CLINICAL RESEARCH

Glycaemic threshold for changes in electroencephalograms during hypoglycaemia in patients with insulin dependent diabetes

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Abstract

The relation between blood glucose concentration, the symptoms and signs of hypoglycaemia, and electroencephalographic changes in diabetic patients is not known. The effect of hypoglycaemia on brain function was studied in 13 patients with insulin dependent diabetes. During a gradual fall in blood glucose concentration induced by a bolus injection of insulin followed by an intravenous infusion of insulin, during 60 minutes of biochemical hypoglycaemia, and after restoration of normoglycaemia with intravenous glucose electroencephalograms were evaluated continuously by period-amplitude analysis; blood samples were taken every 10 minutes throughout. No changes were seen in electroencephalograms when the blood glucose concentration was above 3 mmol/l. At a median blood glucose concentration of 2.0 (95% confidence interval 1.7 to 2.3) mmol/l alpha activity decreased abruptly in the electroencephalograms concomitant with an increase in theta activity, reflecting neuronal dysfunction in the cortex. When the blood glucose concentration was further lowered changes were observed in the electroencephalograms indicating that deeper brain structures were affected. A normal electroencephalogram was re-established at a blood glucose concentration of 2.0 (1.8 to 2.1) mmol/l. There was no significant correlation between the blood glucose concentration at the onset of changes in the electroencephalograms and age, duration of diabetes, insulin dose, haemoglobin A_{1c} concentration, initial blood glucose concentration, rate of fall in blood glucose concentration, and appearance of symptoms and signs of hypoglycaemia.

Changes in electroencephalograms during hypoglycaemia

appear and disappear at such a narrow range of blood glucose concentrations that the term threshold blood glucose concentration for the onset of such changes seems justified.

Introduction

Patients with insulin dependent diabetes are prone to develop hypoglycaemic episodes, particularly during "tight" metabolic control.¹ Hypoglycaemia influences brain function,² which is important as patients with diabetes depend on having normal mental function when trying to avoid hypoglycaemic episodes. Recently we reported that cognitive function deteriorated in most diabetic patients at a blood glucose concentration of about 3 mmol/l, at which none of the patients had subjective feelings of hypoglycaemia.² Furthermore, Herold *et al* showed that the reaction time is prolonged in some diabetic patients at this blood glucose concentration.³ Electroencephalographic recordings mirror the functional state of the brain,⁴ and hypoglycaemia has a well established ability to cause electroencephalographic abnormalities in subjects with⁵ and without⁶ diabetes.

We therefore set out to describe the relation between changes in the electroencephalogram as evaluated by computerised period-amplitude analysis, blood glucose concentrations, and the symptoms and signs of hypoglycaemia in patients with insulin dependent diabetes during a controlled reduction of the blood glucose concentration to hypoglycaemic values. In particular, we looked for a possible threshold blood glucose concentration at which important changes occurred in the electroencephalogram.

Subjects and methods

Thirteen patients with insulin dependent diabetes who were otherwise healthy (10 men, three women), were not taking any drugs apart from insulin, and had normal electroencephalograms participated after giving their informed consent. The study was approved by the regional medical ethical committee. All patients were prone to ketosis and had been treated with insulin from the time of diagnosis; in all patients the disease had started before the age of 31 and a random C peptide concentration was below 0.1 nmol/l. Their median age was 28 (range 20-40), and they had had diabetes for a mean of eight years (range 2-28). The patients were of normal

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weight (mean body weight index 96 (range 74-121)) and received a mean dose of insulin of 0.54 IU/kg body weight/day (range 0.31-1.08 IU/kg body weight/day). Mean haemoglobin A_{1c} concentration was 8.8% (range 6.5-11.4%) (normal range 4.1-6.4%). None of the patients had persistent proteinuria or any symptoms of autonomic neuropathy.

The patients were attending the outpatient clinic regularly (three or more times a year) and were treated with two or three daily insulin injections. The evening before the study they omitted their intermediate acting insulin and were treated overnight with small doses of soluble insulin according to their blood glucose concentration to avoid nocturnal hypoglycaemia before the study. From 2200 and throughout the study they were recumbent and fasting but allowed to drink water.

Figure 1 shows the design of the study exemplified by the blood glucose concentration curve for one patient. At 0800 an intravenous injection of a

FIG 1—Study design. Electroencephalograms were recorded continuously and blood glucose concentrations measured every 10 minutes.

bolus of highly purified soluble porcine insulin (Velosulin, Nordisk Gentofte, Denmark) was given through a catheter into an antecubital vein and was followed by a continuous intravenous insulin infusion. The infusion rate was adjusted according to the blood glucose concentrations measured every 10 minutes in mixed venous blood samples taken from the other antecubital vein; the catheter in this other arm was kept patent with a slow infusion of saline. The initial blood glucose concentration was allowed to decrease to about 2 mmol/l and was maintained at this value for 60 minutes, when the insulin infusion was stopped. The blood glucose concentration was allowed to rise spontaneously to around 3 mmol/l, and the patients then received an intravenous injection of a bolus of glucose to restore the blood glucose concentration to 6 mmol/l.

Six bipolar derivations of the electroencephalogram from both hemispheres (frontocentral, temporal, and parieto-occipital) were recorded with surface electrodes placed according to the international system.⁷ The electroencephalogram was analysed visually and by a HP-85 computer running a period-amplitude analysis program continuously.⁸ At intervals of 10 seconds, which were indicated on the trace, the computer measured each wave of the electroencephalogram according to its period and amplitude, determined by zero crossing and detection of peaks. The percentage activity time—that is, the cumulative periods as a percentage of the interval analysed—calculated for each of the 21 frequency bands covering the frequency range 0.5-28.6 Hz constituted a frequency spectrum from which the amount of activity in the frequency bands of delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-28.6 Hz) waves could be derived. The mean values in five to 10 of the 10 second intervals without artefacts, analysed in close conjunction with the blood samples, were taken as the values for given blood glucose concentrations. All patients were awake throughout the study and did not undergo activation procedures.

Important changes in the electroencephalogram were defined as a consistent decrease in the proportion of alpha activity over 30 minutes concomitant with an increase in the proportion of theta activity, both varying more than two standard deviations from baseline values. The threshold blood glucose concentrations for the appearance and disappearance of changes in the electroencephalogram were calculated as the mean of the blood glucose concentrations measured immediately before and after the appearance and disappearance of these changes.

The patients were asked to indicate whether they experienced any signs of hypoglycaemia. In addition, they were asked if they felt hypoglycaemic every tenth minute when blood was taken. Finally, the patients were closely

observed for usual signs of hypoglycaemia such as sweating and tremor⁹ by two trained observers (SP, BT).

Blood glucose concentrations were measured in plasma by a glucose oxidase method (Yellow Spring Instruments, California, USA). Haemoglobin A_{1c} concentration was determined as described elsewhere.¹⁰

Results were analysed by linear regression analysis. The level of significance was preset to 95% (two tailed). The results are given as medians (95% confidence intervals) unless otherwise stated.

Results

All patients had normal electroencephalograms before and after the study whether evaluated visually or by period-amplitude analysis. No changes were seen in the electroencephalogram in any patient when the blood glucose concentration was above 3 mmol/l. The median blood glucose concentrations immediately before and after the appearance of—significant changes in the electroencephalogram were 2.3 (95% confidence interval 2.0 to 2.6) mmol/l (fig 2 (A)) and 1.9 (1.4 to 2.1) mmol/l (fig 2 (B)), respectively. The threshold blood glucose concentration for the appearance of changes in the electroencephalogram was 2.0 (1.7 to 2.3) mmol/l. The changes in the electroencephalogram were seen in all but one patient (the lowest blood glucose concentration in this patient was 2.2 mmol/l); in all leads, predominantly parieto-occipitally and temporally; and with no interhemispheric differences. In 10 of the patients the blood glucose concentration continued to fall after the appearance of changes in the electroencephalogram, and a minimum blood glucose concentration of 1.4 (1.3 to 1.6) mmol/l was reached. In these 10 patients the electroencephalogram deteriorated further, and five patients developed bisynchronous bursts of frequency 2-4 Hz fronto-temporally (fig 3).

During recovery, after the infusion of insulin had been stopped, the changes in the electroencephalogram persisted up to a blood glucose concentration of 1.9 (1.5 to 2.1) mmol/l (fig 2 (C)). The electroencephalogram returned to normal at a blood glucose concentration 2.1 (1.8 to 2.4) mmol/l (fig 2 (D)). The threshold blood glucose concentration for the disappearance of changes in the electroencephalogram was 2.0 (1.8 to 2.1) mmol/l. No

FIG 2—Blood glucose concentrations in 12 patients immediately before and after appearance (A and B) and disappearance (C and D) of appreciable changes in electroencephalograms.

FIG 3—Electroencephalograms at different blood glucose concentrations from one patient, showing bisynchronous bursts of activity of 2-4 Hz, especially in frontotemporal region.

further changes in the electroencephalogram were observed after the intravenous injection of the bolus of glucose.

There was no significant correlation between threshold blood glucose concentrations for the appearance and disappearance of changes in the electroencephalogram and age, duration of diabetes, dose of insulin, haemoglobin A_{1c} concentration, initial blood glucose concentration, and rate of fall in blood glucose concentration during the infusion (all $r < 0.21$). All patients developed symptoms and signs of hypoglycaemia during the study. Subjective feelings of hypoglycaemia were present at a blood glucose concentration of 2.0 (1.5 to 2.1) mmol/l. The appearance of symptoms and signs was not correlated with the threshold blood glucose concentration for the appearance or disappearance of changes in the electroencephalogram. The one patient who showed no changes in the electroencephalogram had clear symptoms and signs of hypoglycaemia. After the study most of the patients complained of tiredness.

Discussion

Our study shows that biochemical hypoglycaemia in conscious patients with diabetes is accompanied by changes in the electroencephalogram. The combined decrease in alpha activity and increase in theta activity set in abruptly at a mean blood glucose concentration close to 2 mmol/l and within such a narrow range of blood glucose concentrations that it seems reasonable to talk about a threshold. The changes were symmetrically and diffusely spread over the cortex though slightly more pronounced in the recordings from the temporal and parieto-occipital areas. The reason might be that alpha activity normally dominates in these areas. The evenly spread changes in the electroencephalogram contrast with our previous suggestion from studies of neuropsychological function during hypoglycaemia that the frontal lobes are more sensitive to hypoglycaemia.² Moreover, cognitive function had deteriorated appreciably at a mean blood glucose concentration just below 3 mmol/l—that is, at a value at which changes in the electroencephalogram were seldom seen.

With further lowering of the blood glucose concentration the slow wave activity in the electroencephalogram increased and bursts of low frequency activity supervened in some patients, indicating that deeper parts of the brain were affected. This finding agrees with the theory that these phylogenetically older layers of the brain are less sensitive to low blood glucose concentrations.¹¹

The observed changes in the electroencephalogram are not specific to hypoglycaemia. Similar changes may be seen in other metabolic encephalopathies—for example, hypoxia.^{12,13} As the changes we observed were so closely related to blood glucose concentrations, however, they probably reflect neuroglycopenia in cortical cells requiring high energy. Moreover, the magnitude of the threshold blood glucose value lends support to this assumption as glucose is the main, if not sole, substrate for cerebral metabolism and can be stored intracellularly only in small amounts sufficient for only a few minutes' use.¹⁴ Normal function of cerebral neurones therefore depends on a constant supply of glucose from the blood stream. From animal experiments it has been estimated that at a blood glucose concentration of 2 mmol/l the intracellular glucose concentration in brain cells is close to zero.¹⁴

The electroencephalogram became normal when the blood glucose concentration exceeded 2 mmol/l. Although the changes in the electroencephalogram during the comparatively mild hypoglycaemia in these patients were quickly and fully reversible, most diabetologists know of slowly reversible changes or even irreversible brain damage after profound hypoglycaemia. Cortical neuronal damage after hypoglycaemia is well documented in pathoanatomical human studies^{15,16} as well as in animal experiments.¹⁷ Clinically, however, surprisingly few of the many patients with insulin dependent diabetes who experience unconsciousness due to hypoglycaemia—sometimes repeatedly—during their life¹⁸ seem to develop persistent sequelae. Mild or moderate hypoglycaemia is therefore widely considered to be a necessary evil during treatment with insulin: inevitable if strict metabolic control is aimed for¹⁹ but tolerated by patients.¹⁸ The consequences of repeated moderate

hypoglycaemic episodes have not been properly evaluated in patients with diabetes, but in an analogy, doctors would hesitate to prescribe an otherwise effective treatment that frequently led to episodes of cerebral hypoxia.

The safety of treatment with insulin has gained new interest with the introduction of intensified regimens with their inherent risk of an increased frequency of hypoglycaemia.¹ Our results add to the debate about what the lower limit of blood glucose concentrations should be during treatment with insulin. At a concentration of about 2 mmol/l electroencephalograms show neuronal dysfunction in the cortex. We suggest that this concentration be considered to be an absolute lower limit. At a concentration of about 3 mmol/l neuropsychological performance deteriorates^{2,20} and counter-regulatory responses are triggered.^{21,22} This concentration could therefore be considered to be a relative limit to provide a safety margin.

In this and a previous study subjective feelings of hypoglycaemia seemed to develop at around the proposed absolute limit of blood glucose concentration of 2 mmol/l.² We emphasised, however, that during this study the patients were recumbent and relaxing, which might influence their alertness and ability to recognise impending hypoglycaemia and thus differs from what happens during daily life. In fact, we have observed that in patients told to sample blood at home when they felt hypoglycaemic the median blood glucose concentration was 3.5 mmol/l but the range was 1.4–14.9 mmol/l (unpublished observations). Until the relation between the blood glucose concentration and occurrence of symptoms of hypoglycaemia has been established in greater detail confidence in symptoms may be misleading and potentially dangerous. Instead, systematic home monitoring of blood glucose concentrations should be the rule.

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