Acute Hypoglycemia Impairs Nonverbal Intelligence

Importance of avoiding ceiling effects in cognitive function testing

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Acute hypoglycemia causes a progressive, reversible deterioration in cognitive function that becomes detectable at blood glucose concentrations below ~3.0–3.4 mmol/l (1). In an earlier study in nondiabetic subjects, we reported that several facets of attention deteriorated significantly at an arterialized blood glucose level of 2.6 mmol/l (2). However, performance on Raven's Progressive Matrices (RPM) was not significantly impaired at either 20 min or completion of the test (with no time limit). This was unexpected, because, previously, various domains of cognitive function had consistently been impaired at this level of hypoglycemia (1). Additionally, the RPM is acknowledged as being among the best indicators of general fluid intelligence (3) and has a substantial correlation with working memory (4), which is exquisitely sensitive to hypoglycemia (5).

Hypoglycemia disrupts performance on different cognitive function tests to a variable degree, leading to speculation that different mental functions vary in their sensitivity to hypoglycemia. This is complicated by a lack of a universally accepted battery of cognitive measures and variable experimental methodology (6,7). We speculated that the higher-level cognitive skills required for abstract problem solving (as in the RPM) are resistant to the effects of hypoglycemia. However, this contradicted a widely held opinion that higher-level skills are more sensitive to hypoglycemia than simple, repetitive cognitive or motor tasks (1). An alternative explanation was the possibility of a ceiling effect, as the RPM includes a large proportion of easy problems that involve straightforward pattern completion, and mean scores during euglycemia and hypoglycemia were 49.5 and 48.7, respectively, out of a maximum of 60. The present study was designed to test the ceiling effect hypothesis by substituting two more difficult tests of general fluid intelligence that are known to be discriminatory in highly able adults. Raven's Advanced Progressive Matrices (RAPM) (8) uses harder problems than RPM, which consist of geometric designs from which the subject must induce logical rules, hold the rules in working memory, and apply them simultaneously to complete a pattern (9). The Alice Heim 5 test (AH5) similarly requires identification and application of simultaneous patterns to complete verbal, numerical, and geometric sequences (10).

RESEARCH DESIGN AND METHODS

— Sixteen nondiabetic volunteers were studied. Their mean score on the National Adult Reading Test was 40, which approximates to a Wechsler Adult Intelligence Scale-Revised full-scale IQ score of 118. Each subject underwent two hyperinsulinemic glucose clamps, with experimental states of euglycemia (arterialized blood glucose 4.5 mmol/l) and hypoglycemia (2.5 mmol/l), during which subjects completed the RAPM and AH5. Parallel versions were created by separating odd- and even-numbered items, with sets 1 and 2 of the RAPM being combined. Both the RAPM and AH5 were scored after 20 min, with maximum possible scores of 36 for AH5 and 24 for RAPM. Subjects also completed the Trail Making B (TMB) and Digit Symbol Substitution (DSST) tests. The order of euglycemia-hypoglycemia and cognitive test battery was counterbalanced and included as a between-subject factor in repeated-measures ANOVA.

RESULTS

— The scores are given in Table 1 as means (±SD), except TMB, which is given as completion time in seconds. Performance on TMB, DSST, and RAPM deteriorated significantly during hypoglycemia, with a trend toward deterioration on AH5. The effect size of hypoglycemia on RAPM was substantial, amounting to approximately three-quarters of an SD.

CONCLUSIONS

— These results suggest that our earlier findings were indeed due to a ceiling effect (2) and indicate that hypoglycemia does impair general fluid intelligence, but it is necessary to use a test appropriate to the ability level of the participants. Research volunteers tend to be more able than the population they are intended to represent, and the ceiling effect may be common in studies of hypoglycemia. Care should be taken to avoid the ceiling effect, and, while general consensus on cognitive testing is desirable, a single battery of cognitive tests for all subjects may be inappropriate (7).

The different results for RAPM and AH5 may reflect differences in the standard administration of these tests: paper working is permitted for the AH5 but not for the RAPM. Holding and applying rules entirely in working memory is demanding (8), and as we have previously shown that working memory is obliterated by

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Abbreviations: AH5, Alice Heim 5 test; DSST, Digit Symbol Substitution; RAPM, Raven's Advanced Progressive Matrices; RPM, Raven's Progressive Matrices; TMB, Trail Making B.

Table 1 —*Cognitive function scores during euglycemia and hypoglycemia, plus significance level and effect size for comparison*

Test	Euglycemia	Hypoglycemia	*P*	η^2
RAPM	18.9 ± 3.1	16.5 ± 3.5	0.007	0.465
AH5	15.6 ± 5.6	13.9 ± 5.0	0.057	0.269
TMB	38.8 ± 8.2	46.3 ± 16.1	0.037	0.339
DSST	87.7 ± 12.5	79.4 ± 9.3	0.019	0.409

Data are means ± SD.

moderate hypoglycemia (5), it is likely that this had a greater impact on RAPM than AH5.

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