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Hydrogen peroxide generation by monoamine oxidases in rat white adipocytes: role on cAMP production

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Abstract

In rat, white adipocytes monoamine oxidases (EC 1.4.3.4.) generate hydrogen peroxide (H_2O_2). Recent studies suggested that, in addition to its toxic features, H_2O_2 may behave as a cell second messenger. In the present study, using fluorimetric and chemiluminescence (CL) assays, we showed that tyramine degradation by monoamine oxidases in intact adipocytes resulted in the concentration-dependent generation of H_2O_2. In addition, we found that, in the presence of low tyramine concentrations, forskolin-dependent cAMP production was significantly increased as compared to that of the control and this increase was prevented by the monoamine oxidase inhibitor pargyline or by the H_2O_2 trapping system homovanillic acid-peroxidase. Finally, we demonstrated that tyramine degradation by monoamine oxidases increased the ability of isoproterenol to induce cell lipolysis. Taken together, these data suggest that H_2O_2 produced during substrate degradation by monoamine oxidases may participate in the regulation of adipocyte metabolism.

Keywords: Monoamine oxidase; Hydrogen peroxide; Adipocyte, white; Cell metabolism

1. Introduction

The biological sources and fate of hydrogen peroxide (H_2O_2) and reactive oxygen species have been extensively studied in the last few years. Because of the high chemical reactivity of these compounds and their short half-life in biological compartments, their impact on cell functions is mostly characterised by means of indirect assays in which well-known scavengers are used to modulate cytotoxic effects attributed to reactive oxygen species or peroxides. There is also growing evidence regarding the involvement of H_2O_2 and reactive oxygen species as second messengers in various cell events such as activation of adhesion factors (Farticelli et al., 1996) and protein phosphorylation (Heffetz et al., 1990; Rao et al, 1996) leading, in some cases, to cell apoptosis (Jacobson, 1996; Hansson et al., 1996) or proliferation (Burdon, 1996).

The amine-degrading enzyme monoamine oxidase (EC 1.4.3.4.) is a potential producer of H_2O_2. The enzyme exists as two forms, monoamine oxidases A and B, which can be discriminated by their substrate specificity and inhibition by selective drugs (Shih et al., 1999). Recently, we showed that, in intact cells, monoamine oxidases A and B are able to produce H_2O_2 which is not fully scavenged by endogenous antioxidant (Pizzinat et al., 1999a).

White adipocytes contain one of the largest amounts of monoamine oxidase in the body. In human and rat adipocytes, monoamine oxidase A accounts for most of the monoamine oxidase activity (Pizzinat et al., 1999b; Marti et al., 1998). Converging evidence suggests that in adipose tissue, monoamine oxidases may participate to the clearance of circulating catecholamines (Pizzinat et al., 1999b; Elia et al., 1996; Samra et al., 1996).

In the present study, we investigated whether, in intact adipocytes, monoamine oxidases are able to produce H_2O_2 and we studied its consequence on cell function. With this attempt, we determined (1) the ability of monoamine oxidases to metabolise tyramine in intact adipocytes and the consequent generation of H_2O_2, (2) the impact of such

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H_2O_2 on cAMP production, and (3) the potential regulation of isoproterenol-mediated cell lipolysis.

Our results indicate that in intact white adipocytes, tyramine degradation by monoamine oxidases induces hydrogen peroxide production, an increase in forskolin-stimulated cAMP production and the potentiation of isoproterenol-induced glycerol release.

2. Materials and methods

Bovine serum albumin fraction V, collagenase type II, pargyline hydrochloride, sodium azide, tyramine hydrochloride, 5-amino-2, 3-dihydro-1, 4-phthalazinedione, luminol, isoproterenol bitartrate, tyramine hydrochloride, and 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT), isobutylmethylxanthine, forskolin, were purchased from the Sigma Chemical (St. Louis, MO, U.S.A.). Homovanillic acid was from Merck (Darmstadt, Germany). Horseradish peroxidase, adenosine deaminase, and the glycerol UV determination kit were from Roche Diagnostics (Mannheim, Germany). The cAMP determination kit was purchased from Amersham (Amersham Italia, Milan, Italy). Male Wistar rats were from the Morini breeding colony (San Polo D'Elsa, Reggio Emilia, Italy). [^{14}C]tyramine hydrochloride (53 mCi/mmol) was obtained from ICN.

2.1. Radiochemical measurement of tyramine oxidation in intact adipocytes

Male Wistar rats (250–300 g) were killed by cervical dislocation and the epididymal portion of white adipose tissue was used to isolate adipocytes. Mature adipocytes were prepared according to Rodbell (1964).

[^{14}C]Tyramine oxidation in intact adipocytes was assessed following the method previously described (Raimondi et al., 1997). Briefly, 24 μl of purified cells ($1.8 \pm 0.1 \times 10^6$ cells/ml) was incubated at 37°C in a humidified atmosphere. Twenty-five microlitres of labeled tyramine prepared in Krebs-bicarbonate buffer pH 7.4 (Krebs Ringer buffer (KRB), Raimondi et al., 1993) at different concentrations (from 5 to 100 μM) was then added and incubated for an additional 30 min under the same conditions. The reaction volume was adjusted to 50 μl with buffer. Pargyline (1 mM) was preincubated for 30 min with the enzyme preparation before the addition of substrate. Monoamine oxidase activity was calculated as the difference between [^{14}C]tyramine oxidation observed in the absence and in the presence of pargyline.

Reactions were stopped by the addition of 10 μl of 3 N HCl, and the labeled metabolites were extracted with 500 μl of ethylacetate. The radioactivity present in 300 μl of the organic phase was counted in a β-scintillation counter. The recovery of labeled metabolites after extraction with ethylacetate was 85 ± 7%. Results are expressed as nmol of oxidised tyramine/10^6 cells/30 min (nmol/10^6 cells/30 min).

2.2. Measure of H_2O_2 production in intact adipocytes

Hydrogen peroxide generation in intact adipocytes was measured in fluorimetric and chemiluminescence (CL) assays. For the fluorimetric technique, adipocyte suspension ($5.0 \pm 1.3 \times 10^5$ cells/ml) in 500 μl of KRB containing homovanillic acid and horseradish peroxidase (Matsumoto et al., 1982) was preincubated at 37°C in a humidified atmosphere. Tyramine at different concentrations (from 5 to 100 μM) was added and H_2O_2 accumulation in the medium was measured after 30 min. The reaction was stopped by the addition of 2 ml of 0.1 N NaOH. Fluorescence was measured in a Shimazu spectrofluorimeter (λ_{ecc} = 323 nm, λ_{em} = 426 nm). Results are expressed as nmol of H_2O_2 produced by 10^6 cells in 30 min (nmol/10^6 cells/30 min).

For the CL assay, 25 μl of purified adipocytes was preincubated in the presence or the absence of pargyline (100 μM) for 30 min at 37°C in 1 ml of phosphate buffer containing luminol (30 μM) and horseradish peroxidase (0.1 U/ml). After this period, tyramine (5, 10, 20 and 50 μM) was injected and the production of H_2O_2 was followed continuously for 30 min under the same conditions, using a luminometer BioOrbit 1251 (Pizzinat et al., 1999a). Results are expressed as the total CL emission (area under the curve) evaluated for 30 min after tyramine addition.

2.3. Determination of cell viability

Cell viability was measured using the MTT test (Mosmann, 1983). Adipocyte suspension (5×10^5 cell/ml) was aliquoted in KRB. Tyramine up to 100 μM was added and incubated for 30 min at 37°C in the humidified atmosphere as above. Then, MTT (0.5 mg/ml) was added and cells were further incubated for 3 h. The amount of oxidised formazan was evaluated spectrophotometrically at 570 nm after its solubilisation with acidic isopropyl alcohol.

2.4. Measure of total cAMP generation

Adipocyte suspension was preincubated in KRB containing 4% bovine serum albumin , 1 mM 3-isobutyl-1-methylxanthine (IBMX), 2.5 U/ml adenosine deaminase for 30 min at 37°C. Tyramine (10, 25 and 50 μM) was added and incubated with cells for 10 min. The effect of the monoamine oxidase inhibitor, pargyline, of the semicarbazide-sensitive amine oxidase inhibitor, semicarbazide, and of the H_2O_2 trapping system, homovanillic acid/horseradish peroxidase (0.2 mg/ml and 4 U/ml, respectively), was tested by incubation of these compounds with cells for 30 min before tyramine addition. Forskolin (10 μM) was then added and kept in contact with cells for 5 min. Total cAMP production was evaluated in cell

homogenates using a cAMP determination kit according to the manufacturer's instructions.

2.5. Adipocyte lipolysis

Cell suspensions were preincubated for 30 min at 37°C in 500 μl of Krebs-bicarbonate buffer pH 7.4 containing 4% bovine serum albumin, 200 μM NaN_3 in the presence or the absence of pargyline or semicarbazide and then tyramine was added and incubated for 10 min. Glycerol release was induced by isoproterenol (50 nM) and evaluated in cell lysate after a 20-min incubation. The samples were centrifuged at $10{,}000 \times g$ for 10 min and the clear supernatant was used for spectrophotometric determination of the glycerol content using a glycerol determination kit. Results are expressed as nmol of NADH oxidised in 30 min by 10^6 cells (nmol/10^6 cells/30 min). Basal release of glycerol was subtracted from each sample.

2.6. Protein assay

Protein concentration was estimated by the method of Bradford (1976) using bovine serum albumin as standard.

2.7. Statistical analysis

Results for the enzyme assays and for H_2O_2 production in the fluorimetric and CL assays were analyzed by a non-linear least-square fitting procedure (Prism, Graphpad, Coppertino, CA, USA). Statistical analyses were performed using unpaired Student's *t*-test. Values are expressed as means ± S.E.M.

3. Results

The production of H_2O_2 by monoamine oxidases was determined by fluorimetric and luminometric methods and compared to [^{14}C]tyramine degradation by monoamine oxidases. As shown in Fig. 1A, [^{14}C]tyramine was oxidised by intact adipocytes in a dose-dependent manner with maximal oxidation being observed between 50–100 μM.

Results obtained by fluorimetry are shown in Fig. 1B. Incubation of intact adipocytes with tyramine (from 5 to 100 μM) led to a concentration-dependent increase in peroxide accumulation. The plateau of H_2O_2 was obtained at tyramine concentrations from 50 to 100 μM. At higher tyramine concentrations, additional H_2O_2 generation, poorly inhibited by pargyline and following a complex kinetic, was observed (data not shown). Similar results were obtained with the luminometric assay. As shown in Fig. 1C, the CL signal was proportional to the tyramine concentration, reaching a plateau at substrate concentrations between 25 and 50 μM. Consistent with previous studies reporting a large predominance of monoamine oxidase A in rat (Marti et al., 1998), we showed that H_2O_2 generated by monoamine oxidases was inhibited by the monoamine oxidase A inhibitor clorgyline and poorly affected by the monoamine oxidase B inhibitor selegiline (data not shown). Both techniques showed that substrate concentrations required for maximal H_2O_2 generation were in agreement with those found for [^{14}C]tyramine degradation.

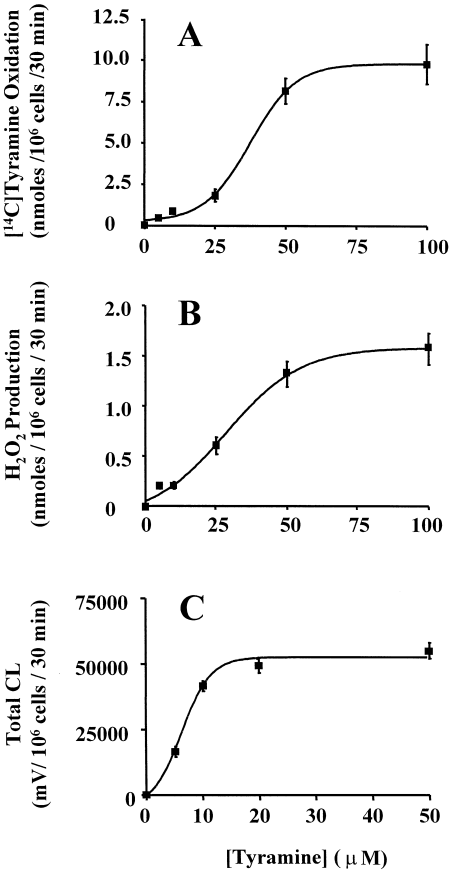

Fig. 1. Monoamine oxidase-dependent tyramine degradation and hydrogen peroxide production in intact white adipocytes. Adipocytes were preincubated in Krebs buffer for 30 min at 37°. Tyramine degradation was followed radiochemically (A) and hydrogen peroxide production was quantified fluorimetrically (B) or by using a continuous luminol chemiluminescent assay (C) as described in Section 2. Results are the means ± S.E.M. of values obtained from four different experiments run in duplicate.

Next, we investigated whether H_2O_2 generation by monoamine oxidases affected adipocyte function. Among the various consequences of H_2O_2 generation on cell function, we investigated the influence on cell death and cAMP generation. In a first series of experiments, we studied the effect of tyramine on cell viability. Adipocyte incubation with tyramine concentrations leading to H_2O_2 generation (from 10 to 100 μM) did not result in a decrease in cell viability as compared to the control (o.d. at 570 nm: control, 1.0 ± 2.1; tyramine 100 μM, 0.97 ± 0.15). In contrast, we observed a modification of forskolin-induced cAMP generation in the presence of tyramine. Indeed, as shown in Fig. 2A, adipocyte incuba-

tion with different concentrations of tyramine significantly increased forskolin-stimulated cAMP production, with the maximal response being observed at 25 μM. As previous reports suggested a role of H_2O_2 generated by semicarbazide-sensitive amine oxidase in the modification of adipocyte function (Marti et al., 1998), we tested the involvement of monoamine oxidases and semicarbazide-sensitive amine oxidase in the regulation of cAMP generation. The increase in forskolin-stimulated cAMP production was fully prevented by pargyline and was unaffected by semicarbazide (Fig. 2B), indicating that only monoamine oxidases were involved in the regulation of cAMP generation. In addition, the observation that the effect of tyramine was also inhibited by the homovanillic–horseradish peroxidase trapping system supports the involvement of monoamine oxidase-dependent

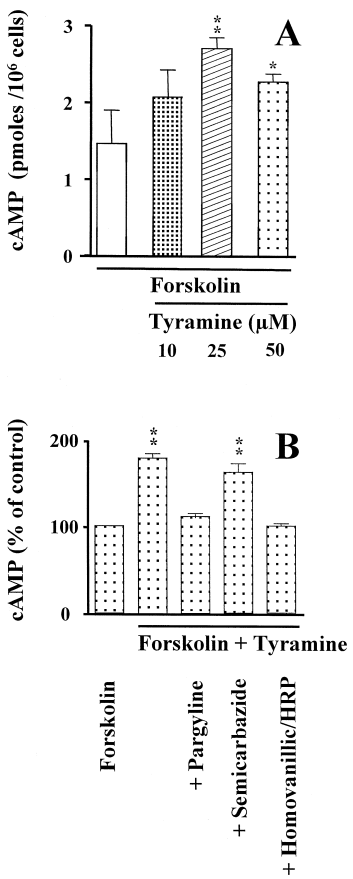

Fig. 2. Effect of tyramine oxidation on forskolin-induced cAMP production. (A) Adipocyte suspensions were incubated in Krebs buffer containing IBMX (1 mM) and adenosine deaminase (2.5 U/ml) for 30 min. Cells were incubated in the presence or in the absence of different tyramine concentrations for 10 min before forskolin (10 μM) addition. Reaction was stopped 5 min after forskolin addition. cAMP production was determined as described in Section 2. (B) Cells were preincubated in the presence or in the absence of pargyline (1 mM), semicarbazide (1 mM), or homovanillic acid plus horseradish peroxidase (0.2 mg/ml and 4 U/ml, respectively) prior to addition of 25 μM tyramine and 10 μM forskolin. Results are the means ± S.E.M. of five different experiments run in duplicate. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus forskolin.

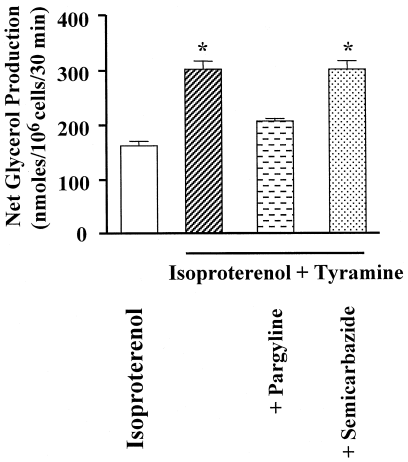

Fig. 3. Effect of tyramine degradation on isoproterenol-dependent lipolysis. Adipocytes were preincubated in Krebs bicarbonate buffer, as described in Section 2, in the absence or in the presence of pargyline (1 mM) or semicarbazide (1 mM) for 30 min. Cells were incubated with 50 μM tyramine for 10 min prior to addition of 50 nM isoproterenol. After 20 min, glycerol release was evaluated spectrophotometrically. Results are the means ± S.E.M. of five different experiments run in duplicate. $^{*}P < 0.05$ versus isoproterenol.

H_2O_2 production in potentiation of forskolin-stimulated cAMP production (Fig. 2B).

In white adipocytes, the increase in cAMP generation is responsible for lipolysis activation. Among the various factors that activate adenylate cyclase in white adipocytes, β-adrenoceptors have been extensively investigated. In this respect, the use of β − adrenoceptors agonist such as isoproterenol, with a non-catechol moiety that prevents oxidation by H_2O_2 as well as degradation by monoamine oxidases, allows the measurement of glycerol release as a consequence of receptor activation. To study the effect of tyramine oxidation on cell lipolysis, we stimulated fat mobilisation with a sub-maximal concentration of isoproterenol (50 nM). As shown in Fig. 3, 50 μM tyramine produced a significant increase in isoproterenol-induced glycerol release. As observed for cAMP generation, this effect was prevented by pargyline but not by semicarbazide.

4. Discussion

In the present study we showed that in intact rat adipocytes, endogenous monoamine oxidases can generate H_2O_2 which may participate in cell modifications occurring during substrate metabolism. Previous studies suggested that some of the monoamine oxidase substrates, such as adrenaline, may induce H_2O_2 generation through a receptor-mediated mechanism (Rosa, 1997). In our study, the use of tyramine, a dietary amine which is also produced endogenously from p-tyrosine metabolism (Bowsher and Henry, 1983; Tillet et al., 1994), allowed us to determine the role of monoamine oxidases in H_2O_2 production

and its consequences on adipocyte function without the interference of receptor-mediated mechanisms and autoxidation processes. Indeed tyramine, unlike catecholamines, lacks the autoxidisable catechol group (Cohen et al., 1997) and does not act through any receptor in mammalian cells (Varma et al., 1995).

Using two different approaches, we demonstrated that relatively low tyramine concentrations induced the concentration-dependent and saturable generation of H_2O_2 in intact adipocytes. Two observations support the role of monoamine oxidases in this phenomenon: first, H_2O_2 production was prevented by the monoamine oxidase inhibitor pargyline and second, the concentration–response curves for H_2O_2 generation were similar to those found for [^{14}C]tyramine degradation. These results also show that, at least for tyramine, substrate transport inside the cells is not a limiting factor for substrate degradation and H_2O_2 generation.

In order to determine whether H_2O_2 generation affects adipocyte function, we first assessed the effect of tyramine degradation on cell viability. Indeed, previous studies showed that H_2O_2 is one of the factors inducing cell death (Hansson et al., 1996). In most cases, the effect of H_2O_2 on cell survival occurred at high concentrations and was dependent on the time of exposure. The mechanisms responsible for H_2O_2-mediated cell death involve different factors including lipid peroxidation and DNA damage (Ramakrishnan et al., 1996). Our results show that the sustained production of tiny amounts of H_2O_2 generated by the metabolism of low concentrations of tyramine did not affect adipocyte viability. Thus, in this case, H_2O_2 generated by monoamine oxidases may behave as a regulatory rather than as a toxic factor. This possibility is supported by our results on cAMP generation and isoproterenol-induced lipolysis. Indeed, we showed that H_2O_2 produced by monoamine oxidases significantly increased forskolin-mediated cAMP generation. The activity of H_2O_2 added to the medium or generated by other enzymes of the seven-transmembrane receptor pathway has been previously reported. Some of these effects have been related to the direct activity of H_2O_2 on receptors or G proteins (Persad et al., 1998). The fact that we directly stimulated adenylate cyclase by forskolin allowed us to rule out this mechanism to explain our results. In contrast, a G protein-independent effect of H_2O_2 on adenylate cyclase (Tan et al., 1995) or on an enzyme involved in cAMP degradation, as reported for phosphodiesterase and phosphatase, could be postulated. Consistent with these results, we also found that tyramine degradation increased β adrenergic/cAMP-mediated lipolysis.

It is noteworthy that the effects of tyramine on both cAMP generation and isoproterenol-mediated lipolysis were completely insensitive to the amine oxidase inhibitor semicarbazide. This result differs from that reported by Tarancon et al. (1998), who showed an effect of tyramine on glucose transporter (GLUT4) trafficking towards plasma membrane of rat adipocytes. Indeed, in this study, in which the amount of H_2O_2 generated was not directly measured, high tyramine concentrations (1 mM) increased glucose uptake and this effect was fully prevented by semicarbazide. This difference with our results may be related to the different tyramine concentrations used and the amount of peroxide generated.

Monoamine oxidases and semicarbazide-sensitive amine oxidase differ in their subcellular localisation (monoamine oxidases in mitochondria and semicarbazide-sensitive amine oxidase in plasma membrane) but both participate in tyramine degradation. Our results show that, over a low range of tyramine concentrations, only the H_2O_2 generated by monoamine oxidases is responsible for the regulation of cAMP production and isoproterenol-mediated lipolysis. This suggests that the specificity of the effects of peroxide on cell function may depend on various factors including substrate concentration and the subcellular localisation of the amine oxidases.

In conclusion, we show that in intact white adipocytes, monoamine oxidases generate H_2O_2 which behaves as a potential regulatory factor. These results open new perspectives in the comprehension of the mechanism of regulation of white adipocyte function by monoamine oxidases and their potential involvement in pathological processes.

Acknowledgements

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