Influence of hypoglycaemia, with or without caffeine ingestion, on visual sensation and performance

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ABSTRACT

Full-field visual evoked potentials and visual information processing were measured in 16 normal, healthy subjects during a hyperinsulinaemic clamp. A randomized cross-over design was used across three conditions: hypoglycaemia and caffeine; hypoglycaemia and placebo; and euglycaemia and caffeine. The latency of the P100 component of the pattern-reversal visual evoked potential increased significantly from rest to hypoglycaemia, but no effect of caffeine was found. Subjects were subsequently divided into two median groups based on the increase in P100 latency in the placebo condition (Group 1, >0.5 ms; Group 2, >5.6 ms). In the absence of caffeine, an inverse correlation between the increase in P100 latency from rest and a deterioration in visual movement detection was found for Group 2, but not for Group 1. Caffeine ingestion resulted in a further increase in P100 latency, from rest to hypoglycaemia, for subjects in Group 2. Hypoglycaemia in the absence of caffeine produces changes in visual sensation from rest to hypoglycaemia. In those subjects most sensitive to the effects of hypoglycaemia (Group 2), the increase in P100 latency was associated with poorer performance in tests of visual information processing. Caffeine ingestion produced further increases in P100 latency in these subjects.

INTRODUCTION

It has been shown previously that caffeine ingestion can significantly alter the magnitude of an individual’s response to hypoglycaemia. The ingestion of caffeine is thought to cause a simultaneous decrease in cerebral blood flow and increase in demand for cerebral substrates, which combine to increase the counter-regulatory hormonal response, and to produce greater subjective awareness of hypoglycaemia [1]. The study of caffeine ingestion during hypoglycaemia is important, as many of the most readily available snacks that might be taken by an individual close to becoming hypoglycaemic, such as coffee, cola or chocolate, contain significant amounts of caffeine. Although some of these products also contain sugar, it is possible that an individual consuming them may actually intensify the effects of borderline hypoglycaemia.

The effects of hypoglycaemia on cognitive performance are also altered following caffeine ingestion. An increase in latency of the auditory oddball P300 component has been found at a blood glucose concentration of 2.8 mmol/l after caffeine ingestion. No similar change in latency was observed in the placebo condition [1]. However, because of the uncertainty concerning the structural origin and functional significance of the P300

Key words: caffeine, hypoglycaemia, visual evoked potential, visual performance, visual sensation.

Abbreviations: EEG, electroencephalogram; TB1 (etc.), test battery 1 (etc.); VCD, visual change detection; VEP, visual evoked potential; VMD, visual movement detection.

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response, the clinical relevance of this type of cognitive function test is uncertain. Also, it is important to understand how sensory events preceding cognition are themselves modified by hypoglycaemia, if appropriate conclusions are to be drawn from studies of cognitive function.

Assessment of the visual system could provide a sensitive measure of the effects of caffeine, if indeed caffeine has an effect over and above that of hypoglycaemia. Visual functions such as visual search, contrast sensitivity and colour vision have all been shown to deteriorate when the blood glucose concentration falls [2–5]. However, it has also been possible to show that very early stages of visual information processing, such as simple visual discrimination and the ability to detect the locus of a discrete change of movement, are altered during hypoglycaemia [3]. In electrophysiology, the P100 component, which is the first major positivity recorded over the occipital cortex following stimulation of the visual field with a reversing checkerboard pattern, increases in latency at blood glucose concentrations of less than 2.5 mmol/l [5].

Increases in P100 latency are not always reported during hypoglycaemia. One study found no significant change in visual sensation, despite hypoglycaemia-induced changes in the electroencephalogram (EEG) [6]. However, in a similar study, subjects presented with a 15° full-field checkerboard which reversed approximately once per second showed a mean P100 latency increase of 10.8 ms at a blood glucose concentration of 2.5 mmol/l or less. This increase occurred in both diabetic and non-diabetic subjects [5]. The pattern-reversal visual evoked potential (VEP) is a sensitive electrodiagnostic indicator of optic nerve dysfunction. An increase in the latency of the P100 indicates that there is a functional deficiency in the transfer of information along the optic nerve to the primary visual cortex.

The present study used tests of visual information processing [3] to examine the simultaneous effects of caffeine and reduced blood glucose. In addition, pattern-reversal VEPs were recorded in an attempt to establish whether any changes during these tests were due to alterations in visual sensation or changes in higher-order visual function.

METHODS

Subjects
A total of 16 healthy subjects participated in the trial. There were eight male subjects with a mean age of 31 years (range 21–37 years) and a mean body mass index of 23.9 kg/m² (19.1–29.2 kg/m²), and eight female subjects with a mean age of 31 years (24–34 years) and a mean body mass index of 22 kg/m² (17.4–30.8 kg/m²). All prospective subjects completed a medical screening questionnaire, which excluded participants on the grounds of a personal or family history of diabetes, or evidence (or history of) cardiovascular or neurological disorders. An ECG was performed to ensure that conduction defects or quiescent cardiac problems were not overlooked, and a blood sample was analysed to check for normal renal function. All subjects had normal body mass and normal visual acuity with correction if necessary. All consumed caffeine on a daily basis and were not taking any regular medication. Intellectual ability was assessed using the National Adult Reading Test [7]. With the exception of one male subject, all were right-handed. The experimental procedure was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association [8], and was approved by the Centre for Human Sciences Ethics Committee. Subjects gave written informed consent.

Experimental design
Subjects were assessed on four separate occasions at least 1 week apart. The first visit was to familiarize subjects with the tests that were to be used during the three experimental conditions, and also to help minimize any practice and learning effects. A cross-over design was adopted, and subjects received all three treatments on separate occasions, in a double-blind fashion. During two of the visits hypoglycaemia was induced, and on the remaining visit euglycaemia was maintained throughout. During the two hypoglycaemic conditions, subjects were given either 200 mg of caffeine at 90 min (the caffeine condition) or matched placebo (the placebo condition). A dose of 200 mg of caffeine was also ingested at this time point during the euglycaemic condition.

Procedure
On each of the experimental visits, the subject attended the laboratory following an overnight fast. They were asked not to consume food and beverages containing caffeine from 18.00 hours on the previous day.

For electrophysiological recording, 15 silver/silver chloride electrodes were fixed to the scalp according to the International 10–20 system [9] at sites Fz, Cz, Pz, F3, F4, F7, F8, C1, C2, C3, C4, P3, P4, T3 and T4. A further electrode was positioned at the inion, in addition to five sites from the ‘Queen Square’ montage; one 5 cm above the inion in the midline, plus electrodes 5 cm and 10 cm to the left and right of this midline electrode. These sites are more optimally placed for an appreciation of pattern-reversal VEP components than electrodes at O1, O2 and Oz, which are not placed optimally with respect to the underlying visual cortex [10]. Activity at all sites was referred to linked earlobes, and impedance was less than 5 kΩ. Electrodes were also positioned around the eyes to monitor eye movements, and ocular artefact was removed off-line [11]. A ground electrode was located mid-forehead.
Hypoglycaemia was induced using a hyperinsulinaemic glucose-clamp procedure [12]. The antecubital site of the non-dominant arm was cannulated for infusion of insulin and glucose. A 20-gauge cannula was placed in the superficial vein in the dorsal surface of the hand, which was then placed in a hand-warming unit maintained at 60 °C to enable sampling of arterialized venous blood [13]. The cannula was kept patent by constant infusion of 154 mmol/l saline. Insulin (Novo-Nordisk Human Actrapid) was infused at a rate of 2 m-units·min⁻¹·kg⁻¹ for a total of 285 min.

The experimental profile is shown in Figure 1. Following cannulation, insulin was infused at a constant rate of 2 m-units·min⁻¹·kg⁻¹ after an initial loading rate of 6 m-units·min⁻¹·kg⁻¹ for 3 min and then 4 m-units·min⁻¹·kg⁻¹ for 4 min. A 20% (w/v) glucose infusion was started 5 min after the insulin infusion. Alterations in the rate of glucose infusion were made in order to maintain euglycaemia (4.5 mmol/l) for 90 min.

Blood glucose measurements were made every 3.5 min. At 90 min after the insulin infusion began, subjects ingested either 200 mg of caffeine or matched placebo, containing lactulose filler. Following this, blood glucose was either maintained at 4.5 mmol/l (euglycaemia) or reduced to 2.5 mmol/l (hypoglycaemia). At 180 min the insulin infusion was stopped, and the glucose infusion rate was increased so that the blood glucose concentration was restored to 4.5 mmol/l by 200 min. The experiment ended when blood glucose had been stabilized for 60 min. At this point the clamp was stopped and subjects received a high-carbohydrate meal.

Plasma caffeine levels were measured by enzyme multiplication immunoassay (EMIT; Behring Diagnostics, Milton Keynes, U.K.) on an Olympus AU560 autoanalyser (Olympus Optical, Eastleigh, Hants., U.K.).

A set of VEPs was recorded at the subject’s own baseline glycaemic concentration prior to insulin infusion (TB1). Subjects then completed further test batteries at 20 min (TB2), 120 min (TB3) and 210 min (TB4) after the start of insulin infusion. The total test battery, which included a number of cognitive tests not reported here, lasted for 60 min, and the tests were performed in a fixed order. Tests of visual information processing and VEPs were included in TB2–TB4.

Tests of visual function
A visual change detection (VCD) task and a visual movement detection (VMD) task [3] were presented at approx. 10 and 15 min respectively after the start of the test battery (TB2–TB4).

VCD
The subject was presented with a stimulus array consisting of 49 identical rectangles displayed on a computer screen. After a variable time of between 14 and 86 ms, a single target rectangle was added. The subject was required to identify the locus of this change by pointing to the added rectangle. There were a total of 50 presentations.

Accuracy rather than speed of response was recorded, and the total number of correct responses was taken as the score (maximum score 50).

VMD
This test was similar in appearance to that for VCD, with the exception that the target rectangle appeared at the same time as the others in the array and then subsequently moved either left or right by a distance equal to its width. The subject had to indicate that they had detected this movement by pointing to the target rectangle. There were a total of 50 presentations. The scoring system was identical with that used for VCD.

Pattern-reversal VEP
VEPs were recorded approx. 30 min after the visual information processing tests. The subject was seated 1 m from a VDU displaying a black-and-white full-field checkerboard which subtended 16° at the eye. Individual checks subtended 50° visual angle and the screen was viewed binocularly. The checkerboard reversed twice per second, and averages were computed from responses to two sets of 100 reversals during each test battery. The sampling rate was 2000 samples per s recorded across a 200 ms epoch. The high-pass filter was set to 1 Hz and the low-pass filter was set to 500 Hz. A 50 Hz notch filter was used.

Data analysis
Blood glucose concentration was analysed immediately after sampling, using a 2300 STATPlus glucose analyser (Yellow Springs Instruments, Yellow Springs, OH, U.S.A.). Correlations between the change in blood glucose concentration and the change in visual function were computed using Pearson’s product moment correlation.

Electrophysiological data acquisition was controlled by Neuro Scan software (Neuro Scan, Inc., Sterling, VA, U.S.A.). The waveforms from two sets of 100 reversals recorded during each test battery were averaged to produce a single VEP. Linear trend was removed from the data using a least-squares approach [14]. The data were re-referenced to the Fz electrode.

Measurements were made of the peak latency N75, P100 and N145 components at the site on the midline 5 cm above the inion. For ease of reference this site will be referred to as Qz. The amplitudes of P100 and N145 were measured from the preceding peak. An overall analysis of the three conditions was carried out. In addition, the euglycaemia and caffeine conditions were
Figure 1 Experimental profile
The experimental profile included four test batteries. Pattern-reversal VEPs were recorded during TB1–TB4, and VMD and VCD were performed during TB2–TB4.

Compared, in order to examine the direct effects of hypoglycaemia, and the effects of caffeine during hypoglycaemia were examined by comparing the placebo and caffeine conditions.

Repeated-measures ANOVA with factors of condition (euglycaemia, placebo, caffeine) and time (TB1, TB2, TB3, TB4) was carried out for latency and amplitude values recorded at the inion and at a midline site 5 cm above the inion. Performance data from the VCD and VMD tests were also analysed using repeated-measures ANOVA. Factors were condition (euglycaemia, placebo, caffeine) and time (TB2, TB3, TB4). ANOVAs were subsequently repeated to test for effects of gender. The Greenhouse–Geisser correction was used where appropriate.

RESULTS

Blood glucose concentrations
Target blood glucose concentrations were achieved in all subjects for each condition. The mean values are shown in Table 1.

Table 1 Blood glucose concentrations achieved
Values are means ± S.D.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Glucose concn. (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Euglycaemia</td>
</tr>
<tr>
<td>Euglycaemia</td>
<td>4.46 ± 0.36</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.60 ± 0.56</td>
</tr>
<tr>
<td>Caffeine</td>
<td>4.45 ± 0.36</td>
</tr>
</tbody>
</table>

Caffeine concentrations
The mean caffeine levels throughout the experiment are shown in Table 2.

VCD scores
The mean scores for VCD are shown in Table 3. Neither absolute nor difference scores changed across the conditions.

VMD scores
There were no differences in the absolute scores for VMD (Table 3), but the direction of change of performance was different across conditions \( F(2,24) = 4.11; P = 0.029 \). This was accounted for by an improvement in performance during euglycaemia, which was not seen during either hypoglycaemic condition. There was no effect of caffeine between the two hypoglycaemic conditions.

There was an interaction during the visual information processing tasks between performance and gender, with females scoring more highly than males \( F(1,11) = 24.36; P = 0.001 \). VMD was most sensitive and, during hypo-
Table 2  Average caffeine levels
Values are means ± S.D.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>+ 20 min</th>
<th>+ 80 min</th>
<th>+ 120 min</th>
<th>+ 180 min</th>
<th>+ 210 min</th>
<th>+ 270 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglycaemia</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>2.6 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>2.5 ± 0.3</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.7 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Caffeine</td>
<td>0.8 ± 0.4</td>
<td>0.8 ± 0.4</td>
<td>0.7 ± 0.4</td>
<td>2.8 ± 0.3</td>
<td>2.5 ± 0.4</td>
<td>2.2 ± 0.4</td>
<td>2.0 ± 0.5</td>
</tr>
</tbody>
</table>

Table 3  Scores for performance during visual information processing tasks for test batteries TB2–TB4
Values are the number correct out of 50, and are means ± S.D.

<table>
<thead>
<tr>
<th>Condition</th>
<th>TB2</th>
<th>TB3</th>
<th>TB4</th>
<th>TB3</th>
<th>TB4</th>
<th>TB2</th>
<th>TB3</th>
<th>TB4</th>
<th>TB3</th>
<th>TB4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglycaemia</td>
<td>27.87 ± 4.73</td>
<td>30.73 ± 4.17</td>
<td>30.29 ± 3.90</td>
<td>2.63 ± 4.26</td>
<td>3.07 ± 4.20</td>
<td>40.68 ± 5.90</td>
<td>43.67 ± 2.35</td>
<td>44.86 ± 4.62</td>
<td>3.27 ± 5.46</td>
<td>4.07 ± 4.85</td>
</tr>
<tr>
<td>Placebo</td>
<td>28.00 ± 4.99</td>
<td>28.67 ± 4.35</td>
<td>0 ± 1.56</td>
<td>1.48</td>
<td>1.19</td>
<td>3.94</td>
<td>4.11</td>
<td>3.70</td>
<td>4.00</td>
<td>3.63</td>
</tr>
<tr>
<td>Caffeine</td>
<td>29.93 ± 3.85</td>
<td>30.20 ± 4.14</td>
<td>29.27 ± 5.59</td>
<td>0.30 ± 4.90</td>
<td>1.06 ± 4.74</td>
<td>42.87 ± 3.42</td>
<td>41.93 ± 4.85</td>
<td>40.27 ± 7.00</td>
<td>1.19</td>
<td>5.28</td>
</tr>
</tbody>
</table>

Figure 2  Increase in P100 latency from baseline to hypoglycaemia for subjects in Group 2
For these subjects, there was a further increase in P100 latency as a result of caffeine ingestion.

Euglycaemia and Caffeine, Hypoglycaemia and Placebo, Hypoglycaemia and Caffeine

Mean baseline VEP (TB1).

TB2 overlaid (in bold) with TB1. No mean change in VEP latency across conditions.

TB3 overlaid (in bold) with TB1. Mean latency of P100 has shifted 5.6 ms in hypoglycaemia and placebo condition. Significant P100 latency shift also evident in hypoglycaemia and caffeine condition.

TB4 overlaid with TB1

An effect of hypoglycaemia was identified by an increase in latency of P100 in a comparison between the euglycaemia/caffeine and hypoglycaemia/caffeine conditions [F(3,33) = 8.59; P = 0.001]. There was no specific effect of caffeine on component latency.

Considerable inter-subject variability in the latency of P100 was noted during the third test battery, at which
The change in P100 latency from baseline to recovery is shown for subjects who were divided into two groups by a median split based on the change in P100 latency during the hypoglycaemia with placebo condition. There were increases in latency for the subjects in Group 2 as a result of both hypoglycaemia and caffeine ingestion. E, euglycaemia; C, caffeine; P, placebo; BL, subjects’ own baseline; EU, experimental euglycaemia; HYPO, hypoglycaemia.

The subjects who showed the largest increase in P100 latency during hypoglycaemia (Group 2) were also the subjects who showed the most significant deterioration in performance of the VMD task [Φ(1,10) = 8.98; P = 0.013] (Figure 4). This deterioration was not reversed during the recovery period.

DISCUSSION

The aim of the present study was to measure the effects of caffeine ingestion on visual function during hypoglycaemia. The data confirm that hypoglycaemia has a significant effect on visual sensory function, as measured by the increase in the latency of P100 from rest to hypoglycaemia. In addition, this study has shown that, in those subjects who are most sensitive to a decrease in blood glucose concentration, caffeine ingestion produces a further increase in P100 latency. For these subjects there is a significant inverse relationship between the increase in P100 latency and the deterioration in performance of a visual information processing task during hypoglycaemia.

Previously, hypoglycaemia has been shown to produce a deterioration in the early stages of visual information processing [3]. However, these results were not replicated in the present study, despite using identical tests of VCD and VMD, and inducing a similar hypoglycaemic profile.

As females were found to perform significantly better on these tests of visual information processing, it is possible that gender accounted for the failure to replicate the results of the previous study [3]. Exactly half of the subjects in the present study were female, compared with only 10% in the McCrimmon study [3]. Analysis by gender of the present data showed that there was a stronger tendency for performance of the VMD test to deteriorate as a result of hypoglycaemia for males compared with females. There were also substantial differences between subjects in their sensitivity to changes in visual function during hypoglycaemia. When subjects were divided into groups based on the median of changes in P100 latency in the hypoglycaemia/placebo condition.
condition, those who showed the greatest deterioration were also those who performed poorly on the visual information processing tasks. It is therefore possible that McCrimmon et al. [3] had a greater number of ‘visually sensitive’ subjects in their study.

The electrophysiological data showed that hypoglycaemia produced a significant mean increase in the latency of the P100 component of the pattern-reversal VEP. Amplitudes were unaffected. This change in latency replicates results reported previously [5]. When compared with subjects’ own baseline concentrations, a decrease in substrate to 2.5 mmol/l resulted in a change in visual function.

The increase in P100 latency has previously been related to a general slowing of cerebral electrophysiological activity recorded in the EEG [5]. However, as the changes in the EEG recovered before the latency of the VEP returned to normal, the authors of that study suggested that cortical changes alone did not account for the increase in latency. A possible alternative explanation is that the changes in P100 are not changes in latency per se, but the ‘unmasking’ of another component of the VEP. Inducing experimental ‘scotomata’ by occluding the central region of the stimulus has previously been shown to result in an almost linear relationship between the radius of the ‘scotomata’ and a reduction in the amplitude of the ipsilateral, half-field P100 [15]. It is possible that a decrease in P100 amplitude can cause the contralaterally maximal P135 to become more prominent. Thus central field deficit can result in the appearance of a latency increase in the positive component.

Although reductions in P100 amplitude were observed in the present study in some subjects, it is not possible to state whether these decreases contributed to the apparent increase in the latency of the P100. Certainly, a central field deficit would explain the deterioration in colour vision that occurs during hypoglycaemia [3]. Without half-field stimulation, it is possible only to conclude that hypoglycaemia produces a change in the P100 which becomes apparent in an increase in the latency of the component.

It is evident from the present study that there were large individual differences in P100 latency during hypoglycaemia, and a median split was carried out, based on the increase in latency. The subsequent analyses produced significant group differences for P100 latency between conditions, indicating that some individuals were more sensitive to a change in visual function as a result of hypoglycaemia. In those subjects who were most sensitive to the effects of hypoglycaemia in the baseline condition, effects of caffeine ingestion were observed, over and above those of hypoglycaemia. In these subjects, caffeine produced further significant increases in the latency of the P100.

The results from the present study indicate that caffeine ingestion can cause increases in the latency of the P100 in those subjects who are visually sensitive to the effects of hypoglycaemia. These results have implications both for healthy individuals and for patients with diabetes. In healthy individuals who may work for long periods in conditions where the most readily available refreshments contain significant amounts of caffeine, consuming food or drink may actually exaggerate feelings of hypoglycaemia, which might be avoided by eating or drinking alternative items. In diabetic subjects the risk of an exaggerated response to hypoglycaemia is even greater, as diabetic individuals are typically hyperglycaemic, and therefore likely to experience a greater absolute reduction in the concentration of glucose. The danger is especially great in cases of asymptomatic hypoglycaemia, where an individual may not be aware that peripheral levels of glucose are already low and that ingestion of caffeine could result in the deterioration of visual symptoms often reported by people with diabetes.

The division of subjects according to the magnitude of the change in P100 latency from baseline to hypoglycaemia resulted in the formation of two groups. Subjects in the group who showed a comparatively large change in latency (5.6 ms) also showed deterioration in performance during one of the visual information processing tests (VMD), and a further increase in P100 latency following caffeine ingestion. Subjects who showed little change in P100 latency (0.5 ms) showed neither of these effects. It therefore appears that there may be individuals in whom the effect of hypoglycaemia is more severe than others. The consequences of this difference in visual information processing are evident from the present study. The validity of this difference and its further consequences remain to be established.

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