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Rise of ketone bodies with psychosocial stress in normal weight men

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KEYWORDS
Ketones;
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Summary
Background: Ketone bodies are known as alternative cerebral energy substrates to glucose. During psychosocial stress, the brain of a normal weight subject demands for extra glucose from the body to satisfy its increased needs. In contrast, the brain of an obese subject organizes its need, supply and demand in a low-reactive manner. The present study aimed at investigating (i) whether psychosocial stress increases ketone body concentrations and (ii) whether ketone reactivity to a psychosocial challenge differs between normal weight and obese people.
Methods: Ten normal weight and ten obese 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 serum β-hydroxybutyrate concentrations and stress hormone profiles.
Results: Our main finding was that social stress markedly increased concentrations of serum β-hydroxybutyrate by 454% in normal weight men. The increase in ketone bodies during stress in normal weight subjects was associated with an increase in ACTH, norepinephrine and epinephrine concentrations. Interestingly, we could not detect any increase in serum β-hydroxybutyrate concentrations during stress in obese men.
Conclusion: Normal weight men showed high ketone reactivity to a psychosocial challenge.

1. Introduction

It was shown experimentally that during acute mild mental stress, the energy supply of the human brain increases by 12% (Madsen et al., 1995). Furthermore, cerebral energy need has been found enhanced during acute psychosocial stress (Hitze et al., 2010).

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The existence of an active cerebral demand process is indispensable to explain such stress-related adjustments in brain energy metabolism. The force with which the brain actively demands energy from the body is referred to as "brain-pull" (Peters and Langemann, 2009). Recently, evidence was provided for two brain-pull mechanisms that may cover cerebral extra needs during stress (Hitze et al., 2010; Kubera et al., 2012a). One of these brain-pull mechanisms is referred to as 'cerebral insulin suppression' (CIS). Cerebral activation of the sympatho-nervous system (SNS) (Woods and Porte, 1974; Ahren, 2000) and the hypothalamus-pituitary-adrenal (HPA) axis (Billaudel and Sutter, 1982; Hitze et al., 2010) suppresses insulin secretion from pancreatic beta cells. As a consequence, the insulin-dependent glucose uptake via glucose transporter GLUT4 into body periphery becomes limited. At this point, glucose is available via insulin-independent GLUT1-transport across the blood–brain barrier (Hasselbalch et al., 1995; Seaquist et al., 2001). Thus, CIS allocates energy to the brain in order to safeguard brain energy homeostasis.

The other detected brain-pull mechanism is referred to as 'cerebral lactate demand' (Kubera et al., 2012a). Plasma lactate is regarded as an alternative cerebral energy substrate to glucose (Qu et al., 2000; Bouzier-Sore et al., 2003; Smith et al., 2003). Cerebral activation of the SNS has been shown to increase lactate production in muscles (James et al., 1999; Hamann et al., 2001; Meyer et al., 2005). Lactate IV leads to a 17% reduction of global brain glucose uptake in PET studies suggesting that lactate may traverse the blood–brain barrier and take over energy procurement of the brain, which is usually covered by glucose (Smith et al., 2003). Indeed, it has been shown recently that psychosocial stress induces a rise in plasma lactate concentrations, suggesting that lactate is used to satisfy increased cerebral needs during stress (Kubera et al., 2012a).

Ketone bodies are also known to function as alternative cerebral energy substrates to glucose. Only in special situations, such as hyponutrition, the organism produces significant amounts of alternative ketones (Mansell and Macdonald, 1989) that can traverse the blood–brain barrier and assume a role in supplying energy to the brain. In 1967, Owen and coworkers showed that ketone bodies replace glucose as the brain's primary fuel during starvation (Owen et al., 1967). Previous studies suggest that ketone bodies may also increase with activation of the SNS. Infusion of norepinephrine (Kurpad et al., 1994), epinephrine (Marker et al., 1998) and glucocorticoids (Schade et al., 1980) have been shown to increase ketone bodies. Moreover, cerebral challenges or diseases such as hypoglycemia (Davis and Tate, 2001) or aneurismal subarachnoid hemorrhage (Tamaki et al., 2008) have been demonstrated to induce a rise in ketone bodies. We therefore hypothesize that ketone body concentrations also increase during psychosocial stress.

There is evidence supporting the notion that the brain of normal weight subjects demands for extra energy from the body during stress by using CIS, and that CIS is not operative in obesity (Kubera et al., 2012b). As early as 1987, Bray and coworkers showed that rats resistant to dietary obesity display increased transport of 3-hydroxybutyrate across the blood–brain barrier compared to obesity prone rats after eating a high-fat diet (Bray et al., 1987). If ketones do rise in stressed normal weight subjects, do they also rise in stressed obese subjects? To test these hypotheses, we challenged ten normal weight and ten obese men with the Trier social stress test (TSST).

2. Methods

2.1. Study population

Ten normal weight men (BMI 20–25 kg/m^2) and ten obese men (BMI $> 30\ kg/m^2$) of Caucasian descent were recruited by notice board postings as in detail described elsewhere (Kubera et al., 2012b). 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 two weeks and no blood donation during the past four weeks prior to the study.

The study was approved by the local medical ethics committee of Lübeck University. All subjects provided their fully informed and written consent before participation.

2.2. Study protocol

Each subject participated in two sessions (stress intervention and non-stress control session) with an interval of seven to fourteen days between these two sessions as in detail described elsewhere (Kubera et al., 2012b). The order of sessions (stress intervention and non-stress control session) was balanced across subjects, i.e. half of the subjects started with stress intervention and vice versa.

After a fasting period of 2½ hours, participants arrived at the medical research unit at 1230 h. A medical exploration was conducted, consisting of a physical examination concerning physical well-being, circular flow and reflexes as well as a routine blood sample (e.g. electrolytes, blood lipids, liver enzymes, blood cells). Afterwards, a standardized meal was offered to the subjects (potatoes, mixed vegetables, butter, chicken breast, margarine, gravy and tomatoes with yoghurt dressing). 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 (see below); the other cannula was connected to a long thin tube that enabled blood sampling from an adjacent room without awareness of the subject. At 1500 h, each subject received a 250 ml Ringer-infusion (isomolar, consisting of sodium chloride, potassium chloride, calcium chloride and water) to adjust the fluid balance and to compensate for the following blood loss. Between 1500 and 1600 h blood samples were taken every 15 min for stress hormone analyses. Baseline blood samples for serum β-hydroxybutyrate concentrations were taken at 1500 h. At 1600 h, a Ringer-infusion was applied with an infusion rate of 7.5 ml/h/kg body mass for 40 min.

At 1600 h, the Trier Social Stress Test (TSST) began as in detail described elsewhere (Kubera et al., 2012b). Subjects were introduced to the task they would have to perform at 1600 h and then taken to another room, where an audience already sat at a table, and a microphone as well as a 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