A Survey of Cognitive Functioning at Different Glucose Levels in Diabetic Persons

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Cognitive functioning was assessed in diabetic patients during hypoglycemia (60 mg/dl), euglycemia/control (110 mg/dl), and hyperglycemia (300 mg/dl). Blood glucose levels were set and maintained to within 4% of targeted levels by an artificial insulin/glucose infusion system (Biostator). Attention and fine motor skills, assessed by visual reaction time, was slowed at altered glucose levels. Performance was less impaired during hyperglycemia than hypoglycemia when a longer interstimulus interval was used, although it was still slower than normal. The time required to solve simple addition problems was increased during hypoglycemia, although reading comprehension was not affected. The possibility that some automatic brain skills are disrupted at altered glucose concentrations is discussed, while associative or inferential skills may be less affected. DIABETES CARE 6: 180–185, MARCH–APRIL 1983.

Glucose provides the major source of energy to the brain and central nervous system. Although fatty acids can be utilized for energy, the shift to these alternative substances requires a significant period of metabolic adaptation. Since relatively little glucose can be stored in the brain, it is critically dependent on ambient blood glucose supplies for normal neuronal functioning.[1–3] Disruption in neuronal activity has been reported during glucose deprivation; alterations in cortical cellular and EEG activity occur. Evidence suggests that hypoglycemia results in decreased excitatory and increased inhibitory postsynaptic potentials.[4] Further, EEG patterns are characterized by slow rhythm activity associated with decreased vigilance.[5]

Although the interrelationship between blood glucose deprivation and brain function is widely accepted, few systematic studies are available to describe the behavioral manifestations of resultant disrupted brain activity. It is known that responding becomes increasingly impaired as blood glucose concentrations fall from 40 mg/dl to 10–15 mg/dl. Speech becomes slurred, convulsions may appear, and coma often occurs.[6] However, there is little information about behavioral responding in the hypoglycemic range of 60 mg/dl, a level which occurs more commonly in the labile daily glucose concentrations of diabetic individuals.[7] Russell and Rix-Trott[8] demonstrated slowed motor responding on a pegboard task at low blood glucose levels. Relatively simple recall of words also was reduced, compared with subjects' performance at a control/euglycemia period. Although accuracy on a more cognitively complex task involving logical reasoning was not impaired, problem-solving was slowed. Nondiabetic subjects in these studies were injected with insulin to produce hypoglycemia. Resulting blood glucose values varied widely from 25–90 mg/dl during the 30-min testing period, making it difficult to discern the relative impact of hypoglycemia versus fluctuating glucose levels on performance. Similar findings and methodologic problems are encountered in a study by Flender and Lifshitz.[9] Their results further suggested that high blood glucose levels may facilitate some types of fine motor and memory performance. However, their brief abstract does not provide sufficient detail of tasks and method of inducing hyperglycemia for comprehensive analysis. An analogue study with rats, evaluating insulin-induced hypoglycemia, indicated that a learning criterion of 90% accuracy on a T-maze task took longer during hypo- than euglycemia. Speed of running was also reduced.[10]

In contrast to these earlier studies, we attempted to maintain greater control over blood glucose levels while testing cognitive performance. We proposed to use an artificial insulin/glucose infusion system (i.e., Biostator, Ames Co., Elkhart, Indiana) to obtain more precisely targeted concentrations of blood glucose for study. Further, we felt that the Biostator device could accurately maintain glucose concen-

trations, once obtained, and help minimize the effects of fluctuations in blood glucose during testing. With this methodologic alteration, we hoped to achieve a clearer evaluation of the relationship between cognitive function and specific levels of blood glucose concentrations.

A variety of psychological skills, ranging from simple sensory/motor responding to complex cognitive skills of reading and mathematics, were assessed at each of three selected blood glucose levels. These tasks were selected because the tasks themselves (i.e., reading) or the component skills required to perform them are routinely encountered in daily functioning, particularly learning situations. This line of research may ultimately yield information with potential implications for diabetic functioning in academic or career settings. It was predicted that the performance of diabetic individuals would be relatively impaired at low (60 mg/dl) compared with normal (110 mg/dl) blood glucose levels. We were uncertain as to the relationship between high (300 mg/dl) blood glucose concentration and performance skills due to the paucity of previous research.

METHOD

Subjects

Twelve type I (juvenile-onset insulin-dependent) diabetic subjects were recruited from the student population of the University of Iowa. Subjects were obtained by advertisement in the student newspaper, duration of disease, glucose control, and insulin management regimen not being criteria for selection. University matriculation was a criterion for participation to insure a relatively homogeneous study population with respect to educational background and at least average intellectual ability. Although this is an oversimplification, the fact that the subjects were used as their own controls (i.e., control period = blood glucose at 110 mg/dl) reduced the influence of intersubject variability on group results.

Procedure

Subjects were admitted to the Clinical Research Center on the day prior to study to obtain a history, physical examination, and written informed consent. Routine dietary and insulin regimens were maintained during the day prior to study.

After an overnight fast at approximately 0730 h, subjects were started on the Biostator, a glucose-controlled insulin infusion system. This unit was used to provide appropriate intravenous glucose or insulin to achieve desired concentrations of blood glucose required by the protocol design. During the 6-h study period, all insulin was given by the Biostator, routine morning insulin being withheld.

Cognitive function was assessed at three concentrations of blood glucose: namely 60 mg/dl, 110 mg/dl, and 300 mg/dl. The sequence of study at the three glucose concentrations was determined by a balanced crossover study design. Sequences used were (note: L = glucose 60 mg/dl, M = glucose 110 mg/dl, H = glucose 300 mg/dl):

	Period		
	1	2	3
Subject 1	L	M	H
Subject 2	M	L	H
Subject 3	H	L	M
Subject 4	H	M	L
Subject 5	L	H	M
Subject 6	M	H	L

Six female subjects and six male subjects were assigned to the above sequences, the total study population being 12 subjects. Subjects were not informed of the specific testing sequence they received, nor were they given any information about their blood glucose levels or test performance adequacy during the study.

The intravenous catheters required to establish the Biostator glucose clamp were affixed to subjects' nondominant arm. The dominant arm and hand were free to engage in the study tasks requiring hand motor activity (e.g., key pressing, pointing, drawing, etc.). Although the restrictions placed on the nondominant arm and hand probably slowed subjects' responding on tasks requiring hand motion, particularly drawing, this performance effect was constant at all glucose levels, including the average range used for control comparison purposes.

Each period of study was 2 h long, the last half hour being used for the cognitive testing protocol. The initial 1½ h was used to establish the desired concentration of blood glucose and a period of constant blood glucose concentration. Upward changes in blood glucose concentration were made by a combination of food ingestion and Biostator-controlled intravenous glucose infusion. No additional food was provided during the study period; however, noncaloric beverages were provided ad libitum.

On completion of the study, subjects were weaned from the Biostator, with care being taken to avoid unwanted hypoglycemia. Routine or supplemental insulin was given subcutaneously prior to the evening meal to ensure that normal diabetic control was maintained. Subjects were discharged from the Clinical Research Center after the evening meal once blood glucose control was adequate.

Assessment Measures

Three equivalent but different forms of the following tasks were employed to assess subjects' cognitive performance at different glucose levels. These tasks included both standardized clinical measures to allow ready comparison with normative groups, and frequently used experimental tasks that often are more sensitive to subtle changes in performance. All tasks were selected, in part, because they are less subject to practice effects that could facilitate performance in the later trials. The order of task presentations was also random-

ized to further minimize systematic practice effects.

Memory tasks. (1) Digit supraspan. An auditory memory test for digits in which subjects have twelve trials to correctly repeat a sequence of nine digits.[11] Digits are read at the rate of 1 per second. (2) Rey auditory verbal learning test. An auditory memory test for words in which subjects have five trials to correctly repeat 15 words.[12] Words are read at the rate of 1 per second.

Attention tasks. (1) Matching familiar figures test (MFFT). Standardized match-to-sample task was used as a measure of attention.[13] Visual discrimination skills and sustained attention to detail are required. Both accuracy (number of errors) and latency (time elapsed before responding) measures are obtained. (2) Delayed reaction time. A reaction time apparatus (Lafayette #60133) with a key press response was used to assess sustained visual attention. After the onset of a neutral (white) warning light, which signaled the beginning of a new trial, subjects were instructed to wait and press a telegraphic key as quickly as possible after a colored (red) target light appeared. A white warning and red target light were used throughout the study. Speed of responding was recorded. Both short (2–4 s) and long (6–8 s) interstimulus intervals (ISI) or delay periods were evaluated. The ISI represented the amount of time that elapsed from the warning light to the onset of the target light. Short and long ISI trials were blocked such that the 10 short test trials occurred together as did the 10 long test trials. In each instance, the 10 test trials were preceded by 3 practice trials. Order of presentation of short and long ISI trials was counterbalanced across subjects such that each was given first in equal number of times.

Visual spatial tasks. Benton Visual Retention Test (administration C). Clinical task used to assess visuomotor perceptual skills.[14] Subjects copied complex geometric designs. An accuracy score was calculated based on the manual's scoring criteria.

Academic tasks. (1) Nelson Denny Reading Test. Standardized reading test for grades 10 through 16.[15] Subjects read 3 passages of graded difficulty and answered 4 multiple choice questions which followed each paragraph. This test was timed with a total of 8 min allowed for administration. Reading comprehension was assessed through the number of questions answered correctly. (2) Mathematical computation. Experimental task consisting of simple computation of math facts. The problems were easy enough to avoid tapping differential levels of math skills among subjects and provided a measure of speeded recall of rote (overlearned) facts. One minute was allotted for this timed test. Number of correctly completed problems and number of problems attempted were recorded to provide an indicator of performance efficiency. These latter two tasks provide a simple analogue to classroom tasks. Both automatic functioning or rote skills (mathematical computation) and associative reasoning or higher level reading comprehension (Nelson Denny Reading Test) skills are assessed.

TABLE 1
Projected and obtained average blood glucose values for all subjects

Blood glucose levels	Blood glucose values (in mg/dl)	
	Projected	Obtained
Low	60	63 (SD = 3.2)
Normal	110	107.5 (SD = 6.1)
High	300	303.6 (SD = 6.4)

TABLE 2
Mean reaction time for short and long interstimulus intervals (in hundredths of a second)

Blood glucose level	Interstimulus interval			
	Short (2–4 s)	Grouping*	Long (6–8 s)	Grouping*
Low	43.6 (SD = 7.6)	A	46.6 (SD = 92)	A
Normal	39.1 (SD = 5.0)	B	39.7 (SD = 6.3)	B
High	41.8 (SD = 8.5)	A	43.6 (SD = 7.5)	C

*Different letter groupings indicate significant differences among means at the $P < 0.05$ level.

RESULTS

Preliminary multivariate analysis indicated no significant sex-related performance differences so the data of males and females were combined for the remainder of the analyses.

The design used in the analyses was a treatment X subjects (3 × 12) analysis of variance[16] with treatment as a repeated factor. The treatments were the following blood glucose levels: low, normal, and high. Subjects' performance at the normal level provided control data for comparison purposes. Projected and obtained mean glucose concentrations are shown in Table 1. Note that obtained levels were very similar to projected levels. Further, during the half hour of psychological testing, blood glucose was maintained to within an average of 4.3% (SD = 3.9%) of targeted concentrations for all subjects at all glucose concentrations.

There were no residual effects of previous glucose level or sequence of treatment effects upon performance for any of the dependent variables. However, several main effects of treatment or glucose levels were found and Duncan multiple comparison procedure was conducted to assess differences between treatment means. All results are reported at the $P < 0.05$ level of significance. Significant differences were obtained on the reaction time task when both a short, $F(2,16) = 13.58$, $P < 0.05$, and long, $F(2,16) = 13.69$, $P < 0.05$, delay or interstimulus interval was employed as

Table 2 reports. In general, reaction time performance was slowed at abnormal glucose levels compared with performance at normal levels. With the longer interstimulus interval, which provided subjects with a longer delay or preparatory period, performance at high compared with low glucose concentrations was significantly faster, although still slower than at normal levels.

The other dependent variable showing a significant effect of treatment or glucose level was number of mathematical calculations correctly completed, $F(2,16) = 7.86$, $P < 0.05$. Multiple comparisons revealed that subjects correctly completed an equivalent number of problems at normal and high blood glucose concentrations, while fewer problems were correctly completed at low glucose levels (see Table 3). In contrast, the percentage of correct math problems to number of problems attempted showed no treatment or glucose-related effects, $F(2,16) = 2.35$, $P > 0.05$. These two findings, taken together, suggest that subjects must have worked slower when their blood glucose was low to maintain the relatively high percentage of accuracy (mean = 95.7%), as was found at normal and high glucose concentrations (mean = 95.8% and 98.1%, respectively). In other words, subjects correctly completed fewer math problems during hypoglycemia because they attempted fewer problems.

DISCUSSION

Different blood glucose levels do affect some types of cognitive functioning. Specifically, we found that attention to and performance on a reaction time task, requiring a rapid motor response to the onset of a visual stimulus, was slowed at both high and low blood glucose levels compared with normal levels. In contrast, no significant glucose-related effects were found on tasks requiring detailed visual perception (MFFT) and self-paced drawing of geometric designs (Benton Visual Retention Test), suggesting that the very quick response required on the reaction time task was more sensitive to glucose-related performance effects. This hypothesis remains speculative, however, since these survey tasks not only varied in degree of task speed required but also varied along several other dimensions (e.g., degree of visual analysis and perception required as well as type of motor response), making clear interpretation difficult. We are in the process of conducting more fine grain analyses to better understand precisely what mechanisms may underlie this impairment.

In contrast to the impaired sensory/motor performance we found at high blood glucose levels, Flender and Lifshitz[9] suggested improved "fine motor coordination" at elevated blood glucose levels. However, their brief abstract does not provide the detail necessary for in-depth analysis. Our work suggests that some performance impairment occurs during hyperglycemia, but this finding is tentative until further replication takes place. The effects of hypoglycemia may be more clear-cut or consistent since our study and the work of Flender and Lifshitz[9] and Russell and Rix-Trott[8] all demonstrate slowed motor responding during low blood glucose levels despite study differences in methodologies and subjects. It is interesting to note that reaction time in the present study was uniformly fastest during euglycemia (110 mg/dl) regardless of whether a short or long preparatory warning interval was employed. Diabetic individuals, even those considered to be in "good" control, typically experience postprandial blood glucose concentrations which on the average exceed 110 mg/dl and routinely are over 200 mg/dl.[7] As reaction time is a component skill underlying more important and complex activities such as operating an automobile, the full implication of this impairment has yet to be evaluated. Additional inquiry may yield important information on the degree of diabetic control that may be desirable for optimal performance on different tasks.

Immediate memory for digits and words was not impaired during abnormal glucose states. These tasks may have been too easy for our subjects, many of whom were involved in post-baccalaureate graduate training. A ceiling effect was obtained in that subjects were able to recall an average of 91% of the digits at any glucose level and showed an average of 93% accuracy in recalling words on the last training trial at any glucose level. Word recall data are provided in Table 4. Even though a ceiling effect was present by the last training

TABLE 3
Mean number of mathematical problems completed

Blood glucose level	Number correct	Grouping*	Percentage correct	Grouping*
Low	18.9 (SD = 9.0)	B	95.8 (SD = 4.8)	A
Medium	21.5 (SD = 10.5)	A	95.8 (SD = 6.5)	A
High	21.7 (SD = 9.9)	A	98.1 (SD = 3.0)	A

*Different letter groupings indicate significant differences among means at the $P < 0.05$ levels.

TABLE 4
Mean number of words recalled across learning trials*

Trial	Blood glucose level		
	Low	Medium	High
Trial 1	7.2 (1.6)	7.1 (1.7)	7.2 (1.4)
Trial 2	9.8 (2.2)	8.8 (2.1)	9.9 (2.1)
Trial 3	11.8 (2.7)	11.6 (1.9)	12.4 (3.2)
Trial 4	12.4 (2.5)	12.6 (2.1)	12.9 (1.6)
Trial 5	12.8 (2.3)	13.2 (2.0)	12.8 (1.7)
Total (Trials 1–5)	53.8 (8.5)	53.2 (7.5)	55.2 (7.0)

*Total words possible recall = 15/trial. SD are in parentheses.

trial, examination of scores from earlier trials suggests that word recall was simply not a sensitive measure of glucose-related effects with these subjects. Russell and Rix-Trott[8] obtained results at variance with our own by showing that recall of words but not digits was reduced during hypoglycemia. Task differences and/or subject differences between studies may explain the divergent finding although fluctuation of blood glucose levels cannot be ruled out either as a potential influence on performance in the former study. Although it seems clear that recall of digits may not be sensitive to changes in glucose levels, the effect of different glucose levels on memory for words will need further evaluation with different populations.

We found evidence that *rate* of remembering information may have been impaired at low glucose levels when performance was timed, as speed of recalling rote math facts was slowed. Subjects who had only 1 min to complete simple addition problems showed slower responding during hypoglycemia than during other blood glucose states. Accuracy did not suffer, but rate of work was slowed. In contrast, timed reading comprehension was not impaired at either of the abnormal glucose levels (see Table 5). Russell and Rix-Trott obtained results similar to ours in that they found during low blood glucose concentrations, accuracy on a complex cognitive task involving reading and logical reasoning was not impaired, although rate of performance was slowed.

There are at least three possible explanations for our findings of slowed reaction time and memory for math facts while reading comprehension, a more complex cognitive skill, was not impaired. First, the impairments we found may reflect reduced conduction of nerve impulses, although this is unlikely as acute changes in metabolism are not thought to have such immediate effects.[17] Second, central processing skills necessary to mediate speed of responding on some sensory, motor, and memory tasks may be impaired although when multiple redundant informational cues are present, such as in reading (e.g., morphology, context, grammar, semantics, etc.), subjects may be better able to compensate for the deleterious effects of abnormal glucose levels on their performance. Third, more automatic brain functioning which involves less complex informational analysis (e.g., perception, simple motor responding, and memory) may be affected by blood glucose differences while higher level or associative cognitive skills such as are required for reading comprehension may experience less detectable or no impairment during abnormal glucose conditions. Present data do not allow us to substantiate one hypothesis versus another. However, we are pursuing more information regarding the underlying causes of performance decrements seen during different glucose states with subjects and tasks that are more carefully chosen to answer the questions raised by this exploratory study.

Our present study has illustrated the potential benefits of using an artificial insulin/glucose infusion system to study cognitive functioning at altered glucose levels. This methodology has been demonstrated to yield reproducible and fairly constant (to within 4%) levels of blood glucose concentration across subjects. The methodology could be improved upon, however, by including a debriefing session after each subject's participation has concluded. Such a session could help determine whether subjects had remained unaware of their blood glucose levels throughout the study, a point that is necessary to avoid unwanted response biases. It is possible that subjects, through awareness of their bodily reactions, may be able to successfully guess their glucose status despite examiner efforts to keep them uninformed as in the present study. The work of Pennebaker, Cox, Gonder-Frederick, Wunsch, Evans, and Pohl[18] suggests it is unlikely that subtle internal cues revealed subjects' glucose status. These researchers found that diabetic subjects had to be systematically and intensively trained over 4–8 days to identify somatic cues reliably related to their glucose status. In a related study, 30% of a follow-up group of patients were unable to reliably discriminate a predictable pattern of glucose associated bodily cues even with practice.[19]

TABLE 5
Mean number of reading comprehension questions completed

Blood glucose level	Number correct	Grouping*	Number attempted	Grouping*
Low	7.2 (SD = 2.9)	A	9.2 (SD = 2.3)	A
Medium	6.5 (SD = 2.5)	A	9.0 (SD = 2.0)	A
High	6.8 (SD = 2.4)	A	9.3 (SD = 2.1)	A

*Same letter grouping indicates that means were not significantly different at the $P < 0.05$ level.

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