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Cortical excitability changes correlate with fluctuations in glucose levels in patients with epilepsy

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ABSTRACT

Objective: We used transcranial magnetic stimulation (TMS) to investigate motor cortical excitability changes in relation to blood glucose levels.
Methods: Twenty-two drug-naïve patients with epilepsy [11 generalized and 11 focal] and 10 controls were studied twice on the same day; first after 12 h of fasting and then 2 h postprandial. Motor threshold and paired-pulse TMS at a number of short and long interstimulus intervals were measured. Serum glucose levels were measured each time.
Results: Decreased long intracortical inhibition was seen in patients and controls during fasting compared to postprandial studies. This effect was much more prominent in patients with generalized epilepsy (with effect sizes of up to 0.8) in whom there was also evidence of increased intracortical facilitation (effect size: 0.3).
Conclusion: Cortical excitability varies with fluctuations in blood glucose levels. This variation is more prominent in patients with epilepsy. Decreased glucose levels may be an important physiological seizure trigger.

1. Introduction

Different mechanisms underlie different types of epilepsy; however, in most cases, there is an interaction between the primary cause and environmental factors [1]. Patients are prone to different physiological and environmental factors that can precipitate seizures in different settings. Among those factors are blood glucose levels. There are several reports of seizures triggered with lack of food or after prolonged exercise [2,3]. Seizures are also very common in patients with impaired transport of glucose across the blood–brain barrier due to deficiency of the major brain glucose transporter GLUT1 [4–6]. These seizures can occur not only in the classical severe GLUT1 encephalopathy but also in milder cases that have otherwise typical idiopathic generalized epilepsy [5,6]. Those patients respond to oral glucose with significant improvement in both clinical seizures and EEG findings [7]. It is also well known that seizures can occur as a complication to severe hypoglycemia induced by excess insulin [8], and epileptiform discharges have been recorded on EEG in the setting of extreme hypoglycemia [9]. These changes are reversed by glucose administration [9].

Blood glucose levels show natural variability, and in general, levels are lower after lack of food for extended periods of time or following exercise. The relationship between these fluctuations and cortical excitability is largely unknown. It could be that variability in blood glucose levels is associated with fluctuations in cortical excitability. These changes may be sufficient to change seizure threshold in certain patients.

Transcranial magnetic stimulation (TMS) is a safe and sensitive tool that can measure relatively subtle changes in the excitatory/inhibitory intracortical neurons in disorders such as epilepsy [10–14]. We previously described syndrome-specific changes in cortical excitability in relation to the time of day [15], sleep deprivation [16], and seizures [17] in patients with epilepsy. In the current study, we used TMS to determine whether there were variations in cortical excitability in relation to fasting in healthy individuals and to evaluate whether this effect is different in drug-naïve patients with new-onset epilepsy.

2. Methods

Here we report the findings from drug-naïve patients newly diagnosed with generalized and focal epilepsy consecutively recruited from the Epilepsy Clinic at St Vincent's Hospital in Melbourne. Only participants aged 14 years and above were included. This is because normal single- and paired-pulse TMS values in children under this age are noncomparable to older participants and have not been established in children with epilepsy [18,19].

The diagnoses were made by at least two experienced epileptologists who were unaware of the study based on clinical history, EEG, and imaging findings.

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Random blood sugar levels were measured prior to recruitment and only nondiabetic subjects (with glucose levels below 10 mmol/L) were included in the study.

The study protocol was approved by the St Vincent's Hospital Human Research Ethics Committee, and written informed consent was obtained from each participant including parental consent from those participants under the age of 18 years.

2.1. Participants

2.1.1. Non-epilepsy controls

Ten healthy control participants (5 females, mean age: 20 years; range: 15–30 years) without a history of diabetes, seizures, or other neurological conditions were included.

2.1.2. Patients with generalized epilepsy

Eleven patients (6 females, mean age: 19 years; range: 16–26 years) were included.

2.1.3. Patients with focal epilepsy

Eleven patients (5 females, mean age: 25 years; range: 14–35 years) were studied.

2.1.4. Inclusion criteria

(a) Antiepileptic drug naïve.
(b) Generalized epilepsy: generalized epileptiform abnormalities (3.5- to 5-Hz spike–wave) on at least one EEG recording and a history of generalized tonic–clonic, myoclonic, and/or absence seizures.
(c) Focal epilepsy: seizure symptomatology (specifically, characteristics of the aura when consistently present) and the EEG showed either a left- or right-sided lateralization. The EEG was considered localizing only if definite and prominent sharp–slow discharges were seen consistently over one region whether it be frontal (Fp1-Fz-F3/Fp2-Fz-F4), temporal (T1–T3/T2/T4), parietal (P3–C3/P4–C4), or occipital (O1/O2). Patients with temporal intermittent rhythmic delta activity (TIRDA) were included only if the activity was consistently recorded over one hemisphere. Nonspecific slow or sharp waves were not considered lateralizing or localizing even if only recorded on one side. Further localizing signs were found on brain MR images, with evidence of hippocampal asymmetry in one patient. (Imaging was only routinely performed on patients thought to have focal epilepsy.)
(d) Normal neurological examination.

2.1.5. Exclusion criteria

(a) Exposure to AEDs.
(b) Suspicion of nonepileptic events (psychogenic nonepileptic seizures, migraine, parasomnias, etc.).
(c) Patients with an undetermined epilepsy syndrome (not clear whether generalized or focal epilepsy).
(d) Seizure foci originating in the vicinity of the motor area (seizure semiology or on imaging).
(e) Bilateral seizure foci.
(f) Previous cortical resections or craniotomies.

2.2. Fasting and postprandial studies

All subjects (non-epilepsy controls and patients) were studied with TMS twice on the same day. The first study was after at least 12 h of fasting, and the second study was carried out 2 h after food ingestion. Serum glucose levels were measured immediately prior to each testing session.

To avoid any effect of diurnal variation in cortical excitability, all studies were performed between 10 am and 3 pm. Care was taken to avoid clustering of any of the participants in a group to a particular time, and the studies were spread evenly over this time interval in all groups. Similarly, to avoid any hormonal effects related to variations across the menstrual cycle, care was taken to avoid clustering of the female participants in each group to a particular phase of the cycle, and they were spread evenly across the two phases (luteal and follicular) in each group. All participants were requested to maintain regular sleep patterns with 7–9 h of sleep the night before the test, and the results were only analyzed after a minimum of two days of seizure freedom on either side of the study was confirmed. This was based on seizure diaries. No patients were excluded as a result of seizures. In addition, no patients suffered a seizure during the TMS study.

2.3. Transcranial magnetic stimulation paradigm

Both hemispheres were studied in each participant (patients and controls). During TMS, the participants sat in a comfortable, reclining chair. Surface electromyographic (EMG) recording was made from the abductor pollicis brevis muscle (APB). Stimuli were delivered to the contralateral cerebral hemisphere by applying the appropriate direction of coil current flow (anticlockwise for left cortical stimulation and clockwise for right cortical stimulation) using a flat circular 9-cm diameter magnetic coil (14-cm external diameter) with the center of the coil positioned over the vertex and held in a plane tangential to it using a pair of Magstim 200 magnetic stimulators (Magstim, Whitland, Dyfed, United Kingdom). Paired stimulation at various interstimulus intervals (ISIs) was performed using a Bistim module to connect 2 stimulators to the coil.

The motor evoked potentials (MEPs) were recorded and digitized online via a CED 1401 interface (Cambridge Electronic Design Ltd, Cambridge, United Kingdom) and stored on a computer for offline analysis. Signal software (Cambridge Electronic Design Ltd, Cambridge, United Kingdom) was used for automated acquisition and marking of the recorded MEPs. Filters for the acquisition were set to a low frequency of 10 Hz and a high frequency of 5 kHz. The sweep speed for threshold determination and paired-pulse TMS at short ISIs was 100 ms, and the sensitivity was set to 100 μV/division. For longer ISIs, the sweep speed was adjusted to 500 ms, and the sensitivity was adjusted to 2 mV/division. The MEP amplitude was measured from peak to peak.

Each experimental session lasted for 60–90 min, and the following parameters were recorded:

Motor threshold (MT): Motor threshold was determined for each hemisphere tested while the participant was at rest and verified by continuous visual and auditory EMG feedback. Stimulation commenced at 30% of maximum output and increased in 5% increments until the MEP was established. One-percent changes in intensity were then used to measure the threshold value. Motor threshold was defined as the lowest level of stimulus intensity which produced a MEP in the target muscle of peak-to-peak amplitude > 100 μV on 50% or more of 10 trials [20].

Intracortical inhibition and facilitation: Cortical recovery curves were derived using paired-pulse TMS. For the short ISIs of 2, 5, 10, and 15 ms, the first stimulus was given at 80% of MT, and the second stimulus was given at 20% above MT. Ten stimuli at 20% above MT without a preconditioning stimulus were also given. For longer ISIs, the stimulation intensity was 20% above MT using paired stimuli in 50-ms increments at ISIs of 100–400 ms. A minimum interval of 15 s was kept between the delivery of each pair of stimuli. Stimuli were given at randomly selected ISIs until a total of 10 stimuli at each ISI were achieved.

Recovery curves at short ISIs (2–15 ms) were constructed for each hemisphere using the ratio of the mean peak-to-peak amplitude of