Life Sciences 168 (2017) 58–64

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Chronic alcohol administration affects purine nucleotide catabolism in vivo

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ARTICLE INFO

Article history:
Received 17 August 2016
Received in revised form 25 October 2016
Accepted 9 November 2016
Available online 10 November 2016

Keywords:
Alcohol dependence
Purine nucleotide
Uric acid
Metabolism

ABSTRACT

Aims: To investigate the relationship between chronic alcohol administration and purine nucleotide metabolism in vivo.
Main methods: Rat models of alcohol dependence and withdrawal were used. The concentrations of uric acid (UAC), urea nitrogen (UREA), creatinine (CREA), and beta-2-microglobulin (β2-M) and creatinine clearance rate (CCR) in plasma were measured. The PLC method was used to detect the absolute content of purine nucleotides in different tissues. Enzymatic activities of adenosine deaminase (ADA), xanthine oxidase (XO), ribose 5-phosphate pyrophosphokinase (RPPPK), glutamine phosphoribosylpyrophosphate amidotransferase (GPRPPAT), hypoxanthine-guanine phosphate ribose transferase (HGPRT), and adenine phosphoribosyltransferase (APRT) in the tissues were analyzed. Real-time PCR was used to determine the relative level of ADA and XO.
Key findings: The renal function of rats with alcohol dependence was normal. Further, the content of purine nucleotides (GMP, AMP, GTP, and ATP) in tissues of the rats was decreased, which indicated that the increased uric acid should be derived from the decomposition of nucleotides in vivo. The activity of XO and ADA increased, and their mRNA expression was enhanced in the alcohol dependence group, but there was no significant difference in the activity of RPPPK and GPRPPAT in the liver, small intestine, and muscle; furthermore, no significant difference in the activity of HGPRT and APRT was observed in the brain.
Significance: These results indicate that chronic alcohol administration might enhance the catabolism of purine nucleotides in tissues by inducing gene expression of ADA and XO, leading to elevation of plasma uric acid levels.

1. Introduction

Ethanol (commonly known as alcohol) is an addictive or dependent substance, and chronic alcohol exposure induces adaptive changes in normal neurocircuitry that lead to dependence [1–3]. At present, alcohol use disorders (AUDs) rank among the leading causes of decrements in disability-adjusted life years and rank third in preventable causes of death in the United States [4,5]. Alcohol-related disorders continue to be a major unmet medical need because appropriate treatment options or effective prevention are still lacking [6]. Therefore, studies of its effects on tissues could be helpful to enhance curative effects. Recent studies have indicated that the molecular mechanism of alcohol function involves adaptations in a variety of ion channels, neurotransmitters, neuropeptides, and intracellular signaling systems [7–10], but there are few reports on the relationship between the effect of alcohol and the metabolism of nucleotides.

An investigation demonstrated that the concentrations of plasma uric acid are increased in frequent drinkers [11]. Some laboratories have reported that alcohol probably metabolizes into lactic acid, which could affect the excretion of uric acid and accelerate the formation of uric acid [12]. Uric acid (UAC) is the final metabolite of nucleotides in humans and higher primates. Changes in the level of UAC may directly reflect the catabolic status of purine nucleotides. We speculated that alcohol dependence may accelerate the production of uric acid by promoting the metabolism of nucleotides.

In this study, the rat model of alcohol dependence and withdrawal was established. Chronic alcohol intake induces changes in multiple system functioning that clinically manifest as dependence symptoms, cirrhosis, gastrointestinal disease, and muscular tremble [13–16]. Thus, four representative research objects (brain, liver, small intestine, and muscle) were selected. Quantification of purine nucleotide and key enzymes of metabolism in these tissues may be an efficient method to study the effect of alcohol on the body function.

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http://dx.doi.org/10.1016/j.lfs.2016.11.008
0024-3205/

Table 1
Total ethanol withdrawal score at the different time of ethanol withdrawal (x ± s).

Withdrawal time	Control group	Alcohol dependence group		
		30 d	60 d	90 d
2 h	1.43 ± 0.47	4.56 ± 1.98*	10.57 ± 3.10*	16.28 ± 2.22*
4 h	1.62 ± 0.78	6.25 ± 2.57*	13.27 ± 2.71*	15.87 ± 3.15*
6 h	1.36 ± 0.50	7.60 ± 2.35*	15.28 ± 1.91*	17.94 ± 2.42*

* $P < 0.01$ vs. control group.

2. Materials and methods

2.1. Animal models

Sixty healthy adult Sprague Dawley male rats weighing 200 ± 20 g were provided by the Experimental Animal Center of Hebei Province. All animal protocols and practices were reviewed and approved in advance by the Hebei Medical University Institutional Animal Welfare. The animal model of alcohol dependence was established according to

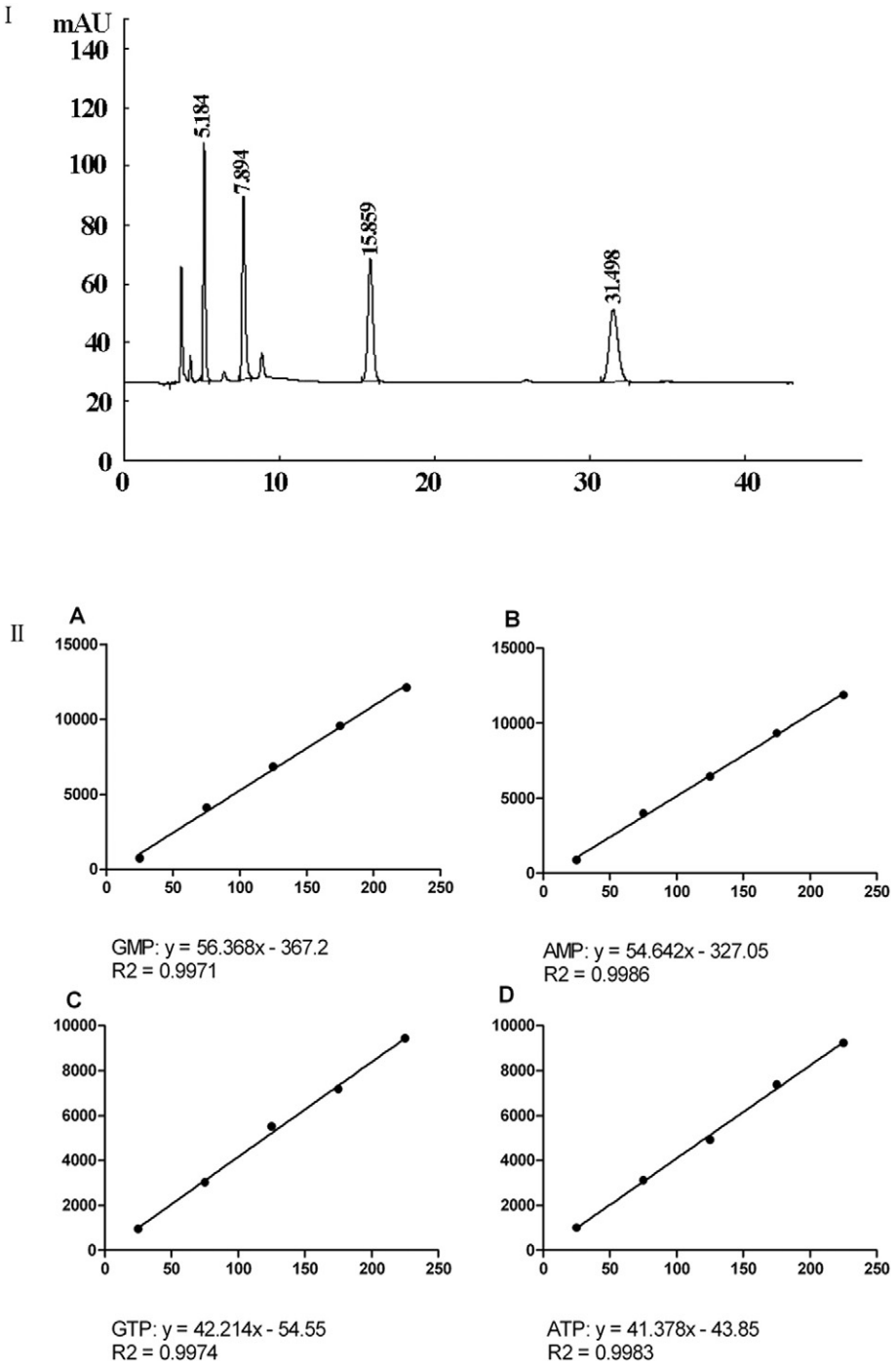

Fig. 1. The chromatogram and standard curve of purine nucleotide standard samples. I) The chromatogram of GMP, AMP, GTP, and ATP standard samples. II) The curve of concentration and peak area of standard samples: (A) GMP, (B) AMP, (C) GTP, (D) ATP.