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The effects of acute insulin-induced hypoglycemia on spatial abilities in adults with type 1 diabetes

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Objective: To examine the effects of acute insulin-induced hypoglycemia on spatial cognitive abilities in adult humans with type 1 diabetes.

Research Design and Methods: Sixteen adults with type 1 diabetes underwent two counterbalanced experimental sessions: euglycemia (blood glucose 4.5mmol/l; 81mg/dl) and hypoglycemia (2.5mmol/l; 45mg/dl). Arterialized blood glucose levels were maintained using a hyperinsulinemic glucose clamp technique. During each session, subjects underwent detailed assessment of spatial abilities from the Kit of Factor-Referenced Cognitive Tests, and two tests of general cognitive function.

Results: Spatial ability performance deteriorated significantly during hypoglycemia. The Hidden Patterns, Card Rotations, Paper Folding, and Maze Tracing tests were all impaired significantly ($p \leq 0.001$) during hypoglycemia, as was the Cube Comparisons test ($p=0.03$). The Map Memory test was not significantly affected by hypoglycemia.

Conclusions: Hypoglycemia is a common side-effect of insulin therapy in people with type 1 diabetes, and spatial abilities are of critical importance in day-to-day functioning. The deterioration in spatial abilities observed during modest experimental hypoglycemia provides novel information on the cerebral hazards of hypoglycemia that has potential relevance to everyday activities.

Hypoglycemia is a common side-effect of insulin treatment of diabetes. Strict glycemic control limits the development and severity of vascular complications of diabetes, but hypoglycemia is a frequent consequence. Strict glycemic control can increase the incidence of severe hypoglycemia by threefold (1). Hypoglycemia has an adverse effect on cognitive functions, as the human brain relies solely on glucose as its source of energy (2). It has a pronounced effect on complex cognitive tasks both in diabetic and non-diabetic humans, whereas simple mental tasks are relatively unaffected (2). Cognitive function deteriorates when arterialized blood glucose concentrations decline below 3.0 mmol/l (3-6). Simple and choice reaction times, speed of mathematical calculation, verbal fluency, attention, memory and psychomotor function have all been demonstrated to suffer during hypoglycemia (7-10). The recovery of different aspects of cognitive function may vary from between 40 and 90 minutes following restoration of blood glucose to normal (2, 11).

Whereas hypoglycemia impairs many domains of cognitive function, the effect of hypoglycemia on spatial cognitive abilities has not been investigated in detail, although spatial ability is undoubtedly a component of some of the tests used to assess other aspects of cognition (12). Spatial abilities may be defined as the ability to generate, retain, retrieve, and transform or manipulate structured visual images in order to orientate and interpret the surrounding environment. In real life terms, spatial ability is concerned with how human beings deal with issues concerning two- and three-dimensional objects, space, navigation, and pathfinding. Practical daily cognition often involves inferring how shapes and objects will appear and function when they are rotated or otherwise oriented or viewed differently. In everyday interactions with the environment, this process is very important, with particular relevance for complex tasks such as driving and map reading. A large variety of mental tests are available for the assessment of spatial abilities. Largely, these tests can be separated into tests of *spatial perception*, namely the ability to determine spatial relations despite distracting information, *spatial visualisation*, which is the ability to manipulate complex, multi-step spatial information, and *mental rotation*, which is the ability to rotate two or three dimensional figures in one's mind (13). The present study was designed to investigate the effects of acute insulin-induced hypoglycemia on spatial abilities in adults with type 1 diabetes, utilizing a well-characterised battery of spatial tests which incorporates all of these components of spatial cognition.

RESEARCH DESIGN AND METHODS

Subjects: Sixteen adults with type 1 diabetes (7 male, 9 female) participated in the study. Subjects were recruited from the diabetes clinic at the Royal Infirmary of Edinburgh. Baseline demographic characteristics were a median age of 28 years (interquartile range 25-37.5 years), median duration of diabetes of 10 years (IQR 4.2-19 years), BMI (mean [SD]) 26.4 (4.01) kg/m^2 and HbA1c 7.91 (0.92) %. HbA1c was measured by high performance liquid chromatography (non-diabetic reference range 5.0-6.05%; Bio-Rad Laboratories, Munich, Germany), and was DCCT-aligned. The subjects had no history of hypertension or macrovascular disease, and microvascular disease was excluded prior to recruitment. The presence of retinopathy was sought using digital retinal photography, neuropathy was assessed by clinical examination, and nephropathy was identified by the presence of microalbuminuria. Subjects were excluded if they had a history of impaired awareness of hypoglycemia, or a history of previous severe reaction to hypoglycemia. None of the participants had a history of head injury, seizure, blackouts, alcohol or drug abuse or psychiatric illness. Subjects were not on any medications other than insulin or the contraceptive pill. All subjects gave written informed consent before participating in the study, which had been approved by the local Research Ethics Committee.

Study Design: Each subject underwent two laboratory sessions, separated by at least two weeks. The study was conducted at the Clinical Research Facility at the Royal Infirmary of Edinburgh. A modified hyperinsulinemic glucose clamp (14) was used to maintain blood glucose at a predetermined level; euglycemia at 4.5 mmol/l (81mg/dl) and hypoglycemia at 2.5 mmol/l (45mg/dl). Each subject underwent a euglycemic study and a hypoglycemic study in a randomized, counterbalanced fashion. The subjects were blinded to the experimental condition.

Study Procedure: The experimental session began at 08:30 hours. All subjects monitored their blood glucose with care for the preceding 48 hours, including bedtime testing, and the study was postponed if they had any blood glucose value below 3.5 mmol/l or any symptoms suggestive of hypoglycemia. After an overnight fast the subjects omitted their morning insulin dose. A retrograde intravenous cannula for regular blood glucose sampling was inserted into the non-dominant hand and was placed in a heated blanket to arterialize the venous blood (15). A further cannula in the non-dominant antecubital fossa was used to infuse soluble insulin (Human Actrapid, NovoNordisk Pharmaceuticals, Crawley, UK) and 20% dextrose. Insulin was infused at a constant rate of 1.5mU/kg/min using a Gemini PCI pump (Alaris Medical Systems, San Diego, CA). Dextrose (20%) was infused at a rate that varied according to the arterialized blood glucose concentration, which was measured at 5 minute intervals using the glucose oxidase method (2300 Stat; Yellow Springs Instrument, Yellow Springs, OH).

On each study day, the arterialized blood glucose was initially stabilised at 4.5 mmol/l for a period of 30 minutes. It was then either maintained at that level throughout the study (euglycemia condition) or it was lowered over 20 minutes to 2.5 mmol/l and maintained at that level for the duration of the study (hypoglycemia condition). The experimental period lasted for 60 minutes, after which time the blood glucose concentration was restored to 4.5 mmol/l. Subjects were given a meal after completion of each study.

Cognitive Function Tests: Tests of spatial ability were drawn from the French and Ekstrom Kit of Factor-Referenced (cognitive) Tests (16, 17). In addition, the Digit Symbol Substitution test and Trail Making B test were administered in order to confirm the recognized effect of hypoglycemia on cognitive function, as described previously (7-10).

Spatial Ability Tests

Hidden patterns test - The Hidden Patterns Test requires subjects to identify a figure that is hidden among other lines. The figure is the same throughout, with the same orientation, and subjects have 3 minutes to correctly identify as many of the patterns in which the figure is concealed as possible.

Card rotations test - The Card Rotations test requires the subject to look closely at a shape on the left hand side of a page, and then assess whether the 8 shapes on the right hand side are the same shape, rotated through a variable number of degrees, or whether the shapes are different, and have in fact been reversed or are a mirror image of the initial shape. Three minutes are allowed to complete as many items as possible.

Cube comparisons test - This test involves pairs of cubes, such as the wooden building blocks played with by children, with a letter or shape of each facet of the cube. Subjects have 3 minutes to analyze as many pairs of cubes as possible, and must determine whether the 2 cubes could be the same cube viewed from different sides, or whether they must be different cubes if the letters on the sides did not correspond with each other had the cube been turned over.

***Paper folding test* -** The Paper Folding test involves showing participants a sequence of folds in a piece of paper, through which a set of holes is then punched. The participants must choose which of a set of punched and unfolded papers corresponds to the one they have just seen.

***Map memory test* -** This is a test of the subject's ability to remember the position of buildings on a street map. Four minutes are permitted to memorize the map, and then a further 4 minutes to place the buildings correctly on a blank version of the map.

***Maze tracing test* -** This is a test of the subject's ability to find a path through a maze quickly. A pencil line must be drawn through the maze without crossing any of the 'walls'. The maze is broken down into blocks, and the score is the number of blocks that are successfully navigated in 3 minutes.

Other Cognitive Function tests

***Digit Symbol Substitution test* -** This test is from the Wechsler Adult Intelligence Scale-III and assesses the ability of the subject to perform coding as quickly as possible. The subject is given a key of numbers 1-9 which each have a corresponding symbol. They must then fill in as many symbols as possible for a list of numbers in 120 seconds.

Trail Making B. - The Trail Making B test is a computerized version of the test, and similar in principle to the classic test from the Halstead Reitan battery. It is used to assess complex visual processing, and also assesses motor function with regards to visual motor tracking. It is performed on a handheld computer. The subject is presented with a grid containing letters and numbers in a random order, and must connect the numbers and letters in numerical and alphabetical order, alternating number with the letter in the fashion '1-A-2-B-3-C…' etc.

Hypoglycemia Symptom Score: The Edinburgh Hypoglycaemia Scale was used to assess the symptoms experienced by subjects during each experimental session. It is a validated self-rating questionnaire comprising a list of common symptoms of hypoglycemia which can be classified into autonomic, neuroglycopenic and non-specific symptoms. Each symptom is scored on a Likert Scale from 1 (not present) to 7 (intensely present) (18).

Statistical Analysis: Results were analysed using SPSS version 15.0 for Windows (SPSS, Chicago, IL). A general linear model (repeated measures ANOVA) was used, with order of session (euglycemia-hypoglycemia or hypoglycemia-euglycemia) as a between-subjects factor, and condition (euglycemia or hypoglycemia) as a within-subjects factor. A p-value <0.05 was considered to be significant. Effect sizes were calculated using partial eta-squared to assess the degree to which hypoglycemia accounts for the variance in results, and Cohen's d was utilized to establish the extent of any effects of hypoglycemia on spatial abilities. Results are expressed as mean (SD) unless stated otherwise.

RESULTS

Blood glucose: The target blood glucose levels were achieved for each experimental condition. The blood glucose concentration achieved during the hypoglycemia condition was 2.46 (0.22) mmol/l, and during the euglycemia condition was 4.53 (0.24) mmol/l.

Symptom Scores: Significant increments occurred in total autonomic ($p<0.001$), total neuroglycopenic ($p<0.001$), and malaise symptom scores (<0.001) during hypoglycaemia.

General Cognitive Function: In the present study, scores achieved in the Digit Symbol Substitution task were significantly lower during the hypoglycemia study period

(72.4 (20.2)) when compared with euglycemia (84.6 (20.7)) ($p<0.001$), confirming that a standard measure of speed of information processing was significantly impaired at blood glucose concentrations of 2.5 mmol/l. The performance on the Trail Making B test was statistically not impaired by hypoglycemia, with a score of 50.4 (20.9) seconds during hypoglycemia and a score of 38.9 (11.5) seconds during euglycemia ($p=0.07$).

Spatial Ability: Hypoglycemia resulted in a significantly lower score on all of the spatial ability tests except the map memory test (Table 1).

The Cohen's d results have shown that the impact of hypoglycemia on these spatial abilities was of medium to large effect. Moreover, the partial eta-squared values indicate that the hypoglycemia condition accounted for a large proportion of the variance in the results (Table 1).

No significant effects were observed of order of exposure to glycemic condition or test battery.

CONCLUSIONS

Acute, insulin-induced hypoglycemia causes significant decrements in most spatial cognitive abilities examined here in a group of adults with uncomplicated type 1 diabetes. This impairment of function was accompanied by a deterioration in speed of mental processing as demonstrated by the decrement in score for the Digit Symbol Substitution task. The effect sizes obtained indicate the development of medium to large decrements in spatial abilities during hypoglycemia in adults with type 1 diabetes.

The present study examined a group of subjects with type 1 diabetes, and did not include a control group of non-diabetic subjects. While this is a limitation of the present study, in reality it is the everyday effect of hypoglycemia on this group of people that is of clinical importance.

Other studies assessing the effects of hypoglycemia on aspects of cognitive function have utilised tests that require a spatial ability component (12), but to our knowledge no previous study has utilised a test battery specifically examining spatial abilities, although it has clear importance in the safe conduct of tasks such as driving, which rely heavily upon the interpretation of the surrounding environment.

The Map Memory test was not affected significantly by the glycemic condition. This test assesses both spatial ability and visual memory. This finding is consistent with previous studies that examined memory function using visual memory tests from the Wechsler Adult Intelligence Scale, which also showed that visual memory is preserved during acute hypoglycemia (19). It is also notable that the Map Memory test, unlike the other tests used here, does not have multiple items, and so its scores might be more idiosyncratic.

Spatial ability relies on cerebral pathways that predominantly involve the right cerebral hemisphere, particularly the parietal lobe. The frontal cortex, thalamus and to some extent, the cerebellum, are also involved in the co-ordination of spatial cognition (20, 21). Neuroimaging studies during hypoglycemia have shown attenuation of functional response, e.g. blood oxygenation level dependent activation, in the pre-motor and supplementary motor cortex, consistent with recognised areas of importance in spatial functioning (22). In addition, it has been shown previously that general fluid intelligence is impaired during hypoglycemia, and it is fluid intelligence, rather than crystallised intelligence, that is responsible for spatial cognition (10).

In conclusion, the present study has shown that acute hypoglycemia has an adverse effect on spatial abilities. These novel data are important for two reasons. First, with regard to our understanding of the domains of cognitive function that experience decrements during hypoglycemia, spatial abilities were a lacuna that has now been partly filled. Second, spatial abilities are relevant to the everyday activities of people with type 1 diabetes, and there are now data to show that part of the inability to manage complex tasks during hypoglycemia is the inability to efficiently carry out spatial cognitive operations.

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Table 1: Spatial ability test scores (results shown as mean [SD]; significance level p<0.05; effect sizes computed as Cohen's *d* and partial eta-squared (η_p^2))

Spatial test	Euglycemia score	Hypoglycemia score	P-value	Cohen's *d*	η_p^2
Hidden patterns	94.5 (21.8)	73.7 (21.0)	<0.001	0.97	0.627
Card rotations	51.9 (15.5)	40.4 (18.7)	0.001	0.67	0.580
Cube comparison	11.7 (4.1)	9.4 (5.7)	0.03	0.46	0.298
Paper folding	6.0 (1.9)	4.7 (2.0)	0.001	0.67	0.604
Map memory	8.6 (3.1)	7.8 (2.1)	0.3	0.30	0.081
Maze tracing	11.1 (3.0)	9.4 (2.5)	<0.001	0.62	0.621