Suppressive Effect of Administrated Glutathione-Enriched *Saccharomyces cerevisiae* FF-8 on the Oxidative Stress in Alcoholic Fatty Liver

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Glutathione is a well known chemotherapeutic agent for liver disease and is a popular nutritional supplement in the United States. Previous our studies reported the suppressive effects of glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain (FF-8GY) on carbon tetrachloride- and alcohol-induced hepatotoxicity. The primary objective of this study was to investigate the comparative effects of FF-8GY and commercially available glutathione-enriched yeast extract (GYE) against the oxidative stress in alcohol-induced fatty liver of rats. The lipid peroxidative index (thiobarbituric acid-reactive substances, TBARS) and antioxidant status (reduced glutathione level) were used to monitor those protective roles of FF-8GY or GYE treatment. When the rat was treated alcohol, the TBARS levels in the whole liver and the subfractions of microsomal and mitochondria were significantly increased but these were significantly decreased by FF-8GY treatment and tended to be lowered by GYE treatment. The concentration of hepatic glutathione is known to be closely associated with antioxidant system and this was slightly deplete in the alcohol-induced rats, but this was recovered by treating with FF-8GY. However, the glutathione concentration was more significantly decreased in the GYE supplementation in alcohol feeding rats. Alcohol treatment also negatively affected the serum total protein and albumin, but these were significantly increased near normal levels in FF-8GY coadministered rats. These results suggest that glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain may have positively mediate the alcohol-induced oxidative stress, and this effect was more pronounced in FF-8GY compared to GYE.

Key words : Glutathione, yeast, alcohol, oxidative stress

Introduction

Alcohol is a major public health problem by long-term excessive consumption that causes diseases and toxicity of multiple organs [5,10,18] and it is metabolized in the liver without stored in the body [21]. Oxidative stress plays a major role in the initiation and progression of alcoholic liver disease [5]. Organisms have evolved a series of antioxidant mechanisms to maintain and protect their intercellular redox homeostasis [16]. Since glutathione is one of the most abundant cellular antioxidants and is a major determinant in setting the intracellular redox potential, measuring the intracellular reduced and oxidised forms of glutathione [7,12,13,36]. Alcoholic liver disease is characterized by the excessive generation of free radicals contributing to oxidative stress, resulting in an increase of glutathione con-

sumption, a major intracellular antioxidant [17,29]. Although many organisms possess antioxidant defense and repair system, which are not effective enough to totally prevent the damages [31].

Glutathione has widely been used as medicine and foodstuffs or supplements for the treatment of liver injury and as additives in functional health food, thus its commercial demand has been expanding. Recent study has well demonstrated that the reduced form of glutathione-enriched yeast extract showed the dose-dependent hepatoprotective effects, but this could not be observed with the low levels of glutathione contained bread yeast extract [34]. Previous our studies reported the suppressive effects of glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain (FF-8GY) on carbon tetrachloride- and alcohol-induced hepatotoxicity [30]. A previous *in vitro* study with the intercellular glutathione-containing cell free extracts from *S. cerevisiae* FF-8 has also observed antioxidative effects [19].

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The purpose of the present study was to investigate the comparative effects of glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain and commercially available glutathione-enriched yeast extract (GYE) on ethanol-induced hepatic oxidative damage in rats.

Materials and Methods

Glutathione-containing yeast strain

High glutathione-containing yeast *S. cerevisiae* FF-8 strain (FF-8GY) isolated from the Korean traditional rice wine showed the hepatoprotective effect on carbon tetrachloride-induced hepatotoxicity [26,30]. This strain also showed hepatoprotective effects on alcoholic liver injury, in our preliminary study. The glutathione concentration in this strain contained 256 mg/l by large scale bioreactor fermentation using the glutathione maximum producing medium under the optimal culture conditions [4].

Animal experiments

Sprague-Dawley strain rats, 4~5 weeks old, were purchased from Hyochang Science Animals Co., Ltd. (Daegu, Korea). Rats were housed individually in the suspended stainless steel cage and maintained under standard controlled conditions of $22\pm 2^{\circ}\text{C}$, relative humidity 50~60% and 12 hr light:dark schedule. Rats were randomly divided into four experimental groups and were fed a normal diet without or with glutathione-enriched yeast *S. cerevisiae* FF-8 strain or commercially available glutathione-enriched yeast extract (GYE) (Kohjin Co., Ltd., Tokyo, Japan). FF-8 GY and GYE supplementation was replaced with equal amount of casein.

The normal rats administered with water, the alcoholic control rats administered with water/ethanol 30% (v/v), the Alcohol+GYE rats administered with water/ethanol 30% and 5% GYE, and the Alcohol+FF-8GY rats administered with water/ethanol 30% and 5% FF-8GY. Each experimental group consisted of six rats that were fed appropriate diet for a 4-week period.

The concentration of liver marker parameters

After 4 weeks supplementation, rats were sacrificed by withdrawing blood from the abdominal aorta under light diethyl-ether anesthesia. Blood and liver were collected. Serum was obtained by centrifuging the blood. Serum total protein and albumin levels were measured by enzyme

methods in Neodin Medicinal Institute (Seoul, Korea).

Determination of glutathione concentrations

The concentration of glutathione was determined using 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) reagent by the method of Beutler *et al.* [2]. The concentration of glutathione was spectrophotometrically determined at 412 nm. Total glutathione concentrations were expressed as nmol per g liver.

Preparation of tissues homogenate and subcellular fractions

Portions of fresh livers from individual rats were homogenized in ice-cold 0.25 M sucrose solution containing 10 mM Tris-HCl buffer (pH 7.4), 1 mM ethylenediamine tetraacetate (EDTA) and 0.2 mM dithiothreitol. Microsomal and mitochondrial fractions were prepared as described previously [3].

The protein concentrations of liver homogenate, microsomal and mitochondrial fractions were determined by the method of Lowry *et al.* [23] using bovine serum albumin as a standard.

Determination of lipid peroxidation (TBARS)

The lipid peroxidation concentrations produced in liver subcellular fractions were determined according to the spectroscopic technique by the previously described method [8]. Reaction mixture containing tissues homogenate solution or each fractions and thiobarbituric acid (TBA) incubated at boiling water for 30 min, and absorbance read at 532 nm. The concentrations of the thiobarbituric reactive substances (TBARS) expressed as the extent by nanomoles of malondialdehyde (MDA) production.

Statistical analysis

The data from animal experiments are presented as the mean $\pm$ S.E., and were analyzed using one way analysis of variance (ANOVA), with the differences analyzed using the Duncan's new multiple-range test [9]. A *p* value <0.05 was accepted as being a statistical significance of difference.

Results and Discussion

Oxidative stress is known to play an important role in the pathogenesis of liver disease by long-term excessive alcohol consumption [6,22,38]. Alcohol administration caused a

significant increase in hepatic lipid peroxidation, one of oxidative stress indicator in association with hepatic injury [6]. The alcohol administration led to an increase in hepatic MDA level indicating an enhancement in the lipid peroxidation potential of the whole liver as compared to the normal rats (Fig. 1), this result was in agreement with these findings [25]. Lipid peroxidation level in the microsomal and mitochondria subfractions of alcohol treatment control rats were also observed (Fig. 2). Administration of FF-8GY to alcohol-treated rats showed an efficiency to attenuate MDA

Fig. 1. The concentration of TBARS measured in terms of malondialdehyde in liver of rats. Values with different letters are significantly different at $p < 0.05$. (mean $\pm$ S.E., $n=6$). N: Normal rats administered with water, C: Alcoholic control rats administered with water/ethanol 30%, GYE: Alcohol+GYE rats administered with water/ethanol 30% and 5% GYE (commercially available glutathione-enriched yeast extract), FF8GY: Alcohol+FF-8GY rats administered with water/ethanol 30% and 5% FF-8GY (glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain).

formation in the liver as compared to the alcohol administered rats and tended to be lower by GYE treatment. This observation demonstrates that glutathione-enriched FF-8GY strain may have positively mediate the alcohol-induced oxidative stress, and this effect was more pronounced in FF-8 GY compared to GYE. A previous *in vitro* study with the intercellular glutathione-containing cell free extracts from FF-8GY have also observed highly antioxidative effects [19]. In addition, administration of FF-8GY significantly inhibited lipid peroxidation of liver homogenate fractions in the carbon tetrachloride treatment rats [30]. In this respect, Manna *et al.* also reported that the powerful antioxidative components in *S. cerevisiae* effectively participated in attenuation of the oxidative stress caused by flutamide metabolites [24]. From these evidences we may conclude that the hepatoprotective effect of glutathione-enriched yeast may be due to its antioxidant activity.

Glutathione is a ubiquitous tripeptide in living organisms that play a central role in co-ordinating the antioxidant defense process in our body. In addition, glutathione plays a central role in cellular anti-oxidant defense; oxidized glutathione (GSSG) accumulates inside the cells, while reduced glutathione (GSH) is decreased by oxidative tissue damage [1]. It is involved in the maintenance of normal cell structure and function, probably through its redox and detoxification reaction [14]. Many studies have found glutathione is an antioxidant and high concentration of glutathione is contained in yeast strains [4,19,26]. Glutathione from microorganisms have been found to inhibit those chemicals-induced oxidant stresses *in vitro* and *in vivo* such as ethanol, carbon tetrachloride and acetaminophen [1,4,16,30,32]. Present study observed a lower

Fig. 2. The concentration of TBARS measured in terms of malondialdehyde in liver mitochondria and microsome fraction of rats. Values with different letters are significantly different at $p < 0.05$. (mean $\pm$ S.E., $n=6$). N: Normal rats administered with water, C: Alcoholic control rats administered with water/ethanol 30%, GYE: Alcohol+GYE rats administered with water/ethanol 30% and 5% GYE (commercially available glutathione-enriched yeast extract), FF8GY: Alcohol+FF-8GY rats administered with water/ethanol 30% and 5% FF-8GY (glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain).

Fig. 3. Concentrations of liver glutathione in rats. Values with different letters are significantly different at $p < 0.05$ (mean $\pm$ S.E., $n=6$). N: Normal rats administered with water, C: Alcoholic control rats administered with water/ethanol 30%, GYE: Alcohol+GYE rats administered with water/ethanol 30% and 5% GYE (commercially available glutathione-enriched yeast extract), FF8GY: Alcohol+FF8GY rats administered with water/ethanol 30% and 5% FF8GY (glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain).

level of hepatic glutathione in alcohol treatment rats (Fig. 3) and it has been considered as an evidence supporting the hypothesis that reactive oxygen intermediates generated during the metabolism of ethanol lead to glutathione oxidation and lipid peroxidation. This result suggests that enhanced oxidative stress induced by alcohol which results, at least in part, in an increase of glutathione consumption. But the hepatic glutathione concentration was more significantly decreased by the GYE supplementation in alcohol feeding rats. However, the hepatic concentration of glutathione in the FF-8GY coadministered rats showed significantly recovered as high as the normal (Fig. 3) and it showed the antioxidant ability of glutathione. A study with rats caused hepatic damage by acetaminophen found that glutathione-enriched yeast extracts to be effective for the protection of liver from hepatic damage dose-dependently and suggested the provision of precursors for glutathione biosynthesis in the liver would derive hepatoprotective effects [34]. The hepatic glutathione level in rats fed carbon tetrachloride+FF-8GY was slightly increased compared to CCl_4 treatment without statistically significant in the our previous study [30].

The liver protective effect of FF-8GY may also be due to the level of its contents like amino acids. Recent reports have indicated that methionine or cysteine as precursors of glutathione metabolism in the liver played key roles in the

intercellular glutathione synthesis [33,35], and the administration of cysteine and cysteine-containing compounds increased glutathione concentrations in the liver [15], thus glutathione production in the liver might be regulated by the availability of cysteine or methionine. Some kinds of dietary amino acids, such as serine, glycine, asparagine, histidine, and tyrosine were also effective to protect the galactosamine- and alcohol-induced liver injury [20,37]. The constitutional-amino acids in FF-8 GY contained mainly glutamic acid by 11.51 %, aspartic acid by 5.46 %, arginine by 3.20 %, alanine by 3.59 %, and glycine by 2.93 %, and this suggested that high concentration of these amino acids in *S. cerevisiae* FF-8 strain showed protective effect on the carbon tetrachloride-induced oxidant stress [30]. Thus, in the present study, the suppressive effect of alcoholic oxidative stress by FF-8GY administration may be due to the high levels of its concentrational amino acids, because FF-8GY contained high glutathione levels from a large scale bioreactor fermentation. The ability of FF-8GY to enhance the levels of antioxidants along with its antilipid - peroxidative activity suggest that this compound might be potentially useful in counteracting free radical-mediated injuries involved in the development of liver damage caused by alcohol abuse.

Albumin is a key component of serum proteins and is synthesized in the liver, it is one element that is used to monitor both the degree of liver damage [11] and the hepatic function parameters [27]. The concentrations of serum total protein and albumin decreased significantly in alcohol

Fig. 4. Concentrations of serum total protein and albumin in rats. Values with different letters are significantly different at $p < 0.05$ (mean $\pm$ S.E., $n=6$). N: Normal rats administered with water, C: Alcoholic control rats administered with water/ethanol 30%, GYE: Alcohol+GYE rats administered with water/ethanol 30% and 5% GYE (commercially available glutathione-enriched yeast extract), FF8GY: Alcohol+FF8GY rats administered with water/ethanol 30% and 5% FF8GY (glutathione-enriched *Saccharomyces cerevisiae* FF-8 strain).

treatment control rats compared with those in the normal rats (Fig. 4), as reported earlier [28,30]. Decreased total protein in serum reflects the reduction in albumin. It demonstrates the decreased functional ability of alcohol administered rat liver. Significant increase in serum total protein and albumin was observed in FF-8GY coadministered rats and it was an increased near normal levels (Fig. 4). Stabilization of serum protein levels through the co-administration of FF-8GY is further a clear indication of the improvement of the functional status of the liver cells.

We also observed an improvement in the levels of these proteins to near normal values in rats treated with GYE.

In conclusion, alcohol administration caused hepatotoxicity by oxidative stress and yeast strain administration containing highly glutathione concentration provided antioxidant activity by reduced hepatic oxidative stress. These results suggest that a highly glutathione containing yeast strain could be considered as effective agents for alleviating alcoholic liver injury.

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초록 : 알코올 투여 흰쥐의 간 조직 산화스트레스에 미치는 글루타티온 고함유 효모 *Saccharomyces cerevisiae* FF-8 균체의 영향

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글루타티온은 간 질환용 치료제 내지는 영양보충제로 시판되고 있다. 이전 실험에서 글루타티온 고함유 효모 *Saccharomyces cerevisiae* FF-8 균체(FF-8GY) 투여가 사염화탄소 및 알코올성 유발 간독성 개선효과를 나타내었다. 따라서, 알코올성 지방간의 산화 스트레스에 미치는 영향을 조사하기 위하여 시판되고 있는 글루타티온 고함유 효모 추출물(GYE)과 본 실험실에서 분리한 글루타티온 고함유 효모 FF-8GY를 비교실험 하였다. FF-8GY 또는 GYE 투여에 의한 간 조직 중의 산화스트레스 측정지표로서는 과산화지질(TBARS) 및 글루타티온 함량을 측정하였다. TBARS 농도는 간 조직 homogenize 분획에서 알코올 투여 대조군에 비해 FF-8GY 투여 실험군에서 5%수준에서 유의적으로 감소하였으며, GYE 투여에 의해서는 감소경향을 보였다. 간 조직 microsomal 및 mitochondria 분획에서도 같은 경향이 관찰되었다. 이때 간 조직 중의 글루타티온 농도는 정상군 보다 알코올 투여 대조군에서 5%수준에서 유의적으로 감소하였으며, 이러한 감소는 GYE 투여에 의해 더욱 감소되었으나 FF-8GY 투여에 의해서 정상군 수준까지 회복되는 것으로 나타났다. 한편 간조직의 손상정도를 나타내는 또 하나의 지표인 혈청 총단백질 및 알부민 농도는 알코올 처리 대조군에서 낮게 나타난 반면 FF-8GY 투여에 의해 정상군 수준 이상으로 증가하는 것으로 나타났다. 이상의 결과에서 글루타티온 고함유 효모 *Saccharomyces cerevisiae* FF-8 균체(FF-8GY)의 투여에 따른 알코올성 유발 산화스트레스의 경감 효과는 시판되고 있는 글루타티온 고함유 효모 추출물 보다 더욱 현저한 개선 효과가 있는 것으로 확인되었다.