Study on the Relationship between Postprandial Brain Function Decline and Blood Glucose Levels

Yuichi Sato, Yudai Ishikawa, Gaochao Cui, Kosuke Nagano, Fumiya Kinoshita, Hideaki Touyama
Toyama Prefectural University, Information Systems Engineering
Laboratory of Human Information
Imizushi, Japan
e-mail: u155014@st.pu-toyama.ac.jp, u255004@st.pu-toyama.ac.jp, cuigaochao@pu-toyama.ac.jp,
u055016@st.pu-toyama.ac.jp, f.kinoshita@pu-toyama.ac.jp, touyama@pu-toyama.ac.jp

***Abstract*— Post-lunch drowsiness, also known as Post-Lunch Dip (PLD), is a symptom of impaired brain function. Currently, the hypothesis that PLD is caused by an increase in postprandial blood glucose level is supported as a possible explanation for the mechanism of PLD. However, few studies have examined the relationship between postprandial brain dysfunction and blood glucose levels by measuring both simultaneously. In this study, we measured blood glucose levels and Event-Related Potential (ERP) before and after consumption of two foods with different carbohydrate contents, and examined the relationship between postprandial blood glucose fluctuations and PLD. In the high-sugar food ingestion group, two slices of bread and water were given, and the low-sugar ingestion group received low-carbohydrate bread and water. The results showed that the high-sugar food ingestion group had increased sleepiness, prolonged P300 latency, and increased early and late contingent negative variation amplitudes at 40 minutes postprandial ingestion. There were no significant differences in sleepiness, brain function, or blood glucose levels in the low-sugar ingestion group. In contrast, there was a significant increase in blood glucose levels immediately and 40 minutes after eating in the high-sugar food ingestion group resulting in brain function impairment. Therefore, it is suggested the postprandial increase in blood glucose level is related to the development of PLD. In addition, the blood glucose levels at 40 minutes after eating in the high-sugar food ingestion group were significantly lower after ERP measurement than before ERP measurement. This suggests PLD occurs during hyperglycemia and when blood glucose levels fall.**

Keywords-Post-Lunch Dip (PLD); Event-Related Potential (ERP); P300; Contingent Negative Variation (CNV); Blood Glucose Level.

I. INTRODUCTION

The transient decline in brain function caused by Post Lunch Dip (PLD) [1] has been highlighted as a possible cause of human error [2][3], and it is important to establish optimal intervention methods and prevention techniques against PLD. In recent years, research hypotheses that link postprandial brain dysfunction and blood glucose fluctuations have attracted attention as a possible explanation for the pathogenesis of PLD. Although the explanation of blood glucose spikes [4] and neuropeptide inhibition [5] are representative examples, neither hypothesis has been widely recognized as a research hypothesis explaining the mechanism of PLD yet, because the evidence for each hypothesis is insufficient. One of the reasons for this is that there have been few cases in which the decline in brain function due to postprandial sleepiness has been evaluated using quantitative indices. Therefore, our research group focused on electrophysiological responses using event-related potentials, a type of electroencephalogram (EEG), as a quantitative evaluation index for PLD and conducted empirical experiments [6]. In addition to the basic rhythmic components of the EEG, such as alpha and beta waves, there is Event-Related Potential (ERP), which is induced by specific stimuli. Among ERPs, P300 and Contingent Negative Variation (CNV) are used to evaluate cognitive function and attention [7]. Our empirical experiments confirmed that simultaneous measurement of P300 and CNV is an effective objective measure of transient deterioration of brain function, fatigue, and sleep in PLD. Recently, however, Continuous Glucose Monitoring (CGM) devices have emerged that can measure blood glucose levels over time with a single puncture. CGM devices can continuously record the concentration of glucose in the interstitial fluid, which is highly correlated with blood glucose levels, using a sensor implanted in the subcutaneous tissue [8]. The CGM measures the glucose concentration in the interstitial fluid by changing the current in the enzymatic method. It has been highlighted that glucose in the interstitial fluid is slow to follow rapid fluctuations in blood glucose levels [9]. However, CGM has attracted attention as a simple and powerful tool for preventing blood glucose-related diseases because it enables monitoring of blood glucose levels over time.

Therefore, in this study, we investigated the relationship between postprandial blood glucose changes and PLD by recording blood glucose levels, P300, and CNV before and after consumption of high and low carbohydrate foods over time.

The rest of this paper is organized as follows. Section II describes the experimental protocol and the issues arising from the ERP. Section III describes the P300 and CNV analysis methods. Section IV describes the experimental

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results. Section V goes into more detail regarding the relationship between postprandial brain dysfunction and blood glucose fluctuations. Section VI provides a summary of this paper.

II. EXPERIMENTAL PROCEDURE

In this study, experiments were conducted on three groups: 1) A high-sugar food ingestion group, 2) A water-only control group, and 3) A low-sugar food ingestion group. All participants were young and healthy with no history of neurological disease. The high-sugar food ingestion group comprised 20 participants (Mean ± SD, 21.50 ± 0.86 years), the control group comprised 10 participants (Mean ± SD, 22.5 ± 0.85 years), and the low-sugar food ingestion group comprised 10 participants (Mean ± SD, 21.80 ± 1.16 years). The participants were thoroughly informed about the experiment, and their consent was obtained. This experiment was approved by the Ethics Committee of Toyama Prefectural University [R3-6].

The measurement items used in this experiment were P300, CNV, electro-oculography, the Stanford Sleepiness Scale (SSS), and reaction time from stimulus presentation to pressing the button switch. Subjects were instructed to press the button switch with their dominant hand. Blood glucose levels were measured in subjects who belonged to the high-sugar food ingestion group and the low-sugar food ingestion group. Blood glucose levels were measured in 10 subjects (Mean ± SD, 21.80 ± 1.16 years) in the high-sugar food ingestion group and in all subjects in the low-sugar food ingestion group. A FreeStyle Libre (Abbott Japan LLC), a CGM device, was used to reduce the measurement burden on subjects and to minimize measurement error due to needle puncture position. CGM records the glucose concentration in the interstitial fluid, not the blood glucose concentration. However, since the glucose concentration in the interstitial fluid has been reported to have a high correlation with the blood glucose concentration, the glucose concentration in the interstitial fluid is hereafter referred to as the blood glucose level. The sensor for measuring blood glucose was attached to the side of the upper arm opposite the dominant hand of each subject.

A g.USBamp (g.tec medical engineering GmbH, Austria) was used to measure biological signals. The sampling frequency of the measurement device was 512 Hz, and a low-pass filter of 0.01 Hz, a high-pass filter of 30 Hz, and a notch filter of 60 Hz were applied for noise reduction. Based on the extended 10–20 method, the electrode positions for the EEG were Cz, which are the predominant areas of CNV, and Pz, which is the predominant area of P300, with AFz as the ground electrode and the left earlobe as the reference electrode. To exclude electrical noise associated with blinking, electrodes were affixed above and below the left eye, and the electro-oculogram was measured. To eliminate artifacts based on spatial independence, EEG measurements were also taken for Fz, F1, F2, C1, C2, P1, and P2.

The experimental protocol is shown in Figure 1. Four ERP measurements were taken before (pre-consumption), immediately after (Post 1), 40 min after (Post 2), and 80 min after (Post 3) the meal, and the SSS was administered before each measurement. Blood glucose levels were measured once before and after each ERP measurement, and the mean value was used as the representative value at each measurement time. A previous study reported that intense sleepiness occurs after ingestion of high-sugar foods [10]. Therefore, the dietary load used in the high-sugar food ingestion group was white bread (two x 20 mm thick slices) and water (285 ml), which has a high glycemic index (GI) value indicating the increase in blood glucose levels due to different foods [11]. The control group received only water (285 ml). The low-sugar food ingestion group was given low-sugar bread (approximately 120 g) and water (285 ml) to control for food ingestion and dietary content, and to manipulate the carbohydrate content of the food. The total carbohydrate content of the bread in the high-sugar food ingestion group was approximately 63 g and the low-sugar food ingestion group was approximately 22 g. Eating and drinking were prohibited two hours prior to the start of the experiment, as well as the use of electronic devices, excessive exercise, eating, drinking, and sleeping outside of the measurement time.

The oddball paradigm and the CNV paradigm are widely used for P300-evoked and CNV-evoked tasks, respectively. In the oddball paradigm, subjects were randomly presented with two types of stimuli with different presentation frequencies and were asked to respond only to the stimulus presented at a lower frequency [6]. The CNVs were elicited by presenting the second stimulus (S2) 3–7 seconds after the first stimulus (S1) and requesting a possible behavioral response to S2. In this study, to measure P300 and CNV simultaneously, we employed two types of stimuli for S2 in the CNV paradigm: low-frequency and high-frequency stimuli (see Figure 2). S1 was a pure tone at 1,000 Hz, presented as an auditory stimulus through an earphone attached to the subject's ear; S2 was a visual stimulus presented through an LCD placed 60 cm in front of the subject. The visual stimuli were "A" and "B" images in the center of the LCD screen as the low-frequency and high-frequency stimuli, respectively. Participants were instructed to quickly press a button switch for the low-frequency stimulus.

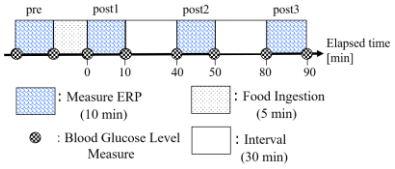

Figure 1. Experiment protocol

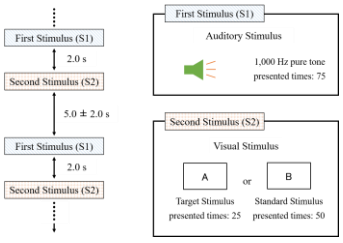

Figure 2. Experimental paradigm

III. ANALYSIS METHOD

A. P300 Analysis

A 0.5–7 Hz bandpass filter was applied to the EEG data at Pz. EEG and electro-oculogram data were then extracted for five seconds before and after the stimulus presentation (10 seconds in total) during each target stimulus. The InfoMax ICA algorithm [12] was applied to the EEG data to remove artifacts associated with blinking, and components with correlation coefficients greater than ± 0.6 with the electro-oculogram during the same time period were excluded. Finally, the baseline was corrected by subtracting the average voltage value during the 0.25 s before the presentation of the target stimulus. In the data of each EEG during target stimulation, we performed additive averaging, excluding trials in which the button switch was pressed incorrectly and where the voltage value exceeded ± 75 μV in the interval from 0.2 s before to 0.8 s after the presentation of the target stimulus. In this study, we identified the positive peak above 2.5 μV that appeared 0.2–0.6 s after presentation of the target stimulus as P300, and derived the P300 latency. The calculated P300 latencies were compared using the Wilcoxon signed-rank test for each value before and after feeding. The significance level was set at $p < 0.05$. A typical waveform of P300 measured in the same subject is shown in Figure 3.

B. CNV Analysis

For CNV derivation, EEG and EOG data at Cz from four seconds before S1 presentation to four seconds after S2 presentation (total 10 seconds) were extracted. To remove artifacts caused by blinking, the extracted EEG data were component decomposed with InfoMax ICA, and independent components with an absolute correlation coefficient of 0.7 or higher with the electro-oculogram at the same time were removed and reconstructed. The EEG data, excluding the effect of blinking, were baseline corrected by subtracting the average amplitude of 0.25 seconds before S1 presentation. For each of the above processed EEG data, an additive average was performed by excluding trials in which no button presses were observed within 0.5 seconds and trials in which the amplitude exceeded ±75 μV. In this study, the interval from 0.4 to 0.8 seconds after S1 presentation was defined as early CNV, and the interval from one second before S2 presentation to one second after S2 presentation as late CNV, and the mean amplitudes of these intervals were derived for each subject [13]. The mean amplitudes of the calculated CNVs were compared before and after feeding using the Wilcoxon signed-rank test for each value. The significance level was set at $p < 0.05$. A typical waveform of CNV measured in the same subject is shown in Figure 4.

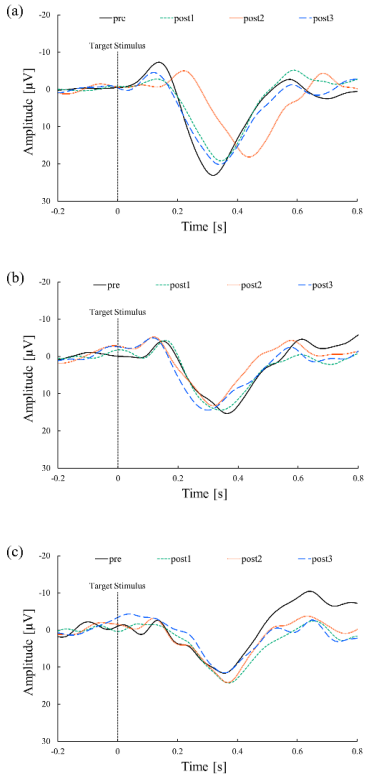

Figure 3. Typical waveform of P300 for one participant: (a) high-sugar food ingestion group, (b) control group, (c) low-sugar food ingestion group

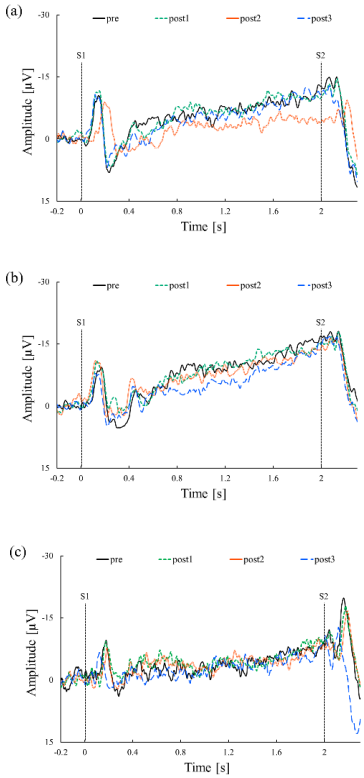

Figure 4. Typical waveform of P300 for one participant: (a) high-sugar food ingestion group, (b) control group, (c) low-sugar food ingestion group

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IV. RESULTS

Figure 5 shows the change over time of the mean value of each analytical index for all subjects.

The mean value of the SSS in the high-sugar food ingestion group was 2.5 for pre-intake, and significantly increased to 3.2 in Post 2 ($p < 0.05$). In the mean values of the SSS in the low-sugar food ingestion and control groups, there was no significant difference between the pre- and post-intake values when compared using Wilcoxon's signed rank test for the pre- and post-intake values, respectively.

Next, the mean reaction time from visual stimulus presentation to button press in the high-sugar food ingestion group was approximately 0.3 seconds at all measurement times, and the Wilcoxon signed-rank test showed no significant difference between the pre- and postprandial values. In the mean reaction time from visual stimulus presentation to button press in the low-sugar food ingestion group and the control group, a comparison using Wilcoxon's signed-rank test between the pre- and postprandial values showed no significant difference between them. Two out of 10 subjects in the low-sugar food ingestion group were excluded from the analysis because the button switch did not work properly.

Next, the mean value of P300 latency in the high-sugar food ingestion group was approximately 0.33 seconds for pre-intake, but was significantly longer in Post 2, approximately 0.36 seconds ($p < 0.05$). In the mean value of P300 latency in the low-sugar food ingestion and control groups, there was no significant difference between pre and post-intake when compared using Wilcoxon's signed rank test for each value in the pre- and post-intake groups.

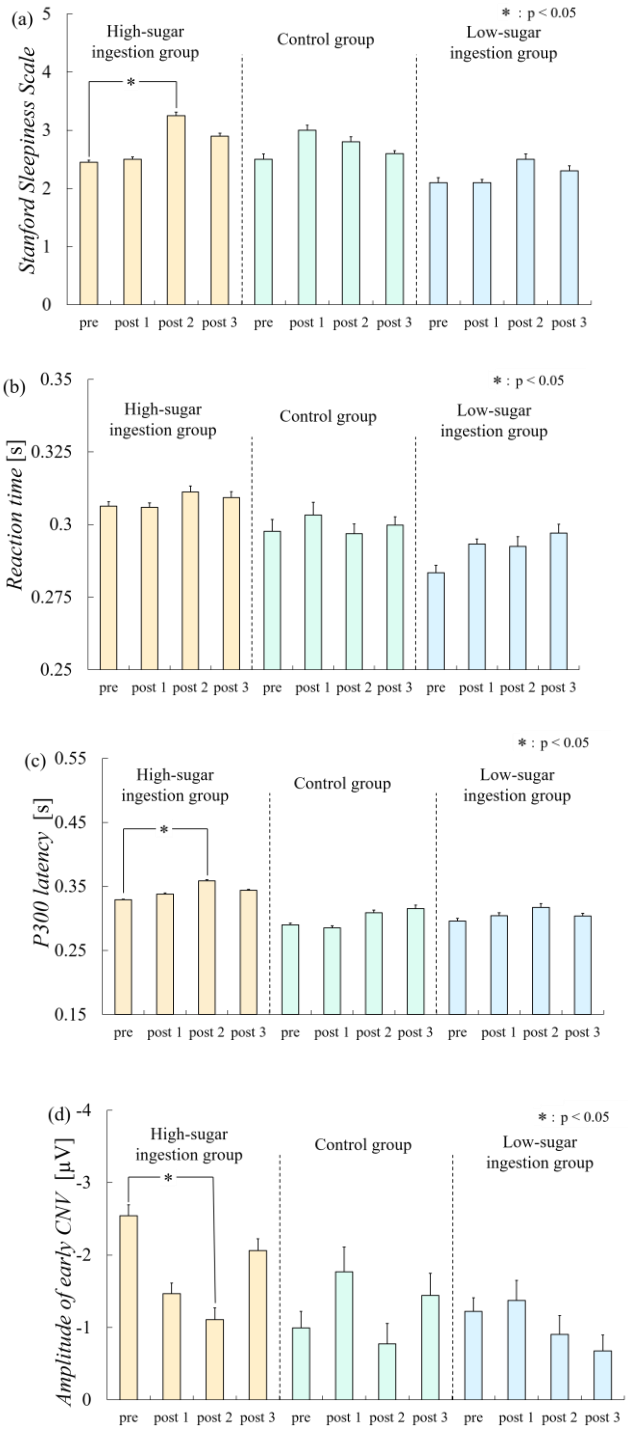
Next, the mean amplitude of the preprimary CNV in the high-sugar food ingestion group was approximately -2.5 μV for the pre-intake, but significantly increased to about -1.1 μV in Post 2 ($p < 0.05$). In the mean amplitude of the early CNV in the low-sugar food ingestion and control groups, there was no significant difference between the pre- and post-intake values when compared using Wilcoxon's signed rank test for each value in the pre- and post-intake groups.

Next, the mean amplitude of late CNV in the high-sugar food ingestion group was approximately -5.2 μV for pre-intake, but significantly increased to about -2.9 μV in Post 2 ($p < 0.05$). In the mean amplitude of late CNV in the low-sugar food ingestion and control groups, there was no significant difference between pre- and post-intake values when compared using Wilcoxon's signed rank test for each value in the pre- and post-intake groups.

The mean blood glucose level in the high-sugar food ingestion group was 97 mg/dL for pre-intake, but significantly increased to 114 mg/dL in Post 1 and 145 mg/dL in Post 2 ($p < 0.05$). Blood glucose levels in Post 2 were significantly higher than those in Post 1 and Post 3 ($p < 0.05$) (see Figure 6). The mean values of blood glucose in the low-sugar food ingestion group showed no significant difference between the pre- and postprandial values using Wilcoxon's signed rank test.

In Post 1, blood glucose significantly increased from 99.7 mg/dL before ERP measurement to 128.8 mg/dL after ERP measurement ($p < 0.05$). The blood glucose level decreased significantly from 152.7 mg/dL before ERP measurement ($p < 0.05$) (see Figure 7).

The mean blood glucose level of all subjects in the low-sugar food ingestion group was 92.5 mg/dL after ERP measurement compared to 99.1 mg/dL before ERP measurement in Post 2, showing a significant decrease in blood glucose level ($p < 0.05$) (see Figure 7).



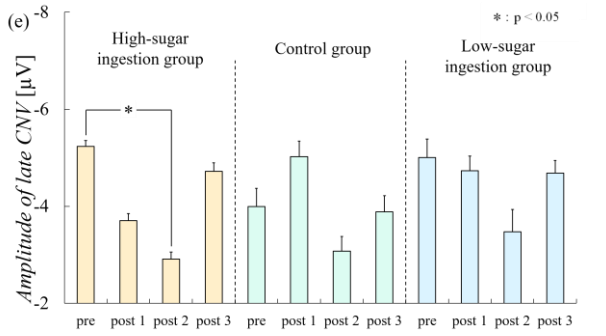


Figure 5. Change over time in each analytical index (Mean ± SE), (a) stanford sleepiness scale, (b) reaction time, (c) P300 latency, (d) amplitude of early CNV; (e) amplitude of late CNV

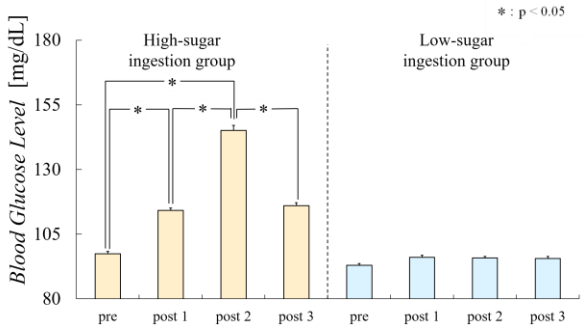


Figure 6. Change over time in blood glucose level (Mean ± SE)

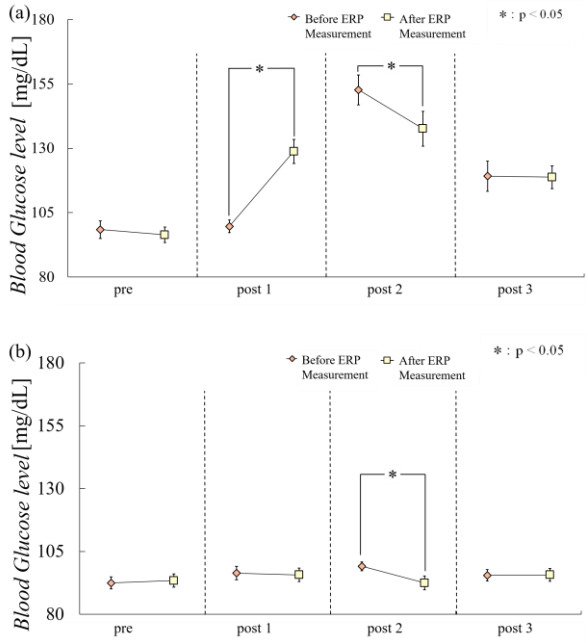


Figure 7. Blood glucose level before and after ERP measurement (Mean ± SE);(a) High-sugar food ingestion group, (b) Low-sugar food ingestion group

V. DISCUSSION

Recent research hypotheses that link postprandial brain dysfunction to fluctuations in blood glucose levels have been proposed to explain the pathogenesis of PLD, and have attracted much attention. Although blood glucose spikes and neuropeptide inhibition are representative examples of such hypotheses, the mechanism of PLD remains to be elucidated. This is due to the fact that there have been few cases in which the decline in brain function caused by postprandial sleepiness has been evaluated using quantitative indices, and where brain function and blood glucose levels before and after eating have been recorded simultaneously. In this study, we investigated the relationship between postprandial brain function decline and blood glucose level fluctuations by measuring ERP and blood glucose levels before and after consumption of two foods with different carbohydrate contents.

In the high-sugar food ingestion group that consumed white bread, a high GI food, there was an increase in the subjective sleepiness score, prolonged P300 latency, and increased early and late CNV amplitude in Post 2 compared to pre-intake. In addition, blood glucose levels measured at the same time were significantly increased in the high-sugar food ingestion group in Post 1 and Post 2 compared to pre-intake. In contrast, there were no significant changes in any of the parameters in the low-sugar food ingestion group before and after the meal. In 1990, Pivonka et al. evaluated postprandial sleepiness after consumption of high-sugar beverages and water using the SSS [14]. The results showed that the group that consumed high-sugar beverages had significantly increased values on the SSS compared to the group that consumed only water. This is consistent with the results of this study, in which PLD was observed only in the high-sugar food ingestion group with significantly increased blood glucose levels. In 2019, Ogata et al. also fed 20 university students with high- or low-GI foods and compared the number of students who fell asleep during lectures after lunch [15]. Ogata et al. also recorded blood glucose levels after lunch using a CGM, similar to this study. The results showed that blood glucose levels increased significantly when students consumed low-GI foods compared to when they consumed high-GI foods. In contrast, the number of students who dozed off during the lecture after lunch did not change even when the GI values of the foods were varied. However, Ogata et al. used the presence or absence of nodding off during lectures as an evaluation index for post-lunch sleepiness, and did not use a quantitative index to evaluate the post-lunch decline in brain function. In this study, in addition to the subjective questionnaire and blood glucose level, we measured ERPs, which were suggested to be useful as quantitative evaluation indices for postprandial brain function decline. As a result, ERP fluctuated significantly with a significant increase in blood glucose level only when high GI foods were consumed, confirming the decline in brain function. Therefore, this study's use of a quantitative evaluation index for postprandial decline in brain function provides new results that support the research

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hypothesis that postprandial blood glucose fluctuations affect brain function.

In the high-sugar food ingestion group, there was a significant increase in blood glucose levels in Post 1 and Post 2 compared to pre-intake. However, increased subjective sleepiness and decreased brain function were not observed in Post 1, but only in Post 2. One of the major research hypotheses explaining the mechanism of PLD is the explanation by neuropeptide inhibition, which is a neuropeptide that regulates arousal level. One of the major research hypotheses to explain the mechanism of PLD, the explanation by suppression of neuropeptides, proposes that PLD is caused by the suppressed secretion of orexin, a neuropeptide that controls arousal level [5]. It is known that orexin secretion is inhibited in response to the degree of blood glucose elevation [16]. Therefore, the inhibitory effect of orexin is small at the degree of elevation of blood glucose level that occurred in Post 1 of this study, and it is considered that brain function did not decrease.

In addition, to investigate the tendency of blood glucose fluctuation during ERP measurement, blood glucose levels before and after ERP measurement were compared in this study. The results showed a significant increase in blood glucose levels before and after ERP measurement in Post 1, and a significant decrease in blood glucose levels before and after ERP measurement in Post 2 in the high-sugar food ingestion group. Therefore, PLD is thought to occur when blood glucose levels fall, not when they rise. The blood glucose spike explanation is a research hypothesis which posits that PLD is caused by the secretion of melatonin, which has hypnotic effects, in association with the additional secretion of insulin in response to the postprandial rise in blood glucose [4]. In other words, in the blood glucose spike explanation, PLD is thought to occur from the peak to the fall of blood glucose levels, when insulin secretion is prominent. In this study, PLD was also observed in Post 2, when blood glucose levels tended to decrease, and these experimental results support the blood glucose spike explanation. However, even in the low-sugar food ingestion group, where brain function did not decline after consumption, a significant decrease in blood glucose levels was observed before and after ERP measurement in Post 2. Therefore, it is possible that the postprandial decline in brain function does not necessarily occur when blood glucose levels fall, but rather when blood glucose levels fall after a postprandial increase to a high level.

VI. CONCLUSION

To elucidate the pathogenesis of PLD, it is important to establish a quantitative evaluation index to assess brain dysfunction caused by eating. Currently, the hypothesis that PLD is caused by an increase in postprandial blood glucose level is sup-ported as a possible explanation for the pathogenesis of PLD. However, few studies have simultaneously measured postprandial brain dysfunction and blood glucose levels, and examined the relationship between the two. In this study, we measured blood glucose levels and ERP before and after consumption of two types of foods with different carbohydrate contents, and examined the relationship between postprandial blood glucose fluctuations and PLD.

The results showed that the SSS values increased significantly in the high-sugar food ingestion group in Post 2 compared to pre-intake. The SSS significantly in-creased in Post 2. The P300 latency was significantly prolonged in Post 2, and the early and late CNV amplitudes were significantly increased in Post 2. However, in the control group without food, there were no significant changes in any of the parameters before or after drinking. Therefore, P300 and CNV are highly useful as quantitative indices to evaluate the transient decline in brain function caused by PLD. There were no significant differences in subjective sleepiness, brain function, or blood glucose levels before and after eating in the low-sugar food ingestion group. In contrast, there was a significant increase in blood glucose levels in the high-sugar food ingestion group with impaired brain function in Post 1 and Post 2 compared to pre-, and a peak increase in blood glucose levels was observed in Post 2. Therefore, it was suggested that the postprandial rise in blood glucose was related to the expression of PLD. In the Post 2 blood glucose levels in the high-sugar food ingestion group, there was a significant decrease after ERP measurement compared to before ERP measurement. This suggests that PLD occurs during hyperglycemia and when blood glucose levels fall.

In the future, we will investigate the relationship between blood glucose and brain function decline in detail, such as when moderate GI foods are consumed and when multiple foods are consumed. If we can clarify the conditions under which PLD is induced by blood glucose levels, it will be possible to estimate the amount of food consumed and the way of eating that reduces the decline in performance after a meal. These research results can be applied to various fields, such as sports science and nutritional science. Furthermore, we aim to establish systematic evaluation criteria for PLD and transient decline in brain function by conducting continuous experiments using the number of chews and the amount of food consumed as factors.

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