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Lactate overrides central nervous but not β-cell glucose sensing in humans

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Abstract

Lactate has been shown to serve as an alternative energy substrate in the central nervous system and to interact with hypothalamic glucose sensors. On the background of marked similarities between central nervous and β-cell glucose sensing, we examined whether lactate also interacts with pancreatic glucose-sensing mechanisms in vivo. The effects of intravenously infused lactate vs placebo (saline) on central nervous and pancreatic glucose sensing were assessed during euglycemic and hypoglycemic clamp experiments in 10 healthy men. The release of neuroendocrine counterregulatory hormones during hypoglycemia was considered to reflect central nervous glucose sensing, whereas endogenous insulin secretion as assessed by serum C-peptide levels served as an indicator of pancreatic β-cell glucose sensing. Lactate infusion blunted the counterregulatory hormonal responses to hypoglycemia, in particular, the release of epinephrine ($P = .007$) and growth hormone ($P = .004$), so that higher glucose infusion rates ($P = .012$) were required to maintain the target blood glucose levels. In contrast, the decrease in C-peptide concentrations during the hypoglycemic clamp remained completely unaffected by lactate ($P = .60$). During euglycemic clamp conditions, lactate infusion did not affect the concentrations of C-peptide and of counterregulatory hormones, with the exception of norepinephrine levels that were lower during lactate than saline infusion ($P = .049$) independently of the glycemic condition. Data indicate that glucose sensing of β-cells is specific to glucose, whereas glucose sensing at the central nervous level can be overridden by lactate, reflecting the brain's ability to rely on lactate as an alternative major energy source.
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1. Introduction

Glucose is the most important energy source in the central nervous system [1]. Besides glucose sensors localized at insulin-secreting β-cells of the pancreas, glucose sensors within the central nervous system are essentially involved in maintaining the organism's energy homeostasis by regulating neuroendocrine function and food intake [2]. In addition to glucose, lactate serves as an alternative energy substrate to neurons [3] and has been shown to interact with central nervous glucose sensing [2]. During hypoglycemia, lactate infusion attenuates neuroendocrine counterregulatory and neurocognitive responses in humans [4-7]. Comparable results were obtained in rats after intraventricular lactate infusion [8]. Under euglycemic conditions, intraventricular lactate administration markedly decreases blood glucose levels by reducing hepatic glucose output and increasing peripheral glucose disposal, thereby mimicking the effects of intraventricular glucose infusion [9]. The underlying signaling pathway to the periphery is not known, but mediation via neuroendocrine and autonomic mechanisms appears likely.

It is also not known whether an elevation of circulating lactate levels under euglycemic conditions affects the secretion of glucose-regulating hormones and, in particular, of counterregulatory, insulin-antagonistic hormones. In one study [10], glucagon levels during euglycemic lactate administration did not differ significantly from those during placebo infusion (46.6 ± 2.2 vs 60.4 ± 4.7 pg/mL); but the lack of statistical significance appeared to be

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partly due to the small size of the subject sample (n = 6). During hyperinsulinemic-euglycemic clamp experiments, lactate infusion distinctly increased the rate of glucose infusion required for maintaining euglycemia [11]. This finding suggests that lactate enhances insulin sensitivity, probably as a result of down-regulated neuroendocrine counterregulatory hormone secretion that was not assessed in that study.

Similar to β-cell glucose sensing, central nervous glucose sensing essentially relies on adenosine triphosphate (ATP)–sensitive potassium channels (K_{ATP}) [12,13] that close in response to adequate glucose levels [14]. In glucose-sensing neurons as well as in β-cells, glucose is metabolized to pyruvate, which, after conversion to acetyl–coenzyme A, is transferred into the tricarbon acid cycle to produce ATP [15]. Glucose and lactate sensing share a common pyruvate-dependent pathway in that lactate is converted to pyruvate by lactate dehydrogenase. Accordingly, lactate mimics the effects of glucose in hypothalamic glucose-responsive neurons as indicated by in vitro recording of neuronal firing rates [16,17]. However, whether lactate can similarly override β-cell glucose sensing has not been systematically investigated in humans. In the present experiments, we scrutinized the effect of lactate infusion on β-cell glucose sensing as indicated by responses in circulating C-peptide concentrations under euglycemic and hypoglycemic conditions. We also examined whether central nervous glucose sensing as reflected by neuroendocrine counterregulatory hormone secretion (epinephrine, norepinephrine, growth hormone, cortisol, and glucagon) responds to lactate infusion under euglycemic conditions.

2. Methods

2.1. Subjects

Ten healthy young men aged 20 to 40 years (mean ± SEM, 24.6 ± 0.7 years) with a mean body mass index between 20.0 and 26.2 kg/m^2 (23.3 ± 0.6 kg/m^2) were examined. Exclusion criteria were chronic or acute illness, current medication of any kind, smoking, alcohol or drug abuse, marked overweight or obesity (body mass index >27 kg/m^2), and diabetes in first-degree relatives. The study protocol was approved by the ethics committee at the University of Luebeck, and all participants gave written informed consent.

2.2. Study design

Participants were tested on 4 different conditions spaced at least 1 week apart and performed in balanced order. Each condition comprised a 30-minute baseline period followed by a 30-minute period of intravenous lactate or placebo (saline 0.9%) infusion and a subsequent 75-minute hypoglycemic or euglycemic clamp while the infusion of lactate/placebo was continued. Conditions were as follows: (*a*) placebo infusion/euglycemic clamp, (*b*) lactate infusion/euglycemic clamp, (*c*) placebo infusion/hypoglycemic clamp, and (*d*) lactate infusion/hypoglycemic clamp. Experiments were performed in a double-blind fashion with respect to the infusion condition (lactate/placebo). In addition, participants were blinded with regard to the glycemic condition.

2.3. Lactate/placebo infusion and clamp procedure

After an overnight fast of 10 hours, subjects arrived at the research unit at 7:30 AM. They had to abstain from eating until the end of experimental sessions. During the sessions, subjects were sitting on a bed with the trunk in an almost upright position (~60°) and their legs stretched out. A cannula was inserted into a vein on the back of the hand that was placed in a heated box (50°C-55°C) to obtain arterialized venous blood. A second cannula was inserted into an antecubital vein of the contralateral arm. Both cannulae were connected to long thin tubes that enabled blood sampling and adjustment of the glucose infusion rate from an adjacent room without awareness of the subject. After a 30-minute baseline period starting at 8:00 AM (t = −60 minutes), the infusion of lactate or placebo was started (at −30 minutes). Lactate was infused at a rate of 50 μmol/min per kilogram of body weight (BW) for the first 20 minutes. Thereafter, the infusion was continued at a rate of 30 μmol/min per kilogram of BW until the end of the session, that is, for another 85 minutes. In the placebo conditions, an equivalent volume of 0.9% saline solution was infused.

At 9:00 AM, that is, 30 minutes after the onset of lactate infusion, glucose clamps started (t = 0 minute) with administration of a bolus of 0.01 IU per kilogram of BW human insulin (Insuman Rapid; Aventis, Strasbourg, France) over 2 minutes. Thereafter, insulin was infused at a constant rate of 1.5 mIU per kilogram of BW per minute until the end of the clamp. A 20% glucose solution was simultaneously infused at a variable rate to control blood glucose levels. Arterialized blood was drawn at 5-minute intervals to measure blood glucose concentrations (HemoCue B-Glucose-Analyzer, Ängelholm, Sweden). In the euglycemic conditions, blood glucose levels were kept at approximately 5.0 mmol/L, whereas in the hypoglycemic conditions, blood glucose levels were allowed to drop to a nadir of 2.8 mmol/L during the first 25 minutes and were kept on this level for the next 50 minutes. Thereafter, insulin infusion was stopped; and blood glucose levels were normalized within 10 minutes by increasing the glucose infusion rate.

Blood samples for the determination of C-peptide and counterregulatory hormones (growth hormone, cortisol, glucagon) in plasma and serum, respectively, were drawn during baseline (−60 minutes), 20 minutes after starting the lactate infusion (−10 minutes), and then every 15 minutes until the end of the clamp period (+75 minutes). For determination of catecholamines, blood was sampled at t = −60, −10, +45, +60, and +75. Blood was centrifuged immediately, and plasma and serum were frozen at −80°C until assay.

2.4. Assays

Plasma lactate was measured by AEROSET Analyzer (Abbott Laboratories, Abbott Park, IL) with intra- and interassay coefficients of variation (CVs) less than 1.1% and less than 0.9%, respectively. Serum C-peptide, cortisol, growth hormone (all Immulite; DPC, Los Angeles, CA), and glucagon (Adaltis, Montreal, Quebec, Canada) concentrations were measured by commercial enzyme-linked immunoassays with the following intraassay and interassay CVs: C-peptide, less than 7.6% and less than 10.5%; cortisol, less than 5.8% and less than 6.3%; growth hormone, less than 5.8% and less than 5.5%; and glucagon, less than 8.0% and less than 8.2%. Plasma epinephrine and norepinephrine were measured by standard high-performance liquid chromatography with electrochemical detection (Chromosystems, Munich, Germany). Intraassay and interassay CVs were less than 2.9% and less than 4.2% for epinephrine and less than 2.6% and less than 3.9% for norepinephrine.

2.5. Statistical analysis

Values are expressed as mean ± SEM. Analysis was based on analyses of variance (ANOVAs) for repeated measures, including the factors "hypo" (euglycemia vs hypoglycemia) and "lactate" (infusion of lactate vs placebo) and the factor "time" (for repeated measurements during the session). Where appropriate, the 2 euglycemic and 2 hypoglycemic clamp conditions were compared separately, thus omitting the respective ANOVA factor hypo. For pairwise comparisons between conditions at single time points, paired Student t tests were used. A P value less than 0.05 was considered significant. All calculations were done with SPSS 12.0 for Windows (SPSS, Chicago, IL).

3. Results

3.1. Blood glucose, lactate, glucose infusion rates, and C-peptide

Blood glucose levels were well comparable between the 2 euglycemic and hypoglycemic conditions (Fig. 1A). Lactate infusion induced plasma lactate levels of approximately 3.6 mmol/L that were distinctly higher than those in the 2 placebo conditions (Fig. 1B). There was no difference in glucose infusion rates required to maintain blood glucose levels at the target levels between the 2 euglycemic conditions (total amount of infused glucose, 57 ± 8 vs 53 ± 5 g; $P = .72$; Fig. 1C). In contrast, during hypoglycemia, the glucose infusion rate was significantly higher in the lactate than in the placebo condition (total amount of infused glucose, 27 ± 3 vs 23 ± 2 g; $P = .012$).

Serum C-peptide levels did not significantly differ among the 4 conditions during baseline ($P = .19$, Fig. 1D). During the hypoglycemic clamps, C-peptide levels markedly decreased, whereas they remained essentially unchanged during the euglycemic clamps ($P = .014$ for hypo × time interaction).

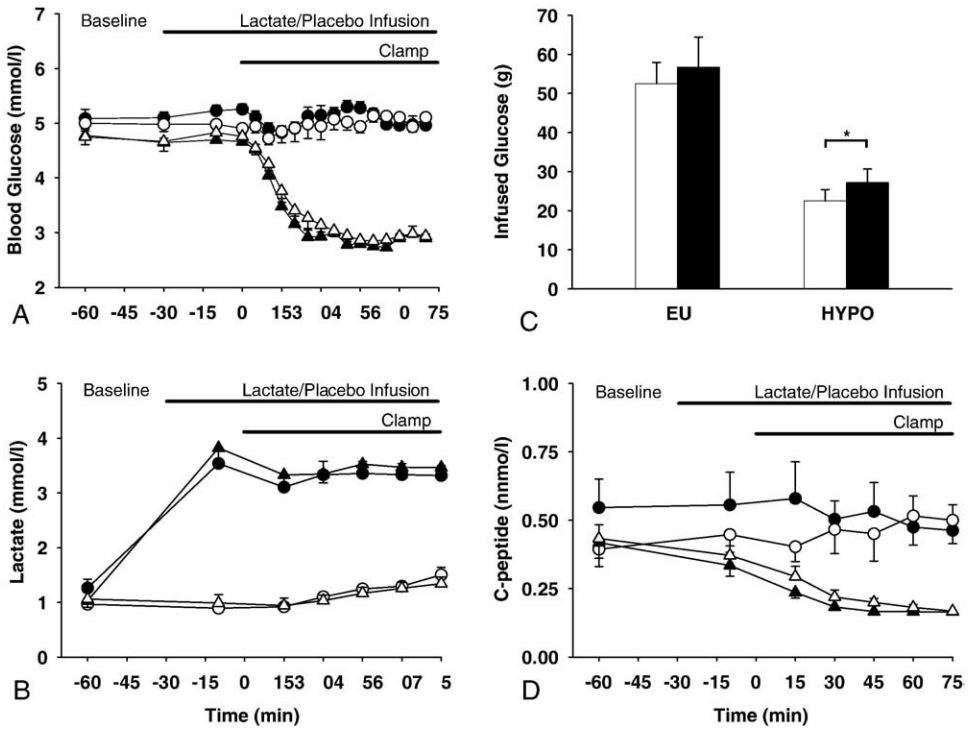

Fig. 1. Mean (±SEM) concentrations of (A) blood glucose, (B) plasma lactate, and (D) C-peptide, and amount of infused glucose (C) during baseline, lactate/placebo infusion, and hyperinsulinemic hypoglycemic and euglycemic clamps in 10 healthy men. White symbols/bars indicate placebo; and black symbols/bars indicate lactate infusion, with circles depicting euglycemic and triangles depicting hypoglycemic conditions. *$P < .05$.

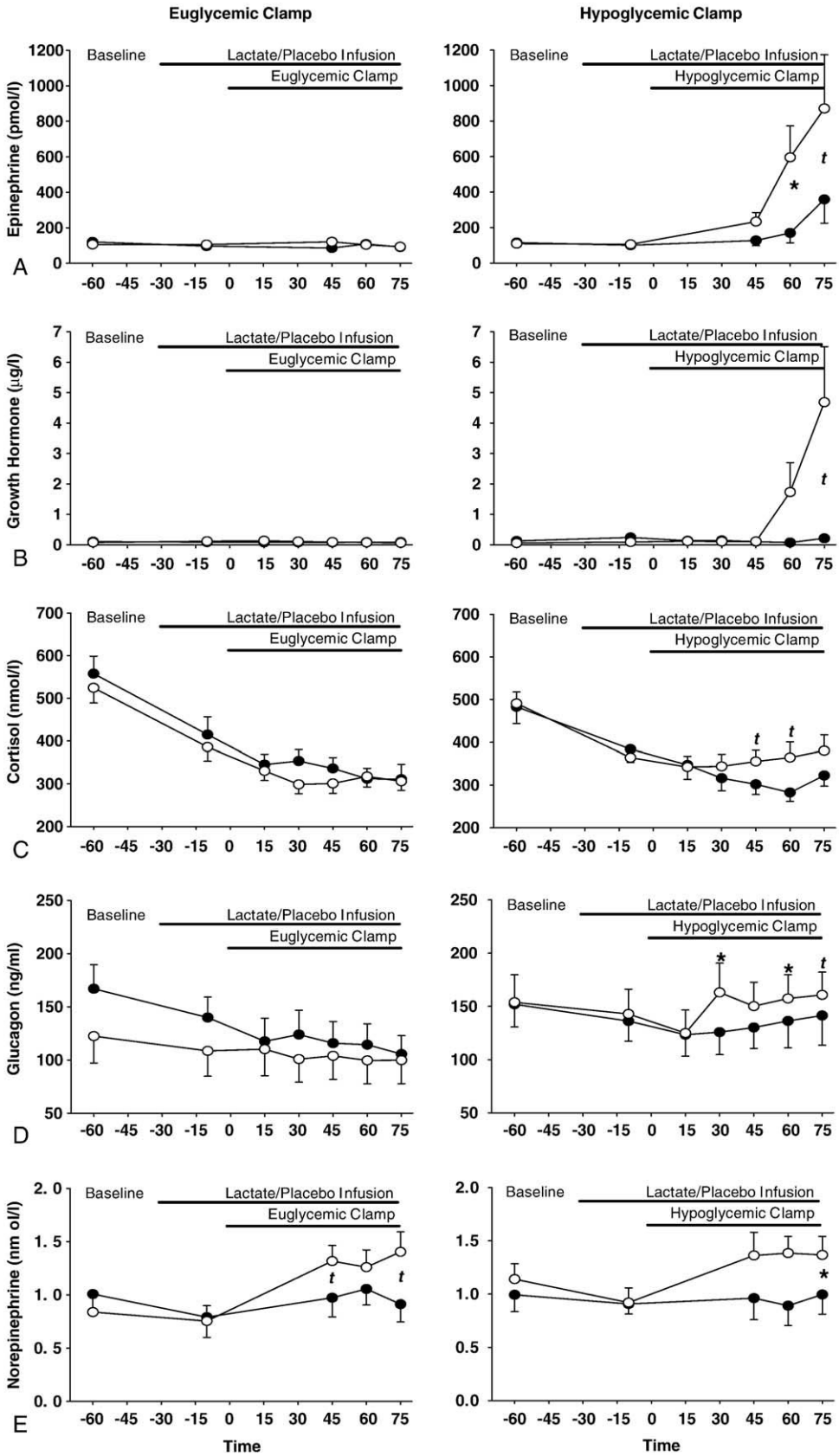

Fig. 2. Mean (±SEM) concentrations of (A) epinephrine, (B) growth hormone, (C) cortisol, (D) glucagon, and (E) norepinephrine during the euglycemic (left) and hypoglycemic (right) clamp experiments with concomitant lactate/placebo infusion in 10 healthy men. White symbols indicate placebo, and black symbols indicate lactate infusion. $^{t}P < .10$, $^{*}P < .05$.

Overall, lactate infusion did not influence the course of C-peptide levels during the clamps ($P = .17$ for the hypo × time × lactate interaction). Separate analyses of the euglycemic and hypoglycemic clamps confirmed that lactate infusion affected β-cell C-peptide secretion neither under euglycemic nor under hypoglycemic conditions ($P = .28$ and $P = .60$, respectively, for time × lactate).

3.2. Counterregulatory hormones

There were no baseline differences between conditions in any of the counterregulatory hormones ($P > .20$ for all comparisons). As expected, hypoglycemia distinctly increased plasma epinephrine levels ($P < .001$ for the hypo × time interaction); but this increase was markedly reduced by lactate infusion ($P = .007$ for the hypo × time × lactate interaction, Fig 2A). Separate analyses of the euglycemic and hypoglycemic clamps indicated that lactate infusion significantly attenuated the rise in epinephrine during hypoglycemia ($P = .004$ for time × lactate interaction), whereas it had no influence on epinephrine levels in the euglycemic condition ($P = .31$ for time × lactate, Fig. 2A).

Growth hormone levels showed a similar pattern because counterregulatory secretion in response to hypoglycemia was distinctly reduced by lactate infusion ($P = .004$ for hypo × time × lactate, Fig. 2B). Again, separate analyses of the euglycemic and hypoglycemic clamps indicated that lactate infusion significantly blunted the rise during hypoglycemia ($P = .004$ for time × lactate), whereas it did not influence growth hormone levels in the euglycemic condition ($P = .14$ for time × lactate, Fig. 2B).

The pattern of circulating cortisol (Fig. 2C) and glucagon (Fig. 2D) concentrations was comparable with that of epinephrine and growth hormone, although statistical analyses revealed less clear-cut results. After a marked circadian decrease in all conditions, serum cortisol levels increased in response to hypoglycemia ($P = .041$ for hypo × time, Fig. 2C). Overall, ANOVA indicated a significant suppressing influence of lactate infusion on cortisol levels ($P = .041$ for time × lactate) independently of the glycemic condition ($P = .633$ for hypo × time × lactate). However, separate analyses of the euglycemic and hypoglycemic clamps did not confirm significance for the time × lactate interactions ($P = .29$ and $P = .18$, respectively). Probably because of great variability, statistical analyses of glucagon levels shortly failed to reveal a significant effect of hypoglycemia ($P = .08$ for hypo × time, Fig. 2D); and there was also no significant effect of lactate infusion ($P > .36$ for lactate main effect, time × lactate, and hypo × time × lactate interaction terms).

Interestingly, plasma norepinephrine levels showed a pattern distinctly different from the other counterregulatory hormones (Fig. 2E). Norepinephrine levels increased over time ($P < .002$ for time); and this increase was reduced by lactate infusion ($P = .10$ for time × lactate), but did not appear to be substantially influenced by the glycemic condition ($P = .30$ for hypo × time). In separate analyses of the euglycemic and hypoglycemic clamps, the lactate-induced decrease in norepinephrine levels approached significance in the euglycemic condition ($P = .09$ for time × lactate) and achieved significance in the hypoglycemic condition ($P = .021$ for lactate main effect, Fig. 2E). Focusing on the 3 norepinephrine values assessed during the clamp, ANOVA confirmed a significant reduction in norepinephrine levels after lactate infusion across both conditions ($P = .049$ for lactate main effect) that did not depend on the glycemic condition ($P = .39$ for hypo × lactate interaction).

4. Discussion

Lactate infusion attenuates the neuroendocrine counterregulatory response to hypoglycemia, with a particular impact on epinephrine and growth hormone secretion. In addition, during concomitant lactate infusion, a higher glucose infusion rate is required to maintain glucose levels at the hypoglycemic target level that further indicates an overall reduced counterregulatory activity due to lactate administration. In accordance with previous findings [6, 7], these results suggest that lactate interacts with central nervous glucose sensing that mediates counterregulatory hormone release. In contrast, lactate infusion does not alter C-peptide levels under euglycemic as well as under hypoglycemic conditions, suggesting that lactate has no impact on β-cell glucose sensing. Thus, our findings indicate that lactate overrides central nervous but not pancreatic β-cell glucose sensing.

Although the suppression of neuroendocrine counterregulatory hormone release by lactate infusion most likely results from lactate acting on central nervous glucose sensors, it cannot be excluded that peripheral glucose sensors, for example, in the carotic bulbs [18] or portal vein [19], contribute to this effect. In rats, elevating portal vein concentrations of lactate attenuates the sympathoadrenal response to hypoglycemia [20]. However, because the activation of neuroendocrine counterregulatory systems relies on hypothalamic mechanisms [21,22], lactate most probably exerts its suppressing effect on hypoglycemia counterregulation at the central nervous level [8].

In contrast to this central nervous effect of lactate, administration of the substance did not alter pancreatic insulin secretion as assessed by C-peptide levels under euglycemic as well as hypoglycemic conditions. With respect to euglycemia, this finding is in line with previous data showing that lactate does not stimulate insulin secretion in isolated human pancreatic islets [23]. In vivo studies in humans [10,11] also failed to reveal any stimulatory effect of lactate on insulin secretion, which may be due to the low expression of plasma membrane monocarboxylate transporters [24,25] and intracellular lactate dehydrogenase [25,26] in pancreatic β-cells [27]. Surprisingly, however, lactate infusion also did not attenuate the hypoglycemia-induced decrease of C-peptide levels that reflects the concomitant

suppression of endogenous insulin secretion. Previous studies have shown that the acute onset of even mild hypoglycemia around 3.6 mmol/L completely blocks endogenous insulin secretion as indicated by C-peptide levels less than 0.03 nmol/L [28]. In contrast, C-peptide levels remain distinctly higher (~0.40 nmol/L) when a comparable hypoglycemia slowly develops during prolonged fasting [29]. This contrast indicates that the suppression of β-cell insulin release is an immediate response that strongly depends on the temporal dynamics of emerging hypoglycemia. We have previously hypothesized that a decrease in blood glucose concentrations is signaled to the β-cell via neuronal and hormonal inputs from the brain [29]. The present results, however, do not support the assumption of a tight link between central nervous and β-cell glucose sensing but favor the idea of a β-cell response to hypoglycemia that is not exclusively dependent on central nervous glucose sensing [21]. Thus, β-cells per se might be sensitive to the temporal dynamics of decreasing blood glucose levels, adjusting endogenous insulin secretion to conditions such as acute hypoglycemia and prolonged fasting. Alternatively, a putative central nervous influence on β-cell insulin secretion during hypoglycemia could be driven by glucose-sensing neurons that respond differentially to lactate than to glucose [30].

Lactate infusion blunted the increase in plasma norepinephrine levels that was observed in both the euglycemic and hypoglycemic placebo conditions. Although the lack of a non–insulin infusion control condition in our study does not allow to pinpoint the exact mechanisms behind this increase in norepinephrine levels in the 2 placebo conditions, it might be assumed that it was a consequence of the well-documented stimulatory influence of insulin on the sympathetic nervous system [31]. It has previously been shown that lactate infusion increases glucose infusion rates required to maintain normal glucose levels during a hyperinsulinemic-euglycemic clamp, indicating that lactate infusion increases insulin sensitivity [11]. An attenuating influence of lactate on sympathetic nervous system activity as suggested here by the reduced norepinephrine levels after lactate infusion could well explain this improvement in insulin sensitivity. However, it should be noted that, in the present study, glucose infusion rates were increased by lactate infusion during hypoglycemia but not during the euglycemic clamps. This failure to confirm lactate-induced insulin sensitization during euglycemia may be best explained by the shorter duration (75 minutes) of our clamps in comparison with those in previous studies (120 minutes [11]). Therefore, the observed reduction of norepinephrine levels, although suggesting an enhancing effect on insulin sensitivity, clearly calls for further investigation.

In sum, our data point to a distinct difference between central nervous and β-cell glucose-sensing mechanisms in humans. Whereas β-cell glucose sensing is not influenced by lactate administration, central nervous glucose sensing shows a clear response to this alternative energy substrate. Thus, β-cell glucose sensing may be considered highly glucose specific, whereas central nervous glucose sensors may rather be assumed to be sensitive to a broader range of energetic substrates used by the brain.

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