Main ethanol metabolizing alcohol dehydrogenases (ADH I and ADH IV): biochemical functions and the physiological manifestation

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Abstract The range of the biochemical reactions which can be catalyzed by ADH I and ADH IV is extremely wide. The most characterized functions of these enzymes are protection against excess endogenous acetaldehyde, products of lipid peroxidation, exogenous alcohols and some xenobiotics. It was found also that ADH I and ADH IV are important members of the enzyme system synthesizing retinoic acid (especially during embryogenesis). They can oxidize some steroids and participate in bioamine and prostaglandin metabolism but so far the extent of their contribution to the latter processes is under discussion. Recent data suggest a correlation between the activity of ADH I in some organs and fine physiological processes including behavior regulation and craving for alcohol in albino rats.

Key words: Alcohol dehydrogenase; Retinol; Steroid; Craving for ethanol; Acetaldehyde; Lipid peroxidation; Xenobiotic

1. Introduction

There are six known classes of mammalian alcohol dehydrogenases (ADH), but only ADH I and ADH IV can be characterized as principal participants of ethanol metabolism. It is not surprising that these enzymes are extremely well studied because the investigation in this area was inspired by the problem of alcoholism. However, many questions regarding ADH I and ADH IV functions still remain: Are ethanol metabolizing enzymes the protectors or provocators of alcoholism? What is the overall range of alcohols and xenobiotics dealing with ADH I and ADH IV? Is the ethanol metabolizing role of these enzymes their main function? Last decade brought a lot of new data in this area.

2. Protective functions

The array of protective functions of ADH I and ADH IV is extremely wide. Ethanol oxidation to acetaldehyde catalyzed by ADH I and ADH IV in vivo is reversible. Moreover, in the absence of exogenous ethanol the equilibrium is shifted towards the reduction of endogenous acetaldehyde. Thus ADH I together with acetaldehyde dehydrogenase play an important role in controlling the level of this toxic metabolite. As shown recently, ADH I can also catalyze the dismutation of acetaldehyde into ethanol and acetate [1]. Along with acetaldehyde, ADH I can detoxicate some other endogenous compounds which may be harmful, e.g. lipid peroxidation products, such as 4-hydroxyalcenals [2].

Under conditions of high ethanol consumption, the role of ADH I and ADH IV is particularly important. The first barrier on the usual way of exogenous ethanol is formed by ADH IV in stomach and intestine mucosa [3]. The second barrier, which is the principal one, is formed in liver. There are two main metabolic pathways that are involved in the oxidation of exogenous ethanol in liver: ADH I-dependent and cytochrome-dependent pathways. In non-alcoholized animals, these pathways have about equal importance while after alcoholization of an animal the chronic metabolic deficit of NAD^+ is created and the role of cytochrome system increases.

ADH I takes part in the metabolic degradation of many xenobiotics, including numerous aliphatic and cyclic alcohols and some other toxic compounds widely distributed in a contemporary human environment. For example, ADH I is able to oxidize 1,3-butadiene derivatives, which are toxic and cancerogenic products detected in cigarette smoke, gasoline and used in synthetic rubber manufacture [4].

Considering protective function of ADH I and/or ADH IV, we have to take into account their very wide distribution in the organism. Besides liver (90% of total ADH I), considerable amounts are in skin, stomach and intestine mucosa. A significant pool of these enzymes was found in several endocrine organs and blood vessels [5–9].

3. Participation in retinol and steroid metabolism

All data described above characterize the role of ADH I and ADH IV in protecting the organism from a wide range of compounds. However, data have accumulated describing the involvement of ADH I and ADH IV in many reactions which are not directly related to the protective functions and associated with other major biochemical and physiological processes.

A special role of ADH I and ADH IV in the synthesis of retinoic acid and their derivatives was discovered. Retinoic acid is presently considered to be a hormonal factor, which is involved not only in vision pathway but also in morphogenesis of skin, digestive and respiratory systems, and in certain processes of immune, nervous and hematopoethic systems. Retinoids were found to be useful for the treatment of

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Abbreviations: ADH, alcohol dehydrogenase; SDR, short-chain dehydrogenases/reductases

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certain skin diseases, diabetes and as additional medication for cancer treatment. All this information inspired a search for key enzymes of retinol oxidation, which revealed that both ADH I and ADH IV can effectively catalyze these reactions, ADH IV being more active [10,11]. Interestingly, these enzymes are able to oxidize only free retinol, which is not linked to specific protein carriers, while bound retinol is oxidized by a recently described large family of short-chain dehydrogenases/reductases (SDR) [11]. It was shown recently that during embryogenesis of the adrenal gland, ADH I and ADH IV play a specific role and their concentration is high on certain stages. Of note, the adrenal gland was shown to be one of the main endocrine centers where the intensive synthesis of retinoic acid takes place [12]. Skin epithelial cells are also characterized by the ADH IV- and/or ADH I-dependent synthesis of retinoic acid [7,13]. Therefore, the existence of SDR does not depreciate the independent role of ADH I and ADH IV in retinol metabolism. Both families have their specificity.

To date, a lot of data which demonstrate the ability of ADH I to oxidize hydroxysteroids have accumulated [14–17]. Of note, only the γ-isoenzyme of human ADH I is active in steroid transformation [17]. However, since SDP (mentioned above as alternative enzymes for retinoic acid synthesis) can also catalyze many reactions of hormonal steroid oxidation, it is not clear whether ADH I or ADH IV plays the key role in these processes. SDP seem to be more specific in oxidation of certain hormonal steroids [18–21].

4. Possible participation in neuromediator metabolism

There are certain indications for the ADH I and ADH IV participation in the metabolism of several neuromediators and prostaglandins. ADH I effectively catalyzes in vitro the transformations of several alcohols and aldehydes which are involved in the metabolism of dopamine: 3,4-dihydroxyphenylethanol, 4-hydroxy-3-methoxyphenylethanol and corresponding aldehydes (ADH II and ADH III do not have such an activity) [22]. ADH I also oxidizes some glycols, which take part in norepinephrine metabolism, but in this case ADH I is less active by comparison with ADH II [23]. ADH I can also catalyze the oxidation of serotonin catabolite, 5-hydroxytryptophol [24]. These data are potentially interesting concerning the suggestion described below about ADH I involvement in the regulation of craving for ethanol. However, it is not clear yet how important these reactions are in catecholamine and serotonin metabolism in vivo: they can represent some collateral metabolic pathways.

5. Putative role in craving for ethanol

There are certain indications for indirect involvement of ADH I and ADH IV activity in the highest physiological processes, behavior regulation and craving for ethanol in particular. ADH I is not found in brain, so the only way it can affect the central nervous system is the penetration of the products of ADH I activity through the blood-brain barrier. However, some contradictions exist considering the behavioral activity of ADH I main product, acetaldehyde. A lot of data obtained on different human races and populations show that fast accumulation of acetaldehyde forced by the particularly active ADH I isozymes and under reduced activity of acetaldehyde dehydrogenase cause aversive behavioral reactions to ethanol. Potent ADH I inhibitor cimetidine (well known antiulcer drug) provokes ethanol consumption [25]. Therefore high ADH I activity seems to be a defensive factor against alcoholism development. Surprisingly, not all ADH I inhibitors increase the craving to alcohol. On the contrary, some of them (e.g. metronidazole) reduce alcohol motivation [26]. As this latter inhibitor could affect the craving for alcohol through some other mechanisms, autoantibodies to ADH I were used to reveal ADH I role [27–29]. The autoantibodies were produced in albino rats, immunized by horse liver ADH I. The autoantibodies decreased the ADH I activity in liver and blood vessels, but a particularly significant decrease of enzyme activity was observed in adrenal medulla. A reliable long-term decrease of rat craving for ethanol was demonstrated. The effect was quite specific, since similar decrease in alcohol motivation was demonstrated in rats after the administration of antibodies to an ADH epitope (S_{265}FFVIGRLDTMV$_{276}$) or after active immunization using conjugates of this peptide with an antigen carrier. This phenomenon may have two explanations: the decrease in ADH I activity reduces the acetaldehyde/ethanol ratio or affects other reactions involving ADH I. The first explanation is not very likely since acetaldehyde is well known to be a factor suppressing the craving for ethanol, thus decreasing its concentration can even have an opposite effect. The second explanation is in accordance with the ADH I role in the synthesis of retinoic acid, hormone steroids and some neuromediators. Interestingly, one of the most characterized ADH I activities, the oxidation of retinol, is located in adrenal glands, where the most significant ADH I suppression in experiments with autoantibodies was observed. Changes in neuromediator and steroid concentration associated with ADH I are also possible. However, for the moment all these suggestions are extremely speculative because of insufficient data, and the most illuminating result would be revealing the situation when ADH I acts as provocator of craving for ethanol.

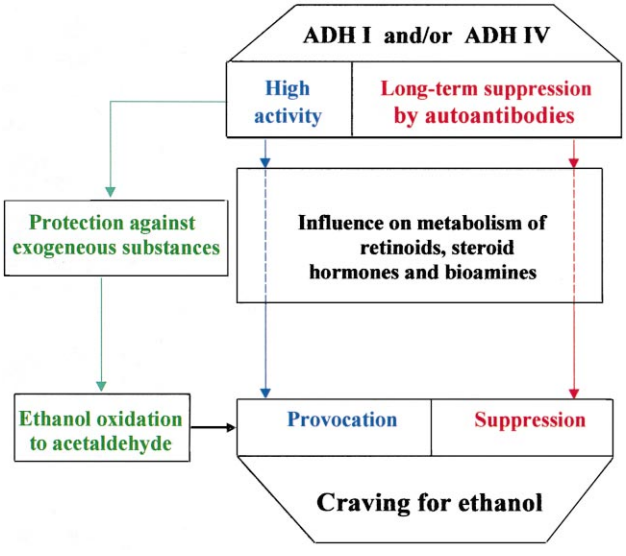

Fig. 1. Different ways of influence of ADH I and/or ADH IV activity on craving for ethanol.

6. Conclusion and perspectives

To summarize, there are several different manifestations of major biochemical and physiological functions of ADH I and ADH IV (Fig. 1): (1) defence against exogenous alcohols and some xenobiotics, detoxication of endogenous acetaldehyde and lipid peroxidation, (2) role in retinol oxidation, particularly during embryogenesis of adrenal glands and skin, (3) contribution to hydroxysteroids oxidation, (4) possible involvement in neuromediator metabolism, (5) effects on craving for ethanol. The phenomenon of long-term suppression of craving for ethanol after induction of autoantibodies to ADH I seems to be particularly interesting for the study of the molecular mechanism of alcoholism. Further investigation of the distribution of functions between short-chain dehydrogenases/reductases, ADH I and ADH IV is promising for better understanding their role in hormonal and neuromediator regulation.

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