CONTEMPORARY REVIEW

Aldehyde dehydrogenase 2 and arrhythmogenesis

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Cardiac arrhythmia is a common cardiovascular disease that leads to considerable economic burdens and significant global public health challenges. Despite the remarkable progress made in recent decades, antiarrhythmic therapy remains suboptimal. Aldehyde dehydrogenase 2 (ALDH2), a critical detoxifying enzyme, catalyzes toxic aldehydes and protects individuals from damage caused by oxidative stress. Accumulating evidence has demonstrated that ALDH2 activation has potential antiarrhythmic benefits. The correlation between ALDH2 deficiency and arrhythmogenesis has been widely recognized. In this review, we summarize recent research on the potential role of ALDH2 activation and antiarrhythmic protection, as well as the role played by the ALDH2*2 polymorphism (rs671) in promoting arrhythmic risk. Additionally, we discuss important new findings illustrating the use of ALDH2 activators, which may prove to be promising antiarrhythmic therapy agents.

KEYWORDS Aldehyde dehydrogenase 2; Aldehyde detoxification; Arrhythmia; Arrhythmic treatment; Mechanisms

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Introduction

Cardiovascular diseases (CVDs) are the principal causes of morbidity and mortality worldwide, resulting in tremendous global health and economic burdens.1 Notably, arrhythmias, defined as a group of abnormal cardiac rates and rhythms due to altered origins of heart activity and conduction disturbances, constitute a significant subgroup of CVDs.2,3 Almost all arrhythmias are pathologic and can be further classified according to heart rate as irregular (dysrhythmia), too fast (tachycardia), or too slow (bradycardia).2 During an arrhythmia, systemic hemodynamics are blocked, which potentially can cause serious damage to the body.3 Current treatment options for arrhythmias have been rapidly advanced. These treatments include antiarrhythmic drugs, radiofrequency catheter ablation, implantable cardioverter-defibrillators for ventricular tachycardia/ventricular fibrillation, and cardiac resynchronization therapy.3,4 However, these therapies have exhibited limited effectiveness and can cause adverse effects.5 Therefore, we need to continuously explore the mechanisms underlying arrhythmogenesis and potential corresponding antiarrhythmic therapeutic targets.

Aldehyde dehydrogenase 2 (ALDH2) is most commonly associated with alcohol metabolism and plays a prominent role in combating CVDs.6,7 The mechanisms and functions of ALDH2 in heart failure, atherosclerosis, ischemic cardiomyopathy, and alcoholic heart disease have been previously reported, indicating that ALDH2 is a cardioprotective enzyme.6–10 After phosphorylation, the increase in ALDH2 activity prevents arrhythmias via related mechanisms.11,12 In this review, we summarize the potential mechanisms underlying the beneficial effects of ALDH2 activation in attenuating arrhythmias, the increased risk of arrhythmogenesis in individuals with the inactive ALDH2 rs671 polymorphism, and possible future research directions with respect to ALDH2 activation in arrhythmia treatments.

ALDH2 and ALDH2 gene polymorphism

ALDH2

Nineteen types of aldehyde dehydrogenases (ALDHs) have been identified in the human body, and one particularly crucial enzyme, ALDH2, has attracted the most attention. The liver is widely considered to be the organ with the highest ALDH2 expression and the main site of ethanol metabolism. However, the liver is not the only organ with ALDH2 expression; ALDH2 is also expressed in the skin, stomach, lung, and kidney.13 As a tetrameric allosteric mitochondrial enzyme, ALDH2 is located in the mitochondrial matrix and exhibits 3 major enzymatic functions: dehydrogenase, reductase, and esterase activity. As a dehydrogenase, ALDH2 has critical functions in ethanol metabolism and aldehyde detoxification.14,15 In the process of alcohol detoxification, it catalyzes the acetaldehyde produced through ethanol oxidation into nontoxic acetic acid.15,16 ALDH2 not only metabolizes toxic acetaldehydes to acetate but also detoxifies endogenous aldehydes, including 4-hydroxynonenal (4-HNE) and malondialdehyde, thereby reducing toxic aldehyde damage to the heart.17 Aldehydes...
have been increasingly deemed a causal risk factor in burden-some CVDs. Under conditions of increased aldehyde production and impaired aldehyde detoxification, aldehyde stress is triggered, causing changes in cardiovascular structure and function. However, ALDH2 can modify this cascading pattern.  

**ALDH2 gene polymorphisms**

ALDH2 is located on human chromosome 12q24, has a total length of 44 kb, and contains 13 exons and 12 introns. ALDH2 has been confirmed to be expressed with >5000 polymorphisms, including 220 missense variants; however, notable phenotypic differences have been observed only for the rs671 polymorphism in the 12th exon. In this variant, the amino acid at position 487 is replaced in mature ALDH2 and at position 504 in precursor ALDH2 (Glu487Lys or Glu504Lys). This gene mutation eventually modifies the structure of ALDH2, resulting in impaired enzymatic activity. The change is partially due to impaired binding of nicotinamide adenine dinucleotide to the enzyme and dehydrogenation weakening. Therefore, the following ALDH2 variant genes expressing a mutation at this locus are formed as ALDH2*1/*1 normal homozygotes, ALDH2*1/*2 heterozygotes, and ALDH2*2/*2 mutant homozygotes. Interestingly, previous studies have shown significant differences in the distribution of ALDH2 rs671 alleles across populations. Compared with that in western populations, a much higher mutation frequency (approximately 40%) is found in Asian populations. Individuals carrying this gene polymorphism present with only minor ALDH2 activity, which leads to capillary dilation due to the accumulation of acetaldehyde. The clinical presentation of diminished ALDH2 activity is called Asian flush syndrome and consists of tachycardia, palpitations, and headaches. The details explaining the reasons why ALDH2 rs671 is common in Asian populations are not completely understood; however, this frequency may be related to long-term adaptation between Asian populations and local migratory events.

**ALDH2 and arrhythmias**

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is characterized by excessively rapid atrial activation, dyssynchronous atrial contraction, and an irregular ventricular rate. In addition to a remarkable symptom burden and poor quality of life, patients with AF have an elevated risk of stroke. Heavy alcohol consumption is associated with a high risk of AF. In a previous meta-analysis, moderate alcohol intake was found to increase slightly the risk of AF. Alcohol consumption has been positively correlated with AF. Hsu et al investigated the susceptibility of ALDH2*2 mice for developing AF after programmed electrical stimulation. A 4F lead was inserted into the esophagus of a mouse and connected to an isolation stimulator of atrial pacing. Approximately 10 days after ethanol exposure, approximately 70% of the ALDH2*2-carrying mice presented with AF compared to approximately 20% of the wild-type control mice, which demonstrated that ALDH2 deficiency created a predisposition to AF. Examining isolated rat hearts, Dudek et al found that alpha-lipoic acid (α-LA) attenuated oxidative stress and limited I/R-related arrhythmias through a mechanism that involved restoring ALDH2 activity in vitro.

**Potential functions and mechanisms of ALDH2 in arrhythmias**

**Aldehyde toxicity and oxidative stress**

When excessive generation of reactive oxygen species (ROS) overwhelms the ability of the endogenous antioxidative system, myocardial oxidative stress is triggered. From the mechanistic perspective, a high level of ROS release in mitochondria can prolong the action potential duration, inducing early afterdepolarization, and trigger arrhythmias in cardiomyocytes. Similarly, excess ROS are known to be related to AF because of their influence on major ionic effects, electrical coupling of myocytes, and abnormal molecular mechanisms.
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(+) = facilitate; (-) = inhibit; 4-HNE = 4-hydroxynonenal; AF = atrial fibrillation; ALDH2 = aldehyde dehydrogenase 2; Ang II = angiotensin II; CaMKII = calcium/calmodulin-dependent protein kinase II; HMC-1 = human mastocytoma cell-1; MC = mast cell; NE = norepinephrine; RAS = renin–angiotensin system; SCN5A = sodium voltage-gated channel alpha subunit 5; TGF-β1 = transforming growth factor-β1.
Aldehydes can be subdivided into exogenous and endogenous compounds, and humans are frequently exposed to both types. Exogenous aldehydes are ubiquitous in the environment, being derived from vehicle exhaust fumes, smoke, and raw materials used for industrial production. More importantly, endogenous aldehydes are involved in the body’s physiological catabolism, lipid metabolism, and carbohydrate metabolism. Among these endogenous aldehydes, 4-HNE and malondialdehyde, reactive endogenous aldehydes, have attracted considerable attention with respect to CVDs because of their toxicity and high content in the human body. Specifically, reactive aldehydes can modify crucial enzymes and genes by forming covalent compounds, resulting in the accumulation of damaged proteins in cells. Reactive aldehydes also inhibit electron transport chain, damaging the function of mitochondria and reducing the ability to repair damaged macromolecules in cells. Interestingly, reactive aldehydes in turn trigger higher ROS levels. For example, 4-HNE is produced by the lipid peroxidation reaction of mitochondria and the plasma membrane; specifically, it is generated through the reaction of ROS with polyunsaturated fatty acids in biomembranes and induce oxidative stress. Notably, 4-HNE cannot be considered as a sole pivotal sign of cardiac oxidative stress because it participates in the progression of CVDs because of their toxicity and high content in the human body. Specifically, reactive aldehydes can modify crucial enzymes and genes by forming covalent compounds, resulting in the accumulation of damaged proteins in cells. Reactive aldehydes also inhibit electron transport chain, damaging the function of mitochondria and reducing the ability to repair damaged macromolecules in cells. Interestingly, reactive aldehydes in turn trigger higher ROS levels. For example, 4-HNE is produced by the lipid peroxidation reaction of mitochondria and the plasma membrane; specifically, it is generated through the reaction of ROS with polyunsaturated fatty acids in biomembranes and induce oxidative stress. Notably, 4-HNE cannot be considered as a sole pivotal sign of cardiac oxidative stress because it participates in the progression of CVDs, including arrhythmias, and exerts different influences on a wide number of pathologies. Several studies have indicated that aldehydes may contribute to harmful arrhythmias. For example, in a study of adult rats, Bhatnagar speculated that 4-HNE induced a severe decline in myocardial intracellular ATP concentration [ATP], and caused electrophysiological changes involved in arrhythmia development. In addition, Horakova et al found that acetaldehyde significantly inhibited inward rectifier potassium currents (IK1) in rat ventricular myocytes, which were the cellular basis of triggered AF.

Figure 1 Function and mechanism of aldehyde dehydrogenase 2 (ALDH2) in arrhythmias. 4-HNE = 4-hydroxynonenal; Alda-1 = ALDH2 activator; Ang-II = angiotensin II; AT1 = angiotensin II receptor type 1; CaMKII = calcium/calmodulin-dependent protein kinase II; NE = norepinephrine; PKCe = protein kinase Ce; RA/RAR = retinoic acid/retinoic acid receptor; RAS = renin–angiotensin system; ROS = reactive oxygen species; RyR2 = ryanodine receptor 2; S1P = sphingosine-1-phosphate; S1P/R = sphingosine-1-phosphate receptor subtype 1; SCNA5 = sodium voltage-gated channel alpha subunit 5; SR = sarcoplasmic reticulum; TGF-β = transforming growth factor-β.

ALDH2 polymorphisms and alcohol consumption

The most common single-point mutation in human ALDH2 [Glu504Lys (rs671) ALDH2] is expressed in 2 allelic subtypes and 3 possible genotypes. ALDH2*1/*2 and ALDH2*2/*2 both are ALDH2-deficient variants. A recent retrospective, single-center study by a Japanese team reported that ALDH2*1/*2 itself was irrelevant to AF but that ALDH2*1/*2 carriers with habitual alcohol consumption showed a higher incidence of AF due to slow alcohol metabolism. In both ALDH2 wild-type and ALDH2*1/*2 allele carriers, sustained alcohol consumption led to an increase in the odds ratio (OR) of AF risk. In contrast, the incidence of AF among ALDH2*2/*2 carriers was low because of the negligible activity of ALDH2 in patients who did not regularly consume alcohol. This finding contradicts previously articulated conclusions suggesting that high ALDH2 activity confers a protective effect on the myocardium.
Hsu et al. identified the underlying mechanism of ALDH2-deficient variant–alcohol interactions in AF. In vivo experiments indicated that ALDH2*2 knock-in mice expressed higher levels of transforming growth factor-β1 (TGF-β1) than wild-type mice after chronic ethanol consumption. This increase in TGF-β1 expression resulted in a shortened atrial refractory period in atrial fibrosis and severe atrial remodeling, greatly promoting the development of AF. However, expression of the ALDH2*2 allele led to low ALDH2 activity, causing low aldehyde detoxification efficiency and higher accumulation of 4-HNE and ROS compared to wild-type carriers, which further aggravated oxidative stress and substrate remodeling in the atria of variant carriers. Another study of 182 patients with only AF and 914 controls (age < 60 years and without hypertension) reported that both ALDH2 and ADH1B single nucleotide polymorphisms were associated with an increased risk of AF (P = 0.013, OR 0.7; and P = .0007, OR 1.4, respectively). This study demonstrated a relationship between alcohol-metabolizing enzyme gene polymorphisms and the risk of AF. Thus, abstinence from alcohol may reduce AF attacks in people who are ALDH2-deficient. Recent studies have only reported conclusions on ALDH2 gene polymorphisms and AF prevalence. Therefore, future studies should be based on a better design to verify the correlation between the ALDH2 rs671 gene polymorphism and different arrhythmias, as well as ventricular and other atrial arrhythmias, and clarify the underlying mechanisms and their correlations. Additionally, further randomized controlled trials with adequate sample sizes would greatly reinforce the reliability and efficacy of the findings.

Mast cell degranulation and renin–angiotensin–aldosterone system activation

Because toxic aldehydes stimulate cardiac mast cells (MCs) to degranulate and release renin, the renin–angiotensin–aldosterone system is activated inappropriately, causing excess norepinephrine release and ultimately inducing arrhythmias. Therefore, the removal of toxic aldehydes plays a critical role in reducing oxidative stress and increasing neurotransmitter release in response to reperfusion arrhythmia. Koda et al. found that when ischemic preconditioning (2 × 5-minute I/R cycles) was performed before ischemia (20 minutes)/reperfusion (30 minutes), the adenosine released by various cells activated A2A/A3-receptors on the MC surface. Subsequently, the activation/translocation of protein kinase C (PKCε), which is translocated from the cytosol into the mitochondrial membrane and phosphorylates ALDH2 at 3 sites (T185E, S279E, and T412E), regulates and increases ALDH2 catalytic activity. Hence, PKCε-mediated ALDH2 activation confers cardioprotection against the renin–angiotensin system, which effectively prevents toxic aldehyde degranulation and renin–angiotensin system activation, reduces the formation of angiotensin II, and ultimately prevents reperfusion arrhythmias. Similar follow-up studies have suggested that in the isolated heart of guinea pigs, activation of Gα-coupled sphingosine-1-phosphate receptors through a PKCε-dependent ALDH2 phosphorylation in MCs has been proved beneficial against cardiac MC degranulation and renin release, ultimately conferring antiarrhythmic effects.

Ca2+ handling

Ca2+ handling is considered to play a critical role in the initiation and maintenance of arrhythmic activity by regulating ROS levels in cardiomyocyte mitochondria. During an increase in physiological variations of workload, myocytes exhibit an increased rate and magnitude of cytoplasmic Ca2+ transients, resulting in increased energy demand and expenditure in atrial tissue. This process accelerates the uptake of Ca2+ by mitochondria, but the Ca2+ excretion rate is slow; subsequently, Ca2+ accumulates. The accumulation of Ca2+ promotes the generation of reduced forms of nicotinamide adenine dinucleotide and flavin adenine dinucleotide as well as electron slippage from the electron transport chain, which increases the production of myocardial superoxide (O2·−). In this case, the rate of mitochondrial ROS generation greatly exceeds cellular ROS scavenging capacity, resulting in oxidative stress. Oxidative stress seems to facilitate afterdepolarization and cause arrhythmias. It is involved in potential ROS-induced mechanisms that increase intracellular Ca2+ levels. For example, sarco-/endoplasmic reticulum Ca2+-ATPase and other potential mechanisms are impaired, affecting rymodine receptor function via calcium/calmodulin-dependent protein kinase II (CaMII) activation and sarcoplasmic reticulum leakage. The antioxidant properties of ALDH2 exert a broad spectrum of effects on Ca2+ regulation, and many of these effects are associated with antiarrhythmic activity. For example, the activation of ALDH2 by Alda-1 is a key regulatory mechanism in Ca2+ signaling because ALDH2 can act upstream of Ca2+-channels. Subsequently, detoxification of O2·− and O2-induced reactive aldehydes can increase the sensitivity of myofilaments, reduce CaMII activation, restore calcium signaling, and improve cardiac function.

ALDH2 activators

Given that normal ALDH2 activation plays a protective role in the heart, the therapeutic potential of ALDH2 has attracted great attention. A genetic association study in Japan showed that Asian flush syndrome was a reliable clinical indicator of the ALDH2*2 genotype. Therefore, ALDH2-targeted therapies are expected to be combined with traditional antiarrhythmic treatment in the future, especially in individuals who lack the ALDH2 enzyme. In recent years, several small-molecule activators have been developed to target increasing activity of mitochondrial ALDH2, providing novel options for individualized antiarrhythmic therapy. Alda-1, the most representative ALDH2 activator, has been investigated in many animal studies; however, it lacks clinical applications. Alda-1 reduces mitochondrial ROS production, detoxifies reactive aldehydes, normalizes calcium
cycling in the heart, and inhibits cardiac fibroblast proliferation and collagen synthesis.\textsuperscript{51,57} Emerging evidence suggests that Alda-1 reduces AF inducibility by attenuating TGF-β1 expression and subsequent atrial fibrosis.\textsuperscript{53} It effectively mediates the cell cycle, eliminates mitochondrial ROS, and significantly alleviates myocardial fibrosis induced by isoproterenol.\textsuperscript{54} Interestingly, Alda-1 directly binds near the exit of an aldehyde-binding site, which is considered the inhibitor.\textsuperscript{55} Kinetic experiments illustrated that Alda-1 played 2 roles in regulating ALDH activity: it was an activator at high concentrations and a negative regulator at low concentrations.\textsuperscript{56} Attention needs to be directed to the different concentrations of Alda-1 to predict its potential ALDH2-activating effects \textit{in vivo}.

\(\alpha\)-LA is another ALDH2 activator. Mounting evidence suggests that \(\alpha\)-LA can restore impaired ALDH2 reductase activity by reducing disulfide bonds at active sites.\textsuperscript{57} Recent research by Li et al\textsuperscript{58} revealed that \(\alpha\)-LA can separate disulfide bonds from a redox-sensitive group, thus preventing the deactivation of ALDH2. Additionally, \(\alpha\)-LA can activate FUN14 domain-containing 1 signaling and treat heart failure induced by pressure overload in an ALDH2-dependent manner.\textsuperscript{59} \textit{In vitro}, the antiarrhythmic effect of \(\alpha\)-LA is mediated by the opening of K\textsubscript{ATP} channels, which reduces the occurrence of postperfusion arrhythmias.\textsuperscript{60} Moreover, exogenous lipoic acid may play a potential role in treating acute arrhythmias, especially attenuated arrhythmias (extrasystoles and atrioventricular blocks) induced by ethanol. Bilska-Wilkosz et al\textsuperscript{61} indicated that lipoic acid inhibited the activity of ALDH by forming mixed disulfides. Further research is required to confirm S-thiolation.

Recently, the application for Alda-1 in antiarrhythmic therapy have been constantly explored. A study revealed that the cardiomyocyte Nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, a mature signaling pathway, activates a series of arrhythmic events, including frequent ectopic activity and AF susceptibility.\textsuperscript{60,61} Studying cardiomyocytes treated with high glucose, Cao et al\textsuperscript{62} found that Alda-1 activated ALDH2, which weakened the activation signal of the NLRP3 inflammasome, thereby inhibiting NLRP3-induced inflammation and reducing cardiotoxicity induced by high glucose levels. The influence of immune inflammation is a complex research area for which further mechanistic studies are required.

**Conclusion and perspectives**

ALDH2 has been shown to protect the body from toxic aldehydes, and recent evidence suggests ALDH2 plays an important role in arrhythmic models and patients (Table 1). This review discussed a possible beneficial effect of ALDH2 activation in arrhythmias, especially arrhythmias involved in AF and I/R arrhythmia. This study provided insight into a novel therapeutic antiarrhythmic target. Multiple complex underlying mechanisms, such as oxidative stress, sympathetic activity, renin–angiotensin–aldosterone system hyperactivity, and high levels of cardiomyocyte Ca\textsuperscript{2+} seem to be involved (Figure 1). ALDH2 gene polymorphisms are prevalent in East Asians individuals, affecting almost 40% of the East Asian population. The ALDH2*2 variant predisposes individuals to AF. Understanding the effect of the ALDH2*2 variant on AF will shed light on possible unknown arrhythmic mechanisms. However, the roles played by ALDH2*2 in other types of arrhythmias and populations remain unclear. Clearly, modulation of ALDH2 activity is an attractive and novel antiarrhythmic treatment. The limitation of recent research relates to the lack of ALDH2 activator data from evidence-based clinical practice from which to determine ALDH2 activator safety and efficacy in antiarrhythmic therapy. Additionally, low ALDH2 activity may exert severe proarrhythmic effects. The novel mechanisms of ALDH2 activation in antiarrhythmic targeted therapy need be investigated in future research.

**References**