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Article

Nutritional status and diet style affect cognitive function in alcoholic liver disease

Ye Rin Choi[1*], Hyeong Seop Kim[1*], Sang Jun Yoon[1], Na Young Lee[1], Haripriya Gupta[1], Ganesan Raja [1], Yoseph Asmelash Gebru[1], Gi Soo Youn[1], Dong Joon Kim[1], Young Lim Ham[2†], Ki Tae Suk[1†]

1 Institute for Liver and Digestive Diseases, Hallym University College of Medicine, Chuncheon, Republic of Korea; dpfls3020@gmail.com (Y.R.C), kimhs2425@gmail.com (H.S.K), ysjtlhuman@gmail.com (S.J.Y), na0lee0218@gmail.com (N.Y.L), phr.haripriya13@gmail.com (H.G), vraja.ganesan@gmail.com (G.R), yagebru@gmail.com (Y.A.G), gisu0428@hallym.ac.kr (G.S.Y), djkim@hallym.ac.kr (D.J.K), ktsuk@hallym.ac.kr (K.T.S)

2 Department of Nursing, Daewon University College, Jaecheon, Republic of Korea; eouhyun@hanmail.net

* Correspondence: Ki Tae Suk; ktsuk@hallym.ac.kr; Tel.: +82-10-5365-5700; FAX: 033-248-3481

Abstract: Malnutrition and cognitive dysfunction are typical features of alcoholic liver disease (ALD) and are correlated with the development of complications. The aim of this study is to explore the effect of nutritional state and diet on cognitive function in ALD. A total of 43 patients with compensated alcoholic cirrhosis were enrolled, and neuropsychological test was assessed according to body mass index (BMI, <22 and ≥22). In the ALD animal study, mice were divided into 5 groups (n=9/group; normal liquid, 5% EtOH+regular liquid, 5% EtOH+high-carbohydrate liquid, 5% EtOH+high-fat liquid, and 5% EtOH+high-protein liquid diet) and fed the same calories for 8-week. To assess cognitive function, we performed T-maze studies weekly before/after alcohol binging. In cognitive function (BMI <22 /≥22), language score of Korea mini-mental state (7.4±1.4/7.9±0.4), Rey-complex figure (72.0±25.9/58.4±33.6), Boston naming (11.7±2.7/13.0±1.8), forward digit span (6.7±1.8/7.5±1.6), Korean Color Word Stroop (24.2±26.5/43.6±32.4), and interference score (33.9±31.9/52.3±33.9) revealed significant differences. In the T-maze test, alcohol significantly delayed the time to reach food, and binge drinking provided a temporary recovery in cognition. The alcohol-induced delay was significantly reduced in the high-carbohydrate and high-fat diet groups. Synaptic function exhibited no changes in all groups. Cognitive dysfunction is affected by nutritional status and diet in ALD.

Keywords: alcoholic liver disease; cognitive function; calorie intake; nutrition; BMI

1. Introduction

Alcoholic liver disease (ALD) is the third most common cause of chronic liver disease and with mortality worldwide [1]. The number of alcohol-related deaths remains high at 2.5 million annually, constituting 4% of all deaths worldwide [2], and death from ALD constitutes approximately 25% of deaths [3]. Excessive alcohol consumption has many adverse health and social consequences [4,5]. Alcohol abuse among older people is common and occurs more frequently among men. Moreover, it is associated with cognitive impairment and independently with short-term mortality [6].

Most patients with ALD consume a regular diet but exhibit malnutrition [7]. Malnutrition is a major complication of ALD that has been studied, especially in patients with alcoholic hepatitis [8]. Malnutrition worsens clinical outcome in ALD, and nutritional support improves nutritional status and may improve clinical outcome. Possible reasons for malnutrition include metabolic disturbance, nausea, vomiting, or unbalanced diet [9].

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Alcohol consumption can cause functional abnormalities and frontal lobe changes given that alcohol has a toxic effect itself [10-12]. Neuropsychological dysfunction due to frontal lobe abnormalities is similar to that noted in chronic alcohol abuse. Consequently, chronic alcohol consumption and liver disease are independently correlated with changes in neuropsychological dysfunction. In this regard, maintaining an adequate nutritional status is essential for ALD patients.

Many studies show that nutrition status is associated with cognitive function. A high-calorie diet reduces hippocampal synaptic plasticity and impairs cognitive function through brain-derived neurotrophic factor-mediated effects on dendritic spines [13]. Furthermore, dietary fat intake at midlife affects cognitive performance. Based on this evidence, a patient's nutritional state is essential to prevent complications, and important lifestyle factor that can alter the risk of cognitive impairment in the long-term [14,15].

In our previous report, impaired memory and frontal lobe executive functions and early development of overt encephalopathy were more common in patients with ALD [16]. However, limited data about the relation between malnutrition and cognitive dysfunction in ALD are available. The aim of this study is to explore the effect of nutrition on cognitive function in ALD.

2. Materials and Methods

2.1. Patients

A total of 43 patients with alcoholic liver cirrhosis were prospectively recruited from October 2011 to March 2020 (NCT04557774). The diagnosis of liver disease was performed based on laboratory data, endoscopic findings, medical record review and liver biopsy. Patients who were > 20 years old with liver function test results indicating with an aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 1 and elevated AST (ALT) levels as well as a history of alcohol consumption of greater than 40 g/day for women and 60 g/day for men during the 7 days before screening were enrolled. Their last drinks were consumed within 48 hours prior to admission. Patients with a history of hepatitis virus infection and those who were administered medications for sedation, seizure, head trauma, stroke, dementia, Parkinson's disease, or any kind of focal neurologic deficits were excluded. Any patients who were suspected of alcohol-induced direct neurologic damage, such as Wernicke's encephalopathy, alcohol-induced spinal cord disease, or alcohol-induced peripheral nerve disease, were excluded.

Patients were recruited after receiving the approval of institutional review board of Hallym University Chuncheon Sacred Heart Hospital (2011-36). Caloric intake was considered to affect cognitive function and was arbitrarily divided according to the nutritional status (BMI < 22 and BMI ≥ 22) of 43 ALD patients.

We conducted baseline evaluations, including family and alcohol history, X-ray, electrocardiography, blood tests for electrolytes, liver function, and viral markers. Serum biochemical parameters included total bilirubin, AST, ALT, gamma-glutamyltranspeptidase (γ-GT), alkaline phosphatase (ALP), albumin, blood urea nitrogen, creatinine, α-fetoprotein, prothrombin time, blood glucose, triglycerides, and total cholesterol. Child-Pugh and MELD scores were evaluated based on laboratory and imaging findings.

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To select patients with same medical condition, endoscopy and imaging (abdominal computed tomography [CT] or ultrasound) were performed for all the patients. The hepatic venous pressure gradient was determined by subtracting free hepatic venous pressure from wedged hepatic venous pressure. In addition, a brain CT was performed on patients who consented.

The diagnosis of liver cirrhosis was established by liver biopsy and/or imaging studies, such as ultrasound and/or contrast-enhanced CT, in conjunction with laboratory data and clinical complications of cirrhosis [17].

2.2 Neuropsychological Test

In this study, we performed neuropsychological tests in patients with alcoholic liver cirrhosis to evaluate the effect of BMI on cognitive function. We used the Seoul Neuropsychological Screening Battery (SNSB, Human Brain Research & Consulting Co, Seoul, South Korea) as the neuropsychological test. Attention function (digit-span forward/backward and letter cancellation), frontal/executive function [Controlled oral ward association test (COWAT), Korean color word stroop test (K-CWST)], visuospatial function [Korea-mini mental status examination (K-MMSE) and Ray-complex figure test (RCFT) copy score], verbal memory [Seoul-verbal learning test (SVLT)], and visual memory (RCFT delayed recall) were assessed in all enrolled subjects. The results were compared using absolute scores instead of percentile scores. Test results, including monitoring of scoring, procession and interpretation, were evaluated by one neurology specialist.

2.3. Experimental Animals

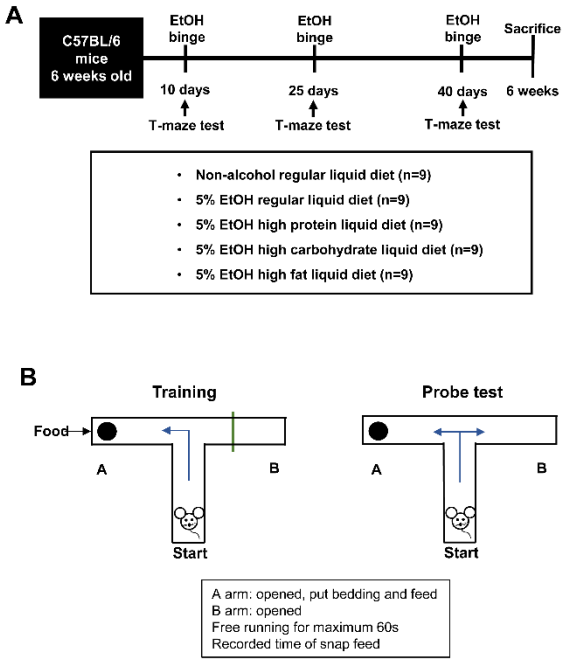

Figure 1. Animal experiment. A. Mice were sub-divided into 4 groups [n=9/group; control (5% EtOH liquid diet), high carbohydrate (5% EtOH + HCD), high fat (5% EtOH + HFD), and high protein (5% EtOH + HPD)] for 8 weeks. B. Schematic of T-maze appliance for working memory study.

After clinical study analyses, we conducted alcohol animal experiments in mice fed a high-protein, high-carbohydrate, and high-fat diet. Six-week-old male C57Bl/6J mice were obtained from

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Dooyeol Biotech (Seoul, Korea). To induce alcoholic liver disease, mice were subdivided into 4 groups (n=9/group; control [5% EtOH liquid diet], high carbohydrate [5% EtOH + high-carbohydrate liquid diet (HCD)], high fat [5% EtOH + high-fat liquid diet (HFD)], and high protein [5% EtOH + high-protein liquid diet (HPD)]) and subject to the indicated conditions for 8 weeks. All animal experiments were performed according to National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of the College of Medicine, Hallym University (Hallym2016-4) (Fig. 1A).

For cognitive function, we performed T-maze studies weekly before and after alcohol binging. We used a T-shape maze constructed of acrylic with opaque sides, and the maximum time was set at 90 seconds. Before alcohol binging, all animals were pretrained to searching the normal chow diet toward the left side blocking one direction. After alcohol binging, we measured the time that mice search for the normal chow diet (Fig. 1B). To assess working memory, we conducted pretraining and poststudy assessments. At the pretrial stage, the mice trained to run from the start to receive a food reward. For the evaluation of the effect of alcohol on cognition, we performed the test before and after alcohol binging at 11, 25, and 44 days during study. In addition, we measured the mice performance time in each diet group (HCD, HPD, HFD).

The mice were euthanized with ether anesthesia. A midline abdominal incision was created, and blood was collected at the heart. Livers were rapidly resected for pathological assessment and stored at -80 ℃ for the evaluation of liver enzyme profiles.

2.4. Pathology

Specimens were fixed with 10% formalin and routinely embedded in paraffin; the tissue sections were processed with hematoxylin and eosin, Masson's trichrome, and reticulin fiber staining. Fatty liver was classified by the clinical research network scoring system [18]. Fatty liver was classified from grade 0 to grade 3 (0: < 5%, 1: 5-33%, 2: 34-66%, and 3: > 66% of steatosis). All specimens were blindly analyzed by 1 hepato-pathologist.

2.5. Western Blot Analysis of the Brain

The whole brain was washed with ice-cold PBS and lysed with a modified RIPA buffer containing 50 mM Tris-HCl pH 7.4, 150 mM NaCl, 1% Triton X-100, 0.1% sodium dodecyl sulfate (SDS), 0.5% sodium deoxycholate, 1 mM ethylenediaminetetraacetic acid (EDTA), protease inhibitors (Pierce Biotechnology, Rockford, IL, USA), 1 mM Na_3VO_4, and 1 mM NaF. Brain homogenates were centrifuged at 15,000 × *g* for 15 min at 4 °C, and the protein concentrations in the supernatants were analyzed using a BCA Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA). Equal amounts of proteins (40 μg/lane) were separated using sodium dodecyl sulfate-polyacrylamide electrophoresis, transferred onto 0.45-μm pore polyvinylidene fluoride (PVDF) membranes (Merck Millipore, Lake Placid, NY, USA) and blocked with 5% skim milk in 1 × PBS containing 0.1% Tween 20 (PBST) for 1 h at room temperature. The following primary antibodies were added to the membranes, which were incubated overnight at 4 °C: anti-Synapsin, anti-Synaptophysin, anti-SNAP25, anti-PSD95, anti-Synaptotagmin (Abcam, Cambridge, MA, USA), anti-Vamp2 (Cell Signaling Technology, Beverly, MA, USA), anti-β-actin (Sigma-Aldrich, St. Louis, MO, USA). The membranes were washed with PBST thrice for 10 min each and then incubated with the following secondary antibodies for 1 h: goat anti-mouse IgG or goat anti-rabbit IgG (Thermo Fisher Scientific)

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conjugated with horseradish peroxidase (HRP). The immunoreactive bands were visualized on digital images captured with an ImageQuantTM LAS4000 imager (GE Healthcare Life Sciences, Piscataway, NJ, USA) using the EzwestLumi plus western blot detection reagent (ATTO Corporation, Tokyo, Japan). The band intensities were quantified using the ImageJ (NIH) program. Statistical analyses were performed using GraphPad Prism 4 (San Diego, CA, USA).

3. Results

3.1. Patient Characteristics

The mean BMI < 22 and BMI ≥ 22 of patients was 21.9 ± 4.6 and 24.9 ± 3.0 ($p < 0.01$). The proportion of males was 82% (14/17) and 77% (20/26) in the BMI < 22 group and BMI ≥ 22 group. The mean age of patients with ALD was 53.2 ± 10.2 and 50.0 ± 8.0 years. The period of education (9.3 ± 4.0 and 10.8 ± 4.0), AST level (54.6 ± 38.7 and 69.7 ± 50.8 g/dL), and ALT level (25.0 ± 17.8 and 36.8 ± 30.0 g/dL) did not exhibit significant differences (Table 1).

Table 1. Baseline characteristics of patient with compensated alcoholic cirrhosis

Variables (mean)	BMI < 22 (n=17)	BMI ≥ 22 (n=26)	P value
Male n (%)	14 (82)	20 (77)	
Age	53.2 (10.2)	50.0 (8.0)	0.659
BMI	21.9 (4.6)	24.9 (3.0)	0.001
Education period (years)	9.3 (4.0)	10.8 (4.0)	0.302
Hemoglobin (g/dL)	11.7 (2.0)	12.4 (2.5)	0.368
Albumin (g/dL)	3.8 (0.6)	3.6 (0.8)	0.298
Total bilirubin (mg/dL)	0.9 (0.5)	1.7 (1.3)	0.023
AST (IU/L)	54.6 (38.7)	69.7 (50.8)	0.302
ALT (IU/L)	25.0 (17.8)	36.8 (30.0)	0.151
ALP (IU/L)	129.5 (47.7)	135.8 (62.5)	0.726
γ-GT (IU/L)	434.7 (455.2)	333.0 (382.1)	0.434

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyl transpeptidase

3.2. Body Mass Index and Cognitive Function

The neuropsychological tests of 43 patients, including visuospatial functions by digit span forward score (6.7 ± 1.8 and 7.5 ± 1.6), K-MMSE (language, 7.4 ± 1.4 and 7.9 ± 0.4), language score K-BNT (11.8 ± 2.7 and 13.0 ± 1.8), attention by RCFT copy score (72.1 ± 25.9 and 58.4 ± 33.6) and Stroop test (color reading time per items [24.2 ± 26.5 and 43.6 ± 32.4] and interference score [33.9 ± 31.9 and 52.3 ± 33.9]), revealed high scores in patients with BMI ≥ 22 ($p < 0.05$). Other neuropsychological tests did not exhibit significant differences between two group ($p > 0.05$) (Table 2 and supplementary Table 1).

Table 2. Neuropsychological tests related cognitive function

Variable	BMI <22 (n=17)	BMI ≥22 (n=26)	P- value
Visuospatial function			

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Digit span forward	6.7 (1.8)	7.5 (1.6)	0.039
Digit span backward	3.8 (1.3)	4.3 (1.5)	0.138
Stroop test			
Color reading correct	72.4 (27.1)	83.8 (26.0)	0.079
Color reading time	119.3 (3.4)	116.4 (9.4)	0.076
Color reading correct response rate	1.0 (0.1)	1.0 (0.1)	0.432
Color reading time per items	24.2 (26.5)	43.6 (32.4)	0.006
Interference scores	33.9 (31.9)	52.3 (33.9)	0.017
Attention			
RCFT copy scores	72.1 (25.9)	58.4 (33.6)	0.048
K-MMSE			
K-MMSE, language	7.4 (1.4)	7.9 (0.4)	0.037
Language			
K-BNT	11.8 (2.7)	13.0 (1.8)	0.017

RCFT, Ray-complex figure test; K-MMSE, Korea-mini mental status examination; K-BNT, Korean version-Boston naming test

3.3. Changes in the Body Weight and Pathology

In the comparison of body weight, HPD and HCD groups showed improvements compared with the alcohol group. In the analysis of the liver/body weight ratio (%), the HFD group (5.60 ± 0.40) exhibited significant changes compared with the control group (4.52 ± 0.31) ($p < 0.01$). The HPD (5.10 ± 1.04) and HCD (4.85 ± 0.44) groups did not exhibit differences in the liver/body weight ratio.

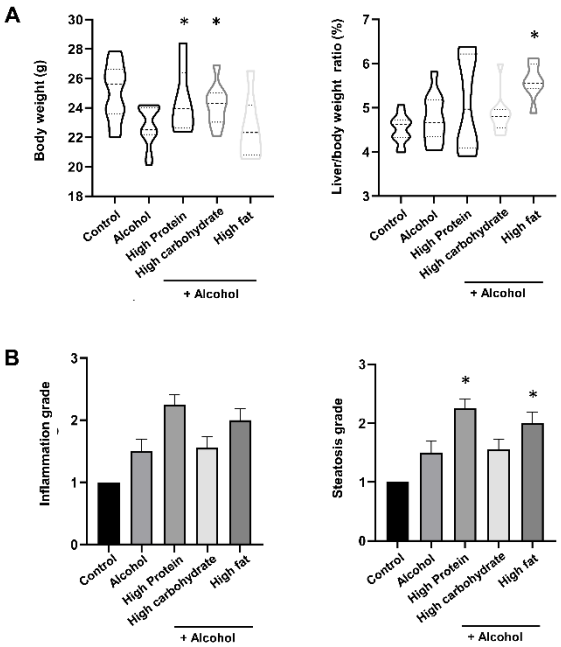

Figure 2. Pathological result according to diet group. A. Liver/Body weight ratio (%), B. Pathological result of diet group. * $p < 0.05$

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In the pathological results, each group did not exhibit differences in the inflammation grade. The HPD (2.3 ± 0.5) and HFD (2.0 ± 0.5) groups exhibit significant increases in steatosis compared with the alcohol group (1.5 ± 0.7) (Fig. 2).

3.4. Cognitive Function Based on Diet Groups

Compared with mice fed a control diet, alcohol induced an increase in time in the T-MAZE results. Mice spent less time searching for food in the HFD group. The reduction in cognitive function was proportional to the period of alcohol administration. Temporary recovery of cognitive function occurred during binging, but cognitive function resumed one day after binge.

Depending on the diet, cognitive function improved in the HCD and HFD groups compared with the alcohol group. In particular, the HCD group exhibited improvement in cognitive function that was proportional to the duration of administration (Fig. 3).

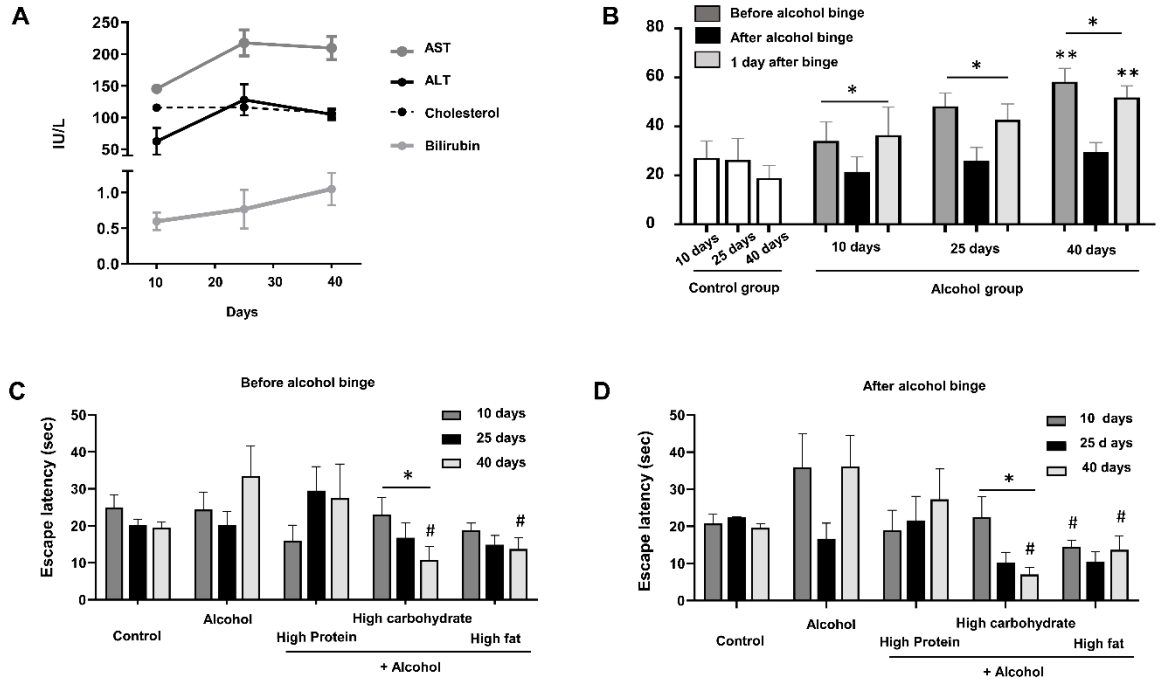

Figure 3. Liver enzyme and T-maze test. A. The serum level of liver enzyme in alcohol group mice. B. Change of T-maze test in alcohol mice. C. T-MAZE before alcohol binge. D. T-MAZE after alcohol binge. * $p < 0.05$ difference in the group, **$p < 0.05$ difference compared with 10 days, 25 days, and 40 days # $p < 0.05$ difference compared with alcohol group

3.5. Brain Markers in the High-Protein Diet Group

The levels of the synapsin-1, synaptophysin, SNAP25, PSD95, synaptotagmin, and Vamp2 were measured by band quantification and normalized with the levels of B-actin. Synapsin-1, synaptophysin and SNAP25 represent presynaptic markers. PSD95 is postsynaptic marker. Synaptotagmin and Vamp2 represent vesicle markers. Vesicles function as pouches that store and transport substances within cells and digest cellular products.

Synapses exhibit mechanical and functional properties, transmit signals and process information in the brain. Synapses are responsible for overall brain function and is also related to cognitive function

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[19,20]. To evaluate synaptic function, we conducted western blotting using samples from the HPD group and alcohol-induced mice. The result shows that synaptic function did not change in the alcohol and HPD groups (Fig. 4).

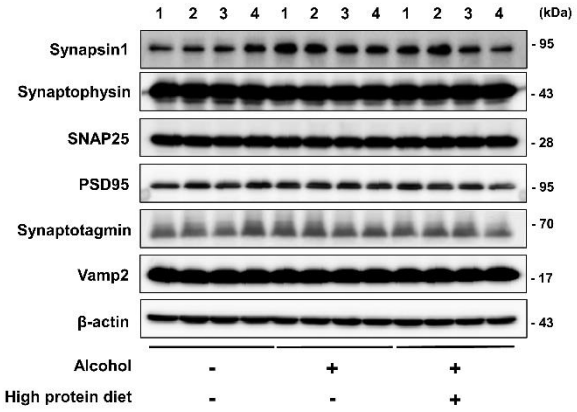

Figure 4. Expression of synaptic neuron in alcohol induced high protein diet group. Representative western blot of mouse hippocampus homogenate.

4. Discussion

BMI has been used as an index of an individual's fat levels and nutritional state in various disease. Accordingly, a high BMI is related with brain atrophy and cognitive dysfunction in some brain diseases [21-24]. Regarding ALD, a negative relationship is noted between alcohol consumption and BMI [25]. Most patients have a low BMI index due to insufficient calorie intake. Few studies are available on the association between cognitive dysfunction and BMI in alcoholic liver disease. In this study, patients (BMI ≥ 22) with cirrhosis exhibited improved cognitive functions, such as visuospatial function, Stroop, attention, MMSE, and language tests, compared with patients with low BMI (< 22). Therefore, we suggest that BMI is closely related with cognitive function in ALD patients.

Chronic alcohol consumption results in brain damage, especially in the frontal lobe [26]. Alcohol use disorder is related with chronic impairment in emotion recognition and reasoning [27]. Problematic alcohol drinking activity is correlated with an increased risk of cognitive dysfunction [28]. Other report suggested that consumption of a small amount of alcohol may reduce the risk of cognitive dysfunction in woman [29]. ALD severity is dependent on the amount and duration of the alcohol intake [30]. In our T-maze test results utilizing male mice, chronic alcohol intake decreased cognitive function. Taken together, chronic alcohol intake affects cognitive function, but gender differences exist.

An interesting fact is that mice exhibited a temporarily reduced T-maze time after alcohol binging in all groups. In our results, the reduced time in T-maze tests after binging worsened after one day. These result are consistent with a recent clinical trial demonstrating that alcohol improved creative problem solving but not divergent thinking [31]. Another study demonstrated that moderate alcohol drinking reduced working memory capacity but increased performance [32]. Improving of performance and abnormal pleasure is a symptom related to addiction, and it is probably one of the reasons why patients continue drinking alcohol. This result indicates that chronic alcohol intake may

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lead to temporary improvements in cognitive function but ultimately leads to fatal damage. As a result, abstinence is the most important treatment for patients with alcoholic liver disease.

In our results, a high-fat diet yielded the shortest time to find food in the alcohol animal model. HPD increased the time required to find food in the T-maze test. In a previous report, a high-fat diet improved neuro-inflammation and neurogenesis [33]. In addition, a high-fat diet increased lipid accumulation in the cortex and brain sensitivity [34]. Regarding obesity, high-fat diet-induced obesity caused cognitive dysfunction. In this study, the results were different because the effects of diet were observed in alcohol models and not the obesity model. Dietary studies on alcoholic liver disease are limited, suggesting that the HFD in this study serves as a dietary regimen for improving cognitive function in alcoholic liver disease. In this study, dextrin was added instead of fat to standardize caloric intake.

Regarding HCD-related improvement in cognition, we hypothesize that maltose dextrin might increase memory. Another clinical report demonstrated that memory is facilitated by offering lecithin, carnitine and glucose supplements [35]. A low-carbohydrate diet aggravated attention and induced confusion in a previous report [36]. Taken together, HFD or HCD can be used as nutritional therapy in patients with ALD.

Alcohol intoxication reduces brain activity in the cortical and subcortical regions, including the temporal lobe, which contains the hippocampus [37]. In cirrhosis and advanced ALD, atrophic changes in the brain are dominant [16], but functional changes take precedence over structural changes in alcohol use disorder. In our data, pathological examination revealed hepatitis not cirrhosis and did not reveal differences in synapsin1, synaptophysin, SNAP25, PSD95, synaptotagmin, and Vamp2 protein levels in brain. These results suggest that alcohol intake does not result in structural issues in the brain but does reduce cognitive function. In addition, nutritional therapy for ALD should be started at an early stage before brain changes occur.

Our results from an alcohol-induced model demonstrated that a high-fat diet improves working memory. However, the limitation of this study is that HFD is not related to steatosis levels. In addition, in western blot analyses, synaptic functions that have a direct or indirect effect on all processes in the overall brain exhibited no significant differences in the protein diet and alcohol group.

In summary, neuropsychological tests of ALD patients revealed that high BMI patients exhibited relatively increased cognitive function compared with low BMI patients. Similarly, in an alcohol-induced animal model, the high-fat diet group, which consumed enough calories, exhibited improved working memory performance. Further studies are need to explore whether alcohol consumption enhances cognitive function.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, K.T.S.; methodology, K.T.S; software, K.T.S; validation, K.T.S and Y.R.C; formal analysis, H.S.K.; investigation, H.S.K.; resources, G.R., Y.A.G., G.S.Y., and D.J.K; data curation, S.J.Y., N.Y.L., H.G., G.R., Y.A.G., G.S.Y., and D.J.K; writing—original draft preparation; project administration, Y.L.H.; funding acquisition, K.T.S. All authors have read and agreed to the published version of the manuscript.",

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Conflicts of Interest: The authors declare that there is no conflict of interest, including relevant financial interests, activities, relationships, affiliations, and any other conflict of interest as explicitly and implicitly expressed in the Editorial Policies for Authors.

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