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Impairment of long-term potentiation in the hippocampus of alcohol-treated OLETF rats

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ABSTRACT

Type 2 diabetes and chronic heavy alcohol consumption each have been known to be associated with the impairment of hippocampus-dependent cognitive functions. Although both conditions often coexist clinically and there is accumulated evidence of a relationship between the two, the combined effect on hippocampal long-term potentiation (LTP) has not yet been investigated. We compared the effect of type 2 diabetes itself with that of type 2 diabetes with chronic heavy alcohol consumption on the hippocampal LTP using Otsuka Long-Evans Tokushima Fatty (OLETF) rat model, which resembles the characteristics of human type 2 diabetes. Ten of 16-week-old male OLETF rats were randomized into two treatment groups according to weight: the OLETF–Alcohol (O–A, $n=5$) and the OLETF–Control (O–C, $n=5$). The rats in the O–A group were fed Lieber-DeCarli Regular EtOH over a 10-week period and the amount of alcohol consumption was 8.42 ± 2.52 g/kg/day. To ensure the effect of poor glycemic control on LTP, intraperitoneal glucose tolerance test was performed after a 10-week treatment. The hippocampal LTP was measured by extracellular field excitatory post-synaptic potentials at Shaffer collateral (SC) synapses in the CA1 region. Although the O–A group showed significantly lower fasting and postprandial glucose ($P<0.01$ and $P=0.02$, respectively), the hippocampal LTP was more significantly attenuated in the O–A group than the O–C group ($P=0.032$). The results of this study suggested that chronic heavy alcohol consumption could potentiate the impairment of hippocampal LTP in individuals with impaired glucose tolerance or early type 2 diabetes, even though it did not aggravate, but did improve glycemic control. Clinical attention to chronic heavy drinking will be required in preventing cognitive impairment in individuals with type 2 diabetes.

Diabetes mellitus is a prevalent metabolic disorder. Although type 1 and type 2 diabetes have detrimental effects on cognitive functioning [25], type 2 diabetes is more common with ample clinical evidence regarding its association with cognitive decline [3,7]. Type 2 diabetes is characterized by insulin resistance associated with the metabolic syndrome and has been suggested as one of the risk factors of Alzheimer's disease [28]. Indeed, impairment of long-term potentiation (LTP) in hippocampal CA1 region has been observed in some rat models with type 2 diabetes [4,43] except for Zuker Diabetes Fatty rats [8]. Deficits in LTP closely correlated with impairments in hippocampus-dependent spatial memory formation [11] and with synaptic dysfunction in Alzheimer's disease [47]. Although improvement of glycemic control [17,30] and insulin resistance [1] would prevent and ameliorate hippocampus-dependent cognitive dysfunction in clinical trials, underlying mechanisms have not been fully understood [39]. Since cognitive dysfunction in individuals with type 2 diabetes places a heavy burden on patients and their families, prevention is an important clinical concern [39].

Alcohol is a well-known risk factor for the impairment of hippocampal LTP [9,31]. A chronic heavy alcohol consumption caused an attenuation of the magnitude of LTP and this impairment was persistent even after a prolonged abstinence in rat models, once it

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had occurred [14,45]. Individuals with heavy alcohol consumption presented a selective cognitive decline in declarative memory compared to controls [15,18]. Alcohol-induced brain damages were commonly observed even in uncomplicated alcoholics [20], and such damages were hard to recover [14,45], which emphasizes the importance of early detection and prevention.

There has been a permissive atmosphere that encourages alcohol consumption to some degree because moderate drinking was reported to decrease the risk of type 2 diabetes while non-drinking and heavy drinking were accounted for the increase in the risk of type 2 diabetes in general population and individuals at high risk [12,24]. Although the underlying mechanisms are not completely understood, modulation of insulin sensitivity has been suggested to be involved in the effects of moderate and heavy drinking [21,48]. However, a relationship between type 2 diabetes and alcohol consumption has not been studied sufficiently regarding cognitive function despite its clinical importance. The fact that alcohol-induced brain damages and cognitive dysfunction might precede other complications of alcohol also strongly suggests the need for research on their relationship in cognitive function [20].

Based on this background, the present study aimed to investigate the effect of chronic heavy alcohol consumption on hippocampal LTP in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, which is a rat model of spontaneously developing type 2 diabetes [23]. We compared the hippocampal LTP at Shaffer collateral (SC) synapses in the CA1-field of OLETF rats with chronic heavy drinking with that of those who never drank.

Ten 16-week-old male OLETF rats were used in this study. The rats were randomized into two treatment groups according to weight: OLETF–Alcohol (O–A, $n = 5$) and OLETF–Control (O–C, $n = 5$) groups. The rats in the O–A group were fed with Lieber-DeCarli Regular EtOH (Cat. No. 710260, Dyets Inc., USA) over a 10-week period, as recommended by the manufacturer. Since previous studies showed that ethanol ingestion over a 4 week period in rodents is equivalent to chronic drinking in humans [6,40], ethanol ingestion for 10 weeks was assumed to be a chronic drinking. The liquid diet contained 34% fat, 11% carbohydrate, 18% protein, and 36% ethanol. The amount of consumption was measured daily and 100 ml/day of the liquid alcohol diet was given to each rat in the O–A group, which means the average amount of ethanol ingested in the O–A group was 8.42 ± 2.52 g/kg/day. This corresponds to heavy drinking [22]. The rats in the O–C group were fed Lieber-DeCarli Control diet (Cat. No. 710027, Dyets Inc., USA), in which the calories from ethanol were replaced with maltose–dextran. Feeding was performed at 10:00 a.m. The O–A group usually did not to eat all the food provided, whereas the O–C group finished all their food. Therefore, pair-feeding controls were used with a synchronized pellet pair-feeding apparatus to regulate the different caloric intake.

After a 10-week treatment, an intraperitoneal glucose tolerance test (IP-GTT) was performed in all rats. The rats were fasted for 17 h and the fasting glucose level was obtained from the venous blood. Subsequently, an intraperitoneal injection of D-glucose (2 g/kg) was administered and blood glucose levels were obtained 30 and 120 min later. The blood glucose level was measured using an ACCU-CHECK Active (Roche Diagnostics, Korea) portable glucose meter. The experiments were carried out in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals (NIH Publication No. 80-23) revised in 1996.

For extracellular recordings, transverse hippocampal slices (400 μm thick) were prepared from the animals using a manual tissue chopper. The animals were deeply anesthetized (Isoflurane) and decapitated. Hippocampal slices were obtained and maintained in an interface chamber at 28 °C, perfused (1–2 ml/min) with artificial cerebrospinal fluid (ACSF). The ACSF contained 124 mM NaCl, 2.5 mM KCl, 1 mM NaH_2PO_4, 25 mM $NaHCO_3$, 10 mM glucose, 2 mM $CaCl_2$, and 2 mM $MgSO_4$, and was oxygenated with 95% O_2 and 5% CO_2. The slices were incubated in the interface chamber for at least 2 h to recover. After the recovery period, extracellular field excitatory post-synaptic potentials (fEPSPs) were recorded at the Shaffer collaterals (SC) of the area CA1 using a glass pipette electrode filled with ACSF (1 MΩ). The SC pathway was stimulated every 30 s using concentric bipolar electrodes (MCE-100; Kopf Instruments) placed in the CA1 region. The field potentials were amplified, low-pass filtered (GeneClamp 500; Axon Instruments), and then digitized (NI PCI-6221; National Instruments) for the measurements. The data was monitored, analyzed online and reanalyzed offline using the WinLTP program (http://www.ltp-program.com) [5]. For the LTP experiments, the stimulation intensity was adjusted to give fEPSP slopes of approximately 30% of the maximum. Two successive responses, which were elicited twice per minute at this intensity, were averaged and expressed relative to the normalized baseline. After a stable baseline was recorded, high-frequency stimulation (HFS)-LTP (100 Hz stimulation, 1 s, test intensity) was induced.

In LTP analysis, the n values represent the number of slices, and results pooled across the slices were expressed relative to the baseline as the mean ± SEM. To compare the magnitude of LTP between the O–A and O–C group, an unpaired t-test was performed by comparing the mean amplitude of the responses over a 5 min period (75–80 min). The body weight and blood glucose levels of both groups were analyzed using a Mann–Whitney U-test and repeated measures analysis of variance (ANOVA). Statistical significance was set at $P < 0.05$.

Baseline characteristics of body weight and fasting glucose were not significantly different in both groups (Table 1). The results of IP-GTT after a 10-week treatment revealed a significantly lower mean glucose levels at the baseline and 120-min after intraperitoneal glucose injection in the O–A group than those in the O–C group. The difference in mean glucose levels between two groups remained after adjusting for time ($P = 0.016$). Defining normal glucose tolerance as fasting glucose <110 mg/dl and 2-h glucose <140 mg/dl [49], the results of IP-GTT after a 10-week treatment implied a possibility of being in a pre-diabetic state (i.e., impaired glucose tolerance (IGT) or an early type 2 diabetes [36]).

To examine the effects of a 10-week ethanol treatment on the hippocampal LTP in the OLETF rats, fEPSP slope was measured at SC-CA1 synapses and the magnitudes of LTP were compared between the O–C group and O–A group. Basal synaptic responses were comparable between two groups and the magnitudes of fEPSP slope at maximum stimulation intensities were indistinguishable (data not shown). LTP induced by 100 Hz, 1 s tetanic stimulation was significantly impaired in the O–A group compared to the O–C group ($P = 0.032$, see Fig. 1). The impairment of LTP in O–A group was observed at the LTP induction phase and maintained throughout the recording.

The present study demonstrated significantly more impairment of LTP after chronic heavy alcohol consumption in individuals with IGT or early type 2 diabetes than those who had never drunk. Moreover, this impairment of LTP was evident even when fasting and postprandial glycemic controls were favorable in alcohol-treated group compared to non-drinking group. Our results might proposed that chronic heavy drinking might impair the hippocampal LTP further or earlier than non-drinking in individuals with IGT or early type 2 diabetes. We confirm the observations of impaired hippocampal LTP induced by chronic heavy drinking [9,31] and provide preliminary evidence of the association between chronic heavy drinking and type 2 diabetes on cognitive impairment.

According to our results, non-drinking might be suggested as helpful in preventing the impairment of hippocampal LTP compared to heavy drinking in individuals prone to developing type 2 diabetes. This is a noticeable finding because previous researches on diabetic risk in general population showed that both non- and

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Table 1
Body weight, fasting glucose, and the result of an intraperitoneal glucose tolerance test in the OLETF–Alcohol (O–A) and the OLETF–Control (O–C) groups.

	The O–A group ($n = 5$)	The O–C group ($n = 5$)	P
	Mean ± SD	Mean ± SD	
Baseline body weight (g)	490.40 ± 8.61	500.60 ± 16.25	0.91
Baseline fasting glucose (mg/dl)	136.80 ± 4.83	132.80 ± 7.55	0.75
Δ Body weight (g)	0.30 ± 12.59	30.70 ± 7.82	0.11
IP-GTT after 10-week treatment (mg/dl)			
Baseline*	79.00 ± 1.87	96.40 ± 2.83	<0.01
30 min	266.40 ± 22.03	298.20 ± 9.20	0.34
120 min*	145.40 ± 6.89	199.00 ± 18.34	0.02

Δ (delta) values were obtained from immediately before and at the end of the 10-week treatment.
IP-GTT, intraperitoneal glucose tolerance test.
* $P < 0.05$.

heavy drinking are known to be associated with an increased diabetes risk [24]. Although the effect of moderate drinking on hippocampal LTP is need further investigation, our results support the significance of alcohol-induced brain damages [20]. The hippocampus and its related structures have been suggested to be particularly vulnerable to well-known neurotoxicity of alcohol [20,38]. Although both acute and chronic ethanol ingestion can impair LTP, chronic alcohol consumption causes morphological changes of hippocampal structures and decreases the synaptic plasticity in the hippocampal neurons even when the synaptic efficacy is maintained by compensatory reorganization [14]. These structural changes were reported to be long-lasting and difficult to recover, though not impossible [14,45]. Furthermore, even short-term, light drinking can abolish LTP if there are additional vulnerable factors, such as the critical time of brain development [50]. Future studies to confirm whether IGT and type 2 diabetes are vulnerable factors for alcohol-induced neurotoxicity will be required.

Although type 2 diabetes has been suggested to be related to the impairment of LTP [4,43], the hippocampal LTP in OLETF rats of the control group was relatively preserved in this study. This discrepancy might result from a difference in animal models of type 2 diabetes [4,43] and a state of pre-diabetes or early type 2 diabetes. However, the OLETF rat is a reliable model of human type 2 diabetes which develops hyperglycemia after 18 weeks of age [23] and shows overt albuminuria reflecting diabetic nephropathy at 22 weeks [44]. Furthermore, IGT reflects insulin resistance [26] that has been suggested as one of the possible mechanisms underlying cognitive impairment and dementia [46]. Insulin resistance itself was also associated with the impairment of hippocampal LTP in previous studies [35,42], indeed. Hence, 26 week-aged OLETF rats in this study might be assumed as having characteristics of type 2 diabetes. Nevertheless, more prolonged study design will be needed to confirm the deleterious effect of type 2 diabetes on the hippocampal LTP.

Regarding the results of the glucose tolerance test, OLETF rats with chronic heavy drinking showed significantly lower fasting and postprandial blood glucose levels than those without. This is inconsistent with previously reported results in human and rat model with type 2 diabetes [22,41] in which heavy drinking impaired postprandial glucose control [22], while moderate drinking improved fasting glucose level and had no effect on postprandial glucose level [41]. Our findings of improved glycemic control in alcohol-treated rats might be due to some possible confounding factors, such as relatively less weight gain and possible alcohol-induced liver injury [13,29]. Since there are few studies investigating the effect of alcohol on glycemic controls in patients with type 2 diabetes, further well-designed studies will be required to ascertain our findings. Nevertheless, considering that both poor glycemic control and relative obesity in the control group are important risk factors for the

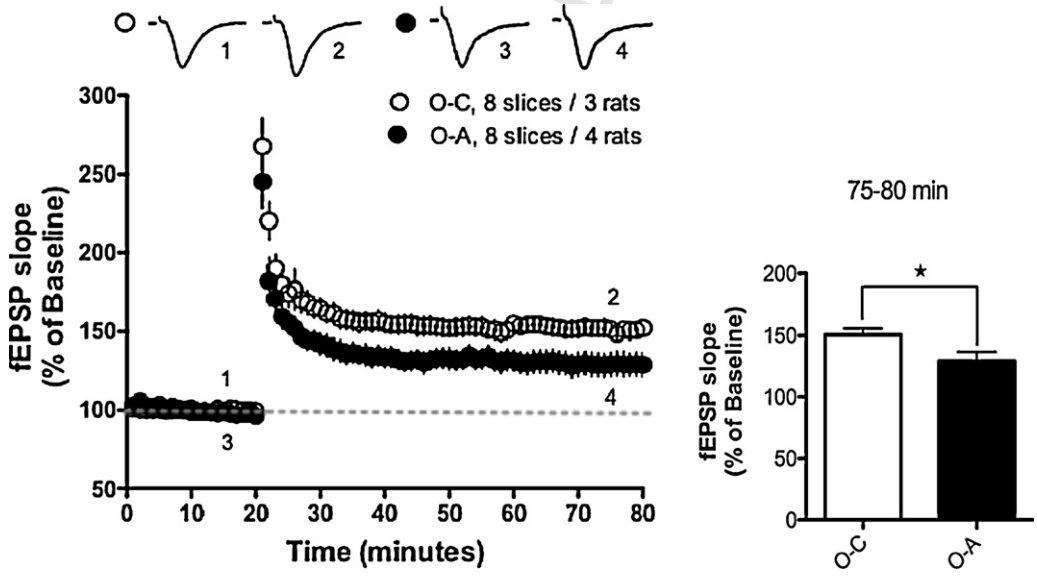

Fig. 1. Effects of chronic alcohol treatment on hippocampal long-term potentiation at the SC-CA1 synapses in OLETF rats. Slice field recording from OLETF rats with alcohol treatment (the O–A group) and control group without alcohol treatment (the O–C group). The data represent the fEPSP slopes (mean ± SEM, % of baseline) for slice field recording. The LTP induced by 1 s train of 100 Hz stimuli is impaired in the O–A group (the O–C group, 150.60 ± 5.07%, $n = 8$ slices/3 rats; the O–A group, 129.20 ± 7.42%, $n = 8$ slices/4 rats; $P = 0.032$, unpaired t-test).

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impairment of LTP [19], the notable impairment of hippocampal LTP in alcohol-treated rats is a more obvious finding. Furthermore, given that the results of IP-GTT are highly correlated with the insulin resistance [10], our results proposed that the impairment of LTP induced by chronic heavy drinking might be mediated by other mechanisms besides worsening of glycemic control and insulin resistance.

The mechanisms underlying the impairment of LTP induced by alcohol consumption and the risk of type 2 diabetes need to be considered. Recently, there have been reports that showed chronic heavy drinking decreased serum BDNF levels in OLETF rats [22]. Moreover, decreased BDNF was also observed in rats displaying insulin resistance and deficits in LTP [42]. BDNF plays a role in the synaptic plasticity and LTP [27] as well as glucose metabolism in diabetes [32]. It could be one of candidate mediators connecting the effects of type 2 diabetes and chronic heavy drinking on the hippocampal LTP. Future researches on potential mediators and their interactions will be expected.

Three caveats to the present study need to be addressed. First, there is no data on the blood alcohol concentration (BAC) to confirm the effect of the ethanol-included diet on blood alcohol level. Lieber-DeCarli Regular EtOH used in this study has been shown to produce a high and relatively constant level of ethanol consumption [33,34]. Additionally, this diet has been effective in examining the effect of chronic ethanol consumption on various physiological measures, such as hippocampal LTP [2,14], acetylcholine in the brain [37], inflammatory cytokines in the plasma [34], and alcohol-induced liver injury [13]. These results might suggest a reliable degree of BAC. However, its measurement should be included in the future study for more accurate interpretations. Second, we did not measure behavioral changes related to hippocampal function. LTP in the hippocampal CA1 region was reported to integrate spatial information by encoding similarities of the shape of spatial environment [16]. Studies investigating behavioral correlates of impaired LTP in the hippocampal CA1 region would be valuable for further clinical implications. Third, the study design did not involve non-diabetic control groups with and without chronic heavy alcohol consumption. Although we draw our conclusive suggestion based on previous results of impairment of hippocampal LTP in rats with type 2 diabetes [4,43] or insulin resistance [35,42], these control groups might help to distinguish the combined effect of alcohol and type 2 diabetes from that of alcohol or type 2 diabetes alone. Despite these limitations, our results provide preliminary evidence about the association between type 2 diabetes and chronic heavy alcohol consumption in the impairment of hippocampal LTP.

In summary, our preliminary results suggest that chronic heavy alcohol consumption could lead to further and/or earlier impairment of hippocampal LTP in individuals with IGT or early type 2 diabetes, even though it did not aggravate glycemic control. Given that the clinical significance of cognitive dysfunction in individuals with type 2 diabetes remains to be accentuated, chronic heavy alcohol consumption would be considered as a risk factor of potentiating cognitive decline in these patients.

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