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Intranasal insulin attenuates the hypothalamic—pituitary—adrenal axis response to psychosocial stress

Andreas Bohringer*, Lars Schwabe, Steffen Richter, Hartmut Schachinger

Department of Clinical Physiology, University of Trier, Johanniterufer 15, 54290 Trier, Germany

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Summary Previous studies have shown that intranasally administered insulin exerts an inhibitory influence on the basal hypothalamic—pituitary—adrenal (HPA) axis activity. To date, however, it remains unclear as to whether intranasal insulin does furthermore affect HPA axis responsiveness in situations of stress. Here, we tested whether intranasally administered insulin attenuates the HPA axis response to psychosocial stress.

Fifty minutes before being exposed to the Trier Social Stress Test (TSST), 26 healthy young male participants received a single intranasal dose of human insulin (40 I.U.) or placebo in a placebo controlled, double-blind between-subject design. Plasma cortisol, saliva cortisol, heart rate, and blood pressure were measured at resting baseline and in response to the TSST.

Plasma cortisol ($P < .001$) and saliva cortisol ($P < .001$) increased in response to stress, as did heart rate ($P < .001$) and blood pressure ($P < .001$). Intranasal insulin did not influence plasma or saliva cortisol, heart rate, blood pressure, blood glucose, and plasma insulin levels at baseline. However, intranasal insulin diminished the saliva cortisol (two-way ANOVA; treatment by time interaction: $P = .05$) and plasma cortisol (two-way ANOVA; treatment by time interaction: $P = .05$) response to the TSST without affecting heart rate, and blood pressure stress reactivity.

Our data show that a single intranasal insulin administration effectively lowers stress-induced HPA axis responsiveness. Intranasal insulin may offer a therapeutic potential to prevent hyperactivity of the HPA system.

1. Introduction

Activation of the hypothalamic—pituitary—adrenal (HPA) axis is crucial for successful regulation of energy homeostasis during situations of stress (Sapolsky et al., 2000). However, hyperactivity of the HPA system is associated with several wide spread diseases like depression, arterial hypertension,

* Corresponding author. Tel.: +49 651 201 3697; fax: +49 651 201 3737.
E-mail address: boeh1303@uni-trier.de (A. Bohringer).

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visceral obesity, and the metabolic syndrome (Chrousos, 2000; Bjorntorp, 2001; Parker et al., 2003; Wirtz et al., 2006), where it contributes to the manifestation of these pathological states. To date our knowledge about the inhibitory control over the HPA axis activity is sparse and identification of factors that inhibit HPA axis activity may help to develop new therapeutic approaches against diseases characterized by HPA axis hyperactivity.

The pancreatic peptide hormone insulin plays a significant role in HPA axis regulation (Fruehwald-Schultes et al., 1999, 2001; Chan et al., 2005). Circulating insulin reaches the central nervous system (CNS) via a saturable active transport mechanism across the blood–brain barrier and binds to brain specific insulin receptors that are found with high density in hypothalamic nuclei and limbic structures (Unger et al., 1991; Plum et al., 2005). These brain structures are known to be involved in the regulation of HPA axis activity (Herman et al., 2005) and animal data indicate that insulin effects on the HPA axis are indeed mediated by actions on central nervous sites (Davis et al., 1995). In humans, intranasal insulin administration is an easy applicable tool for analyzing central nervous insulin effects (Fehm et al., 2000; Hallschmid et al., 2004). Intranasally administered insulin reaches the cerebro spinal fluid (CSF) without being absorbed into the blood stream (Born et al., 2002). Thus, this application method allows investigating central nervous insulin effects without confounding influences of peripheral insulin actions that are seen with systemic insulin infusions. Recently, it was shown that long-term treatment (8 weeks) with intranasally administered insulin reduces the morning HPA axis activity in lean (Benedict et al., 2004) and obese (Hallschmid et al., 2008) individuals and could thus offer a therapeutic way to treat hyperactivity of the HPA axis. Nevertheless, it remains unclear as to whether intranasally administered insulin may affect the HPA axis response to mental stress. This, however, would be of particular interest since human research revealed that HPA axis activation is closely linked to psychosocial challenge (Dickerson and Kemeny, 2004; Schwabe et al., 2008).

The present study examined the role of intranasally administered insulin on the HPA axis response to psychosocial stress. The Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) was used as a psychosocially relevant stressor. This procedure is very effective in activating the HPA axis and has a straight forward relation to every day stress experiences (Dickerson and Kemeny, 2004). Changes in total plasma cortisol, saliva cortisol, heart rate, and blood pressure were measured as indices of HPA axis and cardiovascular responses to the stress challenge, respectively. Based on previous reports about inhibitory influences of intranasal insulin administration on the basal HPA axis activity (Benedict et al., 2004; Hallschmid et al., 2008) we hypothesized that intranasal insulin administration before TSST onset would attenuate the cortisol secretion in response to the stress challenge, as compared to placebo administration.

2. Subjects and methods

2.1. Participants

Twenty-six young, healthy male university students between 20 and 31 years of age participated in this study. Exclusion criteria were as follows: any acute or chronic disease, smoking of cigarettes, familiarity with the TSST, a presence or history of mental illness, use of systemic medication, current participation in another clinical study, fasting glucose above 5.5 mmol/l, body mass index (BMI) below 18 or above 25, the presence of a depressive disorder screened with the German version of the Patient Health Questionnaire (PHQ-D, Loewe et al., 2002). Participants were required to fast for 6 h before arrival in our laboratory. All participants gave voluntary written informed consent and were compensated for their participation. The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethical Committee of the State's Medical Association (Landesärztekammer Rheinland-Pfalz).

One participant of the insulin-group was excluded from further analyses because he showed baseline cortisol values that were two standard deviations above the average baseline cortisol values. Furthermore, one participant of the placebo-group was excluded because he did not meet exclusion criteria as turned out during the experiment.

2.2. Procedure

All participants arrived between 1330 h and 1530 h in our laboratory and were screened for exclusion criteria by the responsible physician. Participants were then randomly assigned to the insulin-group (n = 12) or the placebo-group (n = 12). Afterwards, a catheter (Vasofix, B.Braun, Melsungen, Germany) was inserted in an antecubital vein 105 min before start of the Trier Social Stress Test (TSST) to allow blood sampling at several time points across the experiment. Electrocardiogram (ECG) electrodes were attached according to a standard lead II configuration. The ECG was used for automated detection of heart rate. Fifty-five minutes before the stress challenge the first blood and the first saliva sample were obtained. Directly thereafter (50 min before TSST onset), either 0.4 ml (containing 40 I.U.) insulin (Actrapid® 100, Novo Nordisk) or a corresponding volume of placebo (dilution buffer without insulin; kindly provided by Dr. Manfred Hallschmid, University of Lübeck, Germany) were administered intranasally to the participants. The timing of intranasal insulin administration and the amount of 40 I.U. applied were chosen according to foregoing studies investigating acute effects of intranasal insulin on endocrine and cognitive parameters (Born et al., 2002; Hallschmid et al., 2008). Next, all participants drank 0.3 l of water in order to standardize the intake of liquid. Ten minutes prior to the TSST heart rate monitoring was started. In order to avoid influences of orthostatic reactions on heart rate changes during the TSST all participants were asked to change to a standing position before. Three minutes prior to the TSST the second blood-sample and the second saliva sample were collected and blood pressure was measured. The TSST was started for all participants between 1600 h and 1800 h. Immediately after its termination the third blood and saliva samples were obtained and blood pressure was measured again. Furthermore, participants evaluated on two 10-point rating-scales how stressful and insecure they felt during the TSST. Additional blood and saliva samples were collected 10, 20, 30, 45, 60, and 90 min after termination of the stress