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Hypoglycemia-induced cerebellar dysfunction and quantitative positron emission tomography study

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Articles

Hypoglycemia-induced cerebellar dysfunction and quantitative positron emission tomography study

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Objective: To describe an unusual case of hypoglycemia-induced bilateral cerebellar dysfunction.

Background: The cerebellum is known to be resistant to hypoglycemia, and selective cerebellar dysfunction caused by hypoglycemia has not been reported. Previous studies showed that the ratio between the rate constants for glucose uptake and phosphorylation (K_1 and k_3) is reversed in the cerebellum compared with the cerebral cortex; higher K_1 in the cerebellum and higher k_3 in the cerebral cortex.

Methods: Quantitative dynamic PET scanning with labeled fluorodeoxyglucose (18 F-FDG) was performed to prove altered glucose kinetics in the cerebellum of a patient who presented with episodic cerebellar dysfunction associated with hypoglycemia. Four control subjects underwent the same study.

Results: The ratio between K_1 and k_3 was not reversed in the cerebellum of our patient ($K_1 = 0.082$, $k_3 = 0.192$). On the contrary, the ratio was reversed in the control subjects (mean $K_1 = 0.109$, mean $k_3 = 0.080$). In addition, the patient's cerebellar metabolic rate of glucose ($rCMR_{glu} = 27.9 \mu\text{mol}/100 \text{ g/minute}$) and the rate constant of glucose egress ($k_2 = 0.543$) were relatively increased compared with those of control subjects (mean $rCMR_{glu} = 21.9 \mu\text{mol}/100 \text{ g/minute}$, mean $k_2 = 0.352$).

Conclusions: In a case of episodic bilateral cerebellar dysfunction caused by hypoglycemia, quantitative dynamic PET study demonstrated decreased glucose uptake-to-utilization ratio and increased leak of glucose in the cerebellum. The cerebellum is not invariably resistant to hypoglycemia.

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Introduction

The cerebellum is relatively resistant to hypoglycemia according to studies on the severity of metabolic alteration [1] [2] [3] [4] [5] [6] or pathologic change. [2] [7] [8] [9] In addition, many studies have indicated the following possible mechanisms: a more efficient glucose transporter system, [10] [11] a denser capillary network, [12] or less reduction of the autoregulatory capacity during hypoglycemia [13] in the cerebellum than in other brain regions.

In a PET study of men with diabetes, [14] it was demonstrated that the cerebellum has different glucose kinetics compared with the cerebral cortex; a higher K_1 (rate constant for glucose uptake) and a lower k_3 (rate constant for glucose phosphorylation). Accordingly, the higher rate of glucose extraction from the blood and its lower utilization rate—the rate of phosphorylation and rate of utilization can be used interchangeably [15] —in the cerebellum account for its resistance to hypoglycemia.

We describe a case of selective cerebellar dysfunction due to hypoglycemia and its possible mechanism. We assessed the regional glucose kinetics of the brain with quantitative dynamic PET to explain the unusual vulnerability to hypoglycemia in the patient's cerebellum.

Methods.

Patient history.

A 52-year-old woman presented with dysarthria and ataxia. She had a 24-year history of diabetes mellitus managed with insulin and oral hypoglycemic agents. On the day of admission, she felt a hunger sensation, dizziness, and palpitation on awakening. She could not remain standing without assistance, and her upper limbs trembled when outstretched. Her blood sugar level was 2.98 mmol/L in the emergency room and rose to 5.18 mmol/L after glucose infusion. The palpitation and sweating disappeared after glucose correction, but ataxia, dysarthria, and mild dizziness continued. Three days before admission, she had experienced a similar episode of dysarthria and ataxia outlasting systemic hypoglycemic symptoms, which lasted for 20 minutes. There was no history of ataxia or migraine. No similar neurologic disease was reported in her family.

Her temperature was 36 °C, pulse was 90/minute, and respirations were 18/minute. Initial blood pressure was 160/80 mm Hg. Results of general physical examination were negative. On neurologic examination, the patient was alert and oriented with fluent speech. **Bilateral gaze-evoked nystagmus** and **dysarthria** were observed. Extraocular movements and the remaining cranial nerve functions were intact. Muscle strength and sensory examination were normal. The deep-tendon reflexes were ++ in the four extremities. The plantar responses were flexor. She showed moderate to severe dysmetria on the finger-to-nose test and prominent dysmetria on the heel-to-shin test, bilaterally.

The results of a complete blood count and urinalysis were unremarkable. Chest X-ray and electrocardiography showed no abnormality. Her cerebellar dysfunction disappeared approximately 12 hours after its onset. Brain MRI and angiography (MRA) taken 30 hours after onset revealed no abnormality. Transcranial Doppler (TCD) was normal, and an echocardiography revealed no abnormality except mitral valve prolapse.

Quantitative dynamic PET study was performed, and rate constants for glucose uptake (K_1), egress (k_2), phosphorylation (k_3), and regional cerebral metabolic rate for glucose ($rCMR_{glu}$) were obtained [16] in different brain regions using the three-compartment model described by Sokoloff et al. [17] We also obtained the values for four control subjects. This study was approved by the Institutional Review Board of the hospital. The patient and control subjects gave written consent.

¹⁸F-FDG PET.

¹⁸F-FDG was synthesized and PET scans were performed at the PET center, Seoul National University Hospital, using an ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN; spatial resolution 5.2 mm, 47 contiguous planes, slice thickness 3.375 mm).

Patient preparation.

On the day of the PET scan, the patient fasted after breakfast. After local anesthesia, 20-gauge catheters were placed in the forearm veins of both arms using an aseptic technique. Normal saline was infused slowly to ensure the patency of the IV catheters. One catheter was used for insulin infusion and the other for glucose infusion. After the arterial collateral circulation of the right arm was checked for patency, the radial artery was

cannulated with a 24-gauge catheter using an aseptic technique under local anesthesia. Diluted heparin solution was connected to the arterial catheter using an arterial line set, and the pressure bag was inflated to the sufficient pressure. After preparation of the catheters, the patient was positioned in the PET scanner. The head was immobilized with a restraining strap, and its position was monitored throughout the study using the reference laser system built in the PET scanner.

The initial arterial glucose level was measured at bedside; then, the soluble insulin was diluted to a concentration of 300 mU/mL. At time = 0 minutes, the priming dose of diluted soluble insulin (4.8 mU/kg/minute) was infused continuously, and then the rate was decreased at 1-minute intervals to 1.5 mU/kg/minute at time = 10 minutes. In the next step, the arterial glucose level was measured, and the infusion rate of the glucose was changed every 5 minutes for 20 minutes (time = 30 minutes) in order to maintain an arterial glucose level of between 4.5 and 5.5 mmol/L, with the infusion rate of insulin fixed at 1.5 mU/kg/minute. The arterial glucose level was monitored every 10 minutes after the glucose level was stabilized (from time = 30 minutes to time = 90 minutes). The head position was compared again with the reference laser system and repositioned. The head position was also rechecked every 5 minutes after the scanning was begun.

PET scanning procedure.

Transmission scanning was performed for 20 minutes using three rotating rod sources containing ^{68}Ge between time = 50 minutes and 70 minutes. The patient was asked to stay in the supine position with her eyes closed, in a dimly lit and quiet scanning room for the standardized sensory stimuli.

At time = 90 minutes, when glucose metabolism approximated steady-state with an arterial plasma glucose level of 5 mmol/L under insulin clamp conditions, ^{18}F -FDG PET dynamic scanning was performed to assess glucose early kinetics. ^{18}F -FDG 375 MBq was diluted with normal saline to the total volume of 10 mL. It was infused slowly through the venous catheter that was used for glucose infusion for 30 seconds via an infusion pump. Dynamic scanning began 10 seconds before ^{18}F -FDG infusion and ended 60 minutes after infusion. The dynamic acquisition was comprised of 43 frames: 10 for 5 seconds, 10 for 10 seconds, 5 for 30 seconds, 5 for 60 seconds, 5 for 120 seconds, 8 for 300 seconds. Timed 2-mL hand-drawn arterial blood samples were taken 19 times (at time = 0 ~ 3 minutes every 20 seconds, and at time = 4, 5, 6, 8, 10, 20, 30, 40, 50, 60 minutes) to quantify ^{18}F FDG concentration of arterial plasma.

The arterial blood was collected in EDTA-citrate tubes and immediately put on ice. After centrifuge, the plasma fraction of each blood sample was drawn by 500 μL . Its ^{18}F FDG was counted using a well-type gamma counter (Packard Gamma counter; Cobra, Downers Grove, IL). A portion of the arterial sample was used for glucose monitoring in order to maintain the level at 5 mmol/L.

At the end of the ^{18}F -FDG scan, insulin administration was discontinued. Glucose administration was discontinued when the arterial plasma glucose level became consistently greater than 5.5 mmol/L. The arterial catheter and venous catheters were withdrawn sequentially.

Control subjects.

Four volunteers (F/23, F/21, M/20, M/22) underwent ^{18}F -FDG PET under the same protocol, except that arterialized venous sampling was done instead of arterial sampling.

Measurements and calculations.

Raw data from the emission scanner contained in the sinograms and reconstructed frame images were reviewed to determine any motion of the patient. There was no significant distortion of the image or motion of the patient. Regions of interest (ROI) from the cerebellar cortex and other cerebral cortices were drawn on three sequential slices of PET images and reviewed on MRI scans. Counts of these ROI were measured on each of the 43 frames. The counts of three slices in the same ROI were added together.

The radioactivity count measured with the gamma counter and the PET scanner was converted into absolute radioactivity using conversion factors that had been previously obtained in our PET center. Tracer activity curves (TAC) in arterial plasma and tissue were fitted using nonlinear regression. ^[18]

Results.

As shown in table, the ratio between K_1 and k_3 of the patient was not reversed in the cerebellum compared with that of the cerebral cortex. However, it was reversed in the cerebella of control subjects.

The patient's calculated K_1/k_3 was 0.082/0.192 in the cerebellum and 0.078/0.179 in the cerebral cortex. The mean of K_1/k_3 for control subjects was 0.109/0.080 in the cerebellum and 0.093/0.107 in the cerebral cortex. The cerebellar $rCMR_{glu}$ (27.9 $\mu\text{mol}/100\text{ g}/\text{minute}$) and k_2 (0.543) were relatively increased in the patient compared with those of control subjects (mean $rCMR_{glu}$ = 21.9 $\mu\text{mol}/100\text{ g}/\text{minute}$, mean k_2 = 0.352).

Table 1. Summary of quantitative PET study results

Subjects	Cortex				Cerebellum			
	K_1	k_2	k_3	$rCMR_{glu}$	K_1	k_2	k_3	$rCMR_{glu}$
Patient	0.078	0.387	0.179	32.24	0.082	0.543	0.192	27.90
Control 1	0.081	0.213	0.095	28.75	0.110	0.272	0.099	33.81
Control 2	0.091	0.220	0.105	27.37	0.102	0.301	0.049	13.31
Control 3	0.077	0.194	0.082	22.57	0.083	0.276	0.081	18.53
Control 4	0.123	0.123	0.145	38.07	0.139	0.559	0.089	22.24

The ratio between K_1 and k_3 is not reversed in the cerebellum of the patient, but it is reversed in the cerebella of control subjects. The patient's cerebellar $rCMR_{glu}$ and k_2 were relatively increased compared with those of control subjects.

K_1 = rate constant for glucose uptake; k_2 = rate constant for glucose egress; k_3 = rate constant for glucose phosphorylation; $rCMR_{glu}$ = regional metabolic rate of glucose ($\mu\text{mol}/100\text{ g}/\text{min}$).

Discussion.

Most patients with diabetes should strive to lower glucose levels to reduce the long-term complications associated with diabetes. [19][20] However, this increases the risk of acute hypoglycemia, [19][21] which can bring about diverse neurologic manifestations such as dizziness, behavioral changes, seizures, stupor, coma, or hemiparesis. [22] These may be transient, but irreversible neuronal damage develops when hypoglycemia is severe and prolonged. [7][23][24][25] Among the brain structures, the cerebellum is least vulnerable to hypoglycemia; the association of hypoglycemia and cerebellar dysfunction is of considerable interest.

Because the patient's cerebellar dysfunction lasted for approximately 12 hours without neurologic deficit or MRI abnormality, TIA may be a possible diagnosis. However, most TIA last 10 to 15 minutes, and patients with TIA of longer duration are likely to have relevant cerebral infarcts on MRI. [26][27] Thus, when we also consider that cerebellar dysfunction was repeatedly associated with systemic hypoglycemic symptoms, the diagnosis of TIA is less likely. By excluding other possible diseases such as mitochondrial disorder, familial episodic ataxia, MS, and periodic vestibulocerebellar ataxia by history and clinical findings, the most likely possibility is hypoglycemia-induced cerebellar dysfunction.

Previous studies have reported that the cerebellum is relatively resistant to hypoglycemia. One of the suggested mechanisms of this resistance is its efficiency in using glucose; the higher rate of glucose extraction from the blood and a lower utilization rate in the cerebellum are demonstrated in humans. [14] Thus, we hypothesized that the patient's cerebellar dysfunction was caused by an unusual vulnerability to hypoglycemia, presumably owing to altered glucose kinetics in the cerebellum. To prove this, quantitative dynamic PET scanning of ^{18}F -FDG was performed to determine the regional glucose kinetics of the brain. Contrary to the results of the previous report (cerebellar K_1/k_3 = 0.1356/0.09918; cerebral K_1/k_3 = 0.0993/0.15072) [14] and those of our control subjects, K_1/k_3 was not reversed in the cerebellum of our patient compared with the cerebral cortex. In addition, the cerebellar metabolic rate and the egress rate of glucose were relatively increased compared with those of control subjects. This decreased glucose uptake-to-utilization ratio and increased leak of glucose in the cerebellum explain its vulnerability to hypoglycemia and support our hypothesis. Although our control subjects were younger than the patient, stability of rate constants with age has been reported. [28]

There are some limitations to our study. First, the calculated rate constants might be secondary results of ischemic or hypoglycemic damage to the cerebellum. Severe cerebral ischemia downregulates the glucose transporter kinetics of the blood-brain barrier in the rat, [29] and K_1 is decreased in infarct tissue. [30] Although cerebellar dysfunction disappeared, uncomplicated hypoglycemia can also kill neurons in the brain [8] and may be followed by decreased glucose uptake in the damaged region. In each case,

follow-up brain imaging may be of help, because both ischemic and hypoglycemic brain damage [31] [32] can manifest brain MRI changes over time.

Second, regional differences in the blood flow that supplies the brain's glucose needs were not measured. In addition to MRA and TCD, which showed no abnormalities, quantitative PET scanning of labeled water ($^{15}\text{H}_2\text{O}$) would have been helpful to certify that cerebellar blood flow was not compromised compared with the blood flow in other regions.

What may have caused the altered glucose kinetics in the patient's cerebellum? Glucose uptake depends on the permeability and capillary surface area of absorption. Thus, decreased uptake may be due to problems of the glucose transporter with regard to its affinity for glucose, receptor density, distribution, [33] or the regulation of glucose transporter expression by mRNA. [33] [34] It may also be due to the decreased volume of distribution associated with vascular arrangement or capillary geometry, such as regional differences in capillary length and distribution, or in the ratio of open to closed capillaries. [11] To distinguish cerebellar glucose transporter dysfunction from decreased volume of distribution, another PET study for the calculation of regional volume of distribution is needed. This would require a different tracer, such as ^3O -methylglucose or L-glucose, which are transported into the brain tissue but are not metabolized. Considering increased leak of glucose as well as decreased glucose uptake, dysfunction of cerebellar glucose transporter appears to be a more reasonable answer. Finally, although this is speculative, there is a possibility that increased k_3 reflects a compensatory role for the decreased uptake and increased leak of glucose in the patient's cerebellum.

Despite its limitations, our study suggests that individual variability [2] of cerebellar glucose metabolic capacity may exist. Further studies using a large number of samples are needed to show individual variability in regional glucose kinetics. The wide variability of hypoglycemic symptoms [22] and prognoses [35] among those with similar blood glucose levels may also be explained by these studies.

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