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Effects of phorbol ester and dexamethasone treatment on histidine decarboxylase and ornithine decarboxylase in basophilic cells

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Abstract

Both histamine and polyamines are important for maintaining basophilic cell function and viability. The synthesis of these biogenic amines is regulated by histidine decarboxylase and ornithine decarboxylase, respectively. In other mammalian tissues, an interplay between histamine and polyamine metabolisms has been suspected. In this report, the interplay between histamine and ornithine-derived polyamines was studied in a non-transformed mouse mast cell line (C57.1) treated with phorbol ester and dexamethasone, a treatment previously used to increase histidine decarboxylase expression in mastocytoma and basophilic leukemia. Treatment with phorbol ester and dexamethasone increased histidine decarboxylase expression and intracellular histamine levels in C57.1 mast cells to a greater extent than those found for other transformed basophilic models. The treatment also induced a reduction in ornithine decarboxylase expression, intracellular polyamine contents, and cell proliferation. These results indicate that the treatment induces a co-ordinate response of polyamine metabolism and proliferation in mast cells and other immune-related cells. The decrease in the proliferative capacity of mast cells caused by phorbol ester and dexamethasone was simultaneous to an increase in histamine production. Our results, together with those reported by other groups working with polyamine-treated mast cells, indicate an antagonism between histamine and polyamines in basophilic cells.

Keywords: Histamine; Histidine decarboxylase; Polyamines; Ornithine decarboxylase; Mast cells; Phorbol ester; Dexamethasone

1. Introduction

Mast cells are medium-sized granulated cells releasing chemical mediators (histamine, heparin, proteases, and cytokines). They are effector cells in IgE-associated immune responses, such as those that contribute to asthma and other allergic and inflammatory diseases and to host resistance to parasites. However, mast cells may also influence many other biologic responses, including tissue remodeling and angiogenesis [1,2]. Although metachromatic mast cells are easily recognized in peripheral tissues, little is known about the biochemistry and function of mast cell proliferation/differentiation [3].

Histamine is one of the major mediators produced by mast cells. On the other hand, immature mast cells must proliferate, so they must synthesize ornithine-derived polyamines (putrescine, spermidine, and spermine), which are essential polycations for maintaining macromolecular synthesis and cell viability. The synthesis of both biogenic amine families is controlled by the respective L-amino acid decarboxylase (L-aaDC): histidine decarboxylase (HDC, EC 4.1.1.22) and ornithine decarboxylase (EC 4.1.1.17). A metabolic interplay between histamine and polyamine metabolisms seems to exist in mammalian cells. Common binding proteins to both histamine and polyamines have been described in normal and cancer cells [4], and similar structural changes in nucleic acids elicited by histamine and polyamines have been reported [5]. Simultaneous expression of both L-aaDCs has been reported in different tissues [6–8]. However, the responses to external stimuli are tissue-specific [8,9]. In Ehrlich carcinoma (originally a mammary tumor with undetectable levels of HDC and histamine), we have previously shown that exogenous histamine and other

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Abbreviations: Dex, dexamethasone; PMA, phorbol 12-myristate 13-acetate; L-aa DC, L-amino acid decarboxylase; HDC, histidine decarboxylase; ODC, ornithine decarboxylase; and GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

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diamines are able to reduce ornithine uptake, ODC activity, and polyamine content [10,11].

One of the best-known treatments for inducing HDC in basophilic tumor cells was described by Ichikawa's group: dexamethasone (Dex) is able to induce HDC, and PMA potentiates this induction [12,13]. Katunuma and Kido [14] also described PMA as a "glucocorticoid potency amplifier" with respect to ODC expression. As far as we know, the effect of this treatment on mast cell ODC expression and polyamine metabolism has not been studied yet. However, glucocorticoids are usually included in treatment against immunological disorders for which histamine production and mast cell proliferation must be relevant.

In this report, we studied the effects of PMA + Dex treatment on cell proliferation, HDC and ODC expression and activity, and polyamine levels of mouse C57.1 mast cells derived from C57BL/6J mouse bone marrow cells [15] and transformed basophilic cells, namely mouse mastocytoma P-815 and rat basophilic leukemia models RBL-1 and RBL-2H3.

2. Materials and methods

2.1. Cell cultures

Mouse C57.1 mast cells were cultured in Dulbecco's modified Eagle's medium containing streptomcyin, penicillin, and amphotericin, and supplemented with 10% fetal bovine serum. These cells were kindly supplied by Dr. Fernández-Sánchez from Dr. Galli's lab [15]. Mouse mastocytoma P-815 cells and rat basophilic leukemia cell lines RBL-1 and RBL-2H3 were purchased from the American Type Culture Collection and maintained according to the recommendations given by the supplier. Growth kinetic curves were determined by cell counting in a Coulter Counter (Coulter Electronics). When indicated as the PMA + Dex treatment, 10 nM PMA and 100 nM Dex were added to the cultures and experiments were carried out 12 hr later. In other cases, cells were treated with 10 nM PMA for 3 hr, and then cells were washed and further cultured in the presence of 100 nM Dex for 12 hr before experiments (designated as the PMA/Dex treatment).

2.2. Intracellular amine content

Intracellular content of putrescine, histamine, serotonin, spermidine, and spermine were simultaneously determined by fluorimetry after separation of the dansyl derivatives by reversed-phase HPLC [16]. 1,8-Diaminooctane was used as an internal standard added to the cell extract before derivatization with dansyl chloride. Protein was always estimated by Bradford's method [17].

2.3. Expression of decarboxylases

ODC and HDC mRNAs were detected by Northern blot. Probes were previously described and named as inserts of plasmids ODC71 [18] and pHDC1/512 [19], respectively. HDC protein was detected by Western blots [20]; ODC protein was estimated by immunoprecipitation experiments [18]. Both polyclonal antibody preparations against mouse ODC and rat HDC (K9503) were supplied by Dr. L. Persson (Lund, Sweden). ODC and HDC activities were measured by following the release of $^{14}CO_2$ from (1-^{14}C)-labeled ornithine and histidine as reported [18,19]. HDC activity was measured following the method described by Kishikawa *et al*. [21] with the following modifications: cells were washed twice with PBS, suspended in activity buffer (0.2 mM dithiothreitol, 10 μM pyridoxal 5-phosphate, 10 mg/mL of poly(ethyleneglycol)-300, 100 mM potassium phosphate, pH 6.8), and homogenized in a Branson Sonifier 250 by applying five pulses of 60 watts. Then, extracts were centrifuged at 30,000 rpm in a Beckman Optima TL ultracentrifuge (Beckman) for 30 min at 4°, and HDC activity was assayed in supernatants.

3. Results

3.1. Diamine and polyamine contents

The intracellular amine concentrations in the different cell lines tested were determined during exponential phase of growth. Results are shown in Table 1. Intracellular polyamine (putrescine + spermidine + spermine) contents were higher in transformed cells than in C57.1 mast cells. Higher polyamine contents were detected in the most proliferating cells, as deduced from population doubling times. They were estimated to be 13 hr for P-815 and RBL-1 cells, 22 hr for RBL-2H3 cells, and 24 hr for mouse C57.1 mast cells. On the contrary, the highest diamine content was detected in the non-transformed C57.1 mast cell culture, the serotonin/histamine ratio being higher than 30.

3.2. Effects of PMA + Dex treatment on histamine metabolism

As expected, the PMA + Dex treatment induced expression of HDC in C57.1 cells, as described for other basophilic tumor models (Fig. 1). Indeed, the intensity of HDC mRNA increased when compared to RNA loaded onto each lane, even when GAPDH mRNA signals decreased in response to the treatment. Similar results were obtained with a shorter PMA exposure (only for 3 hr) followed by a 12-hr Dex treatment (PMA/Dex) (Fig. 1B). Characteristic bands of HDC ranking from 74 kDa (primary translation product) to a minimum of 53 kDa (processed polypeptide according to [22,23]) were clearly observed to increase in C57.1 mast cells. These increases correlate very well with those in both

Table 1
Intracellular contents of diamines and polyamines in mast and basophilic leukemia cells

Amine	C57.1	P-815	RBL-1	RBL-2H3
Histamine	< 0.23	ND	< 0.15	0.79 ± 0.21
Serotonin	7.15 ± 1.56	ND	0.84 ± 0.23	0.70 ± 0.15
TOTAL DIAMINES	7.38 ± 1.37	ND	0.95 ± 0.15	1.49 ± 0.05
Putrescine	ND	7.73 ± 1.29	1.64 ± 0.11	< 0.84
Spermidine	18.91 ± 2.47	37.55 ± 5.12	32.69 ± 2.84	29.21 ± 5.28
Spermine	7.76 ± 2.22	10.85 ± 1.25	8.83 ± 0.52	9.71 ± 0.74
TOTAL POLYAMINES	26.67 ± 0.52	56.13 ± 7.66	43.16 ± 3.36	39.48 ± 6.48

Intracellular diamines (histamine and serotonin) and ornithine-derived polyamines in C57.1 mast cells, P-815 mastocytoma cells, and RBL-1 and RBL-2H3 basophilic leukemia cells, at exponential phase of growth, were determined by HPLC as described in section 2. Results are given as pmol amine/μg protein, and are means ± SEM of three independent experiments. ND: non-detectable. Total diamines = Hia + serotonin. Total polyamines = putrescine + spermidine + spermine.

HDC activity (Table 2) and intracellular histamine content, which changed from under 0.23 pmol/μg protein (untreated cultures) to 1.62 ± 0.68 pmol/μg protein (cells treated with PMA + Dex).

In rat leukemia cells, the increases induced by the PMA + Dex treatment in HDC protein were lower than those detected in the non-tumoral C57.1 mast cell cultures (Fig. 1A). Lower relative increases in histamine levels were also observed in these leukemia lines when compared to those of the mast cell line: histamine concentrations after PMA + Dex treatment were 0.45 ± 0.16 (in RBL-1 cells) and 1.47 ± 0.29 pmol/μg protein (in RBL-2H3 cells) (see control values in Table 1).

In the mouse mastocytoma P-815, 74- and 64-kDa HDC protein bands were substantially reduced when compared with the other cell lines (Fig. 1A), and the 53-kDa HDC band, which is thought to correspond to the protein purified from these cells [22], was not observed. Finally, HDC activity with or without the PMA + Dex treatment was non-detectable (results not shown). Curiously, P-815 was also the cell line with the highest intracellular polyamine concentration and growth rate.

3.3. Effects of PMA + Dex treatment on polyamine metabolism and cell proliferation

After treatment, a significant decrease in ODC mRNA and the immunoprecipitated ODC polypeptide signals was observed (Fig. 1, B and C). As for the HDC induction, similar results were obtained with a shorter PMA exposure (PMA/Dex treatment). ODC activity in C57.1 cells was indeed reduced by the PMA + Dex treatment by more than 60% (Table 2). However, the treatment did not induce any significant change in polyamine contents of C57.1 cells (Table 3). On the contrary, changes in the polyamine contents of basophilic cell lines caused by PMA + Dex treatment were clearly observed: the treatment reduced putrescine and spermidine concentrations, and consequently total polyamines (Table 3).

As shown in Fig. 2, the PMA + Dex treatment induced a clear inhibitory effect on the growth of C57.1 mast cells. However, the treatment did not produce an observable DNA fragmentation, typical of apoptosis (results not shown).

4. Discussion

4.1. Diamine and polyamine contents

In spite of the importance of basophilic cells in mammalian physiology, the metabolic interplay between histamine and ornithine-derived polyamines has not been studied on any basophilic cell model so far. In the present work, we used C57.1 mouse-derived mast cells, mouse mastocytoma P-815, and rat basophilic leukemia RBL-1 and RBL-2H3. Some of them have been used by other groups to study HDC expression and protein characterization [22,23].

The observed correlation between intracellular polyamine levels and cell proliferation (see Table 1 and Results) was expected, since a relationship between polyamine content and proliferation rate has been described for other cell types [24]. It is noteworthy that intracellular contents of the diamines typically produced by basophilic cells (serotonin + histamine) inversely correlate to the intracellular polyamine contents of the cultured cell lines.

4.2. Effects of PMA + Dex treatment on histamine metabolism

Different stimuli are known to induce histamine production by transformed basophilic cell models: the HDC induction caused by a 12-hr treatment with 10 nM PMA and 100 nM Dex (PMA + Dex) is one of the most frequently used with transformed basophilic cell cultures [12]. The treatment with Dex leads to an increase in HDC mRNA and protein levels in basophilic cells, and PMA potentiates the induction caused by Dex [12,13].

As expected, the PMA + Dex treatment also induced expression of HDC in C57.1 cells, as shown by mRNA and polypeptide levels (Fig. 1), HDC activity (Table 2), and the

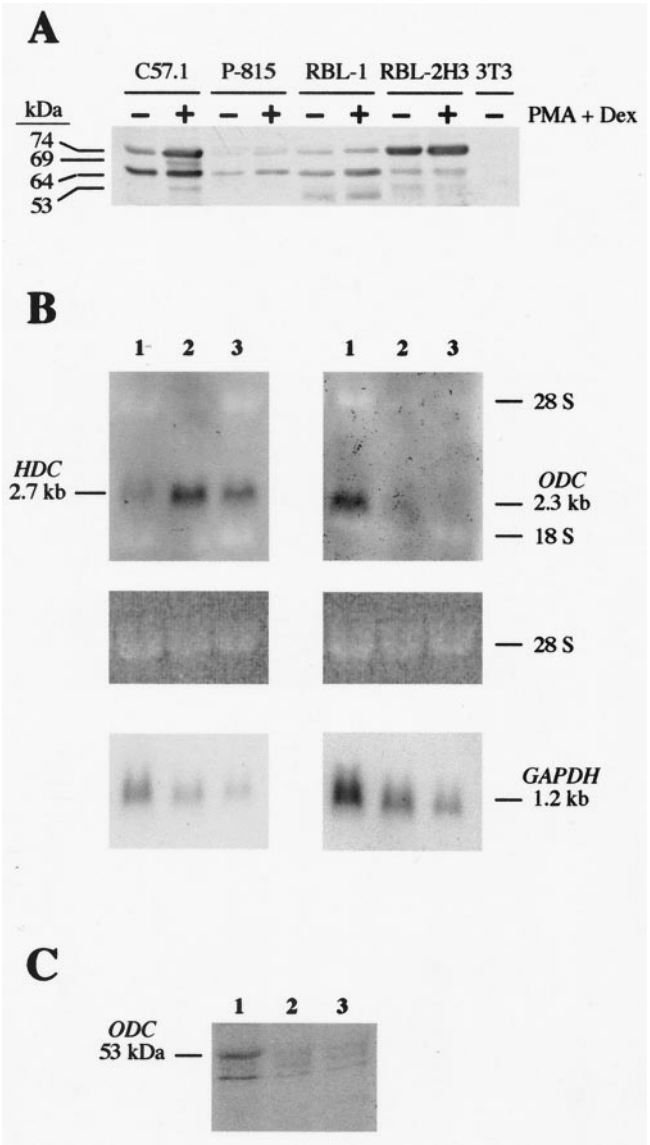

Fig. 1. Expression of ODC and HDC in basophilic cells after PMA and Dex treatment. (A) HDC protein levels in C57.1, P-815, RBL-1, and RBL-2H3 cells treated or untreated with PMA + Dex. Homogenates (30 μg of total protein) were analyzed by Western blot. Untreated NIH/3T3 cells were used as negative control. Estimated relative molecular weights for immunoreactive bands are indicated on the left. (B) HDC (left column, upper panel) and ODC (right column, upper panel) mRNA levels in untreated (lane 1), PMA/Dex-treated (lane 2), or PMA + Dex-treated (lane 3) C57.1 cells. Ribosomal 28 S stained with ethidium bromide on the agarose gel and GAPDH mRNA signals hybridized on the same filter are also shown below. (C) ODC protein levels on untreated (lane 1), PMA/Dex-treated (lane 2), or PMA + Dex-treated (lane 3) C57.1 cells. Immunoprecipitations were carried out on protein from 2×10^6 cells.

7-fold increase in intracellular histamine contents. In C57.1 cells, the induction of HDC expression seems to be mainly at transcriptional level. In fact, the intensity of HDC mRNA increased when compared to RNA loaded onto each lane, even when GAPDH mRNA signals decreased in response to the treatment. Similar results were obtained with a shorter PMA exposure (only 3 hr) followed by a 12-hr Dex treatment (PMA/Dex) (Fig. 1B). In other basophilic cell lines, it has been demonstrated that the increase in HDC expression occurs at the transcriptional level, and the *cis*-element for the response of mouse *HDC* gene promoter to the treatment has been located [13].

Table 2
Effects of PMA + Dex treatment on HDC and ODC activities in C57.1 mast cells

Treatment	HDC activity	ODC activity
None	0.35 ± 0.09	2.93 ± 0.58
PMA + Dex	4.35 ± 1.58*	1.09 ± 0.32*

Exponentially growing C57.1 mast cells were incubated in the presence or absence of 10 nM PMA + 100 nM Dex for 12 hr. HDC and ODC activities in cell extracts were measured as described in section 2. Results are expressed as pmol CO_2/hr/μg protein and are means ± SEM of three independent duplicated experiments.

* Significantly different ($P < 0.05$) from control untreated cells according to a non-parametric Mann–Whitney *U* test.

The induction at the protein level seems to be more dramatic in C57.1 cells than in the other transformed basophilic cell lines tested in parallel. In rat leukemia cells, the increases in HDC protein and the 2- to 3-fold increases in histamine induced by the PMA + Dex treatment were lower than those detected in the non-tumoral C57.1 mast cell cultures.

In the present study, we have also found that the mouse mastocytoma P-815 (purchased in 1998 from the American Type Culture Collection) appear to have lost the basophilic phenotype. Although they were used 8–10 years ago to purify mouse HDC for the first time [22] and to study the induction caused by PMA + Dex [12], we were not able to detect intracellular histamine or serotonin (Table 1). Furthermore, 74- to 53-kDa HDC protein bands were substantially reduced (or absent) when compared with the other cell

Table 3
Effects of PMA + Dex treatment on intracellular contents of diamines and polyamines in mast and basophilic leukemia cells

Amine	C57.1	RBL-1	RBL-2H3
Serotonin	82.1 ± 14.1	260.4 ± 33.3*	166.2 ± 38.5*
Putrescine	—[a]	61.5 ± 7.3*	ND[b]
Spermidine	103.0 ± 15.6	85.3 ± 3.6*	69.3 ± 3.5*
Spermine	101.5 ± 3.5	124.8 ± 5.0*	111.4 ± 10.1
Total polyamines	100.2 ± 10.2	92.4 ± 4.0*	78.7 ± 2.9*

Intracellular contents of serotonin and ornithine-derived polyamines in C57.1 mast cells and RBL-1 and RBL-2H3 basophilic leukemia cells after PMA + Dex treatment were determined by HPLC as described in section 2. Results are expressed as percentages with respect to untreated cells (Table 1), and are means ± SEM of three independent experiments. Total polyamines = putrescine + spermidine + spermine.

[a] The absolute putrescine level in C57.1 cells was <0.24 pmol/μg protein. It cannot be expressed as percentage since some values were below detection level.

[b] ND: non-detectable.

* Significantly different ($P < 0.05$) from control untreated cells according to a non-parametric Mann–Whitney *U* test.

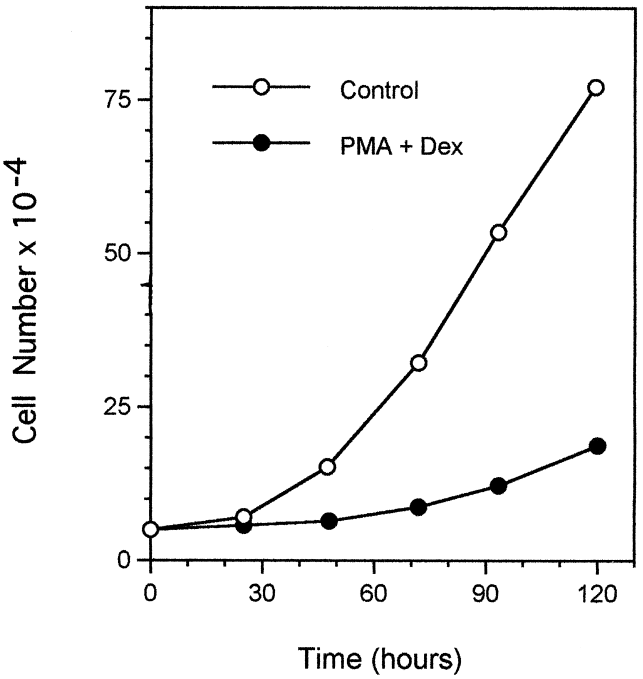

Fig. 2. Effects of PMA + Dex treatment on growth of C57.1 cultures. Growth profiles of untreated C57.1 cells (control, open circles) and cells cultured in the presence of 10 nM PMA + 100 nM Dex (filled circles). PMA + Dex was added at time zero. Data are means of four different cultures. SEM values were smaller than symbol diameters.

lines (Fig. 1A), and HDC activity with or without the PMA + Dex treatment was non-detectable. However, it must be stressed that both 74- and 64-kDa polypeptide bands were induced by the treatment.

4.3. Effects of PMA + Dex treatment on polyamine metabolism and cell proliferation

The efficient induction of HDC activity by PMA and Dex in C57.1 mast cells makes them a good model system to study the interplay between histamine and polyamine metabolism. We have previously reported that perfusion of Ehrlich carcinoma cells with submillimolar concentrations of histamine reduces ornithine uptake, ODC induction, and total tumor polyamine content [10,11]; however, the experimental models (Ehrlich carcinoma cells perfused with PBS and ornithine, and cultured basophilic cells treated with PMA + Dex) are too different to assume that polyamine metabolism of mast cell cultures must respond in a similar way. ODC activity in C57.1 cells was indeed reduced by the PMA + Dex treatment by more than 60% (Table 2). An important decrease in ODC mRNA signals was also observed (Fig. 1B), and the immunoprecipitated ODC polypeptide was greatly reduced by the treatment (Fig. 1C). In our Northern blot experiments, we observed that both ODC and GAPDH transcripts decreased in parallel even when gel lanes were loaded with similar quantities of total RNA. It has been reported recently that stability of GAPDH mRNA can vary in spleenocytes depending on the activation state of the lymphoid cells [25]. In mast cells, it has been shown that Dex treatment induces the degradation of some transcripts [26]. In thymus, dexamethasone has been shown to drastically reduce ODC activity [27], mainly due to induction of antizyme, increasing the ODC turnover rate [28]. On the other hand, PMA has been described as a "glucocorticoid potency amplifier" and as an enhancer of the Dex effects on mouse mastocytoma HDC [12]. Altogether, these data and our own results suggest that the main cause of the reduction in ODC expression could be post-transcriptional instability of the ODC transcript and/or polypeptide in stem-derived cells.

Changes in polyamine contents of basophilic cell lines caused by the PMA + Dex treatment were also observed. In rat basophilic leukemia cells, the treatment not only increased intracellular histamine, but also reduced putrescine and spermidine concentrations, and consequently the total polyamine content (Table 3). This effect was not observed in C57.1 cells 12 hr after the PMA + Dex addition; however, the treatment induced a reduction in the proliferation of cultured C57.1 cells in the longer term, clearly observed one day after treatment (Fig. 2). This result is in agreement with those of other authors reporting that Dex inhibits the cytokine-induced proliferation of non-transformed mouse bone marrow-derived mast cells [26].

4.4. Conclusion

There exists an important quantity of information on the effects of glucocorticoids and phorbol esters on HDC and ODC of different mammalian cell types and tissues, and they seem to be development state- and tissue-specific [6,29,30]. The effects of PMA + Dex treatment on ODC and proliferation of C57.1 mast cells resemble those observed with other lymphoid cells treated with Dex, at least from a phenomenologic point of view. It has been reported that Dex induces a marked decrease in ODC activity in lymphoid tissues (spleen and thymus) and induces apoptosis in lymphocytes [28,31,32]. Here, we observed a significant reduction of ODC expression and mast cell proliferation caused by the treatment. On the contrary, with respect to HDC expression, mast cells show a different response to those detected in other lymphoid cells. An inhibition of histamine production caused by Dex on spleen cells and T lymphocytes has been described [33,34], but here we show that HDC expression is enhanced by treatment. Dex takes part in normal treatment against inflammation and asthma [35]. Taking into account that histamine is one of the mediators of inflammation and asthma [36], the data described here lead us to suggest that treatment with glucocorticoids might lead (especially in the presence of protein kinase C activators) to an "undesirable" short-term increase in histamine production followed by a reduction in mast cell population.

Acknowledgments

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References

[1] Church MK, Clough GF. Human skin mast cells: *in vitro* and *in vivo* studies. Ann Allergy Asthma Immunol 1999;83:471–5.
[2] Galli SJ. Mast cells and basophils. Curr Opin Hematol 2000;7:32–9.
[3] Castells M. Update on mast cells and mast cell precursors and hypersensitivity responses. Allergy Asthma Proc 1997;18:287–92.
[4] Brandes LJ, Queen GM, LaBella FS. Potent interaction of histamine and polyamines at microsomal cytochrome P450, nuclei, and chromatin from rat hepatocytes. J Cell Biochem 1998;69:233–43.
[5] Ruiz-Chica J, Medina MA, Sánchez-Jiménez F, Ramírez FJ. Raman study of the effects of polyamines on DNA: spermine and histamine. J Mol Structure 1999;480–481:455–8.
[6] Araki M, Nakamura M, Takenoshita S, Shoda H, Nagamachi Y, Matsuzaki S. Effects of dexamethasone on the activity of histidine decarboxylase, ornithine decarboxylase, and DOPA decarboxylase in rat oxyntic mucosa. Can J Physiol Pharmacol 1991;69:37–42.
[7] Ding XQ, Chen D, Rosegren E, Persson L, Hakanson R. Comparison between activation of ornithine decarboxylase and histidine decarboxylase in rat stomach. Am J Physiol 1996;270:6476–86.
[8] Bartholeyns J, Bouclier M. Involvement of histamine in growth of mouse and rat tumors: antitumoral properties of monofluoromethylhistidine, an enzyme-activated irreversible inhibitor of histidine decarboxylase. Cancer Res 1984;44:639–45.
[9] Endo Y. Induction of histidine and ornithine decarboxylase activities in mouse tissues by recombinant interleukin-1 and tumor necrosis factor. Biochem Pharmacol 1989;38:1287–92.
[10] Medina MA, Urdiales JL, Matés JM, Núñez de Castro I, Sánchez-Jiménez F. Diamines interfere with the transport of L-ornithine in Ehrlich-cell plasma-membrane vesicles. Biochem J 1991;280:825–7.
[11] Medina MA, Quesada AR, Núñez de Castro I, Sánchez-Jiménez F. Histamine, polyamines and cancer. Biochem Pharmacol 1999;57:1341–4.
[12] Kawai H, Ohgoh M, Emoto S, Ohmori E, Imanishi N, Yatsunami K, Ichikawa A. Synergistic effects of 12-*O*-tetradecanoylphorbol-13-acetate and dexamethasone on *de novo* synthesis of histidine decarboxylase in mouse mastocytoma P-815 cells. Biochim Biophys Acta 1992;1133:172–8.
[13] Ohgoh M, Yamamoto J, Kawata M, Yamamura I, Fukui T, Ichikawa A. Enhanced expression of the mouse L-histidine decarboxylase gene with a combination of dexamethasone and 12-*O*-tetradecanoylphorbol-13-acetate. Biochem Biophys Res Commun 1993;196:1113–9.
[14] Katunuma N, Kido H. Studies on biomodulators of glucocorticoid actions; the nature and the modes of actions of glucocorticoid potency amplifiers. Adv Enzyme Regul 1987;26:191–208.
[15] Young JD, Liu CC, Butler G, Cohn ZA, Galli SJ. Identification, purification, and characterization of a mast cell-associated cytolytic factor related to tumor necrosis factor. Proc Natl Acad Sci USA 1987;84:9175–9.
[16] Matés JM, Márquez J, García-Caballero M, Núñez de Castro I, Sánchez-Jiménez F. Simultaneous fluorometric determination of intracellular polyamines separated by reversed-phase high-performance liquid chromatography. Agents Actions 1992;36:17–21.
[17] Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein–dye binding. Anal Biochem 1976;72:248–54.
[18] Urdiales JL, Matés JM, Núñez de Castro I, Sánchez-Jiménez F. Chlorpheniramine inhibits the ornithine decarboxylase induction of Ehlirch carcinoma growing *in vivo*. FEBS Lett 1992;305:260–4.
[19] Engel M, Olmo MT, Coleman CS, Medina MA, Pegg AE, Sánchez-Jiménez F. Experimental evidence for structure–activity features in common between mammalian histidine decarboxylase and ornithine decarboxylase. Biochem J 1996;320:365–8.
[20] Dartsch C, Chen D, Hakanson R, Persson L. Histidine decarboxylase in rat stomach ECL cells: relationship between enzyme activity and different molecular forms. Regul Pept 1999;81:41–8.
[21] Kishikawa H, Willinger SM, Jackowski S, Barke K, Hough LB. Histidine decarboxylase measurement in brain by $^{14}CO_2$ trapping. Biochem Pharmacol 1991;42:217–22.
[22] Ohmori E, Fukui T, Imanishi N, Yatsunami K, Ichikawa A. Purification and characterization of L-histidine decarboxylase from mouse mastocytoma P-815 cells. J Biochem (Tokyo) 1990;107:834–9.
[23] Tanaka S, Nemoto K, Yamamura E, Ohmura S, Ichikawa A. Degradation of the 74 kDa form of L-histidine decarboxylase via the ubiquitin–proteasome pathway in a rat basophilic/mast cell line (RBL-2H3). FEBS Lett 1997;417:203–7.
[24] Morgan DM. Polyamines and cellular regulation: perspectives. Biochem Soc Trans 1990;18:1080–4.
[25] Aledo JC, Segura JA, Barbero LG, Márquez J. Upregulation of glyceraldehyde-3-phosphate dehydrogenase mRNA in the spleen of tumor-bearing mice. Biochimie 1999;81:1109–13.
[26] Eklund KK, Humphries DE, Xia Z, Ghildyal N, Friend DS, Gross V, Stevens RL. Glucocorticoids inhibit the cytokine-induced proliferation of mast cells, the high affinity IgE receptor-mediated expression of TNF-alpha, and the IL-10-induced expression of chymases. J Immunol 1997;158:4373–80.
[27] Hirvonen A, Immonen T, Leinonen P, Alhonen-Hongisto L, Jänne OA, Jänne J. Effect of dexamethasone on the activity and expression of ornithine decarboxylase in rat liver and thymus. Biochim Biophys Acta 1988;950:229–33.
[28] Stefanelli C, Flamigni F, Carati D, Rossoni C, Caldarera CM. Effects of dexamethasone on spermidine N^1-acetyltransferase and ornithine activities in rat spleen. Biochim Biophys Acta 1987;930:79–86.
[29] Tesoriere G, Vento R, Taibi G, Calvaruso G, Schiavo MR. Biochemical aspects of chick embryo retina development: the effects of glucocorticoids. J Neurochem 1989;52:1487–94.
[30] Bartolome JV, Wang S, Greer NL, Schanberg SM. Glucocorticoid regulation of ornithine decarboxylase in the postnatal rat lung. Life Sci 1999;64:895–904.
[31] Bishop J, Young J, Peng T, Richards JF. An inhibitor of ornithine decarboxylase in the thymus and spleen of dexamethasone-treated rats. Biochem J 1985;226:105–12.
[32] Desiderio MA, Grassilli E, Bellesia E, Salomoni P, Franceschi C. Involvement of ornithine decarboxylase and polyamines in glucocorticoid-induced apoptosis of rat thymocytes. Cell Growth Differ 1995;6:505–13.
[33] Oh C, Nakano K. Inhibition by glucocorticoids of mitogen-dependent histamine biosynthesis caused by histidine decarboxylase in cultured mouse spleen cells and peritoneal adherent cells. Immunology 1988;65:433–6.
[34] Kubo Y, Nakano K. Regulation of histamine synthesis in mouse CD4+ and CD8+ T lymphocytes. Inflamm Res 1999;48:149–53.
[35] Zahnow CA, Panula P, Yamatodani A, Millhorn DE. Glucocorticoid hormones downregulate histidine decarboxylase mRNA and enzyme activity in rat lung. Am J Physiol 1998;275:L407–13.
[36] Holgate ST, Church MK. Asthma. The mast cell. Br Med Bull 1992;48:40–50.