



Emotional changes during experimentally induced hypoglycaemia in type 1 diabetes

Norbert Hermanns*, T. Kubiak, B. Kulzer, T. Haak

Research Institute of the Diabetes Academy Mergentheim (FIDAM), P.O. Box 1144, D-97961 Bad Mergentheim, Germany

Received 20 March 2002; accepted 22 November 2002

Abstract

Emotional changes during experimentally induced hypoglycaemia in type 1 diabetic patients were investigated using a hyperinsulinaemic glucose clamp. In the experimental group ($n = 11$), blood glucose was stabilised at euglycaemia (5.6 mmol/l, phase 1), then lowered to 2.5 mmol/l (phase 2) and raised to 5.6 mmol/l (phase 3). In the control group ($n = 11$), euglycaemia was maintained during all phases. Hypoglycaemia elicited the expected endocrine, symptomatic and neuroglycopenic effects. During hypoglycaemia negative mood states increased significantly, whereas positive mood states decreased. Hypoglycaemia prolonged rating time of emotional stimuli (drawn from IAPS) significantly. The arousal ratings of the slides were higher during hypoglycaemia. Valence and dominance ratings were not affected. Epinephrine and norepinephrine release correlated with a higher arousal rating and a decrease in positive mood states. Deterioration in neuropsychological tasks correlated with an increase in negative mood states. Experimental induction of hypoglycaemia can offer a new research model to study emotional processes.

© 2003 Elsevier Science B.V. All rights reserved.

Keywords: Hypoglycaemia; Emotion; Mood changes; Type 1 diabetes; Emotional processing

1. Introduction

Psychophysiological research has recently focused on emotions and on cerebral mechanisms associated with emotional perception (Lang, 1994; Pinel, 1999; LeDoux,

* Corresponding author. Tel.: +49-7931-594-553; fax: +49-7931-594-89553.

E-mail address: hermanns@diabetes-zentrum.de (N. Hermanns).

1996). Studies use modern imaging techniques like functional magnetic resonance imaging (fMRI) to determine and locate cerebral activity during emotional experiences. Another research strategy is to examine the emotional experiences of specific patient groups with structural brain damage or medical conditions like epilepsy (Kolb and Whishaw, 1996; Pinel, 1999; Birbaumer et al., 1994; Flor et al., 1995).

This study addresses two issues. The main aim of this study is to introduce a new experimental research model to examine emotional changes during hypoglycaemia. Hypoglycaemia can be experimentally induced and provides a highly reproducible physiological state associated with emotional experience. Low blood glucose results in a decrease of the cerebral glucose supply and induces physiological and emotional changes (McCrimmon et al., 1995; Cryer, 1997). From a clinical perspective, these emotional changes have a negative impact on type 1 diabetic patients, who have a high risk to experience hypoglycaemia frequently. Thus, a further objective of the study is to provide a better understanding of these emotional consequences to help patients to cope with hypoglycaemic episodes.

1.1. Hypoglycaemia as a clinical problem

In type 1 diabetic people, irreversible damage to the insulin producing beta cells in the pancreas causes defective autonomic regulation of blood glucose (Chessler and Lernmark, 2000). Patients with type 1 diabetes have to administer exogenous insulin subcutaneously several times a day depending on their carbohydrate intake, exercise, and individual insulin requirement. Unfortunately, insulin treatment in type 1 diabetic patients is not as effective as the autonomic blood glucose regulation in maintaining blood glucose values within a physiological range. Therefore, blood glucose values below the physiological range (hypoglycaemia) can occur as a consequence of hyperinsulinaemia. Hypoglycaemia is a common complication of type 1 diabetes. Severe hypoglycaemic episodes leading to disorientation, seizure, or coma can endanger persons with diabetes, especially if hypoglycaemia occurs during potentially dangerous activities like driving an automobile (Bott et al., 1997; Davidson et al., 2000). The prevention of severe hypoglycaemic episodes is easily possible by an early detection of hypoglycaemic symptoms and an immediate treatment of low blood glucose by the consumption of fast acting carbohydrates. It is essential that the treatment of hypoglycaemia occurs before the effects of neuroglycopenia limit self-treatment.

1.2. Physiological consequences of hypoglycaemia

In non-diabetic people, blood glucose is regulated within a narrow physiological range. This is important for the energy supply of the brain, which relies almost totally on glucose. A glucose concentration above 3.4 mmol/l is crucial for maintaining sufficient energy supply and normal functioning of the brain, because there is a linear relationship between peripheral blood glucose concentration and the cerebral glucose uptake (McCall, 1993). Hypoglycaemia has two different systemic

consequences which may have an impact on emotional experience. (1) Low peripheral blood glucose levels diminish the cerebral energy supply and cause neuroglycopenia of the central nervous system (CNS), and (2) activates the autonomic nervous system. These consequences elicit several physiological sequelae which are depicted in detail in Fig. 1 and described below.

1.3. Neuroglycopenia

Lowering of systemic blood glucose causes a cerebral energy deficit (neuroglycopenia), which results in neurophysiological consequences as well as in a deterioration in neuropsychological tasks.

During hypoglycaemia, a reduction in α -activity and an increase in θ - and δ -activity is observable using electroencephalography. These changes are predominantly present in frontal areas of the brain (Pramming et al., 1988; Tallroth et al., 1990). There is also a great agreement in literature that there are specific consequences in event related potentials. During hypoglycaemia there is a prolongation of the P300 latency, which can be regarded as an indicator for a reduction of information processing speed (Weinger and Jacobson, 1998; Jones et al., 1990; DeFeo et al., 1988; Gallai et al., 1988; Ziegler et al., 1992; Blackman et al., 1990, 1992; Bendtson, 1993). Studies using neuropsychological testing during

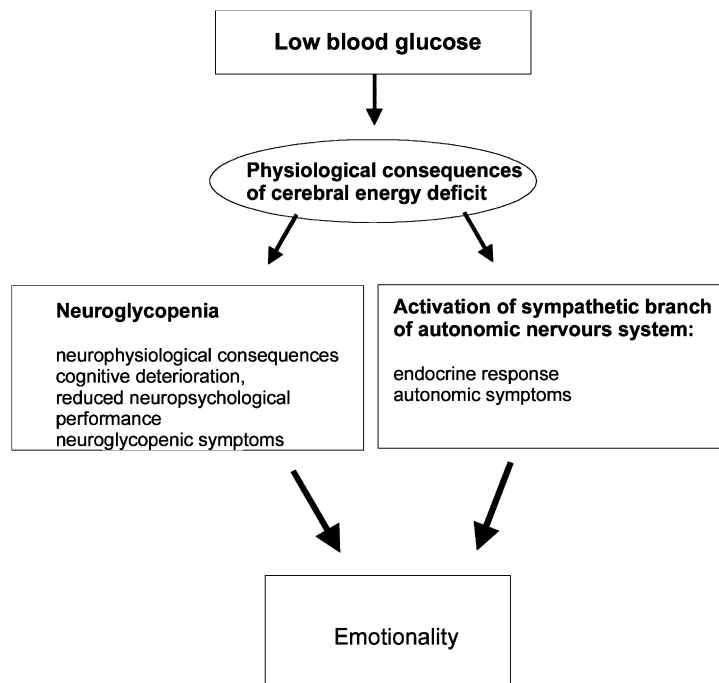


Fig. 1. Systemic consequences of low blood glucose.

controlled hypoglycaemia demonstrated also a deterioration in selective attention tasks, an increase of reaction time in complex reaction tests, a decrease of concentration task performance and fine motor co-ordination (Deary, 1999, 1993; Gold et al., 1995a; Weinger and Jacobson, 1998; Hepburn, 1993). In summary, hypoglycaemia seems to cause deterioration in several cognitive domains. The impairment in attention and complex reaction tasks in combination with the findings of a prolonged P300 latency indicate that hypoglycaemia is associated with a slowing down of information processing speed and characteristic neurophysiological changes (Boyle et al., 1995; Deary, 1999, 1993).

1.4. Activation of autonomous nervous system

There is an activation of the sympathetic branch of the autonomic nervous system and the hypothalamic adrenal axis, triggered by hypoglycaemia. This results in autonomic warning symptoms and a release of catecholamines, cortisol, and human growth hormone. The catecholamine response, epinephrine and norepinephrine, is a part of the activation of the autonomic nervous system, aiming primarily at an increase in peripheral blood glucose levels by endogenous glucose release (Cryer, 2002; Smith and Amiel, 2002; Cryer, 1997; McCall, 1993, 1992; Cryer, 1997). Cortisol and human growth hormone release occurs after prolonged hypoglycaemia and are secondary to hypothalamic activation (DeFeo et al., 1989). These hormonal responses aim primarily at the reduction of peripheral glucose utilisation. In summary, the endocrine responses represent a redundant system of mechanisms aiming at a restoration of euglycaemia either by enhancing endogenous glucose production or by reducing peripheral glucose utilisation (Smith and Amiel, 2002; Cryer, 2002).

1.5. Symptomatic response

The two systemic physiological consequences of hypoglycaemia are resulting in two different types of symptoms. (1) The activation of the autonomic nervous system promotes autonomic warning symptoms such as tachycardia, sweating, and tremor (Hepburn, 1993). (2) The cerebral energy deficit also leads to specific neuroglycopenic symptoms like difficulties in concentration, drowsiness, odd behaviour, co-ordination problems, or confusion. Given that the degree of neuroglycopenia is not too severe, these symptoms can warn the affected individual that immediate action is required. These symptoms worsen with the degree of hypoglycaemia and can, in extreme cases, result in disorientation, stupor, seizure or coma (Frier and Fisher, 1999; Frier, 1993).

1.6. Emotional effects of hypoglycaemia

In one of the first descriptions of hypoglycaemia emotional changes like 'emotional upset', 'marked excitement' and 'emotional instability' have been mentioned as significant symptoms of hypoglycaemic episodes (Fletcher and Campbell, 1922). Since then, there have been many reports of type 1 diabetic

patients describing emotional changes during hypoglycaemia. These include tension, anxiety, depressive feelings, and a decreased sensation of well-being. Sometimes these emotional changes cause conflicts with family members, colleagues, and friends (Gonder-Frederick et al., 1997, 1996; Lincoln and Eaddy, 2001). A field study demonstrated that low blood glucose was related primarily to negative mood changes such as an increase in nervousness, feelings of frustration, worry, and fright. But there were also a few patients reporting positive mood changes like feelings of confidence, relaxation, or energy, indicating that there are large individual differences in emotional responses during hypoglycaemia (Gonder-Frederick et al., 1989). From a clinical perspective, the above mentioned negative emotional changes, induced by low blood glucose, could be a barrier for an early detection of warning symptoms or an immediate treatment of a hypoglycaemic episode. These emotional consequences of hypoglycaemia have not received much attention in research, compared with autonomic and cognitive reactions towards low blood glucose (Gold et al., 1995b,a,c; Deary, 1999, 1993; Gold et al., 1997).

1.7. Experimental findings

There are only a few well controlled experimental studies confirming primarily negative mood changes during hypoglycaemia. Besides large individual differences in emotional changes, these studies demonstrated a significant increase in negative mood states like anger and tension. Furthermore, there was a significant decrease in positive mood states such as feelings of energy or hedonic tone, and a more pessimistic view on life situations (Mebris et al., 1996; Hepburn, 1993; McCrimmon et al., 1999a,b, 1995; Gold et al., 1995c). In summary, there is experimental evidence for negative effects of low blood glucose on internal emotional experience like mood states, which occur independently from external stimuli (Gold et al., 1997). Frequently reported interpersonal conflicts during hypoglycaemic may indicate that there is the possibility that hypoglycaemia does not only affect internal emotional experiences (mood states) but also alters the perception of external emotional stimuli in a negative way.

Furthermore, psychophysiological studies of emotions demonstrated many covariations between physiological variables and the perception of emotional stimuli. A number of physiological parameters like heart rate, corrugator electromyographic activity (EMG), and skin conductance covary with emotional experiences. Changes in heart rate and EMG activity are primarily correlated with the valence ratings of emotional stimuli (Lang et al., 1993, 1998; Bradley, 2000). Studies using positron emission tomography (PET) or fMRI demonstrated changes in cortical activities during the processing of emotional stimuli. The activity in specific cortex areas seems to be dependent from the emotional content (pleasant, neutral, unpleasant) of external stimuli (Lane et al., 1997; Lang et al., 1998). Emotional stimuli (pleasant or unpleasant) have a more pronounced effect on cortical activation than neutral stimuli. These results suggest that activation of autonomic nervous system as well cortical processes contribute to emotional experiences (LeDoux, 1998; Lang, 1994; Cacioppo et al., 1993). From a psychophysiological perspective, changes

in the perception of emotional stimuli during hypoglycaemia are intriguing because low blood glucose causes an activation of the autonomic nervous system and affects central nervous processes (Cryer, 1997).

Therefore, the experimental induction of low blood glucose might provide an interesting new paradigm to study emotional experience, because hypoglycaemia leads to a wide range of physiological consequences which may be involved in emotional responses towards this state.

1.8. Study aims and hypothesis

This study addresses the emotional effects induced by experimentally induced hypoglycaemia on internal stimuli (mood states) as well as on external stimuli by using the International Affective Pictures System (IAPS; Lang et al., 1997). The IAPS is an established tool to elicit an emotional response and it provides a set of normative emotional stimuli for the experimental investigation of emotion. The emotional content of slides is generally scaled along the three dimensions valence, arousal, and dominance. Additionally, the time needed for the rating of the emotional stimuli can be recorded.

(1) According to existing experimental and clinical findings it is expected that experimentally induced hypoglycaemia has a negative effect on internal emotional experiences (mood states), leading to an increase in negative mood states like anger and tension and a decrease in positive mood states like energy and hedonic tone. (2) It is expected that hypoglycaemia will have a negative impact on the perception of emotional stimuli drawn from the IAPS. According to predicted negative mood changes, it is hypothesised that low blood glucose causes also a lower rating of valence and dominance of the slides. The activation of the autonomic nervous system by low blood glucose may induce a higher arousal rating of the emotional stimuli. Furthermore, it can be expected that the prolongation of information processing time caused by neuroglycopenia leads to an increase of time used to rate the emotional content of the slides. (3) Psychophysiological research indicates that the emotional processing of pleasant and unpleasant slides is different from the processing of neutral stimuli. According to the established neuroglycopenic effects of hypoglycaemia, it can be expected that the effects of low blood glucose are more pronounced on pleasant and unpleasant stimuli, compared with neutral stimuli. (4) Additional exploratory analyses look for physiological and neuropsychological correlates of emotional changes (mood and perception of external emotional stimuli) without specific hypotheses.

2. Methods

2.1. Participants

In this study, 22 subjects with the diagnosis of type 1 diabetes according to WHO criteria participated. These inpatients were treated at the Diabetes Centre Mer-

gentheim, Bad Mergentheim, Germany. The participants were randomly assigned either to the experimental or control group. Eleven participants were members of the control group and eleven participants took part in the experimental group. All participants were free of severe diabetic complications or other medical conditions precluding participation in the study. To avoid gender related influences on the dependent variables only male persons participated in this study. The demographic characteristics are depicted in Table 1. There are some differences between control and experimental group. Controls were older, had experienced more severe hypoglycaemic episodes during the past year and had a significant longer disease duration than the experimental group. Years of school education and glycaemic control were comparable in both groups.

Type 1 diabetic patients were asked to participate in an experimental study designed to investigate emotional effects of hypoglycaemia. They were informed that blood glucose was manipulated by a hyperinsulinaemic glucose clamp and that in the experimental group blood glucose was lowered to 2.5 mmol/l whereas blood glucose was stabilised in the control group at 5.6 mmol/l. The participants had also to agree to random assignment to control or experimental group. Furthermore, the participants were informed that they had to rate pictures presented on a screen and that they had to complete questionnaires during the experiment. Participants received a written information about the study and had the opportunity to ask questions. If they agreed to participate they signed informed consent. The study was approved by the local ethics committee.

2.2. Study design

In the experimental group, each subject was studied before, during and after an experimentally induced episode of hypoglycaemia. A hyperinsulinaemic glucose clamp technique was used (see below for details). In the first period euglycaemia (5.6 mmol/l) was maintained. Then, blood glucose was lowered to 2.5 mmol/l and stabilised at this level. After this second phase euglycaemia was restored and stabilised. Each test phase lasted about 40 min. In the control group, euglycaemia was maintained during all three examination periods by the hyperinsulinaemic glucose clamp technique (see Fig. 2). During the experiment all participants were unaware of their status as a member of the control or the experimental group. They

Table 1
Demographic characteristics of control and experimental groups (results of *t*-tests)

Variable	Control group <i>n</i> = 11	Experimental group <i>n</i> = 11	<i>t</i>
Age (years)	38.2 ± 10.8	31.7 ± 9.2 ^{ns}	1.51
Duration of disease (years)	13.9 ± 8.9	7.0 ± 6.5*	2.1*
HbA1c (%)	7.8 ± 2.2	8.2 ± 2.3 ^{ns}	0.51
# of severe hypoglycaemia in past 12 months	2.1 ± 3.0	0.4 ± 0.9 ^{ns}	1.80
Years of school education	10.6 ± 3.9	10.6 ± 3.2 ^{ns}	0.01

* = *P* < 0.05; # = number.

were also blind with respect to their current blood glucose level. During each test period the participants performed a battery of tests consisting of two neuropsychological tests, a symptom checklist, and a mood checklist. In each test phase, blood samples were drawn to determine counterregulatory hormones (epinephrine, norepinephrine, and cortisol). All tests during the experiment were carried out with the participants in a sitting position. Overall, the experiment lasted for 3 to 4 h.

2.3. Preparation of the participants

Previous hypoglycaemia can affect the results of an experimentally induced hypoglycaemia. Therefore, blood glucose levels of the participants were checked seven times per day, 2 days before the study. The night before the experiment, an additional measurement of blood glucose was performed at 03:00 a.m. If blood glucose values lower than 3.3 mmol/l occurred in one of the measurements, the study was postponed. The participants used their ordinary insulin regimens on the day before the experimental study and omitted their injection of long acting insulin on the morning of the study. Carbohydrates consumed during breakfast were covered by an injection of short acting insulin analogue (Humalog[®], Eli Lilly Co., Indianapolis, USA). The glucose clamp was scheduled to commence 2 h after breakfast at 09:00 a.m.

2.4. Hyperinsulinaemic glucose clamp technique

The hyperinsulinaemic glucose clamp technique is the ‘gold standard’ for blood glucose manipulation (Heine, 1993). By use of this technique every physiological

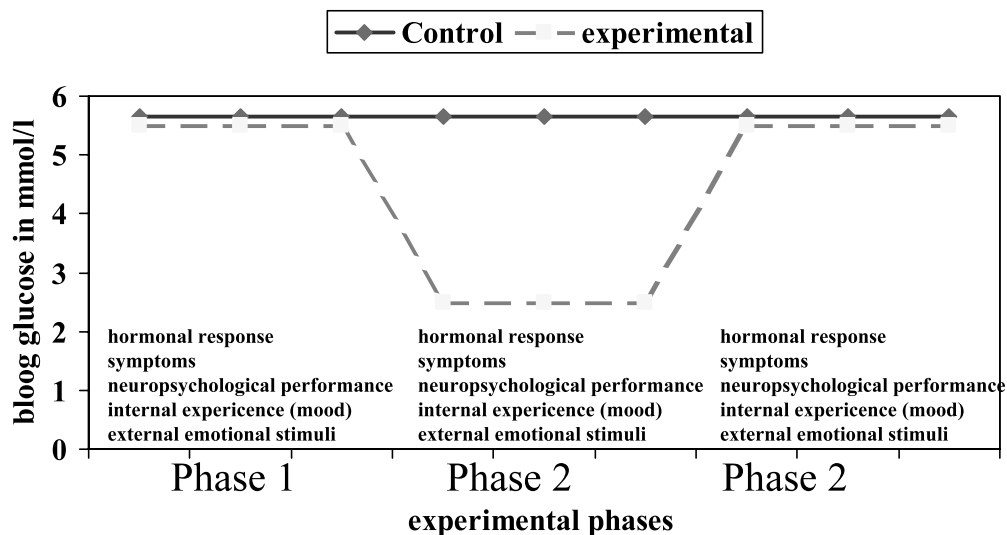


Fig. 2. Experimental design.

blood glucose level can be reached and maintained during the study. Thus, blood glucose manipulation can be standardised and replicated. Insulin is infused intravenously to reach and maintain a constant insulin level. This is necessary to suppress endogenous (hepatic) glucose production in diabetic and non diabetic participants (DeFronzo et al., 1979). Independence from the current blood glucose and the desired blood glucose levels 20% dextrose is infused. To calculate the actual infusion rate of dextrose a standard algorithm is used (see below). According to the blood samples drawn and measured every 5 min this formula calculates a volume component which compensates for the differences between the measured actual and desired blood glucose level. The metabolic component compensates for the current glucose disposal rate of the body. In the current metabolic rate, the metabolic rates of the last two measurements points are taken into account

$$S_i = \underbrace{\frac{(G_d - G_i) \times 10 \times (0.19 \times kg)}{G_{inf} \times 15}}_{\text{volume component}} \times \text{PF} + \underbrace{S_{m_{i-2}} \times \frac{G_i}{G_d} \times F_{m_{i-1}}}_{\text{metabolic component}}$$

Formula for glucose infusion rate (G_d , desired glucose concentration; G_i , glucose concentration at any time; G_{inf} , glucose concentration in the infusate in mg/ml; PF, the infusion pump factor converts the infusion rate in mg/min to that portion of the final dial setting needed for the volume component; $S_{m_{i-2}}$, metabolic component calculated two iterations (10 min) previously, $F_{m_{i-1}}$, correction factor that compensates for the error in the glucose concentration one iteration (5 min) previously.

Before the beginning of the hyperinsulinaemic glucose clamp an antecubital venous cannula for infusion of insulin and glucose was inserted in the dominant arm. Another antecubital cannula was inserted in the non-dominant hand for blood glucose measurement. This hand was placed in a heating box (air temperature 60 °C) for arterialisation of venous blood (Liu et al., 1993). Blood samples were drawn every 5 min and immediately analysed, using a HemoCue®-Photometer (Mallinkrodt Medical, Bad Hoenf, Germany). A constant infusion of insulin (1.5 mU/kg/min) was used to induce hyperinsulinaemia. According to the blood glucose readings a glucose infusion of 20% dextrose was adjusted using the above described algorithm of DeFronzo et al. (1979) to reach and maintain the desired blood glucose levels.

3. Measures

3.1. Mood

For the assessment of mood, a German translation of the well validated UWIST—Mood-Checklist was used (Matthews et al., 1990). This questionnaire assesses hedonic tone, energetic arousal, and tense arousal. In addition to these three scales another scale consisting of anger items (inpatient, annoyed, angry, irritated, grouchy) was created. The German translation was tested in a pre-study with 40 type 1 diabetic persons. The reliability of the translated scales were satisfactory (energetic

arousal Cronbach's $\alpha = 0.85$; hedonic tone $\alpha = 0.90$; tense arousal $\alpha = 0.83$; anger $\alpha = 0.77$).

3.2. Rating of external emotional stimuli

Thirty-six colour slides were selected from the IAPS. Twelve pictures were selected for each of three different valence categories, pleasant, neutral or unpleasant (see Table 2). Three blocks of slides presentation were arranged, so that each block, included four slides of each valence category. Both, the order of the blocks and the order of slides within a block were randomised. Each pair consisting of an experiment in the control and the experimental group had an identical order of slides. During each of the three periods of the experiment one block of slides was presented to the participants.

The participants sat in an armchair about 90 cm in front of the screen. The slides were presented on a 17 in. computer screen for 6 s. The interstimulus interval was set to 10 s. After the first presentation the slides were presented for a second time. Each slide had to be rated according to the affective dimensions of valence, arousal and dominance. For the rating of the slides according to these affective dimensions the participants used a computerised version of Self-Assessment-Manikin (SAM; Cook et al., 1987), an interactive graphics figure yielding responses on a 20-point scale (valence: very unpleasant = 0, very pleasant = 20, arousal: low arousal = 0, very high arousal = 20 and dominance: not strong = 0 and very strong = 20). Additionally, the rating time of each slide was recorded. The participants practised the rating of the emotional content of slides by a computerised version of SAM the day prior to the scheduled experiment.

Table 2
Description of slides and their number according to IAPS

<i>Series 1</i>		<i>Series 2</i>		<i>Series 3</i>	
Slide number	Description	Slide number	Description	Slide number	Description
5200	Flowers	7110	Hammer	7000	Rolling pin
7100	Fire hydrant	3130	Injured body	5660	Mountains
3030	Mutilation	1540	Cat	1300	pit bull
7260	Torte	3010	Mutilation	7570	Skyline
7040	Dust pan	7150	Umbrella	6242	Gang
1710	Puppies	5600	Mountains	2057	dad and baby
3100	Burn victim	5260	Waterfalls	7190	Clock
6313	Attacking	9050	Plane crash	5201	Cherry trees
7004	Spoon	7002	Towel	9250	war victim
7710	Bed	9570	Dog	4650	Couple
3120	Injured body	5760	Outdoors	9410	Soldier
1604	Butterfly	7025	Stool	7060	Trash can

3.3. Symptoms

For the recognition of hypoglycaemia warning symptoms, the symptom checklist, introduced by Hepburn et al. (1991) was used. This checklist contains autonomic symptoms (sweating, trembling, warmness, pounding heart, anxiety, shivering), neuroglycopenic symptoms (inability to concentrate, confusion, weakness, drowsiness, dizziness, tiredness, blurred vision, difficulty speaking, double vision), nonspecific symptoms (hunger, headache, nausea, perioral tingling), and control or ‘dummy’ items (hiccup, bloating, yellow vision, constipated, itching, back pain, pain in the legs, abdominal cramps, difficulty breathing), which have no association to the physiological consequences of hypoglycaemia.

3.4. Neuropsychological tests

Neuropsychological tests on cognitive domains with demonstrated sensitivity to hypoglycaemia were chosen as indicators of neuroglycopenia. Two computerised tests of complex attentional functions (divided attention task and flexibility task) out of the Test battery of Attentional Performance (TAP) were used (Zimmermann and Fimm, 1992). On the day prior to the experimental tests, the participants practised the neuropsychological tests in the laboratory to minimise learning effects during the experiments. In the divided attention task participants had to react either to visual stimuli (appearance of a cross on the screen) or acoustic stimuli (sequence of two identical tones). The mean reaction time and standard deviation (SD) were calculated individually. In the flexibility task participants had to press a button on the same side as a circle which appeared on the screen, or press a contra-lateral button if a square appeared on the screen. The mean reaction time and SD were individually calculated. In both tests, an increase in the mean reactions time indicates a deterioration in these neuropsychological functions.

3.5. Laboratory analysis

For the analysis of epinephrine and norepinephrine High Pressure Liquid Chromatography (HPLC) was used. The analysis was performed with the Tosoh Catecholamin Analyser (HLC-725CA, Eurogenetics, Tessenderlo, Belgium). Plasma cortisol was measured by radioimmunoassay (Multi Kristall Gammacounter, Bertold Co, Bad Wildbad, Germany).

3.6. Statistical analysis

A sum score was calculated from the items belonging to the mood scales and the scales of the symptom-checklist. In each phase of the experiment, 12 slides belonging to three different valence categories (pleasant, neutral and unpleasant content) were presented. The average rating in the three dimensions (valence, arousal and dominance) were calculated for each phase of the experiment and for each valence category.

For the effects of hypoglycaemia on mood states a two-way analysis of variance with repeated measures was carried out with the factors Group (euglycaemia vs. hypoglycaemia) and Phase (first, second, third). The interaction Group \times Phase reveals if there is a different effect of hypoglycaemia or euglycaemia on the course of the mood states in the two groups as expected in hypothesis 1. For testing the effects of low blood glucose on emotional perception a three-way analysis of variance with repeated measures was carried out with the factors Group (euglycaemia vs. hypoglycaemia), Valence (pleasant, neutral and unpleasant) and Phase (first, second, third). According to hypothesis 2 a significant Group \times Phase within effect was expected. A significant three-way interaction Group \times Valence \times Phase would indicate a distinct effect of low blood glucose on the rating of slides with different emotional content (pleasant, neutral, unpleasant) as indicated in hypothesis 3.

Pearson product–moment correlations were calculated to analyse a possible association between the different effects of hypoglycaemia on neuroglycopenia, hormonal counterregulation, symptoms of hypoglycaemia and emotional changes.

According to the exploratory character of this study a minimisation of type 2 error was favoured. Thus, no adjustment for α errors were performed and significance levels were set at $P < 0.05$ for all statistical tests. The statistical analysis was performed by SYSTAT 9.0 (SPSS Inc., Chicago, IL, USA).

4. Results

The effect of the experimental manipulation of blood glucose on blood glucose and the different symptomatic, endocrine, and neuropsychological reactions are depicted in Tables 3 and 4.

4.1. Induction of hypoglycaemia

There is a significant interaction Group \times Phase on blood glucose. Euglycaemia and hypoglycaemia could be reliably induced and stabilised during the experimental phases, as indicated by the low SD (see Table 3 and Fig. 3)

4.2. Symptomatic response

Hypoglycaemia induced a significant and specific symptomatic response in autonomic and neuroglycopenic symptoms, but not in dummy symptoms.

4.3. Endocrine response

The significant epinephrine response (Group \times Phase) indicated an activation of the autonomic nervous system. Norepinephrine levels also increased during hypoglycaemia, but the difference between the two groups was not significant. Cortisol levels declined in the control group as expected from the known circadian

Table 3

Effect of experimental condition on blood glucose, symptoms, endocrine counterregulation and neuroglycopenic effects (data are presented as $M \pm SD$)

Variable	Condition	Phase 1	Phase 2	Phase 3
Blood glucose (mmol/l)	CG	5.7±0.7	5.4±0.2	5.5±0.1
	EG	5.5±0.2	2.5±0.1	5.8±0.3
Autonomic symptoms (score)	CG	7.2±4.9	6.5±3.6	5.5±1.5
	EG	7.3±3.7	11.6±7.2	6.5±2.7
Neuroglycopenic symptoms (score)	CG	13.8±4.8	13.5±4.2	12.0±2.5
	EG	14.1±6.1	26.8±10.8	17.9±8.5
Dummy symptoms (score)	CG	13.4±7.6	12.2±5.6	11.5±4.2
	EG	12.0±2.8	12.3±3.6	12.2±3.1
Epinephrine (per pmol)	CG	0.18±0.1	0.18±0.1	0.16±0.1
	EG	0.19±0.1	0.89±0.7	0.25±0.1
Norepinephrine (per pmol)	CG	0.88±0.3	0.91±0.3	0.84±0.3
	EG	0.86±0.3	1.03±0.5	0.76±0.3
Cortisol (µg/dl)	CG	358±165	304±160	317±181
	EG	375±122	448±246	383±161
Divided attention Test (ms)	CG	705±61	671±45	676±50
	EG	611±49	700±75	627±40
Incompatibility Test (ms)	CG	713±111	729±128	711±121
	EG	645±75	741±174	619±61

CG = control group, EG = experimental group.

rhythm of cortisol levels. In the experimental group, cortisol levels rose slightly during hypoglycaemia, but the change did not reach statistical significance.

4.4. Neuropsychological performance

The baseline reaction time in the two neuropsychological tasks are different. As the control group is 7 years older, this age difference might be responsible for a different level of performance during euglycaemic baseline. The course of performance in the two neuropsychological tasks differs significantly between the groups, indicated by the Group \times Phase effect. There was a deterioration during hypoglycaemia in the experimental group. In this group, the test performance improved above baseline values after restoring euglycaemia.

In summary, there is evidence that blood glucose could be manipulated effectively according to the experimental design. Hypoglycaemia induced an activation of the autonomic nervous system and neuroglycopenia of the CNS, causing a deterioration of neuropsychological functions. As well as activation of the autonomic nervous system, the neuroglycopenic effects of hypoglycaemia were mirrored in a significant increase in autonomic and neuroglycopenic symptoms.

4.5. Effects on internal experiences (mood states)

Fig. 4a–d depict the experimental effects on the mood scales. The negative mood states anger and tension increased in the experimental group during hypoglycaemia

Table 4
Physiological effects of hypoglycaemia (ANOVA results)

Source of variance	<i>df</i>	<i>F</i>	η^2
<i>Blood glucose</i>			
<i>Between effect</i>			
Group	1	215.1***	0.91
Error	20	(23.0)	
<i>Within effect</i>			
Phase	2	147.4***	0.88
Phase \times Group	2	108.8***	0.84
Error	40	(47.0)	
<i>Autonomic symptoms</i>			
<i>Between effect</i>			
Group	1	1.8	0.08
Error	20	(40.6)	
<i>Within effect</i>			
Phase	2	6.6**	0.25
Phase \times Group	2	5.3**	0.21
Error	40	(7.6)	
<i>Neuroglycopenic symptoms</i>			
<i>Between effect</i>			
Group	1	6.7*	0.25
Error	20	(101.4)	
<i>Within effect</i>			
Phase	2	13.8**	0.40
Phase \times Group	2	13.1**	0.39
Error	40	(17.1)	
<i>dummy symptoms</i>			
<i>Between effect</i>			
Group	1	0.1	0.01
Error	20	(59.9)	
<i>Within effect</i>			
Phase	2	1.0	0.01
Phase \times Group	2	1.5	0.07
Error	40	(4.2)	
<i>Epinephrine</i>			
<i>Between effect</i>			
Group	1	9.1**	0.31
Error	20	(0.1)	
<i>Within effect</i>			
Phase	2	12.7***	0.38
Phase \times Group	2	13.0***	0.39
Error	40	(0.1)	
<i>Norepinephrine</i>			
<i>Between effect</i>			
Group	1	0.1	0.01
Error	20	(0.3)	

Table 4 (Continued)

Source of variance	<i>df</i>	<i>F</i>	η^2
<i>Within effect</i>			
Phase	2	4.1*	0.17
Phase \times Group	2	1.5	0.07
Error	40	(0.1)	
<i>Cortisol</i>			
<i>Between effect</i>			
Group	1	1.5	0.07
Error	20	(62757)	
<i>Within effect</i>			
Phase	2	0.2	0.01
Phase \times Group	2	1.5	0.07
Error	40	(15430)	
<i>Divided attention</i>			
<i>Between effect</i>			
Group	1	4.2+	0.17
Error	20	(7679)	
<i>Within effect</i>			
Phase	2	5.7**	0.22
Phase \times Group	2	7.6**	0.27
Error	40	(1922)	
<i>Incompatibility</i>			
<i>Between effect</i>			
Group	1	0.9	0.04
Error	20	(37177)	
<i>Within effect</i>			
Phase	2	8.2**	0.29
Phase \times Group	2	4.1*	0.17
Error	40	(4857)	

Number in brackets represents the mean square of errors. + $P < 0.10$; * $P < 0.05$; ** $P < 0.01$, $P < 0.001$.

and reverted to baseline after restoration of euglycaemia. The positive mood states of energy and hedonic tone decreased during hypoglycaemia in the experimental group.

The results of the analysis of variance are shown in Table 5. For testing the hypothesis 1, the interaction Group \times Phase is of specific interest. There was a significant interaction Group \times Phase in negative mood states like anger and tension and in positive mood states like energy. Hedonic tone failed to reach significance.

4.6. Rating of external emotional stimuli

The rating results of the emotional stimuli in the different valence categories are shown in Figs. 5–7. For testing the hypothesis 2 and 3 the interaction Group \times Phase and the three-way interaction Group \times Valence \times Phase are of specific interest.

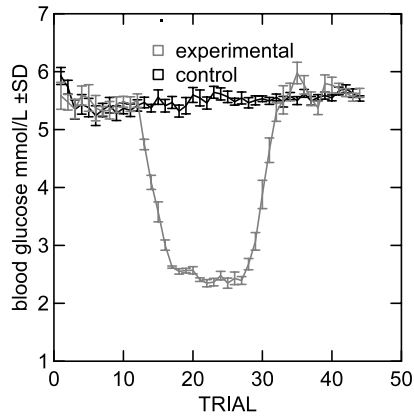


Fig. 3. Course of blood glucose (each trial represents a 5 min interval).

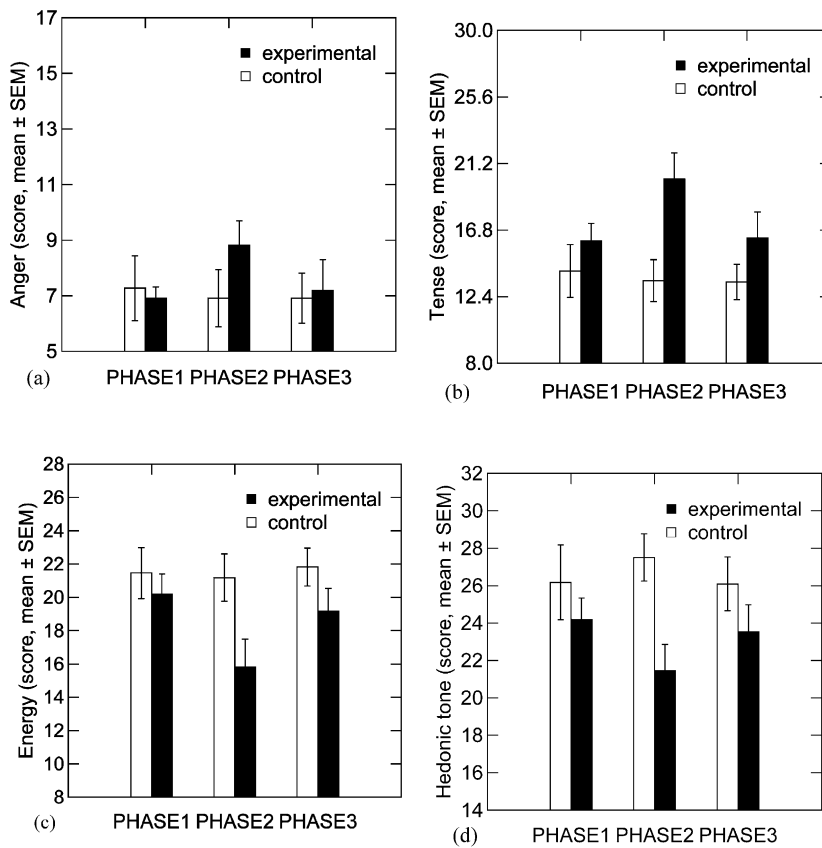


Fig. 4. (a–d) Experimental effects on mood.

Table 5
Effect of hypoglycaemia on mood (ANOVA results)

Source of variance	<i>df</i>	<i>F</i>	η^2
<i>Tense</i>			
<i>Between effect</i>			
Group	1	4.6*	0.18
Error	20	(53.7)	
<i>Within effect</i>			
Phase	2	3.8*	0.16
Phase \times Group	2	5.0*	0.20
Error	40	(6.9)	
<i>Anger</i>			
<i>Between effect</i>			
Group	1	0.3	0.01
Error	20	(22.3)	
<i>Within effect</i>			
Phase	2	2.0	0.09
Phase \times Group	2	3.3*	0.14
Error	40	(2.3)	
<i>Energy</i>			
<i>Between effect</i>			
Group	1	3.3+	0.14
Error	20	(47.4)	
<i>Within effect</i>			
Phase	2	6.5**	0.24
Phase \times Group	2	4.5*	0.18
Error	40	(5.3)	
<i>Hedonic tone</i>			
<i>Between effect</i>			
Group	1	2.3	0.10
Error	20	(67.2)	
<i>Within effect</i>			
Phase	2	3.4*	0.14
Phase \times Group	2	3.1+	0.13
Error	40	(3.5)	

Number in brackets represents the mean square of errors. + $P < 0.10$; * $P < 0.05$; ** $P < 0.01$.

The valence rating varied (Fig. 5a–c) in both groups with the valence categories (pleasant, neutral, unpleasant). Independent from the experimental condition, unpleasant pictures were rated as more pleasant in the second and third experimental phase compared with the first phase. The course of the valence ratings seemed similar in all valence categories during euglycaemia and hypoglycaemia.

Fig. 6a–c shows the arousal ratings in the different valence categories. Arousal ratings in unpleasant slides were remarkably higher compared to neutral and pleasant stimuli. Unpleasant pictures were rated as less exciting during the second and third experimental phase. The course of arousal ratings in the three experimental phases was almost parallel in both groups.

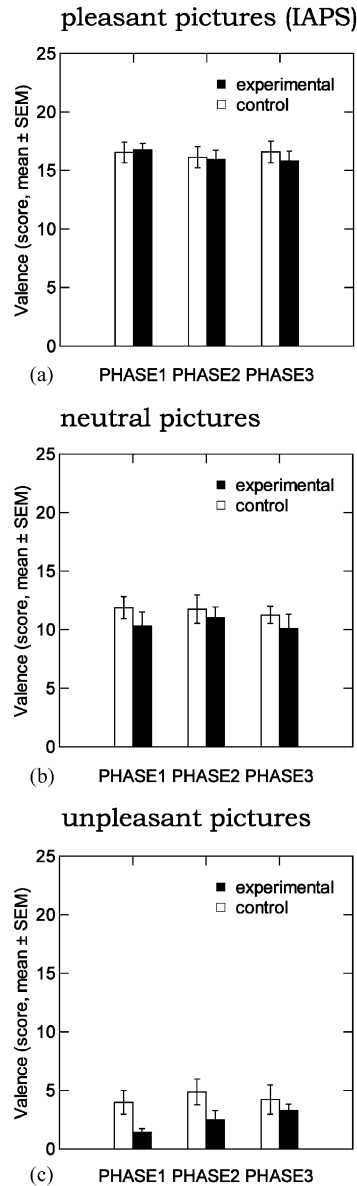


Fig. 5. (a–c) Experimental effects on valence ratings.

Dominance ratings were more pronounced in pleasant and unpleasant stimuli compared with neutral stimuli (Fig. 7a–c). Unpleasant pictures were rated as less dominant in the second and third phases of the experiment compared with the first phase. There was no remarkable difference in the course of the dominance ratings during the experiment between the two experimental groups.

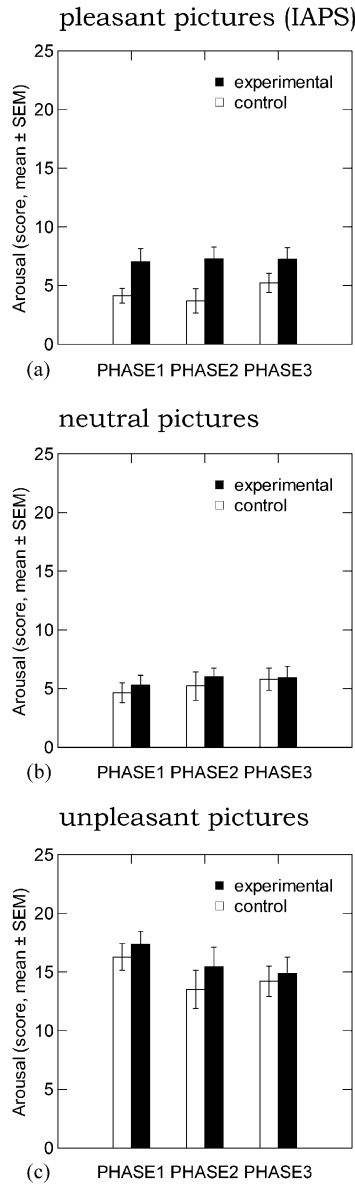


Fig. 6. (a–c) Experimental effects on arousal ratings.

The rating time of emotional stimuli is depicted in Fig. 8a–c. There is a consistent reduction in rating time during phase 2 and 3 in the control group, whereas the rating time remained on the level of phase 1 in the second phase of the experimental group. In the third phase, the rating time of the experimental group dropped to the

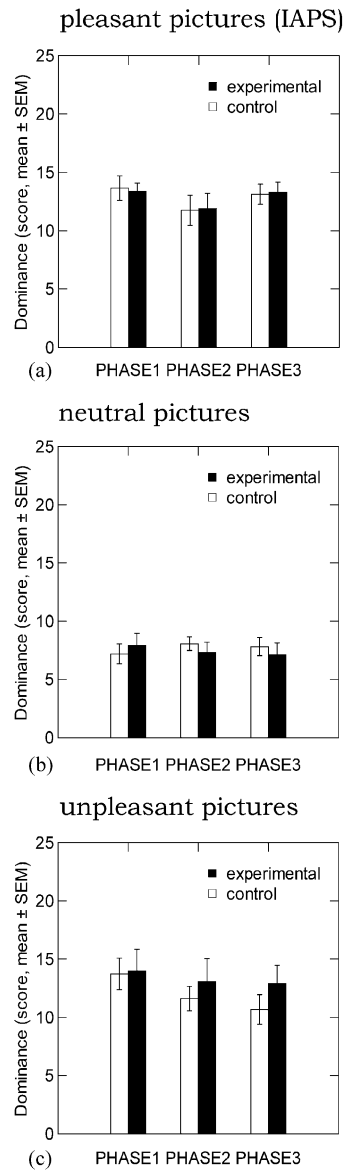


Fig. 7. (a–c) Experimental effects on dominance ratings.

level of the control group. This course of rating time was observable in all three valence categories.

Analysis of variance on the ratings of emotional stimuli are depicted in Table 6. In all three rating dimensions (valence, arousal, dominance), there was a significant effect in Valence. This effect was not unexpected based on numerous studies that

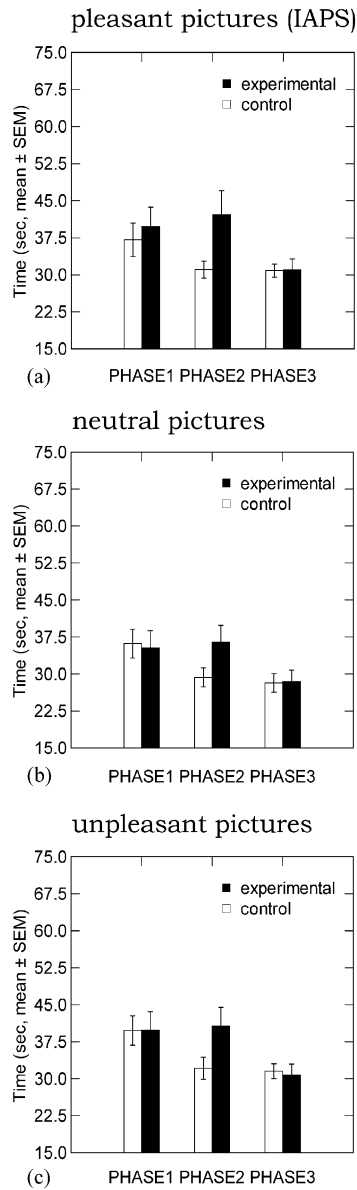


Fig. 8. (a–c) Experimental effects on rating time.

have used the IAPS stimulus set (Lang et al., 1997, 1998). There was also a significant interaction Phase × Valence in all three dimensions, indicating that the repetition of emotional stimuli in different valence categories had a differential effect on their rating.

Table 6
Effect on ratings of IAPS-slides (ANOVA results)

Source of variance	<i>df</i>	<i>F</i>	η^2
<i>Rating time</i>			
<i>Between effect</i>			
Group	1	5.9*	0.09
Valence	2	1.4	0.05
Group \times Valence	2	0.2	0.01
Error	60	(199)	
<i>Within effect</i>			
Phase	2	26.0***	0.30
Phase \times Group	2	12.9***	0.18
Phase \times Valence	4	0.3	0.01
Phase \times Group \times Valence	4	0.3	0.01
Error	120	(36.5)	
<i>Arousal</i>			
<i>Between effect</i>			
Group	1	4.1*	0.06
Valence	2	64.4***	0.68
Group \times Valence	2	0.4	0.01
Error	60	(31.6)	
<i>Within effect</i>			
Phase	2	2.3	0.04
Phase \times Group	2	1.5	0.02
Phase \times Valence	4	4.8**	0.14
Phase \times Group \times Valence	4	0.1	0.01
Error	120	(4.5)	
<i>Valence</i>			
<i>Between effect</i>			
Group	1	2.3	0.06
Valence	2	110.9***	0.79
Group \times Valence	2	0.9	0.03
Error	60	(23.6)	
<i>Within effect</i>			
Phase	2	0.8	0.01
Phase \times Group	2	0.1	0.00
Phase \times Valence	4	2.9*	0.08
Phase \times Group \times Valence	4	1.2	0.03
Error	120	(2.4)	
<i>Dominance</i>			
<i>Between effect</i>			
Group	1	0.1	0.01
Valence	2	14.3***	0.32
Group \times Valence	2	0.1	0.01
Error	60	(38.8)	
<i>Within effect</i>			
Phase	2	4.0*	0.06
Phase \times Group	2	0.1	0.01
Phase \times Valence	4	2.8*	0.08

Table 6 (Continued)

Source of variance	<i>df</i>	<i>F</i>	η^2
Phase \times Group \times Valence	4	0.6	0.02
Error	120	(4.8)	

Number in brackets represents the mean square of errors;. + $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

In the arousal dimension, a significant between effect for Group was observed. Univariate F -tests revealed a significant difference between the arousal ratings of the slides on phase 2 ($F[1, 60] = 5.1$; $P = 0.03$). For testing the hypothesis 2 and 3 the within effect of the interaction Phase \times Group and Phase \times Group \times Valence were of special interest. In all three rating dimensions, there was no significant two-way or three-way interaction observable, indicating that the induction of hypoglycaemia did not change the perception of slides in different valence categories.

There was a significant effect for Group in rating time (see Table 6). Univariate F -tests showed a significantly longer rating time during the second phase ($F[1, 60] = 16.0$; $P < 0.01$). There was also a significant interaction Phase \times Group, confirming the hypothesis 2 for the rating time. In the control group, the rating time for the second phase was significantly shorter than for the experimental group. One possible cause for this could be practice effects in the control group, which seemed to be restricted to the control group. Thus, there was a clear effect of hypoglycaemia on the processing time of emotional stimuli.

4.7. Correlational analysis

The results of explanatory correlational analysis are shown in Table 7. Since there was no distinguished effect of hypoglycaemia on the ratings of stimuli drawn from different valence categories, the average ratings of all stimuli in each phase and in the dimension valence, arousal and dominance were used in the correlational analysis.

Catecholamine and cortisol responses were associated with emotional changes during hypoglycaemia. The higher the epinephrine and norepinephrine responses the more exciting the emotional stimuli were rated. The positive valence and the dominance ratings during hypoglycaemia decreased as less epinephrine was released. Hedonic tone and energy also deteriorated during hypoglycaemia as less epinephrine was released. An increase in anger was associated with a high cortisol response and a deterioration in the divided attention task. A deterioration in the flexibility task showed a strong positive correlation to a prolongation of the rating time of emotional stimuli, suggesting that the slowing down of processing time is a consequence of cerebral energy deprivation (neuroglycopenia). Strong autonomic and neuroglycopenic symptoms were associated with a decrease in positive mood states such as feelings of energy and hedonic tone.

Table 7
Correlation (Pearson coefficient) between emotional changes and physiological consequences of hypoglycaemia in the experimental group ($n = 11$)

	Epi. ^a	Norepi ^a	Cortisol ^a	Aut. sym. ^a	Neu. sym ^a	Div. att. ^a	Flex. ^a
Anger ^a			0.76			0.66	
Tense ^a							
Energy ^b		-0.64		0.67	0.66		
Hedonic ^b	-0.61	-0.78		0.55			
Valence ^b	-0.58						
Arousal ^a	0.63	0.60					
Domin. ^b	-0.58						
Time ^a							0.80

Only substantial correlations $r > 0.50$ and $P < 0.10$ are shown. Epi, epinephrine; norepi, norepinephrine; aut. sym., autonomic symptoms; neu. Sym, neuroglycopenic symptoms; div. Att, divided attention task; flex, flexibility task; domin, dominance rating.

^a Increase from euglycaemia to hypoglycaemia.

^b Decrease from euglycaemia to hypoglycaemia.

5. Conclusions

This study examined the effect of an experimentally induced hypoglycaemia on emotional experiences. Furthermore, we wanted to introduce a new research strategy to study emotional experience by manipulating blood glucose levels.

Experimentally induced hypoglycaemia seems to have different pronounced effects on the perception of internal and external experiences. Positive mood states like energy and hedonic tone decreased whereas negative mood states like anger and tension increased during the hypoglycaemic episode. After the restoration of euglycaemia the mood changes reverted to baseline. These results replicate former findings of negative mood changes during hypoglycaemia. Hypoglycaemia seems to induce a state of 'angry tensed tiredness' (Gold et al., 1997, 1995a; McCrimmon et al., 1999a,b).

Hypoglycaemia is a stimulus which elicits a variety of physiological responses, consisting of the consequences of neuroglycopenia and the activation of the autonomic nervous systems. Correlational analysis reveals that the mood changes seem to be associated with symptomatic, endocrine, and neuroglycopenic responses towards low blood glucose. But since these data are correlational, firm conclusions about the casual direction of these effects cannot be made. Another limitation for the generalisation of these results to all type 1 diabetic patients are differences between control and experimental group in disease duration and exposure towards hypoglycaemia. Longer disease duration and more frequent exposure to severe hypoglycaemia could diminish symptomatic and endocrine responses during hypoglycaemia. Thus, it could be expected that symptomatic and endocrine responses towards low blood glucose may have been smaller as observed, if hypoglycaemia would have been induced in participants of the control group. Generalisation of the observed emotional changes especially to the group of diabetic

patients with a longer disease duration and a more frequent exposure towards hypoglycaemia should therefore be made with caution. Also potential gender differences were not addressed by this study.

From a more clinical perspective mood changes can be meaningful in the context of the treatment of low blood glucose. Mood changes can have an impact on the perception of symptoms, risk appraisal, problem solving, readiness to act, and the perception of other people and situations (Decatanzaro, 1998; Gold et al., 1997). Thus, the observed negative mood changes may delay or prevent an immediate recognition or treatment of hypoglycaemia (Deary, 1999). The negative mood states may also provide a basis for the frequently reported unfavourable communication style and interpersonal conflicts during hypoglycaemia (Lincoln and Eaddy, 2001).

The effect of low blood glucose on the perception of external emotional stimuli was less pronounced. The observed differences in the rating of emotional stimuli were related to the Valence and the interaction Phase \times Valence. Slides belonging to different valence categories induced a different rating along the dimensions of valence, arousal, and dominance. These effects were independent from the experimentally manipulated blood glucose. Ratings of emotional stimuli varying along these valence categories, is an established finding known from other studies using the IAPS. Unpleasant pictures received a more positive valence rating in the second and third phase compared with the first phase of the experiment. This effect could be caused by an adaptation process. Subjects may get used to the unpleasant content of these slides, thus rating them as less aversive.

There is only one Group effect on the arousal ratings of the stimuli. Univariate *F*-tests showed a significantly higher arousal rating during the hypoglycaemic period (second phase) in the experimental group compared with the control group. No other significant differences in the dominance and valence rating of the emotional stimuli were observed.

One reason for the failure to detect significant interaction effects between Group and Phase could be the great variability of emotional experience per se. The power of the test is limited by the great interindividual variance of emotional experience. Due to the invasive character of the hyperinsulinaemic clamp technique only relatively small sample sizes can be investigated. Thus, the small sample size limits the power of this study to detect differences in the perception of external emotional stimuli.

The rating of emotional stimuli can be regarded as a process requiring cognitive abilities. It can be speculated that the hypoglycaemic stimulus was not strong enough to induce a severe impairment of cognitive functions required for the rating of emotional stimuli. The prolongation of cognitive performance tests was about one SD from the baseline, suggesting a rather moderate effect of low blood glucose on cognitive function. With a blood glucose level of 2.5 mmol/l the hypoglycaemic stimulus and the resulting cerebral energy deprivation is moderate. Thus, it cannot be excluded that a lower blood glucose level than that induced in the study would have had more pronounced effects on the perception of external emotional stimuli. For ethical reasons, however, blood glucose cannot be manipulated to more extreme low values to address this question (Fanelli et al., 1998; Amiel, 1998).

One finding of cognitive testing during extraordinary bodily conditions like intoxication, sleep deprivation, and hypoglycaemia is a so called ‘accuracy-speed trade off’, which means that during such extraordinary conditions test performance is maintained at the expense of speed (Wickelgreen, 1977; Rabbitt, 1988; Deary, 1993; Sanders et al., 1982). Analogous to these findings, it can be speculated that the quality of emotional perception is not affected by moderate hypoglycaemia because this maintenance is achieved at the expense of processing speed, indicated by a prolongation of rating time for emotional stimuli. Slowing down the processing time of emotional stimuli may result in a reduced capacity to deal with these emotional stimuli. From a clinical perspective this may contribute to the perception of overstimulation by external emotional stimuli. This may result in a more negative emotional experience and more negative interaction with others during hypoglycaemia.

Correlational analysis shows that the catecholamine response is associated with a higher arousal rating and a less strong deterioration of positive mood states and smaller reductions in the ratings of valence and dominance. Thus, the activation of the autonomic nervous system seems to be associated with an increase in positive mood states and a higher arousal rating of external emotional stimuli. Furthermore, the presence of autonomic and neuroglycopenic warning symptoms may be perceived as aversive and lead to a deterioration of positive mood stages.

On the other hand, the neuroglycopenic consequences of hypoglycaemia seem to be associated with a prolongation of the processing time of emotional stimuli and an increase in negative feelings like anger. It can be speculated that the perception of cognitive deterioration plays a role in the enhancement of feelings like anger. The interpretation of the correlational analysis, however, must be treated with caution because of the small sample size.

From a research perspective experimentally induced hypoglycaemia seems to be a suitable model to study emotional perception. The physiological consequences of hypoglycaemia have two sources, an activation of the autonomic nervous system and a cerebral energy deprivation which is responsible for neuroglycopenia. These physiological consequences have known associations to emotional experiences. Manipulation of blood glucose, therefore, could be an interesting experimental model for investigating the psychophysiology of emotion because low blood glucose elicits these two different physiological responses which are relevant to emotional processes. The experimental induction of hypoglycaemia has the advantage that the onset of these physiological consequences occurs immediately after lowering blood glucose. After restoration of euglycaemia these physiological reactions disappear rapidly. By means of the hyperinsulinaemic clamp technique the hypoglycaemic stimulus can be reproduced reliably and blood glucose can be manipulated precisely.

One drawback of the hyperinsulinaemic clamp technique method is the lack of external validity. Thus the experience of a hypoglycaemic episode under real life circumstances may also modify the perception of external emotional stimuli. The results of the experiment should be transferred only with caution to real life settings. Therefore, experimental methods for investigating emotional experience should be combined with ambulatory assessment in the field, to establish the external validity

of the results (Hermanns, 1999; Fahrenberg and Myrtek, 2001; Kubiak and Hermanns, 2001).

For a better understanding of the emotional consequences of experimentally induced hypoglycaemia applications with fMRI would be favourable. By the use of fMRI and positron emission tomogram (PET) glucose metabolism can be measured directly. This may provide a better understanding of the metabolic effects of low blood glucose on cerebral glucose supply. The regional pattern of energy deprivation might be better understood by use of these imaging techniques and might be related to certain emotional experiences or specific emotional changes.

A selective pharmacological blockade of receptors of the autonomic nervous system could also be a method to distinguish the effects of the autonomic nervous system on emotional experience from those caused directly by neuroglycopenia (Cryer, 1997; Towler et al., 1993; Cryer, 2002).

In summary, hypoglycaemia is a highly reproducible physiological state that has an impact on emotional experience. Further research should address the possible associations between emotional experience and the different physiological consequences of hypoglycaemia by using the above mentioned techniques. This study was a first step to highlight the potential of experimentally induced hypoglycaemia for the examination of emotional experiences.

References

- Amiel, S.A., 1998. Cognitive function testing in studies of acute hypoglycaemia: rights and wrongs. *Diabetologia* 41, 713–719.
- Bendtsen, I., 1993. Neurophysiological changes of hypoglycaemia. In: Frier, B., Fisher, B.M. (Eds.), *Hypoglycaemia and Diabetes. Clinical and Physiological Aspects*. Edward Arnold, London, pp. 72–79.
- Birbaumer, N., Rockstroh, B., Elbert, T., Wolf, P., Dürting-Röth, A., Reker, M., et al., 1994. Biofeedback of slow cortical potential of epilepsy. In: Carlson, J., Seifert, R., Birbaumer, N. (Eds.), *Clinical Applied Psychophysiology*. Plenum, New York, pp. 29–42.
- Blackman, J., Towle, V., Lewis, G., Spire, J., Rolonsky, K., 1990. Hypoglycemic thresholds for cognitive dysfunction in humans. *Diabetes* 39, 828–835.
- Blackman, J.D., Towle, V.L., Sturis, J., 1992. Hypoglycaemia thresholds for cognitive dysfunction in IDDM. *Diabetes* 41, 392–399.
- Bott, S., Bott, U., Berger, M., Mühlhauser, I., 1997. Intensified insulin therapy and the risk of severe hypoglycaemia. *Diabetologia* 40, 926–932.
- Boyle, P.J., Kempers, S.F., O'Connor, A.M., Nagy, R.J., 1995. Brain glucose uptake and unawareness of hypoglycaemia in patients with insulin dependent diabetes. *New England Journal of Medicine* 333, 1726–1731.
- Bradley, M.M., 2000. Emotion and motivation. In: Cacioppo, J.T., Tassinary, L.G., Berntson, G.G. (Eds.), *Handbook of Psychophysiology*. Cambridge University Press, Cambridge, pp. 602–642.
- Cacioppo, J.T., Berntson, D.J., Hatfield, E., 1993. The psychophysiology of emotion. In: Lewis, M., Haviland, E. (Eds.), *Handbook of Emotions*. Guilford Press, New York, pp. 119–142.
- Chessler, S.D., Lernmark, A., 2000. Type 1 (insulin dependent) diabetes mellitus. In: Davidson, J.K. (Ed.), *Clinical Diabetes Mellitus*. Thieme, New York, pp. 37–57.
- Cook, E.W., Atkinson, L., Lang, P.J., 1987. Stimulus control and data acquisition for IBM PC's and compatibles. *Psychophysiology* 24, 726–726.

- Cryer, P.E., 1997. Hypoglycaemia. Pathophysiology, Diagnosis, and Treatment. Oxford University Press, Oxford.
- Cryer, P.E., 2002. Hypoglycaemia: the limiting factor in the glycaemic management of type 1 and 2 diabetes. *Diabetologia* 45, 937–948.
- Davidson, J.K., Anderson, J.H., Chance, R.E., 2000. Insulin therapy. In: Davidson, J.K. (Ed.), *Clinical Diabetes Mellitus*. Thieme, New York, pp. 329–403.
- DeFeo, P., Gallai, V., Mazzotta, G., Crispino, G., Torlone, E., Perriello, G., et al., 1988. Modest decrements in plasma glucose concentration cause early impairment in cognitive function and later activation of glucose counterregulation in the absence of hypoglycemic symptoms in normal man. *Journal of Clinical Investigation* 82, 436–444.
- DeFeo, P., Perriello, G., Torlone, E., Bolli, G.A., 1989. Contribution of cortisol to glucose counterregulation in humans. *American Journal of Physiology* 257, 34–42.
- Deary, I.J., 1993. Effects of hypoglycaemia on cognitive function. In: Frier, B.M., Fisher, B.M. (Eds.), *Hypoglycaemia and Diabetes*. Edward Arnold, London, pp. 80–92.
- Deary, I.J., 1999. Symptoms of hypoglycaemia and effects on mental performance and emotions. In: Frier, B.M., Fisher, B.M. (Eds.), *Hypoglycaemia in Clinical Diabetes*. Wiley, New York, pp. 29–54.
- Decatanzaro, D.A., 1998. *Motivation and Emotion*. Prentice Hall, New York.
- DeFronzo, R.A., Tobin, J.D., Andres, R., 1979. Glucose Cclamp technique: a method for quantifying insulin secretion and resistance. *American Journal of Physiology* 237, E214–E223.
- Fahrenberg, J., Myrtek, M., 2001. *Progress in Ambulatory Assessment*. Hogrefe & Huber, Seattle.
- Fanelli, C.G., Pampanelli, S., Porcellati, F., Bolli, G.A., 1998. Shift of glycemic thresholds for cognitive function in hypoglycaemia unawareness. *Diabetologia* 41, 720–723.
- Fletcher, A.A., Campbell, B.M., 1922. The blood sugar following insulin administration and the symptom complex-hypoglycaemia. *Journal of Metabolic Research* 2, 637–649.
- Flor, H., Elbert, T., Wiesendanger, M., Pantev, C., Knecht, S., Birbaumer, et al., 1995. Phantom limb pain as a perceptual correlate of cortical reorganisation. *Nature* 357, 482–484.
- Frier, B.M., 1993. Hypoglycaemia unawareness. In: Frier, B.M., Fisher, M. (Eds.), *Hypoglycaemia and Diabetes. Clinical and Physiological Aspects*. Edward Arnold, London, pp. 284–301.
- Frier, B.M., Fisher, B.M., 1999. Impaired hypoglycaemia awareness. In: Frier, B.M., Fisher, B.M. (Eds.), *Hypoglycaemia in Clinical Diabetes*. Wiley, New York, pp. 111–146.
- Gallai, V., Mazotta, G., Firenze, C., 1988. A study of the P300 component during minor hypoglycaemia. *Acta Neurologica* 10, 178–186.
- Gold, A.E., Deary, I.J., Thomson, K.F., Frier, B.M., 1995a. Cognitive function during insulin induced hypoglycaemia in humans: short term cerebral adaptation does not occur. *Psychopharmacology* 119, 325–333.
- Gold, A.E., Deary, I.J., MacLeod, K.M., Frier, B.M., 1995b. The effect of IQ level on the degree of cognitive deterioration experienced during hypoglycaemia in normal humans. *Intelligence* 20, 267–290.
- Gold, A.E., MacLeod, K.M., Deary, I.J., Frier, B.M., 1995c. Changes in mood during acute hypoglycaemia in healthy participants. *Physiology and Behavior* 58, 501–511.
- Gold, A.E., Deary, I.J., Frier, B.M., 1997. Hypoglycaemia and non-cognitive aspects of psychological function in insulin-dependent (type 1) diabetes mellitus (IDDM). *Diabetic Medicine* 14, 111–118.
- Gonder-Frederick, L.A., Cox, D.J., Bobbitt, S.A., Pennebaker, J.W., 1989. Mood changes associated with blood glucose fluctuations in insulin-dependent diabetes mellitus. *Health Psychology* 8, 45–59.
- Gonder-Frederick, L., Cox, D.J., Clarke, W.L., 1996. Helping patients understand and recognise hypoglycaemia. In: Anderson, B.J., Rubin, R.R. (Eds.), *Practical Psychology for Diabetes Clinicians*. American Diabetes Association, Alexandria, VA, pp. 83–92.
- Gonder-Frederick, L.A., Clarke, W.L., Cox, D.J., 1997. The emotional, social and behavioral implications of insulin-induced hypoglycaemia. *Seminars of Clinical Neuropsychiatry* 2, 57–65.
- Heine, R.J., 1993. Methods of investigation of insulin induced hypoglycaemia. In: Frier, B.F., Fisher, B.M. (Eds.), *Hypoglycaemia and Diabetes*. Edward Arnold, London, pp. 165–175.
- Hepburn, D.A., 1993. Symptoms of hypoglycaemia. In: Frier, B.M., Fisher, B.M. (Eds.), *Hypoglycaemia and Diabetes. Clinical and Physiological Aspects*. Edward Arnold, London, pp. 93–103.

- Hepburn, D.A., Deary, I.J., Frier, B.F., Patrick, A.W., Quinn, J.D., Fisher, B.M., 1991. Symptoms of acute hypoglycemia in humans with and without IDDM. *Diabetes Care* 14, 949–957.
- Hermanns, N., 1999. Laboratory and field studies. State of the art lecture on the 59th annual meeting of the American Diabetes Association. San Diego, CA.
- Jones, T., McCarthy, G., Tamborlane, W., Caprio, S., Allison, T., Kraemer, D., et al., 1990. Mild hypoglycaemia impairs brain stem and cortical evoked potentials in health subjects. *Diabetes* 39, 1550–1555.
- Kolb, B., Whishaw, I., 1996. *Fundamentals of Human Neuropsychology*. Freeman, New York.
- Kubiak, T., Hermanns, N., 2001. Assessment of hypoglycaemia awareness in type 1 diabetes mellitus. In: Fahrenberg, J., Myrtek, M. (Eds.), *Progress in Ambulatory Assessment*. Hogrefe & Huber, Seattle, pp. 525–534.
- Lane, R.D., Reiman, E.M., Bradley, M.M., Lang, P.J., Ahern, G.L., Davidson, R.J., 1997. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* 35, 1437–1444.
- Lang, P.J., 1994. The varieties of emotional experience: a meditation of James–Lange theory. *Psychological Review* 101, 211–221.
- Lang, P.J., Greenwald, M.K., Bradley, M.M., Hamm, O.A., 1993. Looking at pictures: affective, facial, visceral and behavioral reactions. *Psychophysiology* 30, 261–273.
- Lang, P., Bradley, M.M., Cuthbert, B.N., 1997. *International Affective Picture System (IAPS)*. Technical Manual and Affective Ratings. NIMH Center for the study of emotion and attention, Gainesville, FL.
- Lang, P.J., Bradley, M.M., Bruce, N.C., 1998. Emotion, motivation and anxiety: brain mechanisms and psychophysiology. *Biological Psychiatry* 44, 1248–1263.
- LeDoux, J., 1996. *The Emotional Brain*. Simon & Schuster, New York.
- LeDoux, J., 1998. *The emotional brain*. Simon & Schuster Inc, New York.
- Lincoln, T.A., Eaddy, J.A., 2001. *Beating the Blood Sugar Blues*. American Diabetes Association, Alexandria.
- Liu, Q.Z., et al., 1993. Glycated hemoglobin, plasma glucose and diabetic retinopathy: cross sectional and prospective analysis. *Diabetologia* 36, 428–432.
- Matthews, G.M., Jones, D.M., Chamberlain, A.G., 1990. Refining the measurement of mood: the UWIST mood adjective checklist. *British Journal of Psychology* 81, 17–42.
- McCall, A.L., 1992. The impact of diabetes on the CNS. *Diabetes* 14, 557–570.
- McCall, A.L., 1993. Effect of glucose deprivation on glucose metabolism in central nervous system. In: Frier, B., Fisher, B.M. (Eds.), *Hypoglycaemia and Diabetes*. Clinical and Physiological Aspects. Edward Arnold, London, pp. 56–71.
- McCrimmon, R.J., Deary, I.J., Frier, B.F., 1995. The effect of acute hypoglycaemia on mood anger and personal appraisal in non-diabetic humans. *Diabetic Medicine* 12 (Suppl. 2), S45.
- McCrimmon, R.J., Deary, I.J., Frier, B.M., 1999a. Appraisal of mood and personality during hypoglycaemia. *Physiology and Behavior* 67, 27–33.
- McCrimmon, R.J., Ewing, F.M.E., Frier, B.F., Deary, I.J., 1999b. Anger state during acute insulin-induced hypoglycaemia. *Physiology and Behavior* 67, 35–39.
- Mebris, M.A., Snoek, F.J., Kanc, K., Heine, R.J., 1996. Hypoglycaemia induces emotional disruption. *Patient Education and Counselling* 29, 117–122.
- Pinel, J.P.J., 1999. *Biopsychology*. Prentice Hall, New York.
- Pramming, S., Thorsteinsson, B., Stigsby, B., Binder, C., 1988. Glycaemic thresholds for changes in electroencephalograms during hypoglycaemia in patients with insulin-dependent diabetes. *British Medical Journal* 296, 665–667.
- Rabbitt, P.M.A., 1988. The faster the better? Some comments on the use of information processing rate as an index of change and individual differences in performance. In: Hindmarch, I., Aufemdrinke, B., Ott, H. (Eds.), *Psychopharmacology and Reaction*. Wiley, New York, pp. 79–95.
- Sanders, A.F., Wijnen, J.L.C., van Arkel, A.E., 1982. An additive factor analysis of the effect of sleep-loss on reaction process. *Acta Psychologica* 51, 41–59.
- Smith, D., Amiel, S.A., 2002. Hypoglycaemia unawareness and the brain. *Diabetologia* 45, 949–958.
- Talroth, G., Lindgren, M., Stenberg, G., Rosen, I., Agardh, C.D., 1990. Neurophysiological changes during insulin-induced hypoglycaemia and in the recovery period following glucose infusion in type 1 (insulin-dependent) diabetes mellitus and in normal man. *Diabetologia* 33, 319–323.

- Towler, D.A., Havlin, C.E., Craft, S., Cryer, P., 1993. Mechanisms of awareness of hypoglycaemia: perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 42, 1791–1798.
- Weinger, K., Jacobson, A.M., 1998. Cognitive impairment in patients with type 1 (insulin-dependent) diabetes mellitus. *CNS Drugs* 9, 233–252.
- Wickelgreen, W.B., 1977. Speed accuracy trade-off and information processing dynamics. *Acta Psychologica* 41, 67–85.
- Ziegler, D., Hübinger, A., Mühlen, H., Gries, F.A., 1992. Effects of previous control on the onset and magnitude of cognitive dysfunction during hypoglycaemia in type 1 (insulin-dependent) diabetic patients. *Diabetologia* 35, 828–834.
- Zimmermann, P., Fimm, B., 1992. Testbatterie zur Aufmerksamkeitsprüfung (TAP). Psytest, Würselen, Germany.