Mammalian L-amino acid decarboxylases producing 1,4-diamines: analogies among differences

Mammalian ornithine decarboxylase (ODC, EC 4.1.1.17), histidine decarboxylase (HDC, EC 4.1.1.22) and aromatic L-amino acid decarboxylase (DDC, EC 4.1.1.28) are homodimeric pyridoxal-phosphate (PLP)-dependent enzymes that produce the physiological 1,4-diamines: putrescine, histamine and serotonin (and tryptamine), respectively. Mammalian HDCs and DDCs exhibit structurally related 1,4-diamines: putrescine, histamine and serotonin (and tryptamine), respectively. Mammalian ODCs and other mammalian 1,4-diamines can behave like polyamine analogs: they regulate mammalian ODC, intracellular polyamine levels and cell growth in vivo and in vitro. HDC, like ODC, is a very unstable protein, and there is evidence for a coordinate regulation of ODC and HDC in several mammalian cell lines and tissues. After consideration of all these data, some common structural features might be expected between these enzymes.

By using a computer program developed from the algorithm described by Rogers et al., the deduced primary translation products of the known mammalian mRNAs encoding HDC and DDC were analyzed for the existence of PEST regions. Interestingly, all deduced products contained at least one sequence (Fig. 1a) that satisfies the requirements of the PEST regions found in extremely short-half-life eukaryotic proteins: hydrophilic sequences (between positively charged residues) enriched in P, S/T or D/E tend to reside near the amino or carboxyl termini of enzymes.

(a) N termini

HDC M. musculus P23738 (168-98) VFKGATLKT

HDC R. norvegicus P16453 (168-98) VFKGATLKT

HDC H. sapiens P19114 (168-98) VFKGATLKT

DDC B. taurus P27719 (237-70) EFVVTGL

DDC S. scrofa P80041 (237-70) EFVVTGL

DDC R. norvegicus P14173 (237-70) EFVVTGL

DDC C. porcellus P22781 (237-70) EFVVTGL

DDC H. sapiens P20711 (237-70) EFVVTGL

(b) C termini

HDC M. musculus P23738 (168-98) DVI VGS FYH

HDC R. norvegicus P16453 (168-98) DVI VGS FYH

HDC H. sapiens P19114 (168-98) DVI VGS FYH

DDC B. taurus P27719 (237-70) DVI VGS FYH

DDC S. scrofa P80041 (237-70) DVI VGS FYH

DDC R. norvegicus P14173 (237-70) DVI VGS FYH

DDC C. porcellus P22781 (237-70) DVI VGS FYH

DDC H. sapiens P20711 (237-70) DVI VGS FYH

Figure 1

(a) PEST regions of mammalian HDCs and DDCs. Mammalian species and accession numbers of every deduced sequence in the SWISS-PROT data bank are indicated. The figure reflects the alignment of the PEST sequences by the PILEUP program. PEST regions are shown in boxes; numbers on boxes refer to the first and last residues of the deduced sequences. (b) Multiple alignment of a fragment of mammalian ODC (residues 168-198 in mouse ODC) with fragments of mammalian HDCs and DDCs. Black boxes indicate residues that are identical between ODCs and some other mammalian decarboxylases. Shaded residues in HDC and DDC fragments present a degree of similarity equal to or higher than 0.8 (Gribstov and Burguess's scores) with respect to the aligned ODC residues; residues with similarity scores from 0.2--0.8 with respect to those of ODC are shown in white boxes. The first and last residues of the deduced sequences. (c) Termini.
The amino-terminal PEST regions of HDCs and DDCs overlap (PILEUP3). PEST regions were also detected in the carboxyl termini of the HDC-deduced sequences, in the fragment with no counterpart in DDCs; this fragment is apparently removed during post-translational maturation of the HDC subunits3,4.

The essential residues for ODC activity (Lys169 and His197) occur in conserved fragments of mammalian HDCs (z scores = 8-8.5; 200 local shuffles; window = 10 residues) and DDCs (z scores = 3-3.5, same conditions) (Fig. 1b). A histidine residue followed by a branched-chain residue at the end of these fragments occurs, not only in the mammalian decarboxylases depicted in Fig. 1b, but also in other homologous PLP-dependent prokaryotic and eukaryotic amino acid decarboxylases present in the SWISS-PROT data bank (release 27.0), including glutamate decarboxylases (GDC, EC 4.1.1.15). His197 is the proposed proton donor during PLP-mediated decarboxylation in mouse ODC; to our knowledge the relevance of this histidine residue has not been studied in the other amino acid decarboxylases.

In addition, Glu186 and Ile189 of mouse ODC were aligned with identical residues of the other mammalian decarboxylases shown in Fig. 1b. The consensus sequence [A/V]x[T/S] could be deduced from the amino termini of these fragments (residues 172-177 of mouse ODC). According to the secondary structure prediction of the fragments (PHD method13), these conserved residues are close to loop-enriched zones in all the mammalian ODCs, HDCs and DDCs.

Every ODC described so far from vertebrates has three hydroxylated residues (Ser or Thr) aligning to positions 173, 176 and 177 of the mouse enzyme; this is also the case for ODC of prokaryotic and eukaryotic amino acid decarboxylases depicted in Fig. 1b, but also in other homologous PLP-dependent prokaryotic and eukaryotic amino acid decarboxylases present in the SWISS-PROT data bank (release 27.0), including glutamate decarboxylases (GDC, EC 4.1.1.15). His197 is the proposed proton donor during PLP-mediated decarboxylation in mouse ODC; to our knowledge the relevance of this histidine residue has not been studied in the other amino acid decarboxylases.

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