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SHORT COMMUNICATION

Low glycaemic index diet reduces seizure susceptibility in a syndrome-specific mouse model of generalized epilepsy

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Summary
Purpose: Clinical evidence suggests that low glycaemic index diets are effective at reducing seizure frequency potentially through the stabilization of blood glucose levels. Here we investigate if diets containing carbohydrates with varying glycaemic index (GI) can modulate seizure susceptibility in a mouse model of generalized epilepsy.
Methods: Electrocortical recordings were made from mice harboring the $GABA_A\gamma2$ (R43Q) epilepsy mutation after three weeks on a low-or high-GI diet. Standard rodent diet was used as a control. Occurrence and durations of spike-wave-discharges (SWDs) were measured. An insulin injection was used to reduce blood glucose to levels known to precipitate SWDs in the $GABA_A\gamma2$ (R43Q) mouse on the low and high-GI diets.
Key findings: SWD occurrence was reduced by approximately 35% in mice on the low-GI compared to high-GI diet. SWD occurrence was not different between high-GI diet and a standard diet suggesting that low-GI diet is protective. Weight gain of mice for all diet groups was identical suggesting that they were equally well tolerated. Under low blood glucose conditions SWD occurrence increased in the low and high-GI diets. Importantly, under low glucose conditions the low-GI diet no longer conferred protection against SWDs.
Significance: SWDs were reduced in mice on a low GI-diet suggesting it may be an effective and well tolerated therapy for generalized epilepsy. The lack of effect of low-GI diet when glucose levels are reduced suggests that seizure protection in the $GABA_A\gamma2$ (R43Q) mouse model may be due to the diets ability to stabilize blood glucose levels.
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Introduction

Dietary therapy is now commonly considered a useful treatment option in refractory epilepsy (Levy et al., 2012). Most studies have investigated the high-fat and low-carbohydrate ketogenic diet with varying reports of success (Bailey et al., 2005). Tolerability remains a significant issue, with patients often unable to adhere to the strict dietary regime. The precise mechanism of action of the ketogenic diet is not fully understood, but most likely multi-factorial (Bough and Rho, 2007) potentially including the stabilization of brain glucose levels. Consistent with this, recent evidence indicates efficacy of a low glycaemic index (GI) diet in patients with refractory epilepsy (Pfeifer and Thiele, 2005; Pfeifer et al., 2008; Muzykewicz et al., 2009; Coppola et al., 2011), epilepsy in tuberous sclerosis complex (Larson et al., 2012) and Angelman syndrome-related seizures (Thibert et al., 2012). Small clinical trials in patient populations with severe epilepsy syndromes are feasible because of the large number of seizure events in these patients. These trials become difficult when more heterogeneous epilepsy populations are investigated. Mouse models provide a mechanism for testing varying therapeutic manipulations under conditions in which environmental and genetic factors can be more tightly controlled. Recent genetic discoveries have isolated a number of epilepsy causing genes enabling the engineering of 'syndrome-specific' mouse models based on human mutations. The $GABA_A$ $\gamma2$ (R43Q) mouse model of generalized epilepsy is remarkable in that it recapitulates the two primary seizure phenotypes seen in humans with the disease, including absence epilepsy and febrile seizures (Reid et al., 2013). Further, the $GABA_A$ $\gamma2$ (R43Q) mouse is sensitive to the first-line anti-absence drug, ethosuximide (Tan et al., 2007). We have also recently shown that reducing blood glucose levels, either by overnight fasting or injecting insulin, results in a doubling of spike-and-wave discharge (SWD) events in the $GABA_A$ $\gamma2$ (R43Q) mouse (Reid et al., 2011). This is consistent with the idea that fluctuating glucose levels may also be an important determinant of seizure susceptibility in generalized epilepsy. Here we test the impact of low- and high-GI diets on SWD expression in the $GABA_A$ $\gamma2$ (R43Q) mouse model.

Materials and methods

All experiments were approved by the Animal Ethics Committee at the Florey Institute for Neuroscience and Mental Health in accordance with The Code of Ethics of the World Medical Association for experiments involving animals. The $GABA_A\gamma2$ (R43Q) mutation bred into the DBA/2J background strain mice (>N20 generations) was used between the ages of P42-45. Genotyping was done at P12 using a PCR-based method (Tan et al., 2007). All mice were housed under a 12 h light dark cycle with free access to food and water.

Diet protocols

Pregnant and lactating mothers were kept on a standard rodent diet (Barastoc 8720310, Ridley Corporation Ltd, Australia). At weaning (P21), mice were placed on either a high- or low-GI carbohydrate diet (Specialty Feeds, Glen Forrest, WA, Australia) for the duration of the experiment. These two diets are derived from a standard rodent diet differing only in their carbohydrate type (Table 1). The standard rodent diet was used as a control.

Table 1 Diet composition of low GI and high GI diets.

Ingredients (g/kg)	Low GI	High GI
Casein	200.0	200.0
Starch Waxy Maize: 90% amylopectin + 1% amylose	—	568.0
Starch GelCrisp: 30% amylopectin + 70% amylose	568.0	—
Sucrose	85.0	85.0
Gelatine	20.0	20.0
Soybean oil	50.0	50.0
Cellulose	33.0	33.0
DL methionine	3.0	3.0
Calcium carbonate	13.1	13.1
Sodium chloride	2.6	2.6
AIN93 trace minerals	1.4	1.4
Potassium citrate	2.5	2.5
Potassium dihydrogen phosphate	6.9	6.9
Potassium sulphate	1.6	1.6
Choline chloride	2.5	2.5
AIN93 vitamin	10.0	10.0
Digestible energy, kJ/g	16.1	16.1

Electrocorticogram (ECoG) recordings

Electrode implantation surgeries were performed as previously described (Tan et al., 2007; Reid et al., 2013). Mice were anesthetized with 1—3% isoflurane and two epidural silver 'ball' electrodes were implanted on each hemisphere of the skull. Electrodes were placed 3 mm lateral of the midline and 0.5 mm caudal from bregma. A ground electrode that was not touching the brain surface was placed 2.5 mm rostral from bregma and 0.5 mm lateral from the midline. A differential signal was recorded relative to this common ground. Mice were allowed to recover for at least 48 h after surgery. ECoGs were continuously recorded in freely moving mice for 12 h epochs during the light cycle. For acute modulation of blood glucose experiments, EcoG recordings were made for 2 h prior to the i.p. injection of 1.5 units of insulin (Sigma, Australia) and 2 h following. Data from male and female mice were pooled in this study. Approximately equal female/male ratio were used in this study (5 males and 4 females for low-GI diet and 4 each for high-GI diet) ruling out any potential gender bias. Signals were filtered at 0.1—200 Hz and sampled at 1 kHz using Powerlab 16/30 (ADInstruments Pty. Ltd., Sydney, NSW, Australia). EEG recordings were acquired during daylight hours. A full spike and wave discharge (SWD) was defined as an individual seizure event (Fig. 1). Events were detected by eye with the observer blind to treatment group. Event duration was defined as time from the first to the final peak of the SWD.

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