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Differential processing of mammalian L-histidine decarboxylase enzymes

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ABSTRACT

In the mammalian species studied so far, the L-histidine decarboxylase (HDC) enzyme responsible for histamine biosynthesis has been shown to undergo post-translational processing. The processing is best characterized for the mouse enzyme, where di-asparate DD motifs mediate the production of active ~55 and ~60 kDa isoforms from the ~74 kDa precursor in a caspase-9 dependent manner. The identification of conserved di-aspartate motifs at similar locations in the rat and human HDC protein sequences has led to proposals that these may represent important processing sites in these species also. Here we used transfected Cos7 cells to demonstrate that the rat and human HDC proteins undergo differential processing compared to each other, and found no evidence to suggest that conserved di-aspartate motifs are required absolutely for processing in this cell type. Instead we identified SKD and EEAPD motifs that are important for caspase-6 dependent production of ~54 and ~59 kDa isoforms in the rat and human proteins, respectively. The addition of staurosporine, which is known to pharmacologically activate caspase enzymes, increased processing of the human HDC protein. We propose that caspase-dependent processing is a conserved feature of mammalian HDC enzymes, but that proteolysis may involve different enzymes and occur at diverse sites and sequences.

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1. Introduction

The biogenic amine histamine is produced by the catalytic activity of L-histidine decarboxylase (HDC). When the enzyme was first purified from mouse and rat it was concluded that it was a 110 kDa homodimer containing two monomers of roughly 53/54 kDa in size, depending on the species [1,2]. It wasn't until the cDNA was sequenced however, firstly from the rat [3] and subsequently from the mouse [4], that it became clear that the enzyme is initially translated as a ~74 kDa protein. This then undergoes post-translational processing to generate lower molecular weight isoforms [3,4]. Despite the fact that the protein is translated as a larger protein, there remains little doubt that processed forms of the protein, such as the ~54 kDa isoform used to make the ~110 kDa homodimer, are catalytically active, and may even represent the main catalytic form of the protein in some cell types [5].

A combination of antibody and cDNA expression experiments demonstrated that processing occurs primarily at the carboxyl terminus [6], and studies on the rat and mouse sequences have shown that the maximally truncated form of the protein to retain activity is ~52–53 kDa in size. Isoforms that are smaller than this are inactive [5,7]. Localization of the catalytic activity to the amino end has facilitated numerous biochemical studies to explore the catalytic mechanism. For example, truncated forms of the rat enzyme have been used to characterise the kinetic properties of the enzyme [8], map catalytically important residues in the active site, and to identify a loop domain that is important for catalytic activity [9,10].

Given that the catalytic domain is located at the amino terminus, it is of little surprise that the greatest homology between mammalian HDC proteins exists over the first five hundred amino acids (91% sequence identity between rat and mouse) [4]. However the processed carboxyl-terminus is not without function. It has been shown to target the protein to the endoplasmic reticulum, and it also encodes a degradation promoting PEST domain such that truncated forms of the protein are more stable that the full-length primary translation product [11,12].

Although early studies demonstrated that porcine elastase is capable of cleaving the mouse enzyme *in vitro* [13], the first study to address cellular processing of mammalian HDC's was performed

Abbreviations: HDC, histidine decarboxylase; GI, gastrointestinal; rHDC, rat histidine decarboxylase; hHDC, human histidine decarboxylase; mHDC, mouse histidine decarboxylase.

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with the rat protein [7]. As part of this study it was shown that mutating amino acids SKD from within a DSKD motif at residues 501–504 disrupted production of the ~54 kDa isoform in transfected Cos7 cells. However, the enzyme responsible for processing was not identified at this time [7]. The major advance came when Furuta et al. looked at processing of the mouse enzyme and demonstrated that caspase-9 mediates processing into 55 and 60 kDa isoforms. Mapping of the cleavage sites subsequently revealed the important processing role played by di-aspartate DD motifs at amino acid residues 517/518 and 550/551, respectively [5].

Interestingly, di-aspartate motifs have been identified at the corresponding locations in the rat (519/520, 543/544) and human HDC protein sequences (514/515, 551/552). This has raised the possibility that these could represent caspase-9 cleavage sites in these other species also [5], however a direct comparison between HDC proteins from different mammalian species has not previously been performed. In the current study we aimed to compare the post-translational processing of mouse, rat and human HDC proteins in a single cell type, and to test the hypothesis that di-aspartate motifs located in the rat and human HDC proteins can mediate caspase-dependent proteolysis.

2. Materials and methods

2.1. Cell culture and transfection

Cos7 (ATCC) and AGS-E cells [14] were maintained in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum and 1% penicillin/streptomycin solution (final 100 IU/ml). Cells were cultured in a 5% CO_2 humidified incubator at 37 °C. For transient transfection experiments cells were seeded at a density of 2×10^5 per well on 24 well plates. After 4 h, cells were transfected by the addition of 100 μl antibiotic free Optimem medium (Invitrogen) containing 0.5 μg of plasmid DNA and 1 μl of Lipofectamine 2000 (Invitrogen). The medium was not changed before harvesting of the cells 48 h after transfection. Cells were incubated in the presence or absence of 1 μM staurosporine (Sigma), or 100 μM caspase inhibitors (R&D Systems):- Z-VAD-FMK (pancaspase), z-WEHD-fmk (caspase-1), z-VDVAD-fmk (caspase-2), z-DEVD-fmk (caspase 3), z-YVAD-fmk (caspase 4), z-VEID-fmk (caspase-6), z-IETD-fmk (caspase-8), z-LEHD-fmk (caspase-9), z-AEVD (caspase-10) or z-LEED-fmk (caspase-13), as described in the figure legends.

2.2. Expression constructs and site directed mutagenesis PCR

The cDNA encoding human HDC (described hereafter as hHDC) was amplified from a testes cDNA library. The cDNA encoding mouse HDC (mHDC) was amplified from an MGC clone containing the full-length cDNA (Invitrogen). The rat rHDC was previously cloned using CMV-HDC1.8 as template [3]. The mHDC, hHDC and rat rHDC cDNAs were cloned into the pEP7-ST vector (containing a stop codon). Rat rHDC (encoding both wild type and mutated cDNA as described below) were cloned into the pEP7-HA vector (carboxyl-terminus HA tag). Human hHDC (encoding both wild type and mutated cDNA as described below) were cloned into the pEP7-FL vector (carboxy-terminal FLAG tag). All cloning was performed using HindIII and SalI restriction sites as described previously [7,9,15], and confirmed by sequencing. Site directed mutagenesis was performed using the Quikchange protocol (Stratagene) with sequence specific primers, Phusion thermostable DNA polymerase (Fisher) and DpnI restriction enzyme (Stratagene). Sense primers (5′ → 3′) used for mutagenesis were as follows: rHDC-DD519/520AA, gtc aat gag gga gga gct gcc cca gta cag gtc cgg; rHDC-DD543/544AA, aca atg gat ccc ttt gct gct tgc ttc tca gaa gag; rHDC-SKD502/503/504PNS, ccg gtg acc aga gac tcc aaa gac ctg acc aat ggg cta; hHDC-DD514/515, gtc agt ggg gca gga gct gct cca gtc cag gcc agg; hHDC-551/552, ctg ctg gac cca gtt gct gct tgc ttt tca gaa gag; hHDC-EEAPD556/557/558/559/560AAAA, gac tgc ttt tca gaa gcg gcc gca gct gcc acc aag cac agg.

2.3. Cell lysis and immunoblot analysis

Cell were harvesting by suspension in the culture medium and transferring all the cells to a tube for centrifugation at 3000*g* for 10 min. After centrifugation the medium was discarded and the cell pellets were washed in 500 μl of sterile PBS before centrifuged again at 3000*g*. The supernatant was discarded. Pellets were resuspended in RIPA lysis buffer, which was supplemented with complete protease inhibitors (Roche) and phosphatase inhibitors (1 mM $NaVO_4$ and 10 mM NaF) as described elsewhere [7]. HDC expression and the ratio of processed to unprocessed bands was examined by immunoblotting (EuroDiagnostica) with subsequent quantitation performed using Odyssey imager and software [7]. When appropriate ß-actin expression in cell lysates was examined by immunoblotting (Sigma). All immunoblots are representative of at least three independent experiments.

3. Results

3.1. Mammalian HDC enzymes are differentially processed in transfected Cos7 cells

To further our understanding of the molecular basis for mammalian HDC protein processing we transfected Cos7 cell cultures in parallel to express human, rat or mouse HDC proteins, and analyzed cell lysates by anti-HDC immunoblotting. Despite the recognized homology between the three protein sequences we nevertheless observed that the pattern of protein processing was quite different between the species (Fig. 1A). For the rat protein

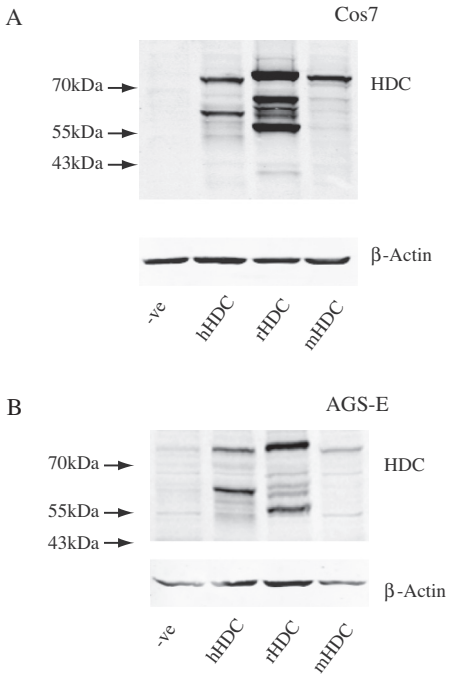

Fig. 1. Cos7 (A) or AGS-E (B) cells were transfected to express human hHDC, rat rHDC or mouse mHDC as indicated (no FLAG or HA tags). 48 h after transfection cells were harvested and proteins analysed by anti-HDC immunoblotting. Gel loading was monitored by probing for β-actin.

the sizes of the processed isoforms were consistent with our previous observations, with rHDC being processed into major 63, 54 and 58/59 kDa doublet bands. Similar sized isoforms have been detected in rat stomach cell lysates and fetal hepatocytes [7,16]. Human hHDC also underwent processing with a major processed band of ~59 kDa being observed in addition to a number of minor bands. In line with observations consistently made by Ichikawa and colleagues [12], the mouse mHDC protein showed comparatively little processing in Cos7 cells, with no major processed band being observed.

We additionally transfected human gastric AGS-E cells (human gastric cancer) to express human, rat and mouse HDC's so as to examine whether the processing patterns were unique to Cos7 cells (monkey kidney). As can be seen in Fig. 1B, the sizes of processed bands was not greatly different from the patterns observed in the Cos7 cells.

3.2. Caspase dependent processing of rat and human HDC enzymes in Cos7 cells does not involve conserved di-aspartate motifs

Conserved di-aspartate motifs have been identified in the rat (519/520, 543/544), human (514/515, 551/552) and mouse (517/518, 550/551) HDC protein sequences. For mHDC, these sites mediate post-translational processing in a caspase-9 dependent manner [5]. To assess the role that these di-aspartate motifs might play in rat rHDC processing Cos7 cells were transfected to express proteins with aspartate to alanine mutations at residues DD519/520 and DD543/544. Cells were additionally transfected to express the rHDC 502/503/504 mutant protein that we have described previously as being of importance for production of the 54 kDa isoform [7]. As can be seen in Fig. 2A, the di-aspartate mutations did not lead to a loss in levels of any of the processed isoforms. Although there was some evidence for a slight change in the size of the 63 kDa isoform expressed from the rHDC DD543/544 mutant, it was only the rHDC 502/503/504 mutant that showed a loss in any of the bands. We wondered if this cleavage was restricted only to Cos7 cells, but as can be seen in Fig. 2B, similar results involving a decrease in the ~54 kDa band were observed when the rHDC 502/503/504 mutant was expressed in AGS-E cells.

We next wondered whether any of the observed cleavages in rat rHDC were mediated by caspase enzymes, and cells transfected to express rHDC-WT were incubated in the presence or absence of the pan-caspase inhibitor z-VAD-fmk. As can be seen from Fig. 2C, the inhibition of caspase enzymes resulted in a decrease in the ~54 kDa band. The band that disappeared following inhibitor treatment was similar in size to the band that is lost for the rHDC 502/503/504 mutant (see Fig. 2C, lane four). These data suggested that processing at the previously mapped rHDC SKD 501/502/503 site is likely to be caspase dependent.

To determine whether conserved di-aspartate motifs facilitate processing of the human hHDC protein we transfected Cos7 cells to express wild type or mutant forms of the hHDC protein where aspartate residues DD513/514 and DD551/552 were mutated to alanines. As can be seen in Fig. 2D, and similar to what we had observed with the rat enzyme, these DD mutations failed to decrease levels of any of the major processed isoforms (Fig. 2D). In contrast, mutation of an EEAPD motif at amino acids 556–560 of the human hHDC protein exhibited a decrease in the ~59 kDa processed band (Fig. 2E, lane 5). Again we wondered whether processing at this site might be mediated by caspase enzymes and transfected cells were incubated in the presence or absence of z-VAD-fmk. As can be seen from Fig. 2E the hHDC 556–560 mutant was comparatively unaffected by caspase inhibition whereas the wild type protein showed a decrease in production of the 59 kDa band and a slight increase in a 61 kDa protein.

These combined data indicated that while both the rat and human HDC enzymes are sensitive to caspase dependent processing, the processing does not seem to involve the di-asparate motifs such as those observed in the mouse enzyme.

3.3. Post-translational processing of rat and human HDC enzymes is caspase 6 dependent

To help establish which of the caspase enzymes is responsible for the observed processing we transfected cells in the first instance to express human hHDC-WT and incubated them in the presence or absence of a panel of caspase inhibitors for 16 h. In three independent experiments the caspase-6 inhibitor consistently had the greatest effect on production of the ~59 kDa processed isoform with an associated increase in the higher molecular weight ~61 kDa band (Fig. 3A). Other inhibitors (including those for caspases 3 and 4-data not shown) had less of an effect. In follow-up experiments we observed that increasing the time course for incubation with the caspase-6 inhibitor almost completed blocked production of the ~59 kDa isoform (Fig. 3B), once again with a slight accumulation of the higher molecular weight ~61 kDa isoform.

A similar set of experiments were conducted with cells transfected to express the rat rHDC enzyme. Once again we observed the greatest effect when cells were incubated with the caspase-6 inhibitor, and increasing the period of time during which the inhibitor was incubated with the cells effectively blocked production of the ~54 kDa isoform (Fig. 3C and D).

Staurosporine is frequently used to induce caspase enzymes including caspase-6 [17]. To test whether staurosporine treatment can influence hHDC cleavage we incubated cells in the presence or absence of the drug for increasing time periods. As can be seen in Fig. 4A and B, this treatment was associated with a significant increase in the ratio of processed to unprocessed hHDC isoforms.

4. Discussion

There is now broad recognition that mammalian HDC enzymes are capable of undergoing post-translational processing with the production of multiple isoforms [5,16,18]. There are frequently differences however in the type and species of cells used in experimental studies, and increasing evidence that different cell types may produce different sized isoforms [19]. In transfection studies involving protein over-expression there is also considerable variability in the species origin of the proteins being tested. This makes it difficult to compare different studies, and there is a tendency to assume that what is observed for one protein is applicable to all the others. Our study, which is the first to directly compare HDC proteins from different mammalian species alongside one another in a common cell type, shows that the mouse, rat and human proteins are differentially processed in Cos7 cells. The differential pattern of processing was not restricted to Cos7 cells, and the generation of similarly sized isoforms was observed in AGS-E cells. We also noted that mutation of the rHDC-SKD502/503/504 residues disrupted production of the ~54 kDa isoform in both Cos7 and AGS-E cell types, suggesting that common cleavage sites, presumably utilizing common proteases, have the capacity to mediate processing in different cell types.

Despite the gross differences that we observed in the banding patterns for the three HDC protein examined, our studies nevertheless point towards a conserved role for caspase enzymes in the processing of mammalian HDC's, with caspase-6 playing a particularly important role for the human and rat proteins. Caspase-6 has been described as an effector caspase that can be activated by caspase-1 [20]. Activation is frequently associated with activation of caspase

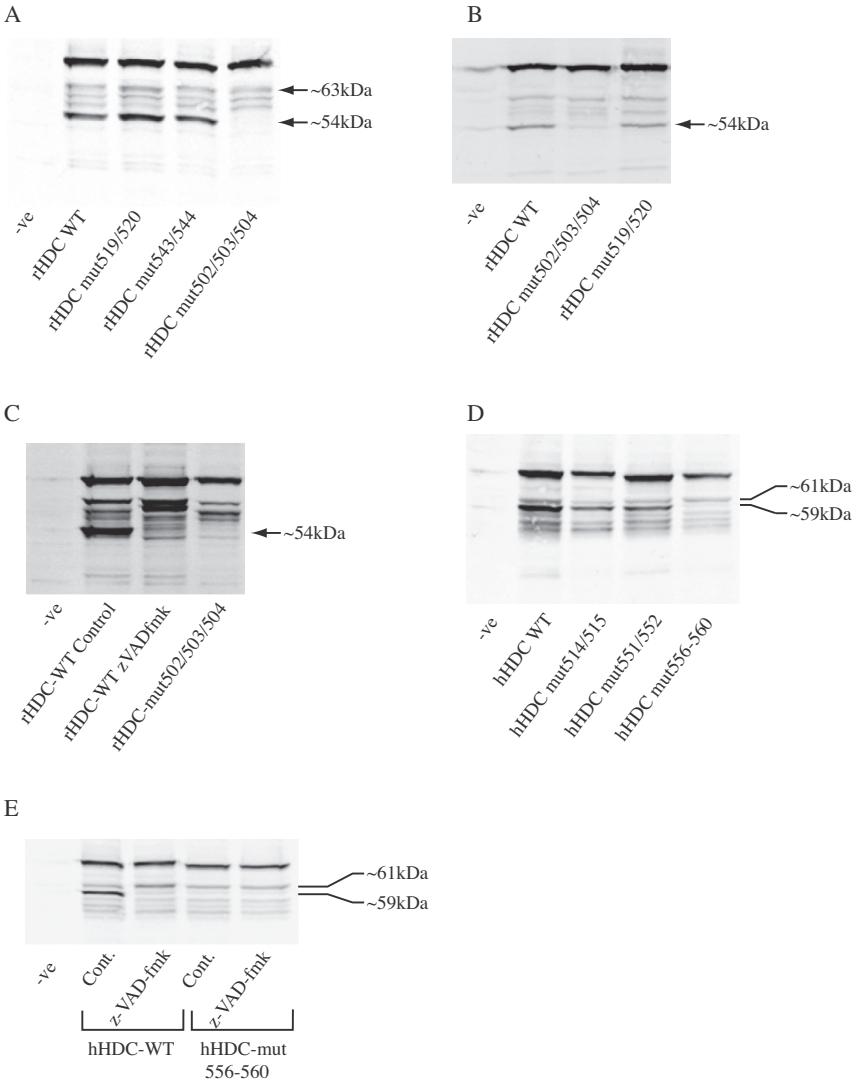

Fig. 2. (A) Cos7 cells were transfected to express wild type rat rHDC-WT or mutant forms of the protein carrying DD519/520AA (rHDC-mut519/520), DD543/544AA (rHDC-mut543/544) or SKD502/503/504PNS (rHDC-mut502/503/504) mutations. (B) AGS-E cells were transfected to express rHDC-WT, rHDC-mut502/503/504 or rHDC-mut519/520. (C) Cos7 cells were transfected to express wild type rHDC-WT or rHDC-mut502/503/504. Cells expressing rHDC-WT were incubated in the presence or absence of 100 μM z-VAD-fmk for 16 h. (D) Cos7 cells were transfected to express either wild type human hHDC or mutant forms of the protein carrying DD518/519AA (hHDC-mut518/519), DD551/552AA (hHDC-mut551/552) or EEAPD 556/557/558/559/560AAAAA (hHDC-mut556–560) mutations. (E) Cos7 cells were transfected to express either wild type or hHDC-mut556–560 mutated human hHDC and incubated in the presence or absence of 100 μM z-VAD-fmk for 16 h. In all cases cells were harvested 48 h after transfection and changes in HDC enzyme processing were analysed by anti-HDC immunoblotting.

3 and caspase 7 and a number of substrates have been described [21]. Activation is not always associated with cell death however [22], and active forms of the enzyme have been detected in the adult GI tract and brain (sites, which are incidentally recognized also for histamine biosynthesis), leading to suggestions for a role in normal cell physiology [23]. *In vitro* proteolysis studies will be required to differentiate whether the HDC processing observed in our study is mediated by caspase-6 or a downstream protease, but a role for caspase-6 is evident from our studies, and it is noteworthy that the cleavage sites identified are not dissimilar to caspase-6 sites that have previously been described [21,24]. Interestingly, the inhibition of caspase-6 in our experiments was frequently accompanied by the accumulation of higher molecular weight HDC isoforms (for example the ~61 kDa form seen for the human hHDC protein in Fig. 3B). It remains possible therefore that processing is a multistage process with an initial caspase-independent cleavage that then facilitates caspase-dependent cleavage.

Although caspase-9 is regarded as an activator caspase, and capable of activating other proteolytic enzymes, Furuta et al. showed that it is involved in the direct proteolysis of mHDC [5]. The fact that we observed very little mHDC processing in Cos7 might therefore suggest that levels of caspase-9 are quite low in this cell type. There may be other instances however where the repertoire of expressed proteases, including for example caspase-9, could result in a very different pattern. Indeed, we cannot rule out the possibility that there may even be cell types where the conserved DD-motifs as described by Furuta et al. play a role in expression of the rat and human enzymes.

Specific treatment of human hHDC expressing cells with staurosporine, a commonly used caspase-6 activator [22], significantly increased the ratio of the ~59 kDa band to the unprocessed band. Although these data suggest that processing events can be regulated, the human hHDC enzyme has not been well characterized and it is difficult to speculate as to what the functional conse-

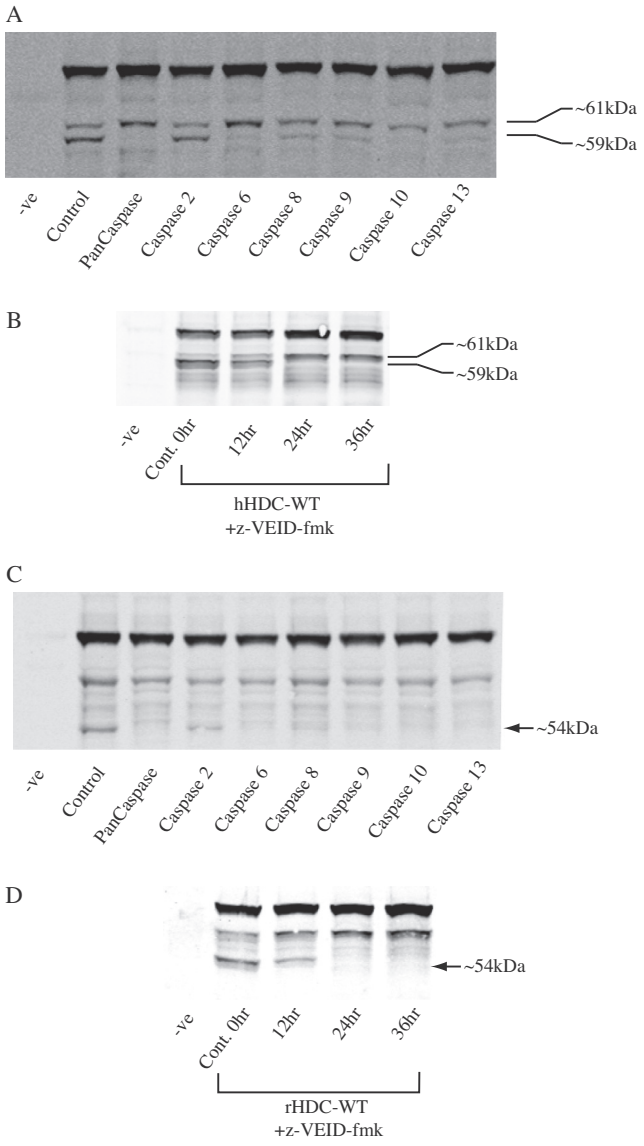

Fig. 3. Cos7 cells were transfected to express hHDC-WT (A) or rHDC-WT (C) and incubated for 16 h in the presence or absence of specific caspase inhibitors (100 μM) as indicated. Cos7 cells were transfected to express hHDC-WT (B) or rHDC-WT (D) and incubated for increasing time periods in the presence or absence of the specific caspase-6 inhibitor (z-VEID-fmk) as indicated. In all cases cells were harvested 48 h after transfection and changes in HDC enzyme processing were analysed by anti-HDC immunoblotting.

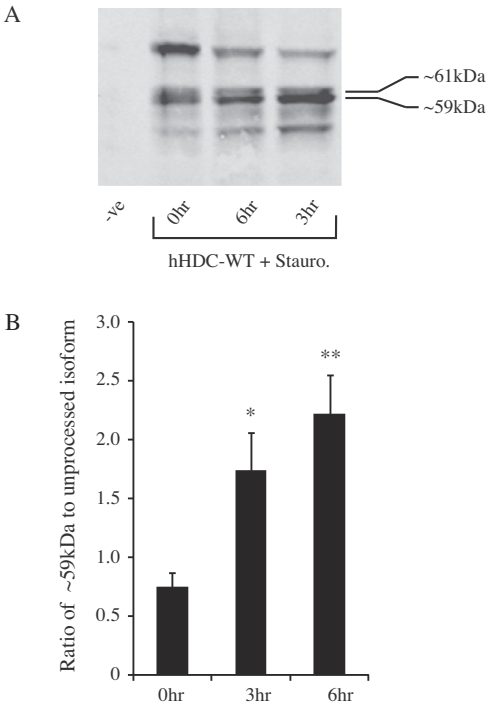

Fig. 4. (A) Cos7 cells were transfected to express hHDC-WT and incubated in the presence or absence of 1 μM staurosporine for 3 or 6 h as indicated before harvesting. Cells were harvested 48 h post transfection and changes in HDC enzyme processing were analysed by anti-HDC immunoblotting. (B) Graph showing changes in the ratio of the ~59 kDa isoform to the unprocessed isoform in response to staurosporine treatment (mean ± S.E.M, $n = 4$, $^{*} = p < 0.05$, $^{**} = p < 0.01$, students t-test).

quences might be. Based on our knowledge of the rat rHDC protein however we can hypothesise that caspase-6 dependent processing at the DSKD site would likely lead to stabilization of the protein [7,11]. There is also evidence from *in vitro* studies that the rat rHDC enzyme (like the mouse mHDC enzyme [5]) is inactive in the absence of post-translational processing [15]. Processing might therefore also be expected to result in activation of the rat protein and lead to increased histamine biosynthesis. What is less clear however is how extensively regulated proteolysis might be during normal cellular conditions, or how closely it is linked to apoptosis. It is noteworthy then that although we didn't specifically look at regulation of rat rHDC cleavage, we have nevertheless observed in Cos7 cultures that detached cells (representing only a small minority of the total cells but potentially in the early stages of apoptosis) showed an increased ratio of the ~54 kDa to the unprocessed ~74 kDa band (data not shown).

In summary our experiments point towards a conserved role for caspase enzymes in processing of mammalian HDC enzymes, however our data highlights that processing may involve different sites and enzymes depending on the species. The functional significance of processing, and the contexts during which processing occurs, remain to be fully elucidated.

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