced with scissors and transferred to a polypropylene tube containing type II collagenase (0·5 mg mL^{-1}; Rodbell 1964). Digestion was performed for 30–45 min at 37°C after extensive oxygenation of tissue pieces with 95% O_2 and 5% CO_2. Floating adipocytes were separated from the undigested tissue by filtration through cotton gauze and left to float to the top of the tube. A supernatant was aspirated and fresh Krebs–bicarbonate buffer (Raimondi et al 1993) pH 7.4, was added. Three or four washings were performed before the cells were used. At the end of the procedure as much medium as possible was aspirated to give a suspension of packed cells.

Bz-SSAO activity measurement

The Bz-SSAO activity of white adipocytes was assayed in cell homogenates. Cells were homogenized using a glass–Teflon homogenizer in Krebs–bicarbonate buffer (1:10 dilution) and then centrifuged at 1000 *g* at room temperature for 10 min. The resulting clear supernatant was used as a source of enzyme (0·3–0·5 mg mL^{-1} protein). Activity was measured fluorimetrically according to the method of Matsumoto et al (1982). Supernatant (0·1 mL) was incubated in 0·5 mL 10 mM phosphate buffer, pH 7·8, containing 1 mM pargyline, peroxidase and homovanillic acid. Mixtures were pre-incubated at 37°C for 30 min before addition of histamine or benzylamine and were allowed to react for a further 30 min at this temperature. The reaction was stopped by the addition of 0·5 M NaOH (2 mL) and H_2O_2 produced was measured fluorimetrically.

The calculation of kinetic constants for histamine and benzylamine oxidation was performed by the method of Wilkinson (1961). K_m and V_{max} for benzylamine oxidation were also compared with values obtained by appropriate graphical analysis of the kinetic data. It was found that although histamine oxidation gave simple hyperbolic kinetics, benzylamine oxidation showed substrate inhibition (Raimondi et al 1995). This problem was minimized by using a low range of benzylamine concentrations (from 1 to 10–20 μM).

When inhibitors of enzymatic activity were added, they were pre-incubated with the enzyme for 30 min before addition of substrates.

Diamine oxidase activity

Pig kidney diamine oxidase (10–20 mg mL^{-1}) was prepared in Krebs–bicarbonate buffer. Enzyme activity was measured by adding enzyme suspension (0·1 mL) to 10 mM phosphate buffer, pH 7.8, containing all the reagents for the fluorimetric measurement of the hydrogen peroxide, as above. Mixtures were pre-incubated for 30 min at 37°C and then histamine (25–100 μM) was added and reacted for a further 30 min at the same temperature.

Monoamine oxidase activity

Mitochondrial monoamine oxidase activity was measured in a mitochondria-enriched fraction of rat liver homogenate prepared as described elsewhere (Buffoni & Ignesti 1975). Enzyme activity was assayed radiochemically using β-phenylethylamine or [^{14}C]hydroxytryptamine as substrates for monoamine oxidases B and A, respectively.

Protein content

The protein content of samples was estimated by the method of Lowry et al (1951) using bovine serum albumin as standard.

Dialysis

Enzyme mixtures (5 mL) incubated for 30 min at 37°C with dimaprit and nor-dimaprit were dialysed against sodium-potassium phosphate buffer (10 mM, pH 7·8; 200 mL) for 24 h at 4°C (three changes). Enzyme activity was measured before and after dialysis.

Results

Histamine-related compounds as substrates of rat white adipocyte Bz-SSAO

Three primary amines structurally related to histamine, active as H_1 and H_2 agonists, were checked as possible substrates of rat white–adipocyte Bz-SSAO. Table 1 shows the kinetic parameters for the oxidation of each compound by rat white–adipocyte Bz-SSAO. All the compounds tested gave linear Lineweaver-Burk plots. Histamine, 4-methylhistamine and 2-methylhistamine showed different apparent affinities for the enzyme, with the affinity being least for 4-methylhistamine. Amtamine, a novel and selective H_2 agonist (Eriks et al 1993), behaved as a high-affinity substrate of Bz-SSAO; the K_m of amtamine was closer to the K_m of benzylamine than to that of histamine.

Table 1. Histamine derivatives as possible substrates for rat white–adipocyte Bz-SSAO.

Compound	K_m (μM)	V_{max} (nmol (mg protein)$^{-1}$ min^{-1})	V_{max}/K_m (mg^{-1} min^{-1} × 1000)
Histamine	122·7 ± 11·4	2·67 ± 0·09	22
4-Methylhistamine	1884 ± 453	1·41 ± 0·30	0·75
2-Methylhistamine	158·2 ± 16·2	1·64 ± 0·05	10
Amtamine	37·2 ± 3·3	0·57 ± 0·09	15
Benzylamine	9·94 ± 1·92	6·10 ± 0·68	613

Bz-SSAO activity was measured fluorimetrically under conditions of monoamine oxidase inhibition by 1 mM pargyline. Histamine (50, 100, 125, 250, 500, 1000 μM), 2-methylhistamine (250, 500, 1000, 2000, 4000 μM), 4-methylhistamine (100, 250, 500, 1000, 2000 μM), amtamine (50, 75, 100, 200, 400, 600 μM) were added and the hydrogen peroxide produced measured after 30 min incubation at 37°C. The calculation of kinetic constants was performed by the Wilkinson (1961) method.

Table 2. Isothiourea derivatives as possible inhibitors of benzylamine oxidation by rat white–adipocyte Bz-SSAO.

Compound	K_i (μM)	Mechanism of inhibition	Effect
Thiourea	> 2000		
Isothiourea	> 2000		
S-Methylisothiourea	> 2000		
Nor-dimaprit	450 ± 35	Hyperbolic mixed non-competitive	Reversible
Dimaprit	400 ± 44	Hyperbolic mixed non-competitive	Reversible
Homo-dimaprit	> 1000		

All the compounds were assayed as possible substrate for or inhibitors of the Bz-SSAO activity of rat white adipocytes. Enzyme preparations were pre-incubated with the molecules (for dimaprit and nor-dimaprit the concentrations used are the same of those used for Figs 1–4, the others were tested up to 2 mM) for 30 min at 37°C in the presence of pargyline (1 mM). Benzylamine (5, 10, 15, 20 μM) was then added and reacted for a further 30 min under the same conditions. For explanation of the mechanism of inhibition and on the calculation of K_i see the figure legends. Enzymatic activity was evaluated before and after the dialysis which led to recovery of 85% activity.

Table 3. Isothiourea derivatives as possible inhibitors of histamine oxidation by rat white–adipocyte Bz-SSAO.

Compound	K_i (μM)	Mechanism of inhibition	Effect
Thiourea	> 2000		
Isothiourea	> 2000		
S-Methylisothiourea	> 2000		
Nor-dimaprit	530 ± 25	Hyperbolic mixed non-competitive	Reversible
Dimaprit	600 ± 50	Hyperbolic mixed non-competitive	Reversible
Homo-dimaprit	> 1000		

All the compounds were assayed as possible substrate for or inhibitors of the Bz-SSAO activity of rat white adipocytes. Enzyme preparations were pre-incubated with the molecules (for dimaprit and nor-dimaprit the concentrations used are the same of those used for Figs 1–4, the others were tested up to 2 mM) for 30 min at 37°C in the presence of pargyline (1 mM). Histamine (100, 200, 500, 1000 μM) was then added and reacted for a further 30 min under the same conditions. For explanation of the mechanism of inhibition and on the calculation of K_i see the figure legends. Enzymatic activity was evaluated before and after the dialysis which led to recovery of 85% activity.

Diamine oxidase activity

We were interested in checking amtamine oxidation by diamine oxidase under our experimental conditions. To this aim we used pig kidney diamine oxidase as a source of enzyme activity. Amtamine (up to 1 mM) did not produce any appreciable amount of hydrogen peroxide when used as a substrate for pig kidney diamine oxidase (data not shown).

Isothiourea derivatives as inhibitors of rat white adipocyte Bz-SSAO

A series of isothiourea derivatives, some active at histaminergic receptors, were assayed as possible substrates or inhibitors of adipocyte Bz-SSAO (Tables 2 and 3). None of the compounds was oxidized by the enzyme.

Of the isothiourea derivatives screened only dimaprit and nor-dimaprit inhibited the oxidation of benzylamine and histamine by white adipocyte Bz-SSAO. All the other compounds showed a small amount of inhibition (20–30%) of benzylamine and histamine oxidation only at concentrations above 3 mM.

Dimaprit and nor-dimaprit were pre-incubated with the enzyme mixture for 30 min before addition of benzylamine (2·5 to 20 μM) or histamine (100 to 1000 μM). The mechanism of inhibition of the oxidation of both amines by dimaprit and nor-dimaprit was assessed by plotting the kinetic data according to Lineweaver–Burk, (Dixon 1953) and Hanes-Woolf. Both compounds inhibited the oxidation of benzylamine and histamine; K_i values were approximately 500 μM (Table 3). Whereas dimaprit inhibited oxidation of both benzylamine (Fig. 1) and histamine (Fig. 2) by a mixed non-competitive hyperbolic mechanism, nor-dimaprit caused mixed, hyperbolic, non-competitive inhibition of the oxidation of benzylamine (Fig. 3) and mixed uncompetitive hyperbolic inhibition of the oxidation of histamine (Fig. 4).

The effect of dialysis

Enzyme mixtures with or without inhibitors (1 mM) were subjected to extensive dialysis against phosphate buffer, as described above. After dialysis 85 ± 5% of enzyme activity was recovered.

Monoamine oxidase activity

All the isothiourea derivatives listed in Table 2 were subjected to screening as possible inhibitors of mitochondrial monoamine oxidase. The compounds (up to 1 mM) inhibited neither [^{14}C]phenylethylamine nor [^{14}C]hydroxytryptamine oxidation.

Discussion

The histaminase property of rat white–adipocyte Bz-SSAO extends also to other histamine derivatives, e.g. 2-methylhistamine and the novel H_2-selective agonist amtamine. Among

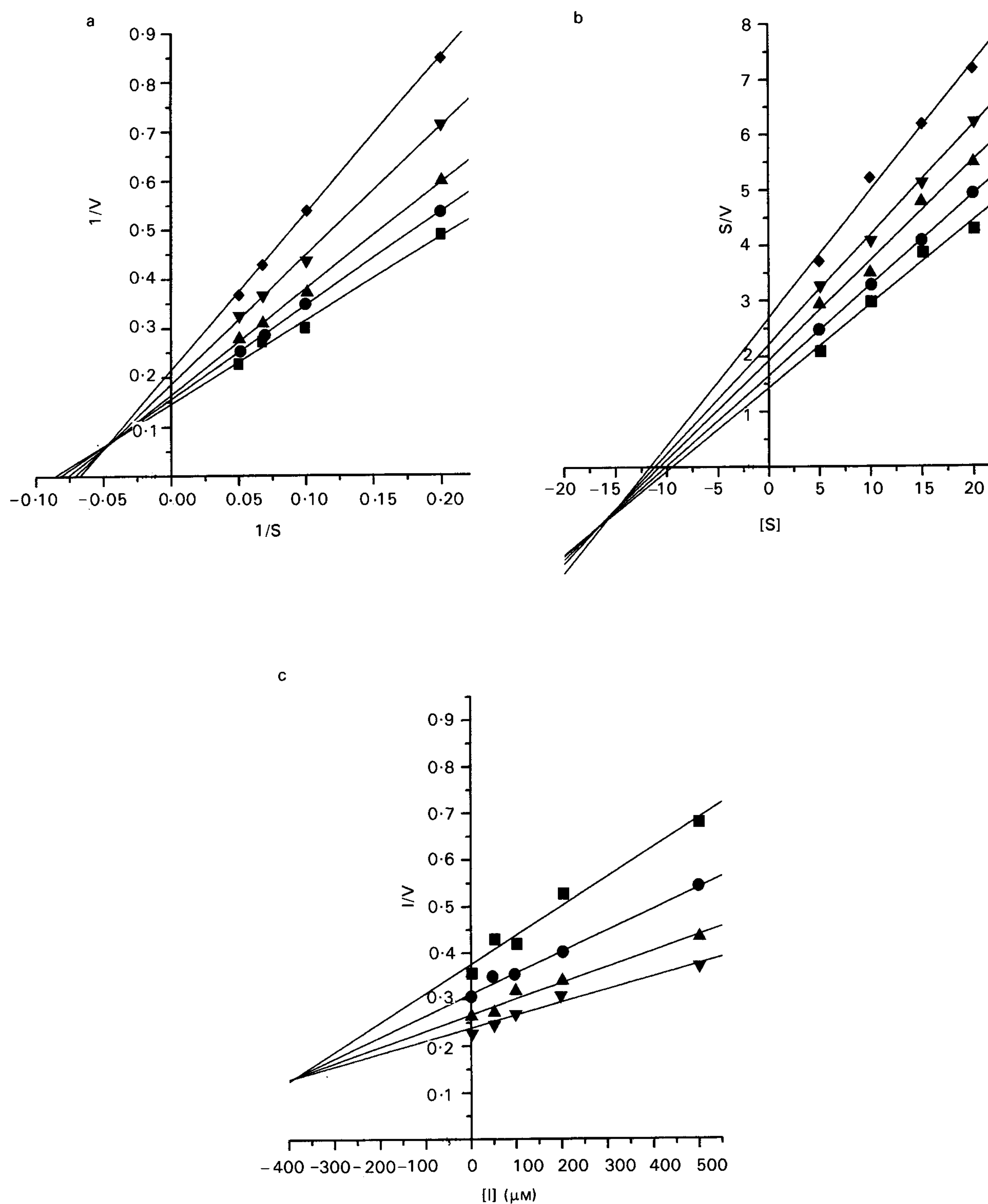

FIG. 1. Kinetic analysis of inhibition by dimaprit of benzylamine oxidation by rat white adipocyte Bz-SSAO. Enzyme preparations were pre-incubated for 30 min at 37°C in the presence of 1 mM pargyline, to inhibit monoamine oxidase activity and in the presence of dimaprit (50, 100, 200, 500 μM). Benzylamine (5, 10, 15, 20 μM) was then added and reacted for a further 30 min at the same temperature. Enzymatic activity was measured fluorimetrically. The K_i values of dimaprit for benzylamine oxidation were calculated according to Segel (1993) to be 400 ± 44 (mean ± s.e.m. of three different values from separate experiments. (a) Results plotted according to Lineweaver-Burk, i.e. 1/(rate of benzylamine oxidation (1/(nmol × (mg protein)$^{-1}$ min^{-1}))) against 1/[benzylamine](μM^{-1}): ■, dimaprit 0 μM, ●, dimaprit 50 μM; ▲, dimaprit 100 μM; ▼, dimaprit 200 μM; ◆, dimaprit 500 μM. (b) Results plotted according to Hanes-Woolf, i.e. [benzylamine]/(rate of oxidation) ((mM)/(nmol × (mg protein)$^{-1}$ min^{-1})) against [benzylamine] (μM): ■, dimaprit 0 μM; ●, dimaprit 50 μM; ▲, dimaprit 100 μM; ▼, dimaprit 200 μM; ◆, dimaprit 500 mm. (c) Results re-plotted according to Dixon (1953): 1/(rate of benzylamine oxidation) (nmol × (mg protein)$^{-1}$ min^{-1}) against [dimaprit](μM): ■, benzylamine 5 μM; ●, benzylamine 10 μM; ▲, benzylamine 15 μM; ▼, benzylamine 20 μM.

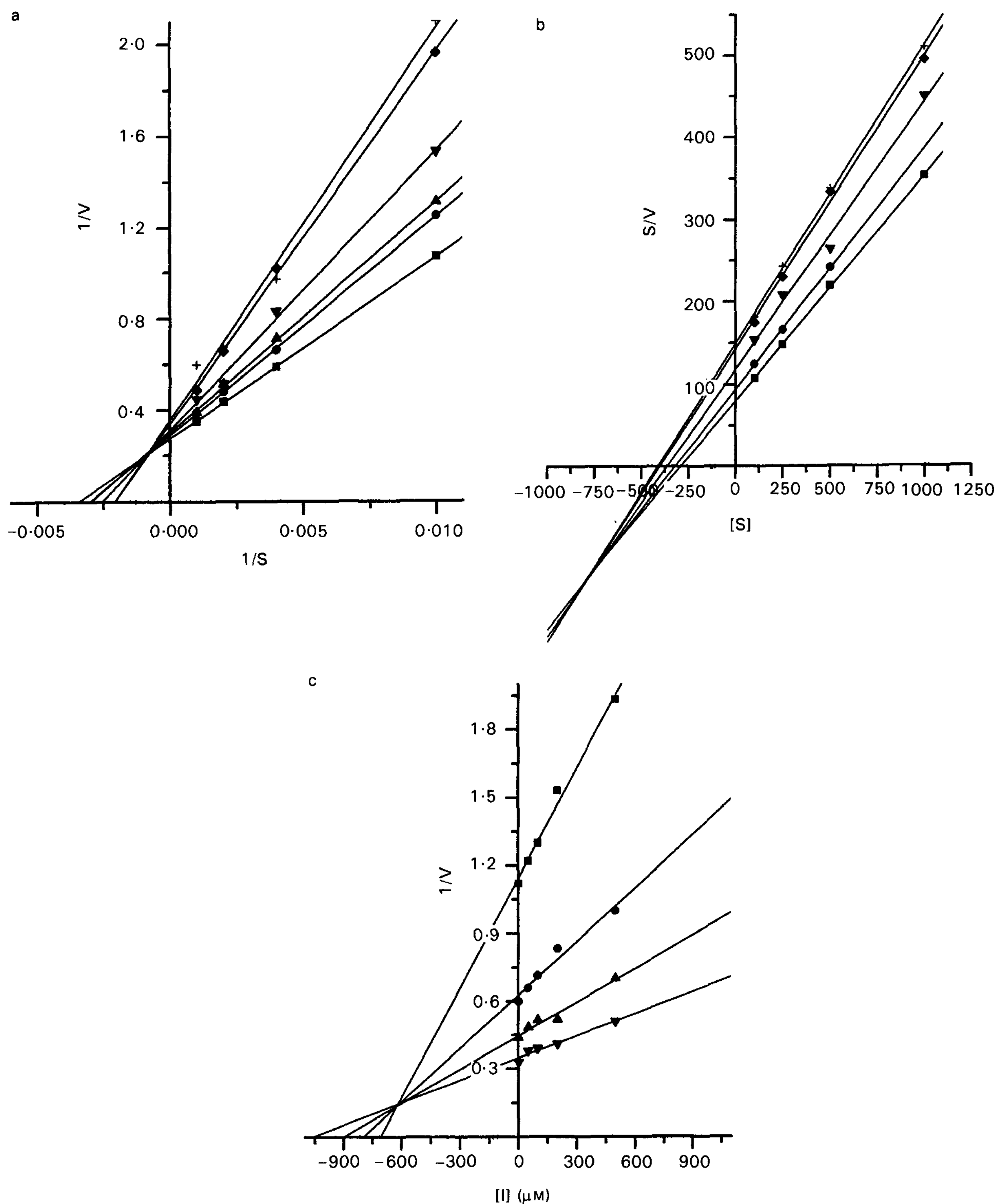

FIG. 2. Kinetic analysis of inhibition by dimaprit of histamine oxidation by rat white adipocyte Bz-SSAO. Enzyme preparations were pre-incubated for 30 min at 37°C in the presence of 1 mM pargyline, to inhibit mitochondrial monoamine oxidase activity and in the presence of dimaprit (50, 100, 200, 500, 1000 μM). Histamine (100, 200, 500, 1000 μM) was then added and reacted for a further 30 min at the same temperature. Enzymatic activity was measured fluorimetrically. A K_i value of 600 ± 50 was calculated according to Segel (1993) and it represents the mean ± s.e.m. of values calculated from three different experiments run in duplicate. (a) Results plotted according to Lineweaver-Burk, i.e. 1/(rate of histamine oxidation (1/(nmol × (mg protein)$^{-1}$ min^{-1})) against 1/[histamine](μM^{-1}): ■, dimaprit 0 μm;●, dimaprit 50 μM; ▲, dimaprit 100 μM;▼, dimaprit 200 μM; ◆, dimaprit 500 μM; + dimaprit 1000 μM. (b) Results plotted according to Hanes-Woolf, i.e. [histamine]/(rate of oxidation) ((mM)/(nmol × (mg protein)$^{-1}$ min^{-1})) against [histamine](μM): ■ dimaprit 0 μm; ◆, dimaprit 50 μM; ▲, dimaprit 200 μM; ●, dimaprit 500 μM; + dimaprit 1000 μM. (c) Results re-plotted according to Dixon (1953): 1/(rate of histamine oxidation) (nmol × (mg protein)$^{-1}$ min^{-1}) against [dimaprit](μM): ▼, histamine 100 μM; ▲, histamine 200 μM; ●, histamine 500 μM; ■, histamine 1000 μM.

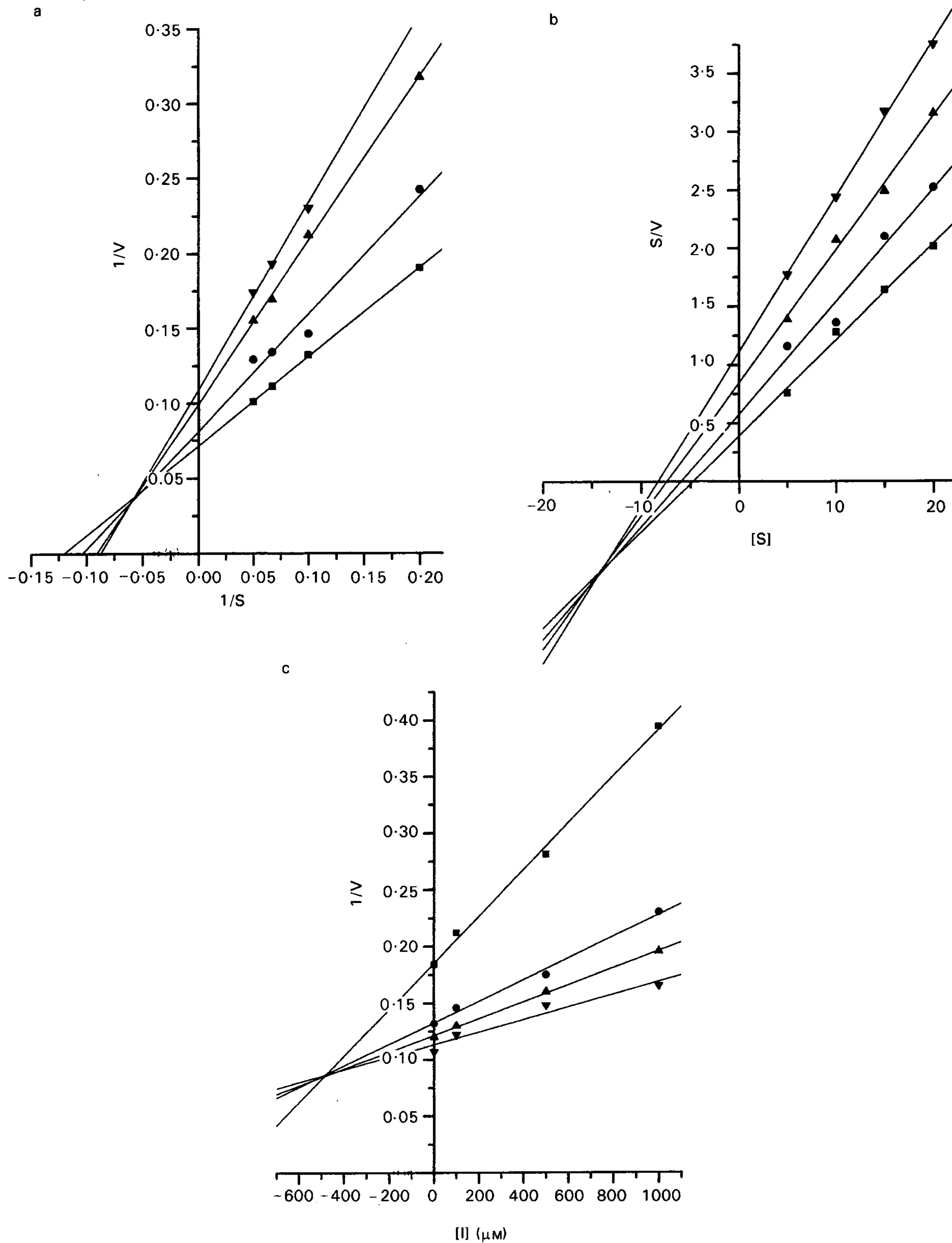

FIG. 3. Kinetic analysis of inhibition by nor-dimaprit of benzylamine oxidation by rat white adipocyte Bz-SSAO. Enzyme preparations were pre-incubated for 30 min at 37°C in the presence of 1 mM pargyline, to inhibit monoamine oxidase activity and in the presence of nor-dimaprit (100, 500, 1000 μM). Benzylamine (5, 10, 15, 20 μM) was then added and reacted for a further 30 min at the same temperature. Enzymatic activity was measured fluorimetrically. A K_i value of 450 ± 35 was calculated according to Segel (1993) and represents the mean ± s.e.m. from three different experiments run in duplicate. (a) Results plotted according to Lineweaver-Burk, i.e. 1/(rate of benzylamine oxidation (1/(nmol × (mg protein)$^{-1}$ min^{-1})) against 1/[benzylamine] (μM^{-1}): ■, nor-dimaprit 0 μM; ●, nor-dimaprit 100 μM; ▲, nor-dimaprit 500 μM; ▼, nor-dimaprit 1000 μM. (b) Results plotted according to Hanes-Woolf, i.e. [benzylamine]/(rate of oxidation) ((mM)/(nmol × (mg protein)$^{-1}$ min^{-1})) against [benzylamine] (μM): ■, nor-dimaprit 0 μM; , nor-dimaprit 100 μM; ▲, nor-dimaprit 500 μM; ▼, nor-dimaprit 1000 μM. (c) Results re-plotted according to Dixon (1953): 1/(rate of benzylamine oxidation) (nmol × (mg protein)$^{-1}$ min^{-1}) against [nor-dimaprit](μM): ■, benzylamine 5 μM; , benzylamine 10 μM; ▲, benzylamine 15 μM; ▼, benzylamine 20 μM.

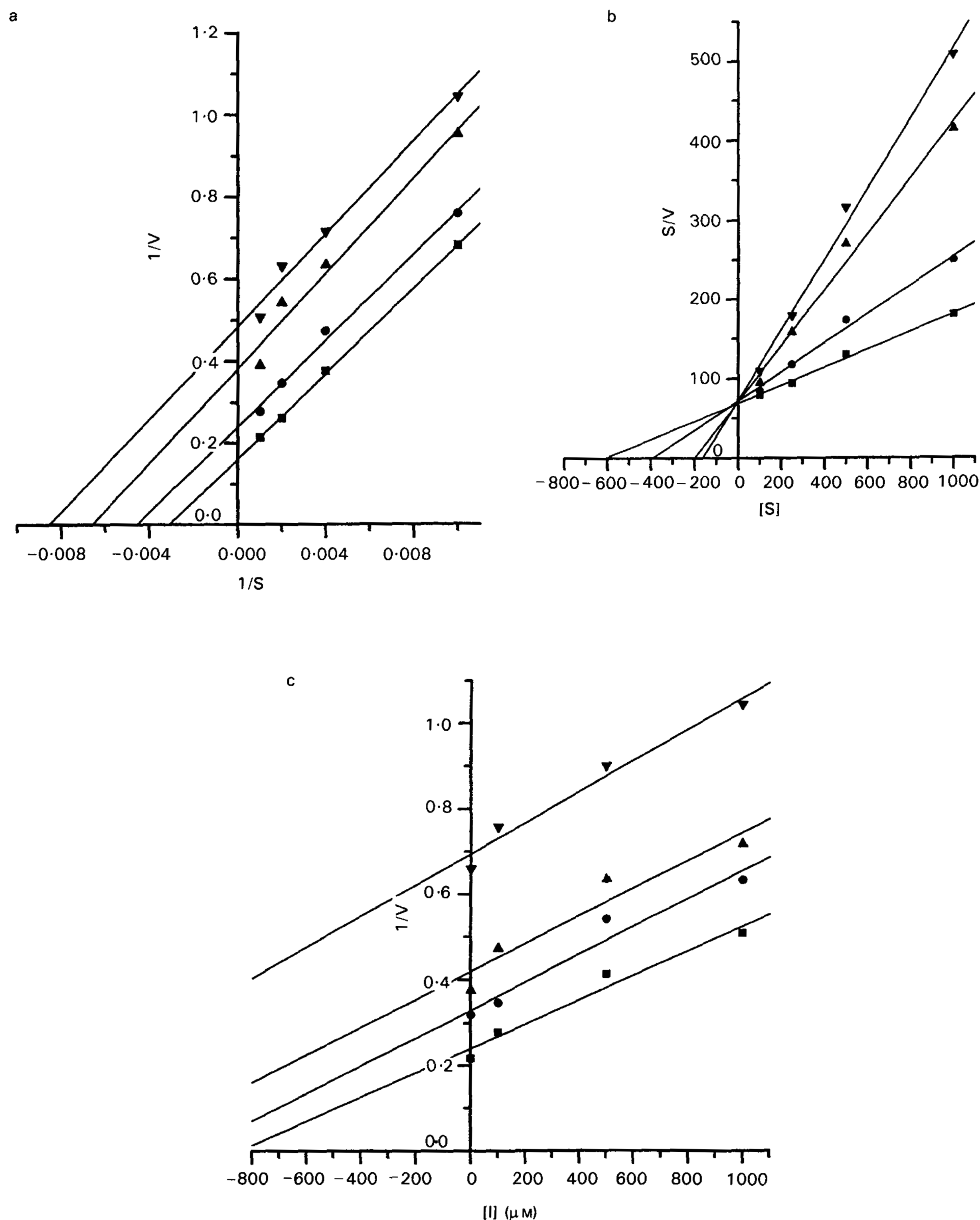

FIG. 4. Kinetic analysis of inhibition by nor-dimaprit of histamine oxidation by rat white-adipocyte Bz-SSAO. Enzyme preparations were pre-incubated for 30 min at 37°C in the presence of 1 mM pargyline, to inhibit monoamine oxidase activity and with nor-dimaprit (100, 500, 1000 μM). Histamine (100, 250, 500, 1000 μM) was then added and reacted for a further 30 min at the same temperature. The enzymatic activity was measured fluorimetrically. The K_i of 520 ± 25 calculated according to Segel (1993) represents the mean ± s.e.m. of values from three different experiments run in duplicate. (a) Results plotted according to Lineweaver-Burk, i.e. 1/(rate of histamine oxidation (1/(nmol × (mg protein)$^{-1}$ min^{-1})) against 1/[histamine](μM^{-1}): ■, nor-dimaprit 0 μM; ●, nor-dimaprit 100 μM; ▲, nor-dimaprit 500 mm; ▼, nor-dimaprit 1000 mm. (b) Results plotted according to Hanes-Woolf, i.e. [histamine]/(rate of oxidation ((μM)/(nmol × (mg protein)$^{-1}$ min^{-1}))) against [histamine](μM): ■, nor-dimaprit 0 μM; ●, nor-dimaprit 100 μM; ▲, nor-dimaprit 500 μM; ▼, nor-dimaprit 1000 μM. (c) Results re-plotted according to Dixon, i.e. 1/(rate of histamine oxidation (nmol × (mg protein)$^{-1}$ min^{-1})) against [nor-dimaprit] (μM): ■, histamine 100 μM; ●, histamine 250 μM; ▲, histamine 500 μM; ▼, histamine 1000 μM.

the amines tested only the 2- and 4-methyl derivatives were active on lipid mobilization from rat white adipocytes (Raimondi et al 1993). Amtamine, in contrast, appears to be a selective, high-affinity substrate for rat white–adipocyte Bz-SSAO (Table 1), but without any ability to mobilize glycerol from cells. The H_2-selective agonist is not oxidized by the classical diamine oxidase. This finding suggests that substitution of the imidazolo group in histamine by a thiazolo group has a favourable effect on the K_m for oxidation by Bz-SSAO.

Amtamine seems also to represent a bridge compound between the aromatic group of histaminergic compounds, still recognized as substrates by the enzyme, and the open-ring, non-aromatic structure of the isothiourea derivatives. It is already known that isothiourea derivatives elicit H_2-and H_3-related effects in different ways (Leurs & Timmerman 1995) and their ability to inhibit enzymes involved in histamine degradation has also been reported (Shaff & Beaven 1977). Under our experimental conditions, among the isothiourea derivatives screened only dimaprit and nor-dimaprit were able to interact with the oxidation of benzylamine and histamine by Bz-SSAO. Kinetic measurements on both substrates were made to distinguish differences between the behaviour of the inhibitors tested. These compounds have been found to be mixed-type inhibitors of the oxidation of both benzylamine and histamine with a similar K_i values (Tables 2 and 3). Whereas both dimaprit and nor-dimaprit behave like mixed non-competitive hyperbolic inhibitors of benzylamine oxidation (Figs 1 and 3), a mixed-uncompetitive type mechanism of inhibition of histamine oxidation was revealed for nor-dimaprit (Figs 2 and 4). Notwithstanding the substrate used, the inhibitors seem to bind to enzyme sites different from those of the substrates.

The fact that only dimaprit and nor-dimaprit interact with the enzyme and elicit a lipolytic response suggests that the distance between the isothiourea and the *N,N*-dimethyl residue is crucial for both types of interaction. Either the elongation (homo-dimaprit) or the shortening (*S*-methylisothiourea) of the carbon atom chain between the two residues led to compounds inactive either as lipolytic agents or as substrates or inhibitors of Bz-SSAO. It is also important to emphasize that both lipolysis and inhibition of Bz-SSAO fall in the same range of concentrations (Raimondi et al 1995).

Homo-dimaprit, dimaprit and nor-dimaprit have been studied as inhibitors of *N*-methyltransferase and of diamine oxidase (Taylor & Snyder 1972; Shaff & Beaven 1977). Whereas K_i for diamine oxidase inhibition by dimaprit was of the same order of that found for inhibition of the activity of Bz-SSAO from rat white adipocytes, homo-dimaprit was a more potent inhibitor of diamine oxidase than was dimaprit or nor-dimaprit. Under our experimental conditions, homo-dimaprit was without any effect on the Bz-SSAO activity of rat adipocytes. This seems to emphasize further the biochemical differences between diamine oxidase and Bz-SSAO.

In conclusion, the histaminase property of Bz-SSAO from rat white adipocytes extends to other histamine derivatives, including amtamine, a novel and selective H_2 agonist, which is deaminated by the enzyme. The oxidative deamination of amtamine by Bz-SSAO represents a pathway of metabolism of the drug in these cells.

Whereas histamine lipolysis was found to be enhanced by the use of Bz-SSAO inhibitors, it seems unlikely that the same enzyme can participate in the metabolism of 4-methylhistamine, dimaprit and nor-dimaprit, which are all stronger than histamine as lipolytic agents. That they are not metabolized by the histaminase can contribute to their pharmacological effect in these cells.

A body of evidence suggests the that pharmacological properties of isothiourea and its derivatives are related to enzyme inhibition (Southan et al 1995). That dimaprit and nor-dimaprit also inhibit the only pathway of oxidative deamination of histamine in rat white adipocytes can extend our knowledge on the properties of isothiourea derivatives and on their possible pharmacological applications.

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