Aldehyde dehydrogenase (ALDH) in Alzheimer’s and Parkinson’s disease

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Abstract Evidence suggests that aldehyde dehydrogenase (ALDH; E.C. 1.2.1.3) gene, protein expression and activity are substantially decreased in the substantia nigra of patients with Parkinson’s disease (PD). This holds especially true for cytosolic ALDH1A1, while mitochondrial ALDH2 is increased in the putamen of PD. Similarly, in Alzheimer’s disease (AD) several studies in genetic, transcriptomic, protein and animal models suggest ALDH involvement in the neurodegeneration processes. Such data are in line with findings of increased toxic aldehydes, like for example malondialdehyde, nonenal, 3,4-dihydroxyphenylacetaldehyde and others. Genetic, transcriptomic and protein alterations may contribute to such data. Also in vitro and in vivo experimental work points to an important role of ALDH in the pathology of neurodegenerative disorders. Aims at investigating dysfunctions of aldehyde detoxification are suitable to define genetic/molecular targets for new therapeutic strategies balancing amine metabolism in devastating disorders like PD and probably also AD.

Keywords Aldehyde dehydrogenase · Alzheimer’s disease · Gene variation · Parkinson’s disease · Proteomic · Transcription

Introduction

Aldehyde dehydrogenase (ALDH; E.C. 1.2.1.3) metabolizes both physiological and pathophysiological relevant aldehydes (Jackson et al. 2011). The removal of toxic aldehydes seems to play a central role of ALDH in the cells, while ALDH enzyme activity is also required for the synthesis of retinoic acid, folate and betaine (Marchitti et al. 2008). In addition to its central detoxification functionality, by its involvement in the retinoic acid synthesis, ALDH plays a role in the modulation of cell proliferation, differentiation and survival (Marchitti et al. 2008). Extending this point, ALDH enzymes exhibit functions that appear to be independent to their enzyme activity, including absorption of ultraviolet irradiation in the cornea by acting as a crystalline and binding to hormones and other small molecules, including androgens, cholesterol, thyroid hormone and acetaminophen (Jackson et al. 2011).

To date, nineteen putatively functional genes were identified in the human ALDH gene superfamily [Jackson et al. (2011); www.aldh.org, the aldehyde dehydrogenase gene superfamily resource center (Black and Vasiliou 2009)]. It was recognized not only that the ALDH gene consists of a great variety of genes, but many of the ALDH genes encode multiple mRNA splice variants (Black et al. 2009). Moreover, over one-hundred copy number
Genomic Variants (DGV, http://dgv.tcag.ca/dgv/app/home) for the human ALDH gene with deletions, duplications and inversions thus increasing the complexity of the functional genetics and these act on enzyme activity and expression (Jackson et al. 2011). Nevertheless, several phylogenetic analyses point to the importance of the gene since it goes back to more than two-thousand million years in the evolutionary tree (Rzhetsky et al. 1997; Strickland et al. 2011). The transcriptional profile of most ALDH genes show spread expression in the brain, in particular, the variants ALDH2 and ALDH1A1 (Fig. 1). Similarly to the mRNA, most of the ALDH proteins have a wide tissue distribution, with some distinct substrate specificity (Vasiliou et al. 2004). The different variants of ALDH proteins are found in different subcellular regions including cytosol, mitochondria, endoplasmatic reticulum and nucleus. In particular, in the central nervous system (CNS), ALDH catalyzes the irreversible oxidation of 3,4-dihydroxyphenylacetaldehyde (DOPAL), a metabolite of dopamine, to 3,4-dihydroxyphenylacetic acid (DOPAC), or 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL), a metabolite of norepinephrine and epinephrine, to 3,4-dihydroxyphenylmandelic acid (DOMA) which can then be further metabolized into homovanillic acid (HVA), or vanillylmandelic acid (VMA), respectively (Fig. 2) (Dedek et al. 1979; Lamensdorf et al. 2000). Several reports point to the disastrous effects of dysregulation in ALDH activity, causing to increase cytotoxicity, oxidative stress, energy deficits, apoptosis and cell death (Marchitti et al. 2008).

Increasing evidence at the genetic, transcriptomic and protein levels suggest the involvement of ALDH in the mechanism associated with neurodegeneration, in particular in Parkinson’s disease (PD) and Alzheimer’s disease (AD) (Marchitti et al. 2008). The evidence for ALDH alterations at various levels in both AD and PD will be described in this review.

Genetic alterations

The mitochondrial ALDH2, a polymorphic enzyme responsible for the oxidation of acetaldehyde to acetate, encoded on chromosome 12, has been often described in Asian population with intolerance to alcohol who carries the inactive subunit, denoted ALDH2*2 (rs671) (Goede et al. 1992; Yoshida et al. 1984). When even one component of the tetramer of ALDH2*1 is replaced by ALDH2*2, its binding ability with NAD+, a coenzyme, is reduced due to a structural change, resulting in loss of the enzyme activity (Larson et al. 2005). Therefore, ALDH2*2 may act in a dominant-negative manner. Moreover, the reduced activity of the mitochondrial ALDH2 causes accumulation of acetaldehyde and 4-hydroxy-2-nonenal (HNE), which has been proposed to be potentially linked with AD (Ohita and Ohsawa 2006; Tanzi and Bertram 2001; Picklo et al. 2001; Shoeb et al. 2014). Nevertheless, both in a recent meta-analysis as well as in www.alzgene.org, the ALDH2 genotype GA/AA or the alleles A vs. G were not found to associate with increased AD risk [odds ratio (OR) = 1.35 95% confidence interval (CI) = 0.75–2.42; OR = 1.23 95% CI = 0.72–2.11, respectively]. In addition, a recent case-control study of Japanese population with or without high alcohol consumption AD could not find any significant association of the ALDH2*2 with AD risk (Komatsu et al. 2014). Similarly to the ALDH2, the mitochondrial ALDH1A1 gene on chromosome 10, was studied for its association with AD risk, but also did not result in significant association (www.alzgene.org, rs4417206; OR = 0.88 95% CI = 0.77–1.01).

To date, neither genome-wide association studies (GWAS) nor single genetic association studies (www.pdgene.org) have reported gene variation on any of the ALDH genes as risk for PD. Nevertheless, Fitzmaurice et al. have described that when combining genetic susceptibility with environmental factors, this increased the risk to develop PD (Fitzmaurice et al. 2014). In more details, the study investigated whether exposure to pesticides, in particularly such known to inhibit ALDH activity, is associated with PD in particularly when probands carry the cluster 2 (haplotype of rs737280, rs968529, rs16941667, rs16941669, rs9971942) of the ALDH2 gene. Indeed they could demonstrate that exposure of ALDH-inhibiting pesticides was associated with increased PD risk, and the genetic variation in ALDH2 exacerbated PD risk (Fitzmaurice et al. 2014). Nevertheless, since this is the first report of such association, it would be important to reproduce this finding in additional populations, as well as to understand the functional effects of these particular genetic polymorphisms.

Transcriptomic alterations

Several studies for the abundance of mRNA expression in fetal and adult human tissue of the various ALDHs have been reported. Stewart et al. reported higher expression of ALDH1 mRNA in liver, kidney, muscle and pancreas, while ALDH2 and ALDH5 mRNA expressed in additional regions as heart and brain also at fetal stages (Stewart et al. 1996). Nevertheless, recent studies using the whole genome transcriptomic studies reported by the Allen Brain Atlas (ABA http://www.brain-map.org; Fig. 1), as well as in the human protein atlas (http://www.proteinatlas.org) demonstrate the wide-spread expression of the different ALDH transcript in the CNS as well as in periphery. From these highly sensitive
methods, the expression of ALDH2, ALDH1A1, ALDH1L1, ALDH5A1, ALDH16A1 and ALDH18A1 mRNAs could be detected in adult human brain (Fig. 1).

To date, there are no reports concerning gene expression alterations for ALDH genes in the CNS of AD patients. Whereas, in peripheral blood samples, several studies report mRNA profiling of ALDH genes (Maes et al. 2009; Grünblatt et al. 2010; Molochnikov et al. 2012). In both reports, ALDH1A1 mRNA expression did not change in AD compared to controls [see GEO data base GDS2601]
and supplementary data in (Grünblatt et al. 2010; Molochnikov et al. 2012), as well as no change in expression profile for ALDH2 mRNA was observed (GEO GDS2601).

In PD, the first to report down-regulation of ALDH1 mRNA in SN of PD was by Galter and colleagues, who studied the expression alterations in post-mortem SN and ventral tegmental area of controls and PD using in situ hybridization technique (Galter et al. 2003). Following these findings, more specifically, the down-regulation of ALDH1A1 mRNA was found by our group using genome-wide transcriptomic assay in SN from PD patients compared to controls (Grünblatt et al. 2004). Following this report, many other groups could consistently confirm ALDH1A1 down-regulation in the SN of PD patients (Durrenberger et al. 2012; Grünblatt 2012; Kotraiah et al. 2013). In the last report by Kotraiah et al. the analysis was extended to the various splice variants of ALDH1A1, which all showed similar down-regulation (Kotraiah et al. 2013). Moreover, they demonstrated a new approach of screening ALDH1A1 activators and inhibitors, which could be a starting point for development of highly specific activator compounds that may restore the metabolism of ALDH1A1 in PD (Kotraiah et al. 2013). Decreased levels of ALDH1A1 have not been reported in the peripheral blood initially (Scherzer et al. 2007) but in two of our studies ALDH1A1 could be demonstrated as being part of a combination of four genes having potential diagnostic value to detect individuals at risk of developing PD (Grünblatt et al. 2010; Molochnikov et al. 2012).

**Protein alterations**

Similar to the transcriptomic patterns of the various ALDH mRNAs, the ALDH protein-expression patterns are widely spread in CNS and peripheral tissues (http://www.proteinatlas.org). Nevertheless, the mitochondrial ALDH2 enzyme was more intensively studied for its alterations in expression and activity in AD or PD brains (Picklo et al. 2001; Michel et al. 2010, 2014), while some reports indicate changes in ALDH1A1 (Werner et al. 2008; Mandel et al. 2007) and ALDH1L1 (Serrano-Pozo et al. 2013). Picklo et al. described a unique distribution of the mitochondrial ALDH2 expression in the gray matter in human cerebral cortex, limited to glia in cerebral cortex and hippocampus (Picklo et al. 2001). Additionally, the immunoreactivity was prominent in senile plaques, in which it was significantly higher in temporal cortex of AD patients compared to controls (Picklo et al. 2001). This was hypothesized as a reaction to the stress induced by senile plaques. In accordance, we could detect a significant increase in ALDH2 activity in the putamen of AD patients, while no difference was observed in frontal cortex compared to controls (Michel et al. 2010).

Recently, activated astrocytes were found to be differentially detected by the fact that these astrocytes express both ALDH1A1 and glial fibrillary acidic protein (GFAP), while resting astrocytes express only ALDH1A1 (Serrano-Pozo et al. 2013). Consequently, higher number of activated astrocytes was exhibited in temporal cortex of AD patients compared to control, while total astrocytes and microglia were similar in both groups (Serrano-Pozo et al. 2013).

In PD, similarly to the transcriptomic alterations of ALDH1A1 mRNA (see transcriptomic chapter), several studies in post-mortem human brain could detect a decrease in the expression of the cytosolic ALDH1A1 protein in PD patients compared to controls (Mandel et al. 2007; Werner et al. 2008). More specifically, in dopaminergic neurons (neuromelanin positive) of the substantia nigra pars compacta (SNpc) diminished immunohistochemical positive ALDH1 signals were demonstrated in PD patients compared to controls (Mandel et al. 2007). Similarly, proteomic analysis using 2D-PAGE and MALDI-ToF–MS of SN homogenates from PD and controls brains, revealed decreased expression of ALDH1 protein (Werner et al. 2008). In contrast to the...
cytosolic isoform, an increased mitochondrial ALDH2 activity was reported in the putamen of PD patients compared to controls, while no alteration was observed in frontal cortex (Michel et al. 2014). These different protein and activity profiles of the cytosolic and mitochondrial ALDH isoforms could be due to the fact that different brain regions were analyzed but also due to their different role in substrate metabolism. It is known that ALDH2 and ALDH1A1 may act on different substrates at different concentrations and they respond differently to different inhibitors (Ryzlak and Pietruszko 1987; Maring et al. 1985; Yoval-Sanchez and Rodriguez-Zavala 2012; Song et al. 2011; Budas et al. 2010).

**Cellular and animal models for AD and PD**

**Cellular models**

Cellular models provide an excellent platform to test hypotheses for mechanisms of action in pathological disorders such as in neurodegenerative disorders including AD and PD. In this manner, the hypothesis that the ALDH2*2 variant causes the neurons to have higher susceptibility to oxidative stress was tested. The effect of the ALDH2*2 mutant was tested in a rat pheochromocytoma model and susceptibility to oxidative stress was tested. The effect of the ALDH2*2 mutant causes the neurons to have higher susceptibility to oxidative stress, e.g. reduced accumulation of protein-HNE adducts and reduced expression of caspase-3, an apoptotic marker (Zhang et al. 2010). Therefore, the protective effect of overexpression of ALDH1A1 in SH-SY5Y cells via reduction of HNE was investigated (Zhang et al. 2010). It was demonstrated that overexpressing ALDH1, the main enzyme metabolizing HNE, protected against toxic events precipitated by oxidative stress, e.g. reduced accumulation of protein-HNE adducts and reduced expression of caspase-3, an apoptotic marker (Zhang et al. 2010), points to the importance of ALDH activity in cell survival. Similarly, Kong and Kotraiah demonstrated that overexpressing ALDH1A1 in PC12 cells increased HNE toxicity, while inhibiting ALDH1A1 by disulfiram reduced its toxicity (Kong and Kotraiah 2012). Moreover, they could show that this was linked to the fact that decrease or increased HNE-protein adducts were formed, respectively. Additionally, 6-methyl-2-(phenylazo)-3-pyridinol, an activator of ALDH1A1, demonstrated cytoprotective effects in PC12 cells (Kong and Kotraiah 2012). At the same line as Zhang and colleagues, Bai and Mei reported neuroprotective effects of overexpression of the mitochondrial ALDH2 against HNE neurotoxicity (Bai and Mei 2011). They could demonstrate that overexpression of ALDH2 in primary rat hippocampal neurons protected the neurons against HNE-induced neurite damage, decreased caspase-3 protein expression, decreased reactive oxygen species (ROS) and decreased the disruption of mitochondrial transmembrane potential (Bai and Mei 2011).

Recent data described the link between amyloid beta peptide (Aβ) toxicity and the mitochondrial ALDH2 activity.
activity (Solito et al. 2013). In human endothelial cell line treated with Aβ they could show loss of mitochondrial membrane potential, increased cytochrome c release and ROS accumulation, that were also associated with HNE accumulation and decrease in ALDH2 activity (Solito et al. 2013). All these data point to the angiogenesis processes also known to occur in AD. Moreover, after treatment with Alda-1, a selective ALDH2 activator, these detrimental effects were abolished, pointing to the importance of ALDH2 activity (Solito et al. 2013).

Animal models

The use of animal models to study effects of genetic variations or neurodegenerative processes on behavior, movements and neurophysiology is widely accepted as a platform investigating CNS alterations. As in the cellular models, several reports indicate the involvement of ALDH in neurodegeneration. Similarly to the experiment conducted in cell lines (Ohsawa et al. 2003), a mice model in which ALDH2*2 was introduced, showed in cerebral cortex primary culture increased cell death when HNE was introduced (Ohta and Ohsawa 2006). Furthermore, 18-months-old ALDH2-deficient mice showed signs of neurodegeneration such as atrophy of the hippocampus and already at 6 months a decreased spatial cognitive ability that was increased even further after 18 months (Ohta and Ohsawa 2006). In a following paper from this group, it was reported that the transgenic mice had decreased ability to detoxify HNE in their cortical neurons and accelerated accumulation of HNE in the brain (Ohsawa et al. 2008). This was also expressed in a shorter life span than control mice expressed with age-dependent neurodegeneration and hyperphosphorylation of tau (Ohsawa et al. 2008). Also the transgenic mice presented cognitive impairment that correlated with the degeneration, which accelerated by apolipoprotein E (APOE) knock-out (Ohsawa et al. 2008).

In the rat model for PD, in which 6-hydroxydopamine (6-OHDA) is injected to lesion the nigrostriatal dopaminergic neurons, it was shown to cause a significant reduction in striatal ALDH activity (Agid et al. 1973). Similarly, a year earlier, a reduction of ALDH activity in the striatum of cats after electrolytic lesion of nigrostriatal tract has been reported (Duncan et al. 1972). A very recent publication by Stott and Barker has looked in the 6-OHDA striatal lesion in mice in a time course of up to 12 days after lesion (Stott and Barker 2014). Since the lesion was done in the striatum they could observe a reduction in the number of dopaminergic neurons in the SN in a delayed manner after surgery. Concurrently to the loss of SNpc dopaminergic neurons a reduction in the level of ALDH1A1 expression was observed 6 days after lesion (Stott and Barker 2014). It seems that this alteration was partly due to the shift in the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern, in which ALDH1A1 was restricted to the expression pattern. In a mouse model in which ALDH1A1 was knocked out, the influence of ALDH1A1 on the function and maintenance of dopaminergic system was assessed (Anderson et al. 2011). The growth and development of SN dopaminergic neurons were not affected by the absence of ALDH1A1 in these mice, nor the protein expression of tyrosine hydroxylase, dopamine transporter or the vesicular monoamine transporter 2 were affected (Anderson et al. 2011). Nevertheless, extracellular dopamine levels were significantly increased in ALDH1A1 null mouse, the effect of amphetamine was altered as well as higher number of tyrosine hydroxylase expressing neurons in the SN were observed in comparison to wild-type mouse (Anderson et al. 2011). Moreover, a double knock-out mouse model of both cytosolic ALDH1A1 and mitochondrial ALDH2 exhibited age-dependent deficit in motor performance that was alleviated by intraperitoneal L-DOPA treatment (Wey et al. 2012). In addition, a significant dopaminergic neuronal loss in the SN was found together with reduction of dopamine and metabolites in the striatum of the double knock-outs (Wey et al. 2012). Besides, they found concomitant increase of HNE and DOPAL in this mouse model (Wey et al. 2012). Similarly, the ratio between DOPAL and dopamine was shown to increase significantly in the striatum of double knock-out mouse, pointing to the increase in neurotoxicity which was similar in the striatum of post-mortem PD patients (Goldstein et al. 2013).

Recently, in a senescence-accelerated P8 (SAMP8) mouse model of aging, the effect of 6 months voluntary wheel running was explored at the gene expression levels (Alvarez-Lopez et al. 2013). One of the genes differentially expressed due to exercise was ALDH1A2 (restored to control levels) in addition to the beneficial effects such as tremor signs abolishment and hippocampal revascularization (Alvarez-Lopez et al. 2013).

Indirectly, Meyer et al. could demonstrate that HNE metabolism diminishes with age in rat brain mitochondria, pointing to the possible decrease in the activity of ALDH2 with age (Meyer et al. 2004).

Conclusions

Aldehydes are increased in the SN of patients with PD. Reasons for this could be loss of gene expression of ALDH1A1 causing loss of enzyme protein and activity. Experimental in vitro and in vivo data point to the conclusion that loss of ALDH activity substantially increases neuronal toxicity in the nigrostriatal tract accompanied by...
significant increase in toxic aldehydes. In AD, ALDH2 seems to be decreased as shown by increased acetaldehyde and HNE concentrations, while meta-analyses as well as gene expression of ALDH genes do not give evidence for ALDH changes. In contrast, immunoreactivity in plaques as well as activity in putamen but not in frontal cortex is increased. These findings are at variance to PD and suggest different behavior of aldehyde induced pathology in these neurodegenerative disorders.

All available information is in line with the suggestion (1) to further elucidate the role of ALDHs in the pathology of neurodegenerative disorders and (2) to strengthen efforts to antagonize the loss of ALDH subtypes by developing respective therapeutic strategies.

Conflict of interest The authors declare neither competing financial interests regarding this review nor conflicts of interest in respect to the content of the article.

References


