Neural dysfunction during hypoglycaemia

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SUMMARY There is controversy over the definition of hypoglycaemia in neonates and children and over its significance when 'asymptomatic'. We measured sensory evoked potentials in relation to blood glucose concentration in 17 children: 13 were fasted or given insulin to investigate endocrine or metabolic abnormalities and four had spontaneous episodes of hypoglycaemia. Abnormal evoked potentials were recorded in 10 of the 11 children whose blood glucose concentration fell below 2·6 mmol/l; five of these 10 children were 'asymptomatic'. No change in evoked potentials was recorded in the six children whose blood glucose concentration remained above 2·6 mmol/l. Our findings suggest that the blood glucose concentration should be maintained above 2·6 mmol/l to ensure normal neural function in children irrespective of the presence or absence of abnormal clinical signs.

Glucose, like oxygen, is essential for normal brain cell function. It cannot now be disputed that hypoglycaemia causes brain damage or that effective management of hypoglycaemia protects from this neural damage.1 2 Thus for example, in 1960 Haworth and Coodin found an incidence of 51% of severe mental retardation among 35 children who had had recurrent 'idiopathic' hypoglycaemia when aged less than 6 months.3 In 1984, Soltesz et al in a review of the outcome of 18 children who had hyperinsulinaemic hypoglycaemia found that the incidence of severe mental retardation had been reduced to 15%.4 They concluded that this improved outcome resulted from early identification, correct diagnosis, and effective management of the hypoglycaemia.

Although there is general agreement on the need to maintain blood glucose concentrations above a 'critical' level in young children and neonates there is no agreement among practising paediatricians and the major paediatric textbooks as to the lowest safe concentration of glucose.5 This difficulty with the definition is understandable in view of the lack of reliable clinical signs when the blood glucose concentrations fall in newborn infants and young children, and in view of the continuing controversy over whether 'asymptomatic' hypoglycaemia causes neurological dysfunction and damage.6 7

To resolve this controversy the lowest blood glucose concentration at which normal neural function is preserved needs to be determined by a correlation between objective measurements of neurophysiological function and blood glucose concentrations. The aims of our study were therefore: (a) to use evoked potentials to measure objectively neural function in relation to blood glucose concentration and (b) to determine if there is a measurable difference in neural function between children who are 'symptomatic' and 'asymptomatic' during periods of low blood glucose concentrations.

Subjects and methods

This study formed part of a project to evaluate the use of evoked potentials in normal and sick newborn infants and children. Approval was obtained from the local health authority ethical committee and informed consent was obtained from the parents before each study.

Seventeen children were studied and were selected from two groups of children. The first group comprised children admitted for investigation of metabolic or endocrine disorders; these children were studied when their investigations included the provocation of hypoglycaemia by either fasting (n=11) or insulin administration (n=2). The second group consisted of children who had recurrent spontaneous episodes of hypoglycaemia (n=4).

In all subjects serial blood samples were obtained. An immediate bedside estimation of the whole blood glucose concentration was made using the Refflux II device (BCL Ltd). Blood samples were obtained at 30 minute intervals while the blood glucose concentration was above 3 mmol/l and at 15
minute intervals if the blood glucose concentration fell below 3 mmol/l. After blood had been withdrawn for clinical diagnostic purposes normoglycaemia was restored by giving glucose or glucagon.

Venous blood was obtained from those subjects in whom an intravenous catheter had been sited, capillary blood was used in the other subjects. From each sample blood was added to fluoride coated tubes for later estimation of the blood glucose concentration using the glucose oxidase method and to perchloric acid for the later estimation of the concentration of ketone bodies (3-hydroxybutyrate and acetacetate) using enzymatic methods on a Cobas Bio Centrifugal Analyser (Roche) in fluorometric mode.

In all subjects, brainstem auditory evoked potentials (n=12) or serial somatosensory evoked potentials (n=5) were recorded immediately after each sample of blood was taken. All the evoked potential recordings were made by one person (THHKG) who did not take part in the clinical management of the child during the study. The evoked potentials were recorded using a portable Nicolet CA1000 Clinical Averager at the patient’s bedside.

Brainstem auditory evoked potentials were elicited using an alternating click (rate 33/s, duration 100 μs) delivered by a Nicolet TIP 10 click generating module. The intensity of the click was determined for each individual subject so that evoked potentials could be elicited reliably in the baseline recordings. The intensity of the stimulus then remained constant throughout each study. To record the evoked potential a silver/silver chloride cup electrode (8 mm in diameter) was placed centrally on the forehead and on the ipsilateral mastoid; an indifferent electrode was placed over the contralateral mastoid. The skin to electrode impedance was maintained at 3 kohms or less. The electroencephalogram was amplified using a Nicolet HGA 200A Physiological Amplifier with a band pass filter of 300–3000 Hz. After each click, 10 ms of the electroencephalogram was sampled and a total of 2000 responses were averaged. Two separate averages of 2000 evoked potentials were obtained and the wave latencies had to agree to within 0-1 ms before these averages were accepted.

To elicit somatosensory evoked potentials a 100 μs square wave pulse of electric current was applied over the right median nerve at the wrist, at a rate of 2 stimuli per second. The intensity of this stimulus was determined for each individual so that a twitch was induced in the muscles of the thenar eminence. To record the evoked potential over the somatosensory cortex silver/silver chloride cup electrodes (8 mm in diameter) were placed over the contralateral parietal region and centrally on the forehead.

Table

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age (years)</th>
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<th>Whole blood ketone bodies (mmol/l)</th>
<th>Evoked potentials</th>
<th>Clinical signs</th>
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bs1 = The lowest blood glucose concentration associated with normal neural function.
bs2 = The blood glucose concentration immediately before the first abnormal evoked potential was recorded.
ketone bodies* = 3-hydroxybutyrate: normal range when normoglycaemic is 0-02-0.49 mmol/l.
ND = not done.
S = Spontaneous hypoglycaemia, F = fasting, I = insulin administration.
with an indifferent electrode placed over the biceps of the right arm. The impedance of the recording electrodes was maintained at 3 kohms or less. The electroencephalogram was amplified by 10⁴ by a Nicolet HGA 200 Physiological Amplifier and a filter bandpass of 30–3000 Hz was used. Fifty ms of the electroencephalogram was sampled after each stimulus was applied to the median nerve and an average of 50 responses was made. Two separate averages of somatosensory evoked potentials were obtained and the latencies of the onset of the first wave (N₁) which is thought to be generated by the arrival of the afferent volley at the cortex were measured. The latencies had to agree to within 0.1 ms for the averages to be accepted.

Both brainstem auditory and somatosensory evoked potentials were plotted onto paper for immediate scrutiny and transferred to a microcomputer for later analysis.

**Results**

The details of the 17 subjects studied are summarised in the table.

Fig 1 shows serial recordings of somatosensory evoked potentials from a 4 month old child studied during an episode of hypoglycaemia provoked by fasting (subject 6). The base line recording of the somatosensory evoked potential shows the latency to the onset of the N₁ complex (20 ms) to be within the normal range for her age (18-9–20.1 ms) when the blood glucose concentration was 4.2 mmol/l. The latency to the onset of N₁ became prolonged (24 ms), and the wave form was less well defined, when the blood glucose concentration fell to 2.3 mmol/l.

After the restoration of the blood glucose concentration to 4.1 mmol/l by an intravenous injection of 25% dextrose (2 ml/kg), the waveform became well defined and the latency returned to lie within the normal range for her age (19.5 ms).

Fig 2 shows serial brainstem evoked potentials recorded from a 2 day old baby who had recurrent 'asymptomatic' episodes of spontaneous hypoglycaemia (subject 4). In brainstem evoked potentials the latency between the waves I and V has been shown to reflect the integrity of brain stem function. Initially the latency between waves I and V (5.03 ms) was within the normal range for a newborn infant (4.81–5.39) during normoglycaemia. The wave I–V interval remained within the normal range until the blood glucose concentration fell to 2.5 mmol/l when the I–V interval was 5.4 ms. There was a progressive prolongation of the wave I to V interval as the blood glucose concentration fell to 1.6 mmol/l when wave V could not be elicited. When the blood glucose concentration was increased to be above 4 mmol/l wave V returned but...
with an abnormal wave I-V latency (5.63 ms). Despite the maintenance of a blood glucose concentration above 4 mmol/l the wave I-V interval continued to be abnormally prolonged for 16 hours (fig 3).

Abnormal changes in the evoked potentials were recorded in 10 of the 17 children studied. The data for these subjects are summarised in the table. Of these 10 children, five were ‘asymptomatic’ (four of whom were newborn infants) and five were ‘symptomatic’; there was no significant difference (0.05<p<0.1, Mann-Whitney U test) in the blood glucose concentration at which the evoked potentials became abnormal between the ‘symptomatic’ and the ‘asymptomatic’ groups (fig 4).

In these 10 subjects normal evoked potentials were recorded at blood glucose concentrations ranging from 5.6-1.9 mmol/l (bs1). The first abnormal changes in the evoked potentials were recorded in these 10 subjects in association with blood glucose concentrations ranging from 2.5 to 0.7 mmol/l (bs2).

The evoked potentials returned immediately to normal in six children after the intravenous administration of 25% dextrose (2 ml/kg) or the intramuscular administration of glucagon (20 μg/kg). In four (subjects 1, 8, 4, and 5) the evoked potentials remained abnormal for 1 hour, 1.5 hours, 16 hours, and two days, respectively, despite the presence of normoglycaemia.

In the remaining seven subjects no changes in the evoked potentials were observed; all but one of these children maintained their blood glucose concentrations above 2.6 mmol/l throughout the study. In subject 15 normal evoked potentials were recorded at a blood glucose concentration of 1.9 mmol/l.

![Fig 3](http://adc.bmj.com/content/63/11/1353/F3)

**Fig 3** The latency between waves I and V in the brainstem auditory evoked potentials recorded in subject 4 in relation to blood glucose concentration and the time from the onset of the study. The shaded area represents the normal range for the wave I-V latency (in ms) in the newborn period.

**Fig 4** (a) The blood glucose concentration that was drawn nearest to the time when the first abnormality in the evoked potentials was recorded in each subject. The subjects have been subdivided into those who were asymptomatic (b) and those who were symptomatic (c). The shaded area identifies the neonatal subjects.

**Discussion**

It is now nearly 30 years since Cornblath and his colleagues established hypoglycaemia to be an important cause of morbidity and mortality in the newborn infant, and yet the definition and the management of hypoglycaemia continues to be a controversial and confused topic in paediatrics.

Glucose has a dual role for normal brain function: as the major metabolic fuel, and as a precursor of essential macromolecules during the rapid phase of brain growth. It is likely, therefore, that hypoglycaemia is particularly harmful in childhood, especially in the newborn period.

It is a common belief that 'asymptomatic' hypoglycaemia is less important than 'symptomatic' hypoglycaemia. This is not supported by our findings where there was demonstrable neural dysfunction in children with blood glucose concentrations of less than 2.6 mmol/l irrespective of whether
there were clinical signs. Clinical signs of disturbed neural function in the newborn baby and young child are often subtle and they may not be noted consistently even by experienced observers. The data from our study suggest the division between 'symptomatic' and 'asymptomatic' hypoglycaemia is artificial and may result in treatment being delayed or withheld.

The belief that 'asymptomatic' hypoglycaemia is not harmful has arisen mainly from the findings of three follow up studies, the largest of which is by Koivisto and his colleagues. In their analysis of the outcome of 151 children who had had blood glucose concentrations of less than 1-1 mmol/l in the neonatal period they found that those babies with no abnormal clinical signs during the hypoglycaemia had a better outcome than those in whom abnormal clinical signs were reported. There was, however, a similar incidence of 'doubtful' outcomes in the 'asymptomatic' and 'symptomatic' groups and if the babies who had hypoglycaemic seizures were excluded from the 'symptomatic' group, there was no significant difference between the outcome of the 'symptomatic' group and the 'asymptomatic' babies. On this basis Koivisto et al in fact recommended 'that asymptomatic hypoglycaemia should be detected by a screening system and if it persists should be treated to avoid possible permanent central nervous system damage'.

The study by Pilides and her colleagues emphasises the need for longer term follow up of the higher mental functions of children after episodes of hypoglycaemia. The results of their psychological tests suggested that as verbal skills became important in the evaluation of intellectual performance (between 5–7 years of age) a larger proportion of the hypoglycaemic children had Stanford-Binet scores below 86 in comparison with the control group. The findings by Haworth and McRae and those of Koivisto's group can be criticised because both had very short follow up periods ranging from eight to 30 months.

Other investigators have studied the acute effects of hypoglycaemia on neurological function as assessed by the electroencephalogram and have shown there to be abnormalities in children during episodes of blood glucose concentrations below 2-2 mmol/l. The electroencephalogram is, however, a non-specific measure of brain function. It is difficult from these studies to determine the blood glucose concentration below which neural dysfunction occurs in neural pathways with a high rate of glucose utilisation.

The recording of evoked potentials allows objective serial measurements of neural function in specific pathways in relation to the blood glucose concentration. In this study we chose to measure the potentials evoked in neural pathways with a high rate of glucose utilisation. Studies investigating local cerebral glucose metabolism in newborn and adult primates have shown that the rate of glucose utilisation is highest in the inferior colliculus (commonly accepted as the generator of wave V in brainstem auditory evoked potentials) and that there are relatively high rates of glucose utilisation in the rest of the auditory pathway. Layer IV of the cortex, the site of sensory afferent fibre input to the somatosensory areas of the cortex, was also shown to have a high rate of glucose utilisation. It is reasonable, therefore, to propose that the measurement of neural activity in the somatosensory and the auditory pathways provides a sensitive index of the lowest blood glucose concentration compatible with normal neural function.

Although abnormalities in evoked potentials have been shown to be of prognostic importance in other clinical situations, there have been no previous studies in children relating acute changes in sensory evoked potentials to the blood glucose concentration.

Our studies show that neural dysfunction occurs in children in association with low blood glucose concentrations. In two subjects (subjects 4 and 7) neural dysfunction was recorded at blood glucose concentrations as high as 2-5 mmol/l (see table; bs). There was intersubject variability, however, with normal evoked potentials being recorded in four subjects (subjects 1, 3, 2, and 15) in association with blood glucose concentrations of 2-4, 2-1, 1-9, and 1-9 mmol/l, respectively (see table; bs). It is possible that several factors contribute to this intersubject variability. First, there may be different critical concentrations of blood glucose for normal neural function in individual subjects. Second, the rate of fall of the blood glucose concentration and the duration of hypoglycaemia may determine the presence and degree of abnormal neural function. Without continuous measurements of the blood glucose concentrations it was not possible in our study to determine the relative importance of these factors. Third, it has been suggested that ketone bodies can be used for energy by the brain and may therefore have a protective effect during episodes of hypoglycaemia. Owen and his colleagues showed in adult man during starvation that alternative substrates particularly ketone bodies can be used by the brain. Cerebral utilisation of ketones has been shown subsequently in children and in young animals.

Our data provide conflicting results concerning the protective effect of high concentrations of blood ketone bodies during hypoglycaemia. Eleven sub-
jects had blood glucose concentrations below 2-6 mmol/l during the study; the concentration of circulating ketone bodies was measured in nine of these children. Seven children (subjects 1, 2, 3, 4, 5, 6, and 8) had hypoketonaemic hypoglycaemia and all had abnormal changes in their evoked potentials in association with low blood glucose concentrations. Two subjects (subjects 7 and 15) had hyperketonaemic hypoglycaemia. Subject 15 had normal evoked potentials with a blood glucose concentration of 1-9 mmol/l and a ketone body concentration of 2-4 mmol/l, suggestive of a protective effect from the hyperketonaemia. Subject 7, however, had abnormal evoked potentials at a blood glucose concentration of 2-5 mmol/l and with a blood ketone body concentration of 5-3 mmol/l. It may be that there is a complex interrelationship for the maintenance of normal neural function not only between blood glucose and ketone body concentrations but also between the concentration of other metabolic fuels and substrates, for example, free fatty acids, lactate, and amino acids.

It is of practical importance to note, however, that no subjects with blood glucose concentrations of 2-6 mmol/l or greater had abnormal changes in neural function. These findings are supported by the study of Harrad et al. who found abnormalities in the visual evoked potentials of adult subjects when the blood glucose concentration was below 2-6 mmol/l.

In all the 10 subjects with neural dysfunction the evoked potentials eventually returned to normal after a rise in the blood glucose concentration. In four of these subjects, however, there was prolonged neural dysfunction for up to 48 hours despite the maintenance of normoglycaemia. Although it cannot be known whether transient abnormalities in the evoked potentials are associated with permanent neural damage, such neural dysfunction cannot be beneficial and it is reasonable to try to prevent it by maintaining blood glucose concentrations at 2-6, mmol/l or above.

All our subjects were well at the time of the study. It is likely that the ‘safe’ blood glucose concentration may vary in different clinical situations, for example, during anoxia, polycythaemia, or convulsions. The non-invasive recording of evoked potentials provides the possibility of obtaining functional definitions of hypoglycaemia in children of different ages under a variety of clinical situations, and further studies are needed to explore these suggestions.

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References


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