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Attentional functioning is impaired during acute hypoglycaemia in people with Type 1 diabetes

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Abstract

Aims To examine the effects of acute insulin-induced hypoglycaemia on different aspects of attention and on general non-verbal reasoning in people with Type 1 diabetes.

Methods A hyperinsulinaemic glucose clamp was used to maintain euglycaemia (4.5 mmol/l) or induce hypoglycaemia (2.6 mmol/l) on separate occasions in 16 adults with Type 1 diabetes each of whom were studied on two occasions in a counterbalanced order. During each study condition, the subjects completed parallel tests of cognitive function assessed by the Test of Everyday Attention and the Raven's Progressive Matrices.

Results Hypoglycaemia caused a significant deterioration in tests sensitive to visual and auditory selective attention. During hypoglycaemia, attentional flexibility deteriorated and speed of information processing was delayed. Sustained attention and intelligence scores were preserved during hypoglycaemia.

Conclusions In people with Type 1 diabetes, hypoglycaemia causes a significant deterioration in attentional abilities, while non-verbal reasoning is preserved. It is likely therefore that many complex cognitive tasks which involve attention will be impaired during moderate hypoglycaemia during everyday life.

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Keywords attention, cognitive function, hypoglycaemia, intelligence, Type 1 diabetes

Abbreviations RAPM, Raven's Advanced Progressive Matrices; RPM, Raven's Standard Progressive Matrices; SD, standard deviation; TEA, Test of Everyday Attention

Introduction

Cognitive function is impaired during acute hypoglycaemia [1–3]. When arterialized blood glucose falls below about 3.0 mmol/l, tests that require attention, concentration, psychomotor skill, access to long-term memory and the ability to ignore distracting information deteriorate in performance [4–8]. Responses to the effects of acute hypoglycaemia vary considerably between individuals, and numerous moderators of cognitive function are recognized, including intelligence [9], the presence or absence of diabetes [5,8,10–12], and glycaemic control [5,12]. Because few cognitive domains in isolation have received detailed examination, recent studies have tried to address how specific cognitive domains are disrupted by neuroglycopenia. Attempts have been made to ascertain how abnormalities of cognitive function that are demonstrable by neuropsychological tests, are related to everyday mental tasks [13–17].

Attention is a complex cognitive domain involving multiple subcomponent processes [18,19]. Because it comprises fundamental cognitive processes that are integral to many neuropsychological tests, it is difficult to examine attentional dysfunction in isolation. A previous study in our centre examined individual attentional processes during hypoglycaemia in non-diabetic subjects, and demonstrated deterioration of attentional flexibility

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and speed of information processing, while sustained attention was preserved [13].

Within the psychometric study of intelligence, general fluid intelligence reflects adaptive, problem-solving ability. Raven's Progressive Matrices [20] is a test of non-verbal reasoning that involves rule induction and application in abstract patterns. It is closely associated with general fluid intelligence [21]. General intelligence is a key finding and theoretical construct in the psychometric structure of human abilities [22], and is an important influence on the quality of performance of many everyday activities [23]. Although a deterioration in aspects of intelligence has been observed during acute hypoglycaemia, both in non-diabetic subjects [24,25] and in people with diabetes [6,26,27], to our knowledge few studies of non-diabetic or diabetic adults have included subtests that were designed specifically to measure aspects of non-verbal reasoning [13,17].

It is uncertain whether the results of our previous study in non-diabetic subjects can be applied to subjects with Type 1 diabetes. Thus, the aim of the present study was to examine the effects of acute, controlled insulin-induced hypoglycaemia on facets of attention and on general non-verbal reasoning in adults with Type 1 diabetes.

Subjects and methods

Subjects

Sixteen adults with Type 1 diabetes were recruited from the diabetes outpatient clinics at the Royal Infirmary of Edinburgh. The median (range) age was 25.5 (18–39) years and duration of diabetes was 8.0 (2.5–15) years with a mean (SD) body mass index of 24.1 (1.8) kg/m^2. The mean (SD) National Adult Reading Test number correct score was 27 (7.8). Thus, the group comprised people whose mean was just above average intelligence, with an overall predicted full-scale intelligence quotient of around 109. Their mean (SD) HbA_{1c}, measured by high-performance liquid chromatography (Variant II Hemoglobin Testing System; Bio-Rad Diagnostics, Hercules, CA, USA) was 7.7 (1.0) % (local Diabetes Control and Complications Trial-aligned, non-diabetic reference range: 4.3–6.5%). None of the participants had a history of chronic disease, hypertension, previous head injury, seizure or blackouts, alcohol or drug abuse or psychiatric disorder. None had any intercurrent illness, nor was taking medication (other than insulin and the combined oral contraceptive pill) and none of the subjects had evidence of microvascular disease. Peripheral neuropathy was excluded by clinical examination, and none of the participants had microalbuminuria. No subjects had impaired awareness of hypoglycaemia. Care was taken to avoid hypoglycaemia in the 48 h prior to the cognitive testing, with regular blood glucose monitoring, including bedtime measurements on the night before each study. The study was deferred for 1 week if there was biochemical evidence of hypoglycaemia (blood glucose < 4.0 mmol/l) at that time.

Study design

Ethical permission for the study was given by the Lothian Medical Ethical Advisory Committee, and all subjects gave their written informed consent. The subjects were studied on two occasions, separated by at least 1 week. The experiment had a repeated measures, counterbalanced design, i.e. half of the subjects underwent the euglycaemia session first, followed by the hypoglycaemia study, and the other half were studied in the reverse order. A modified hyperinsulinaemic glucose clamp technique [28] was used to adjust the blood glucose to a predetermined level. Either hypoglycaemia was induced (blood glucose 2.6 mmol/l) and maintained at this level, or the blood glucose concentration was maintained at 4.5 mmol/l (euglycaemia). During the two study conditions (euglycaemia and hypoglycaemia) tests of cognitive function were administered and the subjects completed a questionnaire on the symptoms of hypoglycaemia. Subjects were blinded as to the order of the studies and to their prevailing blood glucose concentration at all times throughout the procedure.

Procedure

Each session commenced at 08.00 h after an overnight fast, and the subjects omitted their morning dose of insulin. Intradermal lignocaine (1%) was used for local anaesthesia, and two cannulae were placed in the non-dominant arm, one being inserted retrogradely in a distal hand vein. This hand was used for sampling, having been placed in a warm blanket to 'arterialise' venous blood. A second intravenous cannula was placed in the antecubital fossa for infusion of 20% dextrose and human soluble insulin (Humulin S; Eli Lilly, Indianapolis, IN, USA). After a brief priming regimen, insulin in supraphysiological concentrations was infused at a constant rate of 60 mU/m^2/min into a peripheral vein using an IMED Gemini PCI pump. An infusion of 20% dextrose was adjusted according to the blood glucose concentration measured at the bedside (Yellow Springs Instrument 2300 Stat, Yellow Springs, OH, USA). Blood sampling for glucose estimation was made initially at 3-min intervals, then at 5-min intervals once a stable blood glucose concentration had been achieved.

In each study condition, the arterialized blood glucose concentration was stabilized at 4.5 mmol/l (baseline) for a period of 30 min, then either maintained at 4.5 mmol/l (euglycaemia) or lowered to 2.6 mmol/l (hypoglycaemia). An arterialized blood glucose concentration of 2.6 mmol/l was chosen for the depth of hypoglycaemia to be tested because significant impairment of various domains of cognitive function have been demonstrated at this level in previous studies [1]. A period of 20–30 min elapsed between the baseline plateau and the attainment of hypoglycaemia to allow the blood glucose concentration to stabilize. The target blood glucose concentration was maintained for a further 10 min before the tests were administered.

Cognitive function tests

The Test of Everyday Attention (TEA) [29] and the Raven's Standard Progressive Matrices (RPM) [20] were used to measure attention and intelligence, respectively. The order of the tests was identical during each study condition.

Test of Everyday Attention (TEA)

The TEA was devised from the evidence on separable attention systems in the brain [18]; it attempts to measure aspects of the selection and vigilance systems and correlates significantly with existing measures of attention and has been described previously in detail [13]. Briefly, the TEA is divided into eight subtests and has parallel forms. Subjects were asked to pretend that they were visiting Philadelphia in the USA, and were told that they would be asked to perform various tasks such as looking for symbols on maps, consulting telephone directories, and travelling in an elevator. The attention processes examined and their corresponding test(s) are shown in Table 1.

Raven's Progressive Matrices (RPM)

The RPM examine general non-verbal intelligence and specifically measure the inductive ability to find and apply rules that make it easier to bring order to complex situations and events [30]. The Matrices' items are diagrammatical puzzles exhibiting serial change in two dimensions simultaneously. Each puzzle has a part missing which the subject has to locate among the answer options provided. The correct answer is found by discovering and correctly applying the rules governing the changes in each item's pattern. Figure 1 is an example of the type of problem that would be found in the RPM. The test consists of 60 items divided into five sets, each consisting of 12 items. Subjects were scored for the number correct at 20 min and the number correct at completion (no time limit). By doing this, the speed of accurate intellectual work and the total capacity for orderly thinking was assessed.

Symptoms of hypoglycaemia

A validated, subjective self-rating system (The Edinburgh Hypoglycemia Scale) [31] was applied at four time points: baseline, before and after the TEA, and after the RPM. The symptoms of hypoglycaemia were classified as autonomic (palpitations, sweating, shaking and hunger), neuroglycopenic (confusion, drowsiness, inability to concentrate, speech difficulty and blurred vision) and non-specific (nausea and headache). Each symptom was graded on a Likert scale of 1–7 (1 = not present, 7 = very intense). The total for each subgroup of hypoglycaemic symptoms was calculated. A validated scale was used to assess impaired awareness of hypoglycaemia [32].

Statistical analysis

The results were analysed independently for each subtest of the TEA and the RPM. A general linear model (repeated measures analysis of variance) was used with order of session as a 'between subjects' factor with two levels (euglycaemia–hypoglycaemia or hypoglycaemia–euglycaemia), and condition as a 'within subjects' factor with two levels (euglycaemia vs. hypoglycaemia). A similar model was used to analyse the symptoms of hypoglycaemia, with the addition of time as a 'within subjects' factor with four levels. A *P*-value of < 0.05 was considered to be significant. Effect size was calculated using Eta squared (η^2). η^2 is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs. hypoglycaemia). An η^2 score of 0.25–0.5 was considered a moderate effect size. All analyses were performed using SPSS version 11.0 for Windows (SAS Institute, Cary, NC, USA).

Table 1 The subtests and attention processes of the TEA

Attentional process	Test
Selective attention	Map search
Speed of information processing	Telephone search
Attentional switching	Visual elevator
Sustained attention	Lottery counting Elevator counting Telephone search while counting
Divided attention	Telephone search while counting

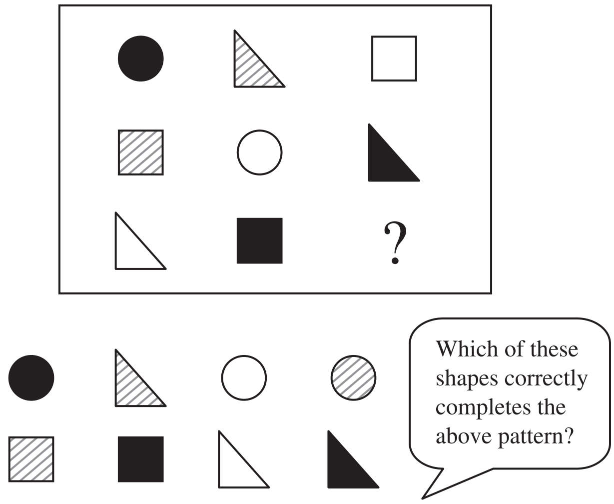

Figure 1 Illustrative example of RPM item. Subjects are asked to identify the piece required to complete the design from the options below. (The item shown here is not from the current range of RPM tests.) With thanks to John Raven for permission to reproduce.

Results

A stable blood glucose plateau was achieved during each condition. The mean (SD) blood glucose concentration during the hypoglycaemia clamp was 2.6 (0.2) mmol/l, and during euglycaemia was 4.5 (0.2) mmol/l. The initial statistical analysis revealed that no significant order effects had occurred.

Symptoms

The autonomic symptom score increased from a mean (SD) of 5.1 (1.2) at baseline to 7.9 (2.8) during hypoglycaemia ($P = 0.002$), and the neuroglycopenic symptom score increased from 6.0 (1.9) to 11.1 (5.4) ($P = 0.001$). A significant increment was also observed in the general malaise symptom scores, which increased from 2.1 (0.3) at baseline to 3.3 (1.8) during hypoglycaemia ($P = 0.01$). No significant changes in symptom scores occurred during the euglycaemia condition.

Tests of attention

The results of the attention tests are summarized in Table 2.

Table 2 Attentional function during euglycaemia and hypoglycaemia in 16 subjects with Type 1 diabetes

Attentional system	Subtest	Euglycaemia	Hypoglycaemia	*P*-value	η^2	η^2 for non-diabetics*
Visual selective attention	Map search symbols in 1 min	50.0 (8.8)	42.6 (10.0)	0.032	0.29	0.32
	Map symbols circled in 2 min	74.1 (4.0)	70.3 (7.7)	0.042	0.26	0.12
	Telephone search time (s)	47.4 (6.0)	52.5 (8.0)	0.022	0.32	0.36
	Telephone search correct symbols	18.5 (2.7)	18.7 (2.0)	0.46	0.04	0.001
	Telephone search raw score (symbols/s)	2.6 (0.6)	2.9 (0.7)	0.003	0.48	0.36
Attentional switching	Visual elevator raw score	9.3 (0.9)	8.8 (1.4)	0.21	0.11	0.03
	Visual elevator timing score (symbols/s)	3.0 (0.6)	3.4 (0.9)	0.04	0.26	0.69
	Visual elevator time (s)	120.0 (20.5)	150.0 (23.4)	< 0.0001	0.78	0.76
Auditory selective attention	Elevator counting with distraction	8.9 (1.3)	7.3 (2.0)	0.001	0.59	0.40
	Elevator counting with reversal	8.0 (1.7)	7.1 (1.8)	0.013	0.39	0.01
Sustained attention	Elevator counting	6.9 (0.3)	6.7 (0.6)	0.15	0.14	0.03
	Lottery tickets	9.6 (0.7)	9.2 (0.9)	0.26	0.09	0.08
Divided attention	TSWC time (s)	55.2 (10.3)	49.1 (7.7)	0.001	0.58	0.13
	TSWC correct symbols	18.4 (1.6)	18.7 (1.6)	0.67	0.01	0.07
	TSWC time/target score	3.0 (0.7)	2.7 (0.5)	0.036	0.28	0.26
	Dual task decrement	0.4 (0.7)	0.4 (0.6)	0.95	0.00	0.01

Values are mean (SD).
η^2 is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs. hypoglycaemia).
TSWC, telephone search while counting.
*Data from McAulay *et al*. [13].

Visual selective attention

The mean number of map symbols circled was lower during hypoglycaemia both at 1 min ($P = 0.032$, $\eta^2 = 0.29$) and at 2 min ($P = 0.042$, $\eta^2 = 0.26$). By contrast, in the telephone search task, no difference was demonstrated between euglycaemia and hypoglycaemia in the number of symbols located ($P = 0.46$). However, the mean time taken to complete the task increased significantly during hypoglycaemia ($P = 0.022$, $\eta^2 = 0.32$).

Auditory selective attention/auditory verbal working memory

With the auditory elevator test with distraction, the achieved score declined during hypoglycaemia with a large effect size ($P = 0.001$, $\eta^2 = 0.59$). Furthermore, the score attained on the elevator test with reversal deteriorated during hypoglycaemia ($P = 0.013$, $\eta^2 = 0.39$).

Sustained attention

Sustained attention did not deteriorate during hypoglycaemia using either the lottery ticket test ($P = 0.26$) or the elevator counting test ($P = 0.15$).

Attentional switching

In the visual elevator task, no difference was observed in the raw score between the two study conditions ($P = 0.21$). However, a significantly longer time was required to complete the visual elevator task during hypoglycaemia with a large effect size ($P < 0.0001$, $\eta^2 = 0.78$).

Divided attention

In the task that involved search of a telephone directory while counting, no significant difference was observed in the number of symbols that were located during either study condition ($P = 0.67$). However, the time taken to complete the task was higher during hypoglycaemia ($P = 0.001$, $\eta^2 = 0.58$). The time per target score, which is the ratio of the number of circled symbols divided by the time taken for the task, was higher during hypoglycaemia with a moderate effect size ($P = 0.036$, $\eta^2 = 0.28$). The dual task decrement was not significantly different between the two conditions ($P = 0.95$).

Non-verbal intelligence

Using Raven's Progressive Matrices, no significant differences were observed between euglycaemia and hypoglycaemia in the scores achieved either at 20 min or upon completion of the test. The mean (SD) RPM score at 20 min was 50.1 (5.6) during euglycaemia and 49.0 (6.4) during hypoglycaemia ($P = 0.24$, $\eta^2 = 0.12$). Upon completion, the mean (SD) score was 51.7 (6.1) in euglycaemia and 50.6 (6.0) during hypoglycaemia ($P = 0.11$, $\eta^2 = 0.22$). No significant differences were observed between the two study conditions in the times taken to complete the test.

Discussion

In the present study, functional impairment occurred in the subdivisions of attention during hypoglycaemia in adults with Type 1 diabetes. A cognitive test battery was employed that was designed specifically to measure multiple facets of attention. Visual selective attention deteriorated during hypoglycaemia with a moderate effect size, whereas auditory selective attention was exquisitely sensitive to hypoglycaemia with a large effect size. Mean scores on the test of divided attention were poorer during hypoglycaemia, whereas no significant effect was evident on sustained attention or non-verbal reasoning.

A previous study, which used an identical design and cognitive function tests, examined the effects of acute hypoglycaemia in non-diabetic adults of similar age and intelligence and observed a broadly similar distribution of cognitive dysfunction during hypoglycaemia [13]. In that study, a decline in the rate of information processing was demonstrable in visual and auditory selective attention and in attentional switching (the ability to switch attention flexibly, e.g. changing the direction of counting). Although the data from both of these studies are congruent with the received wisdom that acute hypoglycaemia slows the speed of processing, the TEA measures additional cognitive processes. Furthermore, the differences observed in these studies provide an insight as to whether diabetes per se moderates susceptibility to cognitive dysfunction during hypoglycaemia [5,8,10].

In the present study, significant decrements occurred during hypoglycaemia in the test scores for auditory selective attention (Table 2). Unlike the other subtests in the TEA, these responses are not timed, so the observed decrements cannot be attributed to slowing of speeded processing. These two subtests measure the ability to manipulate and sequence information in auditory-verbal working memory [29], a mental ability that is very sensitive to moderate hypoglycaemia [14,15]. In the previous study of comparable non-diabetic volunteers, acute hypoglycaemia caused deterioration in performance of the test of the Elevator counting with distraction, but did not affect Elevator counting with reversal [13]. Indeed, the effect size during hypoglycaemia for Elevator counting with distraction was smaller ($\eta^2 = 0.40$) in non-diabetic volunteers, compared with the present study ($\eta^2 = 0.59$), suggesting that the effect is greater in subjects with diabetes (Table 2). An example of a clinical correlate for these tests of auditory verbal working memory is the ability to calculate using complex mental arithmetic.

Important differences were also observed between the current report and the non-diabetic study [13] in the effect of hypoglycaemia on visual selective attention. In both studies, hypoglycaemia produced a similar reduction in the number of map search symbols found in 1 min, but at 2 min a significant deterioration occurred only in the subjects with diabetes. While the Map search subtest is a timed test, and to an extent will measure speed of processing, it also requires selective attention. Supporting evidence for this can be found using principal components analysis, in which the Map search shares the factor structure of visual selective attention, in common with tests such as Trails B [33]. Because the effects on the other tests of speeded processing during hypoglycaemia were similar in the non-diabetic and diabetic subjects, it is possible that acute hypoglycaemia has a greater impact on visual selective attention in subjects with Type 1 diabetes, particularly when the test is prolonged. This premise is supported by a further study in which acute hypoglycaemia caused a significant and marked deterioration in visual information processing [25]. An alternative explanation is that the cognitive 'reserve' for speeded tests, or visual selection tests, is diminished in people with Type 1 diabetes.

In the present study, sustained attention was not impaired during hypoglycaemia, consistent with the previous observations in non-diabetic subjects [13]. Most subjects achieved the highest score possible during both study conditions, suggesting that significant ceiling effects had occurred. While it is possible that a test of longer duration in the present study may have increased the sensitivity of detecting a deterioration, it would appear that sustained attention to detail over a short period of time (10 min) is unaffected by hypoglycaemia.

In the present study, non-verbal intelligence did not diminish significantly during hypoglycaemia. This was unexpected because so many aspects of cognition are affected adversely by hypoglycaemia [2]. Furthermore, the RPM is known to have a substantial correlation with working memory [34], which is very sensitive to hypoglycaemia [15,16]. It is conceivable that the cognitive abilities required for activities such as those tested by the RPM are resistant to the effects of hypoglycaemia, but such a hypothesis would contravene the received wisdom during acute hypoglycaemia that complex tasks are more susceptible to disruption than simple tasks [2]. The brain is unlikely to have adapted to tolerate the effects of hypoglycaemia during the relatively short duration of exposure in this study [35]. A more plausible explanation for the present results is that the standard matrices that were used were too easy for this particular group of subjects. This has been tested in non-diabetic adults by using a more difficult test of general fluid intelligence, the Raven's Advanced Progressive Matrices (RAPM) [17], which showed that acute hypoglycaemia provoked a significant deterioration in the RAPM, suggesting that a ceiling effect had occurred using the standard RPM.

The present study has demonstrated that acute controlled hypoglycaemia causes attentional dysfunction in adults with Type 1 diabetes, while there was a non-significant decline in non-verbal reasoning. The tests of attention that were used in the present study are plausible, realistic and relevant to everyday activities. Tasks utilizing complex intellectual activity that are relevant to everyday life activities, such as procedures at work or the process of driving a car, are likely to be impaired in people with Type 1 diabetes during moderate insulin-induced hypoglycaemia. The severity of the attentional deficit during acute moderate hypoglycaemia was dependent upon which attentional system was being examined. The degree of hypoglycaemia applied in this study does not affect conscious level, so a similar deterioration during hypoglycemia is likely to have important practical implications for many tasks in the everyday lives of people with Type 1 diabetes. When compared with non-diabetic people, the differential deterioration observed in subtests of visual selective attention and auditory verbal working memory in subjects with Type 1 diabetes raises a potentially contentious issue and implies that a diagnosis of diabetes may act as a susceptibility factor to cognitive disruption during hypoglycaemia.

Competing interests

None declared.

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