Alcohol Dehydrogenase: biological function and evolution in metabolism of alcohols

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Introduction

Alcohol dehydrogenase (ADH) is the major enzyme responsible for the oxidation of ethanol but is also a broad substrate-specific enzyme and can oxidize many other substrates.

$$CH_3CH_2OH + NAD^+ \xrightarrow{ADH} CH_3CHO + NADH + H^+$$

Figure 1: First step of the alcohol metabolism. Ethanol catalyzed to acetaldehyde (Cederbaum, 2012).

Objectives

- Characterize the 3 different types of alcohol dehydrogenase and their subtypes.
- Analyze the biologic evolution of the 3 types of alcohol dehydrogenase.
- Identify the genes which express the alcohol dehydrogenases in humans.
- Understand the effects of polymorphic variants in ethanol metabolism and alleged protection against alcoholism.

Classification and evolution

Type II

This enzyme can be found mainly in insects and it is the unique enzyme involved in their ethanol metabolism. There is a link between the emergence of type II ADH and the emergence of angiosperms so it is suggested that it arose as an adaptive mechanism against ethanol exposure to be able to exploit sugars when yeasts started to ferment fruits.

Type III

Primarily identified in microorganisms but has also been found in some vertebrates such as humans. It is characterized by being iron dependent. Evolutionary studies performed suggest that these enzymes did not emerge to metabolize ethanol and their rise precedes ethanol exposure.

Type I

Accounts for most of the ethanol metabolism in vertebrates. These are distributed depending on the phylum.
There is controversy whether these enzymes developed as an adaptive mechanism to counter the fermentation of sugars by yeasts or emerged incidentally.

Genetics of human ADH

Humans have seven different genes that encode for the five classes of type I ADH. ADH1 (with 3 different isoforms), ADH4, ADH5, ADH6 and ADH7 which participate in general detoxification of variety biogenic and dietary alcohols and aldehydes. There has also been found a type III ADH but it has a negligible function in the metabolism of alcohols in humans.

Figure 2: Relative sizes and positions of the seven human alcohol dehydrogenase (ADH) genes on the long arm of chromosome 4 (Edenberg, 2007)

Human possess three different isoforms or alleles for the class I ADH. They are ADH1A, ADH1B and ADH1C. They share most of the sequence but vary among the residues lining the substrate-binding pocket. This causes variances in catalytic efficiency and propensity for a substrate.

There are also single nucleotide polymorphisms (SNPs) in the ADH1B and ADH1C which have caused variants in these genes and effects of them when metabolizing ethanol.

Effects of variants in ethanol metabolism and role in protection against alcoholism

Humans have three variants for ADH1B and two variants for ADH1C. They all vary in the Vmax which is what determines the velocity at which the ethanol is metabolized.

Table 1: Kinetic properties of human alcohol dehydrogenases (Hurley et al, 2002).

Gen (Enzyme)	Km (mM)	V_{max} (min^{-1})
ADH1A	4	20
ADH1B*1	0.05	4
ADH1B*2	0.9	350
ADH1B*3	40	300
ADH1C*1	1	90
ADH1C*2	0.6	40

Which ADH a person carries influences his or her level of alcohol consumption and risk of becoming alcoholic.

Acetaldehyde is a toxic intermediate between ethanol and acetate which causes ailment. It is thought that having a higher rate of oxidation of ethanol, produces a higher amount of acetaldehyde which causes the aversive reaction and protects the individual from continued drinking.
Furthermore, it has been found that the alcohol drinking differs particularly between ethnic groups because there are fewer amounts of alcoholic cases in Asian population than white population.

Table 2: Frequency of ADH Alleles in Racial Populations (Cederbaum, 2012).

	ADH1B*1	ADH1B*2	ADH1B*3	ADH1C*1	ADH1C*2
White-American	>95%	<5%	<5%	50%	50%
White-European	85%	15%	<5%	60%	40%
Japanese	15%	85%	<5%	95%	5%
Black-American	85%	<5%	15%	85%	15%

Conclusions

- Three types of alcohol dehydrogenase exist and are in charge of the ethanol oxidation in organisms and can have other functions.
- In humans, polymorphisms have occurred in class I ADH which has promoted different effects in the metabolism of alcohol. Also the combination of different alleles can have an effect in metabolism of alcohol.
- Nowadays, there are enzymes that remain uncharacterized and alleles that require further studies to fully understand their effects in metabolism of ethanol.

References

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