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COMMENTARY

Histamine, Polyamines, and Cancer

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ABSTRACT. Mammalian ornithine decarboxylase and histidine decarboxylase present common structural and functional features, and their products also share pharmacological and physiological properties. Although accumulated evidence pointed for years to a direct involvement of polyamines and histamine in tumour growth, it has been only in the last few years that new molecular data have contributed to the clarification of this topic. The aim of this commentary is to review the molecular grounds of the role of histamine and polyamines in cancer and to point to possible directions for future research in emerging areas of interest. BIOCHEM PHARMACOL **57**;12: 1341–1344, 1999. © 1999 Elsevier Science Inc.

KEY WORDS. histamine; polyamine; tumour; histidine decarboxylase (HDC); ornithine decarboxylase (ODC); aromatic L-amino acid decarboxylase (DDC); monofluoromethylhistidine (MFMH)

L-AMINO ACID DECARBOXYLASE ACTIVITIES DURING CELL PROLIFERATION

Eukaryotic L-amino acid decarboxylases catalyze the synthesis of biogenic amines involved in different important biologic functions. Most of them are homodimers, PLP†-dependent enzymes. The mechanistic diversity and uniformity of PLP-dependent enzymes have been reviewed recently [1]. ODC (EC 4.1.1.17) is the best known at the molecular level. ODC catalyzes the first and key step in the biosynthesis of polyamines, which are essential for maintaining cell viability and active macromolecular synthesis by interacting with nucleic acids, proteins, and cellular membranes. Thus, the ornithine-derived amines play a key role in tumour proliferation. In fact, several chemotherapeutic protocols are based on the inhibition of tumour ODC. The main inhibitors used thus far are halogenated derivatives of ornithine (i.e. DFMO), which behave as suicide substrates. This strategy suffers two major drawbacks in most cases: the rapid turnover of mammalian ODC and the relatively high expression of ODC in tumours, as compared with the levels of ODC in non-proliferant tissues [2]. This relatively high level of ODC in tumour cells may not be an effect but rather a cause of cell transformation, since it has been described as a proto-oncogene [3].

Histamine is the product of L-histidine decarboxylation by HDC (EC 4.1.1.22). As other biogenic amines, histamine is described as a neurotransmitter; but histamine is involved in other physiological effects: gastric acid secretion, allergic reactions, inflammation, smooth muscle contraction, and cell proliferation. The hypothesis that histamine could be involved in carcinogenesis and tumour proliferation was proposed in the 1960s, but it still remains open [4]. Accumulated evidence has pointed to a direct relationship between HDC activity and tumour growth; in fact, a previous review was devoted to this issue more than 10 years ago [5]. In recent years, new molecular data have contributed to clarifying the structure of HDC and the connections of histamine with cancer and to introducing new perspectives in this old but open hypothesis, as discussed below. Overexpression of HDC has been detected in a wide range of tumours, including leukemia and breast, stomach, and lung cancer [6]. However, evidence for the direct involvement of HDC in cancer progression remains to be obtained. The most direct experimental approaches would be the selective overexpression of HDC in transfected cell lines to observe whether they acquire a tumoural phenotype or in transgenic mice to observe whether or not they develop tumours.

It has been shown that in tumour or stimulated fetal cells, both ODC and HDC are induced simultaneously and that, after the beginning of the logarithmic phase of growth, both activities decay in a parallel fashion [7, 8]. In fact, Bartholeyns and Bouclier [7] observed a similar reduction in the proliferation of several experimental tumours after their treatment with DFMO or monofluoromethylhistidine (MFMH), a suicide inhibitor of HDC. Furthermore, in several non-neoplastic tissues, ODC and HDC are induced by cytokines, 12-*O*-tetradecanoylphorbol-13-acetate (TPA), and second messengers of growth stimuli [8, 9].

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† *Abbreviations:* DFMO, difluoromethylornithine; HDC, histidine decarboxylase; ODC, ornithine decarboxylase; and PLP, pyridoxal-5′-phosphate.

During embryonic development, there are transient and simultaneous tissue-dependent increases in the expression of L-amino acid decarboxylases. Very recently, it has been shown that the 5′-flanking region of the HDC gene contains multiple regulatory elements for HDC gene expression, some of them responsible for the tissue-specific expression of HDC [10]. Furthermore, c-*fos* and c-*jun*, early expressed genes related to cell proliferation, seem to activate the HDC promoter [11].

STRUCTURE OF MAMMALIAN L-AMINO ACID DECARBOXYLASES PRODUCING 1,4-DIAMINES: ANALOGIES AMONG DIFFERENCES

All the known mammalian ODCs have a unique, common mechanism of short-term regulation based exclusively on the modification of their turnover rates. In fact, the levels of ODC activity can change by several orders of magnitude in only a few hours due to changes in the synthesis and/or degradation rates.

HDC is expressed in very low levels in a limited number of cell types. The mature HDC monomer has an apparent molecular mass of 53–57 kDa, very similar to those of other mammalian L-amino acid decarboxylases [12]. The first mammalian HDC cloned was that of the rat, as reported in 1990 [13]; the structure of the human HDC gene was reported in 1994 [14].

ODC shows no significant homology with HDC and aromatic-L-amino acid decarboxylase (DDC, EC 4.1.1.28) in mammals, and their proposed folding models are different [15]; nevertheless, we have detected some common motifs among their cDNA deduced sequences [16]. These include the presence of PEST regions, which are defined as sequence fragments enriched in proline, glutamic acid, serine, and threonine residues in a hydrophobic fragment flanked by cationic amino acids; PEST regions can act as signals providing mechanisms for intracellular degradation of key metabolic proteins [17]. Mammalian HDCs and DDCs present a PEST region located between amino acids 40 and 70. Mammalian HDCs have at least another PEST region located after residue 503, probably in the fragment removed during monomer maturation. ODC is well known to be degraded by proteasome 26S through an antizyme-dependent, ubiquitin-independent mechanism [18]; HDC has been shown recently to be a substrate for proteasome 26S, although it seems to involve a ubiquitin-dependent mechanism [19]. In addition, mammalian HDCs contain a histidine residue (H-274) in a hydrophobic surrounding that is homologous to the residues 193–198 of mammalian ODCs and to other fragments in DDCs. The substitution of this very well conserved histidine residue by site-directed mutagenesis causes significant changes in the affinities of ODC and HDC for their respective substrates [19]. Similar studies are being carried out presently for other L-amino acid decarboxylases.

HISTAMINE, POLYAMINES, AND TUMOUR PROGRESSION, INVASION, AND ANGIOGENESIS

It is firmly established that polyamines play a key role in cell proliferation. In fact, one of the first events in proliferating cells is the induction of polyamine biosynthesis, preceding both nucleic acid and protein synthesis [20]. ODC overexpression beyond some minimum threshold can induce cell transformation and tumour promotion [3]. On the other hand, to maintain cells in a proliferating state, polyamine levels should be kept high but not extremely high because, in this situation, they can induce apoptosis [21]. The return pathway through spermine, spermidine *N*-acetyltransferase, and polyamine oxidase could play a major regulatory role in this bivalent behaviour [22]. This issue deserves further investigation.

Histamine, as well as ornithine-derived amines, is amphipathic; it also has a positive net charge at physiological pH and a 1,4-diamine skeleton with an N–N distance of approximately 6 Å; these features are important for the regulation of ODC activity by 1,4-diamines [23] and suggest a close relationship between both histamine and ornithine-derived amine metabolism.

At the systemic level, histamine shows a bivalent behaviour: it can act as an immunosuppressor through its H_2 receptors and as a stimulator of immune response through its H_1 receptors [5, 7]. Thus, histamine could control tumour growth through its receptors [5, 24]; selective blockage of H_1 receptor or H_2 receptor produces, respectively, stimulation or inhibition of tumour growth [24–26]. It is interesting that histamine, through its H_2 receptor, modulates the expression of c-*fos*, which, in turn, regulates the HDC promoter, as mentioned above [11, 27]. Due to this dual behaviour, the chronic administration of these compounds to allergic patients could run the risk of oncogenesis, and they should be used with extreme caution [28, 29].

Tumour progression, invasion, and metastasis are, clinically, even more relevant than tumour induction. It is well known that tumour invasion and metastasis are processes whose outcome is completely dependent on the capability to induce tumour angiogenesis [30]. Currently, this is one of the most active areas of research in oncology. Histamine has been reported as an angiogenic factor, but its specific biologic functions in connection with angiogenesis remain to be elucidated. Thirty years ago, it was first demonstrated that histamine (and also serotonin, the product of another L-amino acid decarboxylase) can be angiogenic in the rabbit cornea [31]. Later, Fraser and Simpson [32] showed that histamine stimulates angiogenesis when used in the micromolar range, but this effect diminishes with increasing histamine concentrations. Currently, there is accumulated evidence for a dual role of endogenous histamine in angiogenesis, and it seems that histamine can behave as a pro- or an anti-angiogenic modulator, depending on the receptor to which it binds [33]. The bivalent behaviour of

histamine in tumour angiogenesis could be explained, at least in part, as a consequence of its tight relationship with the metabolism of nitric oxide, a potent inducer of increased vascular permeability and blood flow [34]. It has been shown that histamine up-regulates the release of nitric oxide, and, in turn, the increased generation of nitric oxide down-regulates the release of histamine [35]. The role of nitric oxide in tumour angiogenesis is controversial, and there are data pointing to its possible action as an anti-angiogenic mediator or as a pro-angiogenic factor [34, 36].

On the other hand, previous indirect investigations have suggested a pivotal role for polyamines in tumour angiogenesis [20]. In fact, it has been shown that cells overexpressing ODC can induce highly vascularized tumours in nude mice, that DFMO can inhibit tumour-induced angiogenesis, and that polyamines can induce angiogenesis [20, 37]. Very recently, it has been reported that overexpression of ODC triggers mitogen-activated protein (MAP) kinase activity, which, in turn, implies a proportional increase in invasiveness, due to, at least in part, an increased secretion of matrix metalloproteinase-2, one of the key players in extracellular matrix degradation [38]. As was the case for histamine, it seems that there are interesting links between polyamines and nitric oxide. In fact, nitric oxide can induce an extremely fast decrease of polyamine levels in cultured cells [39], and, in turn, nitric oxide synthase can be inhibited not only by spermine or spermidine, but also by agmatine (the product of another L-amino acid decarboxylase) [40, 41]. It has been hypothesized that nitric oxide and polyamines could regulate melanoma angiogenesis differently: during early stages of malignant melanoma, polyamine synthesis should be increased, and this fact could contribute to endothelial cell proliferation; once the melanoma is vascularized, nitric oxide synthase would be induced, decreasing endothelial cell proliferation and maintaining a vasodilator tone in and around the tumour [42].

CONCLUDING REMARKS

In the last 10 years, molecular data have accumulated pointing to the presence of common structural and functional features among ODC and HDC and, most probably, other L-amino acid decarboxylases. The products of these L-amino acid decarboxylases also share pharmacological and physiological properties. A deeper molecular study of the sequence and expression alterations of tumour cell ODC and HDC would have a direct application in the development of new strategies in diagnosis and antitumour therapy. The use of recombinant DNA technology and transgenic mice to confirm whether overexpression or stabilization of HDC can play a role—as ODC does—in the promotion of neoplastic transformation would reinforce the old hypothesis formulated by Kahlson and Rosengren [4] and could open new therapeutic ways to treat tumours whose proliferation is dependent on HDC activity. A complete characterization of the structure/function relationships of mammalian HDC and ODC will contribute to significant advancements in a wide field of applied areas, including not only oncology but also all the others in which histamine and polyamines play relevant physiological roles. On the other hand, the study of the relationships among polyamines, histamine, nitric oxide, and angiogenesis is an emerging area of interest. The current picture of the state-of-the art is complex and somehow confusing [20, 34], and this issue clearly deserves further experimental efforts.

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