Original Article

Rise in Plasma Lactate Concentrations with Psychosocial Stress: A Possible Sign of Cerebral Energy Demand

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Key Words

Brain-pull • Cerebral lactate demand • Social stress

Abstract

Objective: It is known that exogenous lactate given as an i.v. energy infusion is able to counteract a neuroglycopenic state that developed during psychosocial stress. It is unknown, however, whether the brain under stressful conditions can induce a rise in plasma lactate to satisfy its increased needs during stress. Since lactate is i) an alternative cerebral energy substrate to glucose and ii) its plasmatic concentration is influenced by the sympathetic nervous system, the present study aimed at investigating whether plasma lactate concentrations increase with psychosocial stress in humans. **Methods:** 30 healthy young men participated in two sessions (stress induced by the Trier Social Stress Test and a non-stress control session). Blood samples were frequently taken to assess plasma lactate concentrations and stress hormone profiles. **Results:** Plasma lactate increased 47% during psychosocial stress (from 0.9 ± 0.05 to 1.4 ± 0.1 mmol/l; interaction time $\times$ stress intervention: $F = 19.7$, $p < 0.001$). This increase in lactate concentrations during stress was associated with an increase in epinephrine ($R^2 = 0.221$, $p = 0.02$) and ACTH concentrations ($R^2 = 0.460$, $p < 0.001$). **Conclusion:** Plasma lactate concentrations increase during acute psychosocial stress in humans. This finding suggests the existence of a demand mechanism that functions to allocate an additional source of energy from the body towards the brain, which we refer to as 'cerebral lactate demand'.

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Introduction

Stress and eating behavior are closely related [1]. We previously proposed a cerebral supply chain model to study the interactions between central and peripheral energy metabolism [2]. The supply chain of the brain – with the central nervous system as the final consumer – describes the energy fluxes from the remote environment to the near environment through the body and finally towards the brain. The brain appears to regulate overall energy homeostasis via ‘brain-pull mechanisms’, i.e. by initiating allocation of energy from the body towards the brain. We have recently shown that a competent brain-pull, i.e. the brain’s ability to properly demand energy from the body, functions to preserve brain mass when obese people diet [3]. By contrast, an incompetent brain-pull will lead to build-ups in the cerebral supply chain culminating in obesity and type 2 diabetes [2]. In compensation for an incompetent brain-pull, the brain can initiate ingestive behavior. Under these conditions, the brain is supplied by an increased push component from the blood, which may result in weight gain in the medium or long term.

The identification of specific brain-pull mechanisms is central for the ‘Selfish Brain’ theory dealing with the characteristic of the human brain to cover its own, comparably high energy requirements with the utmost of priorities when regulating energy fluxes in the organism [4, 5].

It was shown experimentally that during acute mild mental stress the energy supply of the human brain is increased by 12% [6]. Accordingly, cerebral energy needs were enhanced during acute psychosocial stress [7]. Such stress-related augmentations suggest the existence of an underlying cerebral demand mechanism. Evidence was provided for a mechanism by which the brain under stressful conditions actively demands for extra energy from the body via cerebral insulin suppression (CIS) [1, 7]. Cerebral activation of the sympathetic nervous system (SNS) [8, 9] and the hypothalamus-pituitary-adrenal (HPA) axis with cortisol release [10] suppresses insulin secretion from pancreatic beta cells. The insulin-dependent glucose uptake via glucose transporter GLUT4 into body periphery becomes limited. As a consequence, glucose is now available via insulin-independent GLUT1-transport across the blood-brain barrier [11, 12]. Thus, a competent brain-pull is exerted by limiting the glucose transport into body periphery via CIS, and by enhancing the glucose transport into the brain. In this way, CIS can be interpreted as a brain-pull mechanism that functions to allocate energy from the body towards the brain.

Previous studies suggest that a rise in plasma lactate concentrations may be regarded as another brain-pull mechanism. First, it is known that plasma lactate is increased by activation of the SNS [13–15]. Because of its large mass and metabolic capacity, the muscle tissue is the major producer of lactate [16]. Lactate arises in the muscle tissue from the glycolytic, anaerobic breakdown of glucose. The amount of lactate produced by other tissues such as red blood cells is small [17]. Second, plasma lactate is an alternative cerebral energy substrate to glucose [18–20]. There is growing evidence that lactate even acts as the preferred energy substrate for activated neurons [21]. Lactate i.v. leads to a 17% reduction of global brain glucose uptake in PET studies, indicating that lactate may traverse the blood-brain barrier and take over energy procurement of the brain that is usually covered by glucose [20]. Third, lactate given as an i.v. energy infusion during acute psychosocial stress is able to resolve post-stress neuroglycopenic symptoms [7]. Thus, exogenous lactate is able to compensate the cerebral energy depletion during stress.

A recent study in head-injured patients showed an increase in serum lactate as head injuries became more severe. Moreover, higher lactate levels were associated with better neurological function at hospital discharge [22]. The authors of that study concluded that the increase in serum lactate may be a mechanism by which brain function is preserved [22]. Is

plasma lactate also increased by psychosocial stress? One previous study showed that exam stress increased lactic acid concentrations [23]. It is unknown, however, whether a rise in plasma lactate by psychosocial stress is linked to the stress system and the cerebral need.

The objective of the present study was to examine the hypothesis that plasma lactate is increased by psychosocial stress as another brain-pull mechanism necessary to demand extra energy from the body during a mentally challenging situation. We further aimed at investigating whether peri-stress energy supplementation influences the increase in plasma lactate. Therefore, 30 healthy young men undergoing social stress were examined. Subjects were assigned to three different groups according to the energy provided during or after stress intervention (rich buffet, dextrose infusion and meager salad).

Participants and Methods

Study Population

30 healthy men aged 18.0 to 33.0 years (22.7 ± 0.6 years) with a BMI in the normal range (19.8 to 25.0 (22.7 ± 0.3) kg/m^2) were recruited by notice board postings. Participants met the following inclusion criteria: normal physical examination and routine laboratory tests, no physical or mental disease, no abuse of nicotine, alcohol or drugs, no nightshifts, no disturbed sleep or exceptional stress during the past 2 weeks as well as no blood donation during the past 4 weeks prior to the study. The study was approved by the local medical ethics committee of Lübeck University and was conducted in accordance with the Declaration of Helsinki. All subjects provided their fully informed and written consent before participation.

Study Protocol

Subjects were randomly assigned to three different interventional groups according to the energy provided during or after stress (high-energy groups: 'rich buffet + i.v. control (i.e. Ringer infusion)' and 'dextrose infusion + oral control (i.e. meager salad)' vs. low-energy group: 'meager salad + i.v. control'). Each subject participated in two sessions (stress intervention and non-stress control session) with an interval of 7–14 days between these two sessions. The experiments were performed in a single-blind fashion with the order of sessions balanced across subjects as in detail described elsewhere [7].

Experiments took place in a sound attenuated room with the subjects resting on a bed. One venous catheter was placed in each arm. With one cannula the infusion was applied; the other cannula was connected to a long thin tube that enabled blood sampling from an adjacent room without awareness of the subject. After taking a blood sample, the cannula was infused with a NaCl infusion.

After a fasting period of 2.5 h, participants arrived at the medical research unit at 12:30. Each subject received a 250 ml Ringer infusion (isomolar, consisting of NaCl, KCl, CaCl_2 and water) to adjust the fluid balance and to compensate for the following blood loss. A standardized meal was offered to the subjects (potatoes, mixed vegetables, butter, chicken breast, margarine, gravy, and tomatoes with yoghurt dressing). Between 15:00 and 16:00 blood samples were taken every 15 min. At 16:00, the experimental infusions started, lasting for 40 min. The Ringer infusion was applied with an infusion rate of 7.5 ml/h/kg body mass. Dextrose infusion (500 ml dextrose infusion, 0.25 mol/l) was applied with an infusion rate of 5.4 ml/h/kg body mass, which resulted in an efficient rise of glucose concentrations in both the stress session and the non-stress control session [7].

At 16:00, the Trier Social Stress Test (TSST) began as in detail described elsewhere [7]. Subjects were introduced to the task they would have to perform at 16:00 and then taken to another room where an audience already sat at a table and a microphone as well as video camera were installed. It was announced that a video analysis of the subject's performance would be performed. After a brief preparation period (3 min), the subjects were asked to stand at the microphone and to deliver a free speech as a job applicant who was invited for a personal interview with the company manager (5 min). If the subject finished in less than 5 min, the jury members told the subjects that he had still some time left. If the subject stopped a second time, the audience was quiet for some seconds and then started to ask prepared questions. Afterwards, subjects had to perform a mental arithmetic task consisting of serial subtractions (5 min). On a failure, subjects had to restart [24].

Directly after stress intervention (at 16:25 and 16:30), blood samples were taken and food was offered at 16:30. One group was offered a rich buffet, from which they could choose food for 1 h (for compo-

sition of rich buffet see [7]). Consumed food was analyzed for its amounts of energy and macronutrients by a dietician. As described previously, carbohydrate intake from a rich buffet increased from 149 ± 13 g in the non-stress control session to 183 ± 16 g in the stress session (main effect stress: $F = 6.4$; $p < 0.05$), whereas the intake of total energy ($1,569 \pm 155$ vs. $1,383 \pm 352$ kcal), protein (48 ± 6 vs. 48 ± 4 g) and fat (71 ± 10 vs. 66 ± 6 g) did not differ between stress and non-stress control session (all $p > 0.05$) [7]. The other two interventional groups (meager salad and dextrose infusion groups) received a meager salad only (mean amount of energy: 45.7 ± 4.4 kcal, carbohydrates: 11.1 ± 2.7 g, fat: 0.2 ± 0.0 g, and protein: 1.2 ± 0.1 g). During and after meal ingestion, six blood samples were taken for lactate analysis according to the following schedule: 16:40 and between 17:00 and 18:00 every 15 min.

The procedure in the non-stress control session was the same, except that the TSST was omitted.

Laboratory Methods

All blood samples were immediately centrifuged, and the supernatants were stored at -60°C until analysis. Plasma lactate concentrations were measured by an enzymatic method (Architect, Abbott, Wiesbaden, Germany, inter-assay CV 2%, intra-assay CV $<2\%$). Plasma ACTH and serum cortisol were determined by immunometric assay (ACTH: intra-assay CV 6.7–9.5%; inter-assay CV 6.1–10.0%; cortisol: intra-assay CV 5.2–7.4%, inter-assay CV 7.2–9.4%). Plasma epinephrine and norepinephrine were analyzed by HPLC (Chromsystems Diagnostics by HPLC, Munich, Germany; intra-assay CV 1.7–11.4%, inter-assay CV 3.7–12.7%).

Statistics

Data analysis was performed using SPSS statistical software (SPSS 12.0, Inc., Chicago, IL, USA). Descriptive statistics were given as mean $\pm$ SEM. ANOVA for repeated measures was used to test differences in the variation of time between stress intervention and non-stress control session. In this approach, time and stress intervention were entered as within-subject factors, interventional groups were entered as between-subject factors. Within-group differences were calculated by paired t-test. Percent increase from baseline in response to the TSST was calculated for plasma lactate and each of the stress hormones (epinephrine, norepinephrine, ACTH, and cortisol). The relationship between percent increase in lactate and percent increases in stress hormones during stress was assessed applying regression analyses. A p value (two-sided) of 0.05 was considered significant.

Results

When analyzing all interventional groups, plasma lactate concentrations increased by 47% during stress (fig. 1; interaction time (16:00 vs. 16:25) $\times$ stress intervention: $F = 19.7$, $p < 0.001$; main effect time: $F = 15.0$, $p < 0.01$, main effect stress: $F = 15.0$, $p < 0.01$). There was no difference in the increase in plasma lactate concentrations between the interventional groups (interaction time $\times$ stress intervention $\times$ group: $F = 0.2$, n.s.; main effect group: $F = 0.1$; n.s.; ANOVA for repeated measures). Thus, the stress-induced increase in plasma lactate concentrations was even independent of i.v. non-lactate energy supplementation during stress (i.e. dextrose infusion). Plasma lactate concentrations decreased within approximately 15 min after stress exposure in the high-energy groups (rich buffet and dextrose infusion; fig. 1). By contrast, in the low-energy group (only meager salad) lactate concentrations were still elevated 1 h after stress exposure.

Social stress markedly induced an immediate hormonal stress response (plasma concentrations of epinephrine, norepinephrine, ACTH, and cortisol) in all three interventional groups (fig. 2). Taken all three interventional groups together, social stress increased concentrations of epinephrine by 80% (time $\times$ stress intervention: $F = 12.3$, $p < 0.01$), norepinephrine by 122% (time $\times$ stress intervention: $F = 100.2$, $p < 0.001$), ACTH by 200% (time $\times$ stress intervention: $F = 46.2$, $p < 0.001$), and cortisol by 148% (time $\times$ stress intervention: $F = 160.6$, $p < 0.001$).

Percent increase in lactate concentrations during stress was significantly associated with percent increase in ACTH and epinephrine concentrations (table 1).

Fig. 1. Plasma lactate concentrations by time during stress intervention and non-stress control session in all three interventional groups. Values are means $\pm$ SEM; closed circles, stress intervention and open circles, non-stress control session; * $p < 0.05$, # $p < 0.01$, significantly different from non-stress control session by paired t-test.

Table 1. Relationship between percent increase in plasma lactate and percent increases in stress hormones during stress

	B	SE	R ²	P
Increase in plasma epinephrine, %	0.219	0.078	0.221	<0.01
Increase in plasma norepinephrine, %	0.170	0.115	0.072	n.s.
Increase in plasma ACTH, %	0.153	0.031	0.460	<0.001
Increase in plasma cortisol, %	0.066	0.071	0.030	n.s.

B = unstandardized coefficient; SE = standard error for B; n.s. = not significant.

^aRegression analyses for 30 men

Fig. 2. Hormonal response during stress intervention and non-stress control session for **a** cortisol, **b** ACTH, **c** epinephrine, and **d** norepinephrine concentrations. Values are means $\pm$ SEM; closed circles, stress intervention and open circles, non-stress control session.

Discussion

The present study shows that plasma lactate increases during acute psychosocial stress in humans. This increase in plasma lactate was linked with the hormonal stress response.

The exact origin and mechanism of lactate release cannot be identified by the present data. However, other studies suggest how psychosocial stress may have induced a rise in plasma lactate concentrations. The SNS is activated by psychosocial stress. It is known that upon activation of the SNS by the central nervous system, muscles increase their lactate production [13–15, 25]. Indeed, catecholamines increase muscle glycogenolysis and glycolysis. Such increased plasma lactate passes on to the plasma and erythrocytes [16]. Plasma lactate can be taken up by the brain via monocarboxylate transporter 1 at the blood-brain barrier and then by neurons via the monocarboxylate transporter 2 for oxidation [26].

Cerebral lactate levels cannot be determined by the present data. However, previous studies suggest that increased plasma lactate reaches the cerebral circulation at considerable concentrations: First, transport of lactate across the blood-brain barrier is accelerated in proportion to its plasma concentration [27]. Second, under conditions of cerebral energy deficiency, i.e. systemic hypoglycemia, the brain takes up considerable amounts of plasma lactate [28]. Third, exogenous lactate is able to compensate the cerebral energy depletion during stress [7].

An important question addressed by the present study is whether peri-stress energy supplementation influences the duration of the stress-induced lactate increase. Energy supplementation during stress by an i.v. dextrose infusion did not dampen plasma lactate increase. In the post-stress replenishment phase, however, the duration of the increase in plasma lactate concentrations was prolonged in subjects receiving low compared to high energy. Thus, high energy supplementation is able to compensate for the cerebral energy depletion, whereas in subjects receiving low energy the increase in plasma lactate is maintained.

Integrating these results into the 'Selfish Brain' theory, it seems as if the brain demands for extra energy in order to match the enormous cerebral need during stress. Thereby the brain activates the SNS to increase lactate production in muscles. In this way, our finding of increased plasma lactate concentrations during stress may provide evidence for another brain-pull mechanism, which we refer to as 'cerebral lactate demand'.

What would happen if cerebral lactate demand fails? In a recent population-based cohort study we could show that low fasting lactate concentrations were associated with long-term weight gain and increased postprandial hunger feelings in patients with type 2 diabetes mellitus [29]. These findings suggest that an inadequate cerebral lactate demand may contribute to weight gain. What is the hallmark of an incompetent brain-pull? While a high SNS activity, which mediates cerebral lactate demand, protects against weight gain, inadequate sympatho-adrenal system activity has been shown to result in obesity. In an 18-year follow-up study, a low epinephrine response to a mental challenge was a predictor for body mass gain in men [30]. Other experimental studies confirmed that obese subjects exhibit an inadequate sympatho-adrenal system response to different stimuli such as exercise [31], cold [32], and oral glucose load [33]. Similarly, obesity-prone rats are known to exhibit an inadequate sympatho-adrenal system response to hypoglycemia [34], over-feeding [35], and chronic stress [36]. Thus, a low SNS activity is indicative for an incompetent brain-pull and also predictive for obesity.

In conclusion, the present study shows that plasma lactate is increased by psychosocial stress in humans. When discussing the findings of our study, we strictly referred to the 'Selfish Brain' theory. We found that the lactate data set presented here enlarges the theory's scope of validity. On this background, our findings suggest the existence of another brain-pull mechanism during stress, which we refer to as 'cerebral lactate demand'. Cerebral lactate demand seems necessary to adequately supply the brain with an additional energy source. In this way, both brain-pull mechanisms – CIS [1] and cerebral lactate demand – allocate energy in a synergistic manner to the brain in order to re-establish brain energy homeostasis.

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Disclosure Statement

All authors declare that they have no conflicts of interest.

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