Annals of Genetics and Genomics

Research Article

HSD17B10 Gene-related Disorders are Associated with Abnormalities of Mitochondrial Function, Morphology, Dynamics and Clearance

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Abstract

The type 10 17β-hydroxysteroid dehydrogenase (17β-HSD10), a multifunctional protein was encoded by the *HSD17B10* gene mapping to Xp11.2. An appropriate concentration of mitochondrial 17β-HSD10 is key for the maintenance of normal function of mitochondria, which is necessary for improving cellular bioenergetics and brain cognitive function. A missense and silent mutation in the *HSD17B10* gene cause progressive and non-progressive neurodegeneration, respectively, by disturbing the homeostasis of neurosteroid metabolism. Abnormal quantity or quality of 17β-HSD10 is associated with the pathogenesis of certain types of dementia. Some mutation of 17β-HSD10 could unevenly damage individual functions of this protein, e.g., it was found that 17β-HSD10 (p.A157V) mutant had destroyed 3-hydroxyacyl- CoA and 2-methyl-3-hydroxyacyl-CoA dehydrogenase activity but it retained significant 3α-HSD activity necessary for neurosteroid metabolism. This may explain why such a HSD10 deficiency patient does not suffer apparent neurological handicap, although isoleucine metabolites are excreted from his urine. Since antisera against the same antigen could not behave so disparately as published previously, it indicated that the 'discovery' of ABAD/ERAB in mitochondria was certainly preceded by unreferenced SCHAD/17β-HSD10 reports. It was also found that Aβ does not play a pathogenetic role in the infantile neurodegeneration even if it is critical to the senile neurodegeneration. The last but not the least, elevated levels of mitochondrial 17β-HSD10 itself may serve as a new therapeutic target for the treatment of Alzheimer's disease.

Keywords: Acyl thioester metabolism; Infantile neurodegeneration; Mitochondria disease; Neurosteroid metabolism; Alzheimer disease

Abbreviations

ABAD: Aβ-Binding Alcohol Dehydrogenase; AKR: Aldo-Keto Reductase; ER: Endoplasmic Reticulum; ERAB: Endoplasmic Reticulum-Associated Aβ-Binding protein; HAD: L-3-Hydroxyacyl-CoA Dehydrogenase; HAD2 or HADH II: 3- Hydroxyacyl-CoA Dehydrogenase type 2; HSD: Hydroxysteroid Dehydrogenase; 17β- HSD10: 17β-Hydroxysteroid Dehydrogenase type 10; MHBD: 2-Methyl-3- Hydroxybutyryl-CoA Dehydrogenase; MRXS10: Mental Retardation, X-linked, Syndromic 10; mtRNA: Mitochondrial tRNA; SCHAD: Short-Chain 3-Hydroxyacyl- CoA dehydrogenase; TCA: Tricarboxylic Acid Cycle

Citation: Xue-Ying He, Jerzy Wegiel, R. Frank Kooy, W. Ted Brown, Song-Yu Yang. *HSD17B10* Gene-related Disorders are Associated with Abnormalities of Mitochondrial Function, Morphology, Dynamics and Clearance. Ann Genet Genom. 2021; 1(1): 1005.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Jul 15th, 2021

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Introduction

The *HSD17B10* gene was first cloned from human brain in 1997 and mapped to Xp11.2 [1]. It encodes a *mitochondrial* multifunctional protein with MW = 108 kDa and composed of four identical, simpler molecules [1-4]. Since the first enzymatic function identified for this protein was an L-3-Hydroxyacyl-CoA Dehydrogenase (HAD) activity [1-6], it was designated as Short-Chain 3-Hydroxyacyl-CoA Dehydrogenase (SCHAD), composed of 261 amino acid residues per subunit [1-4]. Meanwhile, a 27 kDa protein consisting of 262 residues was reported as being associated with the Endoplasmic Reticulum (ER) and labeled as being Endoplasmic Reticulum-Associated Aβ-Binding Protein (ERAB) [7]. This appears to be a subunit of SCHAD with an inaccurately reported sequence. It had been admitted [8] that "a recent report concerning properties of human L-3-hydroxyacyl-CoA dehydrogenase... the cDNA sequence of which is identical to that of human ERAB". It was claimed [8] that ERAB deficiency may cause defects in fatty acid β-oxidation such that HADII (3-hydroxyacyl-CoA dehydrogenase type 2) became an alternative name of ERAB. ERAB/HADII was reportedly associated with the endoplasmic reticulum, and further certified by tons of evidence [8,9]. In contrast, the SCHAD/17β-HSD10 was found to be localized in mitochondria because of its N-terminal mitochondrial targeting signal [2-4] rather than associated with the endoplasmic reticulum as reported previously [7-9]. Unfortunately, there was no corrigendum of erroneous ERAB

reports [7,8] but ERAB was then compelled to be renamed as Amyloid beta-peptide Binding Alcohol Dehydrogenase (ABAD) to avoid ER [9]. ABAD had been casted because of the findings of so-called *generalized* alcohol dehydrogenase (C2-C10) activity [8,9]. However, it was revealed that the *generalized* alcohol dehydrogenase activities reported for ABAD/ERAB was non-reproducible [5].

In contrast to other types of 17β-HSD [10-13], 17β-HSD10 is the only one localized in mitochondria [2-4]. Although it was already known that mitochondrial SCHAD/HSD10 is structurally similar to ERAB/ABAD [1-5,8-12] even if ABAD/ERAB was erroneously claimed to be associated with ER [7-9]. The *re-discovering* of ABAD/ERAB in mitochondria was later reported in the *Science* journal as a new discovery [14] without reference to any previously published 17β-HSD10/SCHAD literature [1-6,10,11].

As this gene was officially designated *HSD17B10* by the Human Genome Organization (HUGO) [15], the gene product was, as a matter of course, declared to be type 10 17β-hydroxysteroid dehydrogenase (17β-HSD10) [15-18]. Elevated levels of 17β-HSD10 were found in brains of Alzheimer's Disease (AD) patients and an AD mouse model [4,18,19], which may affect the homeostasis of the neurosteroid estradiol as 17β-HSD10 effectively catalyzes the inactivation of 17β-estradiol leading to oxidative stress of neurons (Figure 1) [20-27]. It may explain why the cytotoxic effects of Aβ on neuroblastoma cells in culture were enhanced by overexpression of 17β-HSD10 but not its inactive mutant [16].

A missense mutation in 17β-HSD10 was found to cause HSD10 deficiency resulting in infantile neurodegeneration [21,23-25]. Since 17β-HSD10 is indispensable for the normal degradation of the essential amino acid isoleucine [12,17-30], the excretion of abnormally high levels of isoleucine metabolites such as tiglylglycine and 2-methyl-3- hydroxybutyrate from urine serves as an indicator of HSD10 deficiency and is also designated as an inborn error in isoleucine metabolism [17,21-25,30-35]. 17β- HSD10/ERAB/ABAD reportedly mediates the neurotoxicity of Aβ and results in Alzheimer's disease [1,4,17-20], the most common form of dementia. Since Aβ was reportedly undetectable in HSD10 deficiency patient's cerebrospinal fluid [35], it suggests that the alteration of the 17β-HSD10 functions itself could be a major pathogenetic factor involved in neurodegeneration. In addition, a silent mutation of the *HSD17B10* gene leads to a syndromic form of X-linked mental retardation, designated as MRXS10 [36]. These patients have a normal organic acid profile [37], indicating that isoleucine seems to be degraded in their mitochondria without a blockade. It will be of great interest to identify additional mitochondrial changes in different *HSD17B10* gene-related disorders.

Here we show that a certain mutation at *HSD17B10* gene could alter individual function of 17β-HSD10 at different extents. More importantly, it was demonstrated that alteration of the quantity or quality of 17β-HSD10 activity has a significant impact on the structure and/or function of mitochondria, which underlie the pathogenesis of *HSD17B10* gene-related disorders.

Results

HAD activity and hydroxysteroid dehydrogenase activity of human 17β- HSD10

The HAD activity of 6xHis-tagged 17β-HSD10 was measured according to the published procedure [1,38] by use of acetoacetyl-CoA as substrate and NADH as coenzyme, respectively. Its 3α-HSD activity was determined by use of allopregnanolone as substrate and NAD^+ as coenzyme as described previously [25]. The data obtained in the absence of inhibitor or activator was taken as 100% for the observation of inhibition or activation of 17β-HSD10 by a mutation or a tested compound.

Uneven damages to HAD and 3α-HSD activities by the p.A157V mutation

HAD and 3α-HSD activities of human 17β-HSD10 and its p.A157V mutant were determined quantitatively. The residual 3α-HSD activity and HAD activity of the HSD10 (p.A157V) mutant were found to be about 19% and 1.5% of the wild type enzyme, respectively, when it was measured at various levels of allopregnanolone and acetoacetyl-CoA as the substrate for the determining of 3α-HSD and HAD activity of this multifunctional protein, respectively (Figure 2).

Destruction of mitochondria in the patient with HSD10 deficiency rather than MRXS10

This study was approved by the Institutional Review Board of New York State Institute for Basic Research in Developmental Disabilities. It was discovered that mitochondria of the HSD10 deficiency patient were smaller than those of the normal control, and their cristae were condensed and shrunken due to a missense mutation in *HSD17B10* [39] (compare Figure 3b to 3c). In contrast, an electron-microscopic study failed to disclose any prominent morphological changes in individual mitochondria of the MRXS10 patient [36,37] even though the total number of mitochondria in the MRXS10 patient cells is several times more than that in the normal control (compare Figure 3a to 3c).

Discussion

17β-HSD10 is also known as Short-Chain 3-Hydroxyacyl-CoA Dehydrogenase (SCHAD) [1-6], Endoplasmic Reticulum-Associated Aβ-Binding Protein (ERAB) [7,8] and Amyloid β-peptide Binding Alcohol Dehydrogenase (ABAD) [9,14]. It was found to have a high affinity to Aβ [22], and to be capable of catalyzing the inactivation of 17β-estradiol [2]. Its involvement in the pathogenesis of neurodegeneration is not only due to the mediation of Aβ neurotoxicity [1,7] but also to its role in the keeping of neurosteroid homeostasis [2,20,21]. Results of this study provided new evidence that appropriate levels of mitochondrial 17β-HSD10 is necessary to the normal structure and function of mitochondria. Abnormal quantity or quality of this mitochondrial multifunctional protein would be harmful to the cognitive function.

ERAB/ABAD was reportedly associated with the endoplasmic reticulum [7-9], and later re-localized into mitochondria without reference to any SCHAD/17β-HSD10 literature [14] As shown in Figure 4e [7], intracellular ERAB could be attracted by Aβ peptide to move to the plasma membrane. Such incredible reports owe the public an explanation regarding the discrepancy between immuno-histological micrographs stained with guinea pig or mouse anti-ABAD (Figure 1d of [14]) and those stained with rabbit anti-ERAB/ABAD, because ABAD and ERAB both are just alternate names for 17β- HSD10 [1-12,14-17]. How could so disparate results shown in in Figures 1 of [14] and 4 of [7] be really obtained with anti-sera against the very same antigen? As shown in Table 1, erroneous information published previously had never be corrected or withdrawn such that it may mislead the public forever.

Multiplex roles of 17β-HSD10/ABAD in neurodegeneration were found not to be limited to its binding to Aβ as previously reported

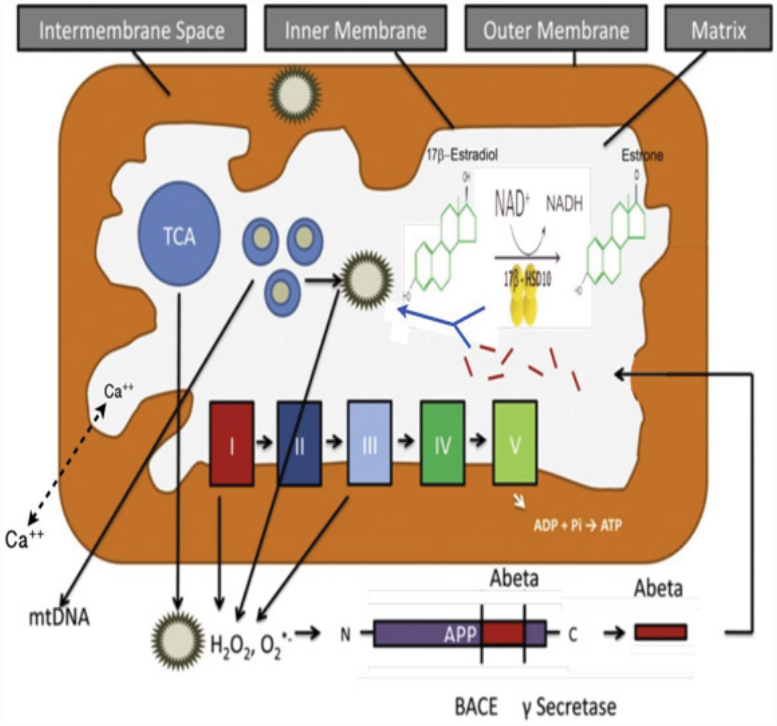

Figure 1: Oxidative inactivation of neuroprotective 17β-estradiol by 17β-HSD10 in brain mitochondria. In senile neurodegeneration patients reduced mitochondrial 17β-estradiol level causes overproduction of reactive oxygen species (*) to reduce the ATP production, and would increase the Aβ generation resulting in damage to the function and structure of mitochondria. The I, II, III, IV and V represent the complexes consisting of the electron-transport chain for the oxidative phosphorylation to generate ATP.

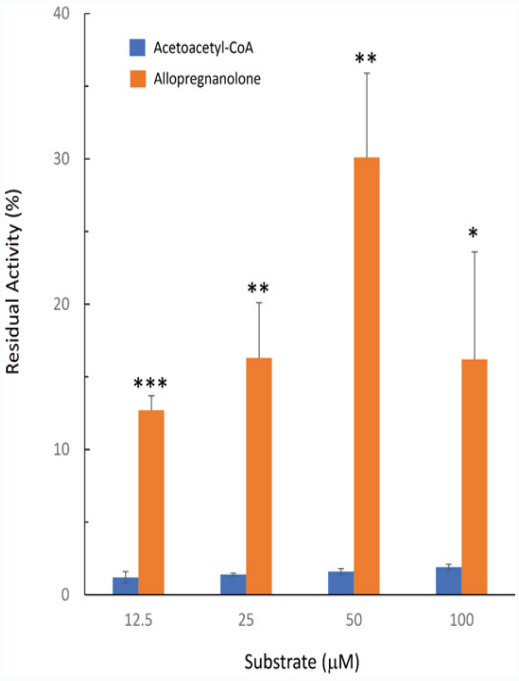

Figure 2: Residual HAD and 3α-HSD activities of HSD10 (p.A157V) mutant. Various concentrations of acetoacetyl-CoA and allopregnanolone (12.5, 25, 50, 100 μM) were used as substrates. Enzyme assays were performed as described in the Experimental Procedure. The residual activity of this mutant was reported as percentage of the wild type enzyme activities. The symbol * indicates P<0.05; **, P<0.005; and ***, P<0.0005.

Table 1: Distribution of 17β-HSD10 in cells†.

Component	Evidenc e Code	Pubs
cytoplasm	TAS	PubMed
mitochondrial matrix	TAS	
mitochondrial ribonuclease P complex	IDA	PubMed
mi†chondrial ribonuclease P complex	TAS	PubMed
mitochondrion	IDA	PubMed
mitochondrion	ISS	
plasma membrane	TAS	PubMed

†Contents displayed in the NCBI/NIH website need to be corrected as shown in red.

[7,14]. The Aβ-binding resulted in reportedly shocking alterations of stereo-structure of 17β-HSD10 from a compacted homo-tetramer to what showed in Figure 4a and b. It indicated that the 17β-HSD10-Aβ complex may have much high free energy than 17β-HSD10. However, no electron density of Aβ was shown in Figure 4a and b [14], and it would be highly questionable how the Aβ bound ABAD could have displayed so many different stereo-structures. It is also not known which one between Figure 4a and b represented a relative stable configuration. Although the dissociation constant for Aβ binding to ABAD/ERAB was reported to be about 65 nM [8], hundredfold higher concentration of Aβ is reportedly required to inhibit the HAD activity of this multifunctional protein [22]. Although 17β-HSD10 serves as the core of RNase P, it was reported [31] that neither RNase P nor methyltransferase activities were specifically affected by the Aβ binding. Therefore, the accuracy of the three-dimensional structures of Aβ-bound ABAD previously published in highly-respected journal [14] needs to be verified independently.

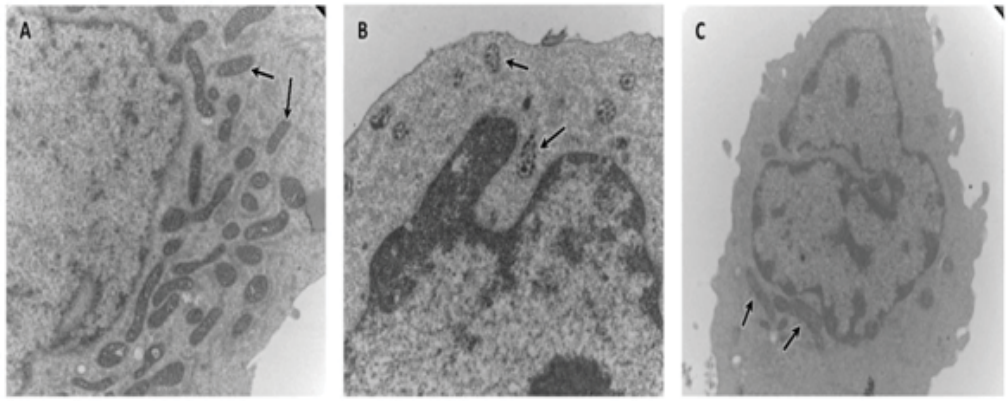

Figure 3: Comparison of electron-microscopic images of lymphoblastoid cells from intellectual disability patients and normal control. (A) patient with mental retardation, X-linked, syndromic 10 (MRXS10) [37], (B) patient with HSD10 deficiency [39], and (C) normal male control. Arrows indicated mitochondria. Magnification: x42,000.

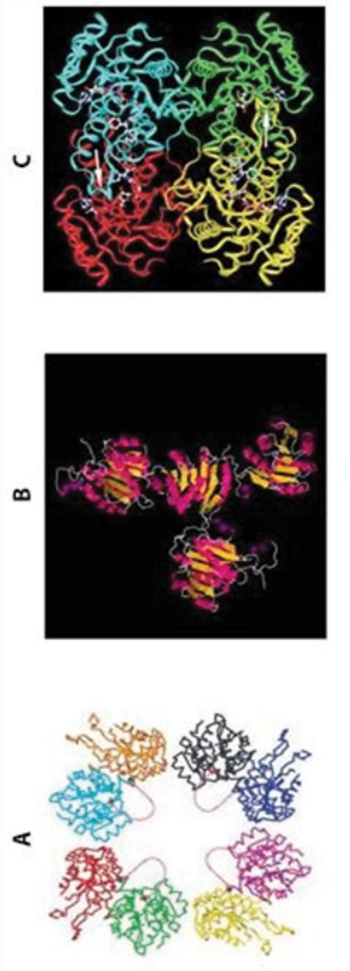

Figure 4: Comparison of crystal structure images of human Aβ-bound ABAD (a, b) to that of human 17β-HSD10/ABAD (c). (a) A section of the crystal packing interactions, showing the large solvent channels. Each ABAD molecule is shown in a different color. The ordered ends of the LD loop, residues 94 and 114 are marked as red and blue balls, respectively, and the hypothetical loops are shown in pink as dotted lines (see Fig. 2D of Ref. 14); (b) PDB: 1SO8 [14] showed only one subunit associated with other three subunits which have no contact with each other; and (c) PDB: 1U7T showed a close association of four subunits in human HSD10/ABAD [16].

HAD was the first enzymatic activity identified in 17β-HSD10 [1], but its characterization was impeded by erroneous but never corrected reports [8,9]. Mitochondrial 17β-HSD10 catalyzes acyl thioester metabolism [1,12,40], e. g., the oxidation of acyl-CoA and methyl-branched acyl-CoA to generate ATP. Since a methyl group and the CoA moiety accounts for approximately 1.7% and 90% of the size of such acyl thioesters, respectively, no one has ever identified a mutation damaging HAD but not the MHBD activity of 17β-HSD10. Residual activities of HAD and MHBD in individual HSD10 mutants appear roughly in parallel.

A missense mutation at the *HSD17B10* gene resulted in a loss-of-function HSD10 mutant that disturbs homeostasis of neurosteroid metabolism [25,26] and the bioenergetics of brain cells [28,40]. Since the p.A157V mutation was found to abolish the HAD activity (Figure 2), it indicated that the MHBD activity of this mutant would also be severely damaged [34]. This was further corroborated by the isoleucine metabolites detected in the patients' urine [42]. HSD10 deficiency patients usually suffered with intellectual disabilities. Half of such patients resulted from a mutation p.R130C in 17β-HSD10 [23] because of a mutation hot spot in the *HSD17B10* gene [43]. Surprisingly, the HSD10p.A157V mutant in a HSD10 deficiency family has not yet resulted in neurological handicap [42]. Therefore, studies on this HSD10 mutant may provide a clue to the pathogenesis of HSD10 deficiency. In contrast to the HSD10(p.R130C) mutant [25], the HSD10(p.A157V) mutant was found to retain a considerable residual 3α-HSD activity indispensable to the homeostasis of neurosteroid metabolism. 3α-HSD was believed to control the relative levels of 5α-DHP versus allopregnanolone as a molecular switch (44). However, the catalytic efficiency (kcat/Km) of human brain 3α-HSD3 for the reduction of 5α-DHP was reportedly about 15-fold greater than that for the oxidation of allopregnanolone [44]. Furthermore, the extremely high ratio of [NADPH/NADP+] in cytoplasm favors a reduction reaction, so that human 3α-HSD3 functions as a reductive 3α-HSD in brain. To close this loophole, human mitochondrial 17β-HSD10 has been found to effectively catalyze intracellular oxidation of allopregnanolone, a steroid modulator of γ-aminobutyric acid type A receptors [26]. The homeostasis of neurosteroid metabolism could be well maintained by the operation of a dual-enzyme molecular switch, consists of two distinct hydroxysteroid dehydrogenases, AKR1C2 and 17β-HSD10. Therefore, findings of this study strongly support the hypothesis that

a disruption of neurosteroid metabolism may play an important role in the pathogenesis of infantile neurodegeneration.

Destruction of mitochondria was found in lymphoblastoid cells from HSD10 deficiency patients, but not the patient with MRXS10 where intramitochondrial 17β-HSD10 levels decreased and the number of mitochondria was several times greater than the normal control. Lymphoblastoid cells of MRXS10 patients reportedly retain about 85% of MHBD activity [36] so that MRXS10 patients have a normal organic acid profile [37]. If a ratio of mitochondrial volume in the MRXS10 patient's cells versus that of normal controls is assessed, a dramatic decrease in intramitochondrial concentrations of 17β-HSD10 in the MRXS10 patient becomes evident. It was recently reported [45] that 17β-HSD10 acts as a member of the Parkin/PINK1 pathway, a biochemical mitochondria quality control pathway determining mitochondrial morphology, dynamics and clearance. Therefore, it is likely that a 17β-HSD10 mutant, e.g., HSD10(p.V65A) [39], would impair mitophagy leading to accumulation of excess mitochondria. Contrary to HSD10 deficiency patients with progressive neurodegeneration, MRXS10 patients suffer only milder and non-progressive intellectual deficiency because a silent mutation does not alter the 17β-HSD10 protein. However, a significant decrease in the intramitochondrial 17β-HSD10 concentration might disturb the homeostasis of neurosteroid metabolism, resulting in interference with the Parkin/PINK1 pathway, and thus interfering with the mitochondrial fission and fusion cycle [45]. Results of this study suggest that the qualitative and quantitative normality of *HSD17B10* gene product in cells is essential for the biochemical mitochondria quality control. Nevertheless, it seems inappropriate to combine MRXS10 with HSD10 deficiency as a single HSD10 disease [46].

It was reported [47] that human 17β-HSD10 serves as a cardiolipin phospholipase involved in the metabolism of cardiolipin, which is an important constituent of the mitochondrial inner membrane [48]. A significant mutation of 17β- HSD10 could disturb cardiolipin metabolism resulting in damages to mitochondrial structure and function. This may explain why some HSD10 deficiency patients suffer cardiomyopathy and a shortened life span [49].

17β-HSD10 exhibits a variety of non-dehydrogenase functions [31,50], in addition to the dehydrogenase functions involved in the metabolism of acyl thioesters [1,40]. It can bind with tRNA methyl transferase and then mitochondrial RNase P protein 3 to form RNase P [50]. A p.K212E mutation in 17β-HSD10 resulted in a general mitochondrial dysfunction, which was probably due to the impairment of 5'- processing and methylation of purine-9 of mitochondrial tRNA [51]. However, it was not known whether cardiolipin phospholipase activity is retained by the 17β-HSD10(p.K212E) mutant, since a missense mutation could damage various functions to different extents as discovered in the present study.

HSD10 deficiency is one of the most complicated, inherited metabolic diseases, and the correlation between genotype and phenotype is unclear. Based on data of this study, it is suggested that MRXS10 and HSD10 deficiency are, indeed, two kinds of *HSD17B10* gene-related disorders. The latter may result from defects in mtRNA maturation or cardiolipin metabolism as well as an imbalance of neurosteroid metabolism. 17β-HSD10 catalyzes the oxidative inactivation of 17β- estradiol, a neuroprotective neurosteroid serving as an anti-oxidant in mitochondria. Elevated levels of 17β-HSD10 found in AD brains are probably harmful to mitochondrial function. This fascinating protein is thus proposed as a new target in therapeutic studies on AD [21,23].

Materials and Methods

Materials

Acetoacetyl-CoA, allopregnanolone, NAD^+, NADH, RPMI, FBS, antibiotics (Penicillin and Streptomycin), and standard biochemicals were obtained from Sigma-Aldrich. The protein assay kit was from Bio-Rad. Human 6xHis-tagged 17β-HSD10 was prepared as previously reported [25], and the 17β-HSD10(p.A157V) mutant was expressed and purified as follows. The c.470C>T mutation was introduced into the plasmid pSBET-6xHis-HSD10 with a pair of mutagenesis primers A157Vmf (5'-CTgCCAgTgTggTTgCCTTCgAggg) and A157Vmr (5'-CCCTCgAAggCAA- CCACACTggCAg) using a Quick Change Site-Directed Mutagenesis Kit (Stratagene) per the instructions of the manufacturer. The sequence of the mutated plasmid, pSBET-6xHis-HSD10(p.A157V), was confirmed by sequencing. It was then transformed into *E. coli* BL21(DE3)pLysS. The transformants were induced by 1 mM IPTG for 6 h. The preparation of cell extracts, and the purification of 6xHis-HSD10 and 6xHis-HSD10(p.A157V) by use of the Ni-NTA fast Start kit (Qiagen) was accomplished as described previously [25].

Protein and enzyme assays

The protein concentration was determined by use of the Bio-Rad reagent according to the manufacturer's instruction. The 3-hydroxyacyl-CoA dehydrogenase (HAD) activity of 6xHis-tagged 17β-HSD10 was determined in the backward direction with acetoacetyl-CoA as substrate and NADH as the coenzyme according to experimental procedure described previously [1,38]. Its 3α-hydroxysteroid dehydrogenase activity was measured according to the previously reported procedure with allopregnanolone as substrate and NAD^+ as coenzyme [25] using a continuously recording spectrophotometer (Hitachi U-3010). Data were then analyzed by the Leonora computer program.

The molar extinction coefficient used for calculating rates is 6220 $M^{-1}cm^{-1}$. A unit of activity is defined as the amount of enzyme that catalyzes the conversion of 1 μmol of substrate to product/min.

EM study

Lymphoblastoid cell lines were established by EBV transformation of B lymphocytes from an HSD10 deficiency patient caused by the missense mutation HSD10p.V65A [39]. Lymphoblastoid cell lines from patient IV-1 with MRXS10, and those from the HSD10 deficiency patient and a normal male control were cultured in RPMI complete with 20% fetal bovine serum and 1% glutamine as well as antibiotics (Penicillin and Streptomycin). EM images of these cells were obtained as described previously [52].

Conflict of Interest

The authors declare no conflict of interests.

Acknowledgement

This work was supported in part by the New York State Office for People with Developmental Disabilities. We deeply indebted to Dr. G.Y. Wen for his invaluable help in the securing of electron-microscopic images.

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