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Oxytocin does not acutely improve glucose tolerance in men with type 2 diabetes

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Abstract

Aim: To assess oxytocin's acute glucoregulatory impact in men with type 2 diabetes in the context of our previous findings that oxytocin improves β-cell responsivity in healthy men.

Methods: In a double-blind, crossover comparison, intranasal oxytocin (24 IU) and placebo, respectively, were administered to 25 fasted men with non-insulin–treated type 2 diabetes (age ± standard error of the mean, 63.40 ± 1.36 years; body mass index, 27.77 ± 0.66 kg/m^2; HbA1c, 6.86% ± 0.08%; Homeostatic Model Assessment of Insulin Resistance (HOMA-IR, 3.44 ± 0.39) 60 minutes before an oral glucose tolerance test (oGTT). Key outcomes were compared with previous results in men with normal weight or obesity.

Results: Oxytocin compared with placebo increased plasma oxytocin concentrations and reduced the heart rate, but did not alter glucose metabolism in the 3 hours after oGTT onset (area under the curve, glucose, 2240 ± 80.5 vs. 2190 ± 69.5 mmol/L × min; insulin, 45 663 ± 4538 vs. 44 343 ± 4269 pmol/L × min; C-peptide, 235 ± 5.1 vs. 231 ± 15.9 nmol/L × min).

Nina Goll and Nina Moszka contributed equally to this study.

Conclusions: This outcome contrasts with the oxytocin-induced attenuation of early postprandial glucose excursions in normal-weight individuals, but is in line with the absence of respective effects in men with obesity. We conclude that insulin resistance in type 2 diabetes is associated with decreased sensitivity to the acute glucoregulatory effect of oxytocin in male individuals.

KEYWORDS
glucose metabolism, oral glucose tolerance test, oxytocin, type 2 diabetes

1 | INTRODUCTION

Experiments in animals and humans indicate that the hypothalamic neuropeptide oxytocin not only regulates reproductive functions and psychosocial processes,[1] but also contributes to metabolic control.[2] In rats[3] and rhesus monkeys[4] with diet-induced obesity, peripheral oxytocin delivery inhibits food intake and reduces body weight. In humans, the intranasal administration of the hormone acutely attenuates food intake in men with normal weight[5] and men with overweight or obesity.[6,7] Moreover, in normal-weight, healthy men, intranasal oxytocin acutely improves glucose tolerance and pancreatic β-cell responsivity.[8] The islets of Langerhans harbour oxytocin receptors[9] and both central and peripheral oxytocin delivery stimulates insulin secretion in rats.[10] Related in vitro experiments have shown that oxytocin secretion from magnocellular supraoptic oxytocin neurons is stimulated by exposure to glucose and insulin, suggesting a role of the hypothalamic oxytocin system in glucose sensing and glucose homeostasis.[11] Accordingly, oxytocin-deficient mice display decreased insulin sensitivity and glucose intolerance.[12] The conclusion that oxytocin administration might be a novel approach to improve glucose homeostasis in states of chronic insulin resistance, including type 2 diabetes (T2D),[2,13] has received support in animal experiments. Peripherally administered oxytocin improves glucose homeostasis and decreases liver and visceral fat mass in mice with diet-induced obesity.[14] In mouse models of prediabetes and diabetes, intracerebroventricular oxytocin reduced insulin resistance and glucose intolerance independently of changes in body weight.[15]

The potential of oxytocin to improve glucose homeostasis in humans with impaired insulin sensitivity has not been systematically investigated. In a previous study in men with obesity, intranasal oxytocin failed to acutely improve β-cell responsivity and glucose tolerance,[16] raising the question whether insulin resistance compromises the beneficial glucoregulatory impact of oxytocin in humans. We investigated the glucoregulatory impact of oxytocin in patients with T2D who do not have obesity, with the aims of untangling the roles of insulin resistance and of increased body weight for oxytocin sensitivity in humans, and of assessing the potential of oxytocin to ameliorate glucose homeostasis in T2D as a state of chronic insulin resistance. For this purpose, we assessed the acute effect of intranasal oxytocin on glucose homeostasis in men with T2D who underwent an oral glucose tolerance test (oGTT) and related our findings to the results in healthy participants and in men with obesity.[8,16] We also measured energy expenditure, cardiovascular function, mood and hunger throughout the experiment.

2 | RESEARCH DESIGN AND METHODS

2.1 | Participants

Twenty-five male patients with T2D participated in the study. They had a mean age (± standard error of the mean [SEM]) of 63.40 ± 1.36 years, a body mass index (BMI) of 27.77 ± 0.66 kg/m^2, an HbA1c value of 6.86% ± 0.08% (51.48 ± 0.84 mmol/mol) and an average disease duration of 7.55 ± 1.03 years. They were treated with lifestyle intervention according to the standards of diabetes care and, if necessary, with antidiabetic medication (metformin, $n = 25$; dipeptidyl peptidase-4 inhibitors, $n = 6$; sodium-glucose co-transporter-2 inhibitors, $n = 5$; glucagon-like peptide-1 receptor agonists, $n = 1$; therapy with insulin, sulphonylureas or thiazolidinediones was an exclusion criterion); additional medication included antihypertensives ($n = 15$) and cholesterol-lowering drugs ($n = 7$; $n < 4$ for other medication). We compared the results of the current experiments with our previous findings in participants with normal weight ($N = 29$; Klement et al.[8]) or obesity ($N = 15$, Brede et al.[16]), which were obtained in studies with an identical design and experimental set-up. All subject characteristics are presented in Table 1. In all three studies, relevant illness, as well as abuse of alcohol, nicotine or drugs, were excluded by medical history, clinical examination and routine laboratory tests during screening. All participants in the current study provided written informed consent prior to its commencement. The study was approved by the Ethics Committee of the University of Tübingen and conformed to the principles of the Declaration of Helsinki.

2.2 | Experimental procedure

Experiments were performed in a double-blind, crossover, within-subject design. Each participant completed two sessions, oxytocin and placebo, which were scheduled at least 14 days apart with a balanced order across participants. Participants were instructed to remain fasted except for drinking water after 08:00 PM on the day preceding each session. Their antidiabetic drug treatment was stopped 12 hours before each experimental session.

The experimental procedure of each session is illustrated in Figure 1. Following the arrival of the participants at the laboratory at 08:00 AM, their body composition was assessed by bioelectrical impedance analysis (Akern, Pontassieve, Italy) and a venous cannula was inserted into each participant's non-dominant arm to enable

TABLE 1 Participant characteristics.

Variable	T2D	Obesity	Healthy	ANOVA factor group
Age (y)	63.40 ± 1.36[a,b]	24.73 ± 0.95	25.17 ± 0.84	$F(2,66) = 415,3$; $P < .001$
BMI (kg/m^2)	27.77 ± 0.66[a,b]	35.29 ± 1.12[b]	22.99 ± 0.21	$F(2,66) = 88,4$; $P < .001$
Lean body mass (kg)	67.56 ± 1.10[a,b]	79.24 ± 1.89[b]	60.50 ± 0.94	$F(2,133) = 52,2$; $P < .001$
Body fat mass (kg)	18.74 ± 0.70[a]	39.79 ± 1.88[b]	16.52 ± 0.37	$F(2,133) = 171,0$; $P < .001$
Fasting plasma glucose (mmol/L)	7.59 ± 0.21[a,b]	5.08 ± 0.09	4.96 ± 0.07	$F(2,66) = 55,4$; $P < .001$
HOMA-IR (mmol/L)	3.44 ± 0.39[b]	3.73 ± 0.44[b]	0.8 ± 0.06	$F(2,135) = 55.5$; $P < .001$
ISI-M	3.52 ± 0.31[b]	3.77 ± 0.48[b]	12.0 ± 0.97	$F(2,133) = 84.2$; $P < .001$
NEFA-ISI	3.99 ± 0.31[a,b]	6.45 ± 0.59	7.70 ± 0.36	$F(2,134) = 48.6$; $P < .001$
IGI	43.67 ± 6.08[a,b]	280.72 ± 33.8[b]	77.55 ± 6.75	$F(2,133) = 61.9$; $P < .001$
$AUC_{insulin/glucose}$ (oGTT $_{0\text{-}120\ min}$, pmol/mmol)	21.13 ± 2.72[a,b]	98.28 ± 12.92[b]	34.03 ± 3.04	$F(2,65) = 35.5$; $P < .001$
$AUC_{C\text{-}peptide/glucose}$ (oGTT$_{0\text{-}120\ min}$, nmol/mmol)	0.10 ± 0.01[a,b]	0.42 ± 0.03[b]	0.29 ± 0.02	$F(2,65) = 69.2$; $P < .001$

Note: Data are presented as mean values ± SEM. Age and measures of body composition were assessed in the screening session; blood parameters were determined during baseline and averaged across conditions or, for AUC, determined in the placebo session. Results of the current experiments in male patients with T2D ($N = 25$) were compared with results in healthy, normal-weight male participants ($N = 29$) and in men with obesity ($N = 15$) from previous experiments[8,16] by ANOVA and post hoc unpaired t-tests ([a,b]$P < .001$ for comparison with men with obesity and, respectively, healthy men). NEFA-ISI is according to Szeto et al.[17]

Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IGI, insulinogenic index; ISI, insulin sensitivity index; ISI-M, insulin sensitivity index according to Matsuda; NEFA, non-esterified fatty acids; oGTT, oral glucose tolerance test; SEM, standard error of the mean; T2D, type 2 diabetes.

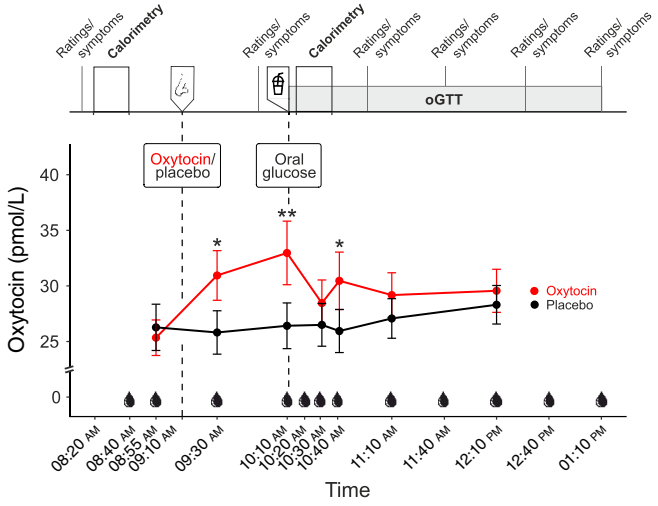

FIGURE 1 Experimental procedure and plasma oxytocin. After baseline assessments of blood parameters and energy expenditure, oxytocin (24 IU) and placebo, respectively, were intranasally administered at 09:10 AM. After the fourth blood collection at 10:10 AM, participants underwent an oGTT. Throughout the session, blood samples were taken (drop symbols), and mood, hunger, thirst, neuroglycopenic and autonomic symptoms were assessed. The bottom panel depicts mean ± SEM concentrations of plasma oxytocin, which were determined at seven representative time points. $N = 25$; *$P \leq .05$; **$P < .01$ for comparisons between conditions (paired t-tests). oGTT, oral glucose tolerance test; SEM, standard error of the mean.

blood collection for the analysis of relevant variables (see the supporting information). Throughout the experiment, blood was repeatedly sampled (with baseline measurements at 08:40 AM and 08:55 AM) and blood pressure and heart rate were measured. At 09:10 AM, 12 0.05-mL puffs (six per nostril) of oxytocin (Syntocinon; Defiante Farmaceutica, Funchal Madeira, Portugal) or placebo (vehicle containing the same ingredients except the hormone) were intranasally administered at 30-second intervals, yielding a total dose of 24 IU oxytocin. This dose had also been administered in our previous studies in men with normal weight or obesity.[8,16] Sixty minutes later, participants drank 300 mL of glucose solution (containing 75 g of anhydrous glucose) within 1 minute. Energy expenditure was measured by indirect calorimetry (Vyntus CPX Canopy, CareFusion, Germany) during baseline and at 10:15 AM, that is, immediately after ingestion of the dextrose solution. Participants frequently rated their hunger, satiety, thirst, current subjective feelings (anxious, happy, stressed, tired), as well as their desire to eat something (in general, something sweet or savoury) on visual analogue scales (VASs; 0-100 mm). They also rated their mood (good/bad), alertness/sleepiness and calmness/agitation on five-point scales[18] and neuroglycopenic (dizziness, tingling, blurred vision, difficulty in thinking, faintness) and autonomic (anxiety, palpitation, hunger, sweating, irritability, tremor) symptoms on 10-point scales.[19]

2.3 | Statistical analyses

Data are presented as mean absolute values ± SEM. Data were analysed and plotted using SPSS and R.[20] Analyses were based on analyses of variance (ANOVAs) with the within-subject factors 'Treatment' (oxytocin vs. placebo) and 'Time'; key results of glucose homeostasis were compared with our previous results[8,16] by introducing the between-subjects factor 'Group' (T2D vs. obesity vs. healthy participants). In supplementary analyses of covariance (ANCOVAs),

the results were adjusted for age, disease duration, BMI, antihypertensive intake and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Degrees of freedom were corrected using the Greenhouse–Geisser procedure. Pairwise *t*-tests and comparisons of areas under the curve (AUCs) covering relevant time periods were used to specify significant ANOVA effects. For parameters without normal distribution, the Wilcoxon test was used. A *P* value less than .05 was considered significant.

3 | RESULTS

3.1 | Glucose homeostasis after oxytocin administration in patients with T2D, men with obesity and healthy men

Baseline concentrations of glucose, insulin and C-peptide were comparable between conditions in patients with T2D ($P > .36$ for all comparisons). Oxytocin compared with placebo administration induced an increase in plasma oxytocin from baseline concentrations of 25.3 ± 1.6 versus 26.3 ± 2.08 pmol/L ($P > .5$) that emerged within 20 minutes, reached peak concentration at the start of the oGTT and was still detectable 60 minutes later ($F(4,87) = 3.07$, $P = .024$ for the ANOVA Treatment × Time interaction; Figure 1). Variables of glucose metabolism showed the expected oGTT-related dynamics, but were generally not altered by oxytocin. Plasma glucose concentrations peaked 90 minutes after the start of the oGTT with no overall differences between conditions ($F(4,91) = 0.69$, $P = .60$ for Treatment × Time; Figure 2A). Exploratory (unadjusted) single time-point comparisons indicated increases rather than decreases in the oxytocin compared with the placebo condition at 20 minutes after oGTT onset ($P = .042$). Insulin and C-peptide concentrations were not altered by oxytocin (each $P > .3$; Figure 2B,C). Adjustment of the glucose, insulin and C-peptide results for age, disease duration, BMI, antihypertensive intake and HOMA-IR values did not alter the results, that is, corroborated the absence of robust glucoregulatory oxytocin effects (all $P > .42$ for respective ANCOVA Treatment × Time terms).

Comparisons of the current results with our previous findings in men with obesity[16] and in healthy male individuals[8] show the expected differences in glucose homeostasis per se, and indicate that

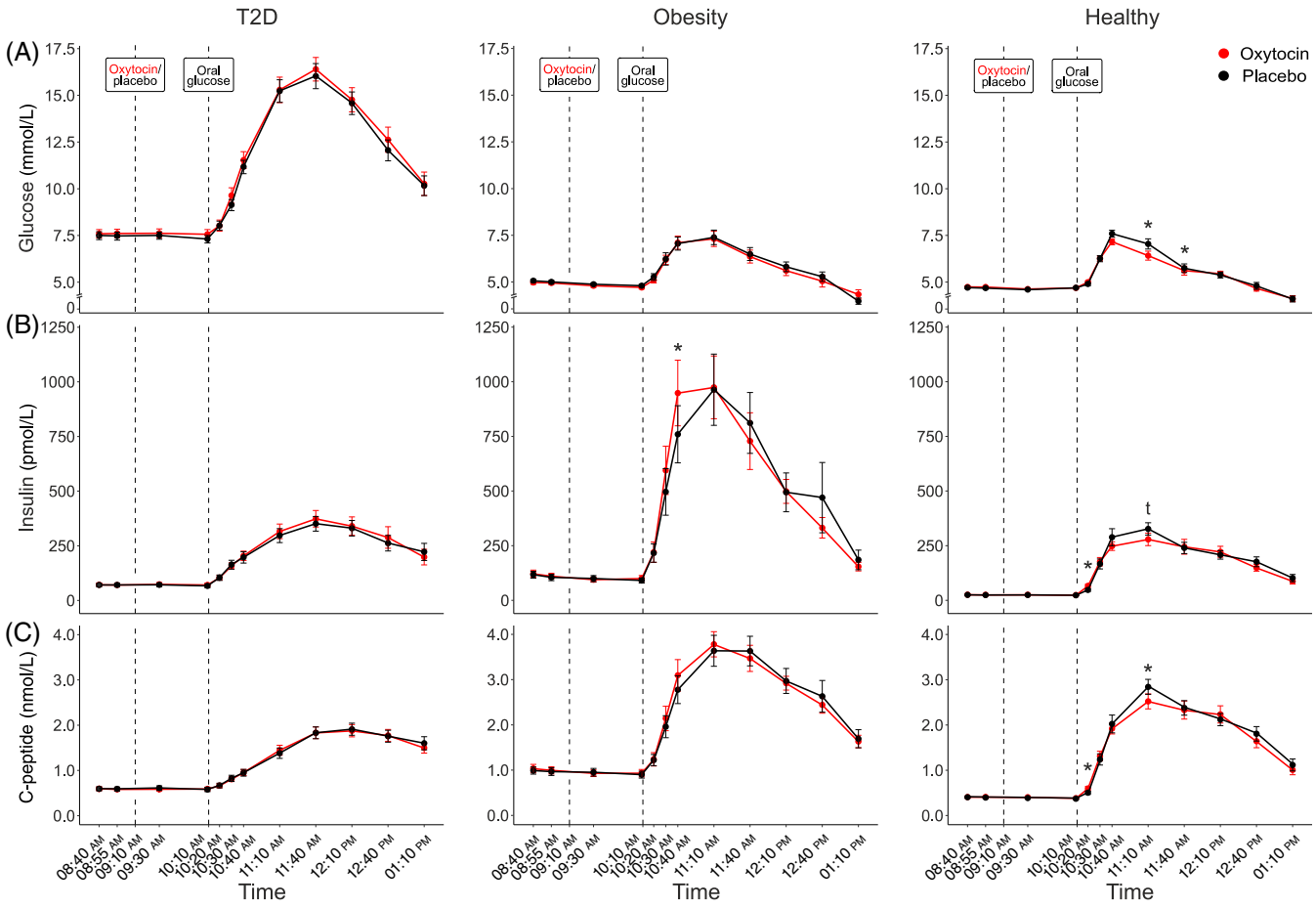

FIGURE 2 Oxytocin effects on glucose metabolism according to study group. Mean ± SEM plasma or serum concentrations of A, Glucose, B, Insulin, and C, C-peptide at baseline and after administration of 24 IU oxytocin (red) or placebo (black) at 09:10 AM followed by the oGTT after the fourth blood collection at 10:10 AM. Results in men with T2D ($N = 25$), in men with obesity ($N = 15$, Brede et al.[16]) and in healthy participants ($N = 29$, Klement et al.[8]) are shown; $^{t}P \le .1$, $^{*}P \le .05$ for comparisons between conditions (paired *t*-tests or Wilcoxon tests). oGTT, oral glucose tolerance test; SEM, standard error of the mean; T2D, type 2 diabetes.

oxytocin exerts a beneficial effect on glucose homeostasis in healthy men that is not found in patients with diabetes and in individuals with obesity. Baseline glucose concentrations were significantly elevated in patients with T2D compared with the other groups ($F(2,66) = 113.3$, $P < .05$ for Group; Figure 2A). Postprandial glucose excursions were significantly higher in men with T2D compared with men with obesity and normal-weight males ($P < .001$); they were attenuated by oxytocin versus placebo in normal-weight men ($P < .005$ for $AUC_{0\text{-}60\ min}$ after oGTT onset), in contrast to the men with T2D ($F(1,52) = 6.02$, $P = .018$ for Group × Treatment). Like in men with T2D, oxytocin did not affect postprandial glucose levels ($AUC_{0\text{-}60\ min}$) in individuals with obesity ($F(1,37) = 1.12$; $P > .2$; $F(2,66) = 2.77$, $P = .07$ for Group × Treatment across the three groups; Figures 2A and S1A).

Baseline insulin concentrations were higher in participants with obesity or T2D compared with normal-weight participants ($F(2,66) = 39.41$, $P < .05$ for Group; Figure 2B). Postprandial insulin concentrations were significantly lower in men with T2D compared with those with obesity ($P < .001$), but not significantly different when compared with values in normal-weight men ($P > .3$; Figures 2B and S1B). In the normal-weight men, serum insulin concentrations increased more quickly, while peak responses were suppressed in the oxytocin compared with the placebo condition, which is in contrast to unaffected or rather slightly elevated responses in the men with T2D or obesity ($AUC_{0\text{-}60\ min}$, $F(2,65) = 5.67$; $P = .005$ for Group × Treatment). Baseline C-peptide values were significantly higher in men with obesity and significantly lower in men with normal weight compared with men with T2D ($F(2,66) = 45.9$, $P < .05$ for Group; post hoc unpaired t-tests, $P < .001$ for all comparisons between groups; Figure 2C). Postprandial C-peptide responses were dampened and less rapid in men with T2D, compared with normal-weight men and men with obesity ($P < .001$; Figures 2C and S1C). In normal-weight men, oxytocin compared with placebo blunted the peak response of C-peptide concentrations ($P < .02$), but did not affect C-peptide concentrations in the men with T2D or obesity ($AUC_{0\text{-}60\ min}$, $F(2,65) = 2.\ 86$, $P = .064$ for Group × Treatment across the three groups).

3.2 | Hypothalamic–pituitary–adrenal axis activity and concentrations of non-esterified fatty acids and lactate

Oxytocin versus placebo administration did not modulate hypothalamic–pituitary–adrenal axis activity, that is, cortisol and adrenocorticotropic hormone (ACTH) concentrations ($P > .05$ for Treatment × Time; Figure 3A,B). However, cortisol concentrations were reduced

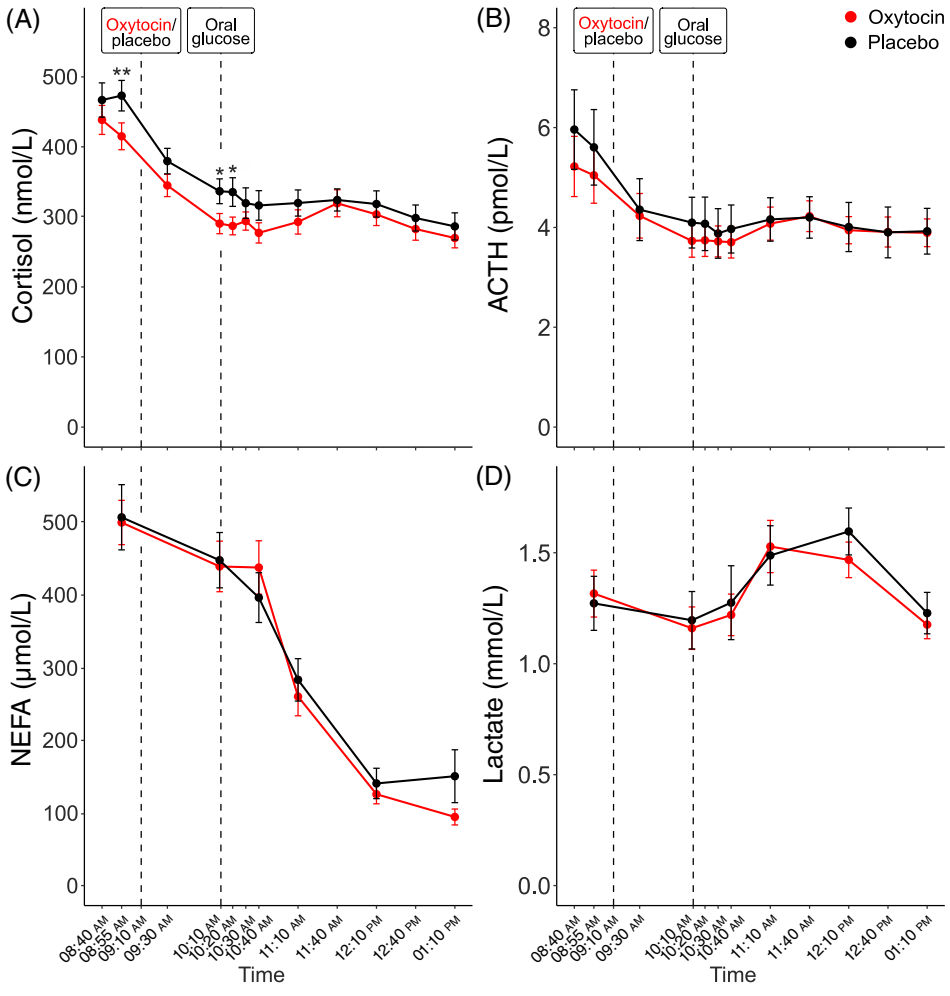

FIGURE 3 Counter-regulatory hormones, NEFA and lactate. Mean ± SEM plasma or serum concentrations of A, Cortisol, B, ACTH, C, NEFA, and D, Lactate in men with T2D at baseline and after administration of 24 IU oxytocin (red) or placebo (black) at 09:10 AM followed by the oGTT after the blood collection at 10:10 AM. $N = 25$; $^{**}P < .01$ for comparisons between conditions (paired t-tests). ACTH, adrenocorticotropic hormone; NEFA, non-esterified fatty acids; oGTT, oral glucose tolerance test; SEM, standard error of the mean; T2D, type 2 diabetes.

in the oxytocin compared with the placebo condition already during baseline (426.72 ± 18.75 vs. 469.90 ± 20.31 nmol/L averaged across the two baseline values; $F(1,22) = 4.632$, $P = .043$ for Treatment; Figure 3A). Note that the results of glucose homeostasis (glucose, insulin, C-peptide) presented above are not markedly altered when adjusted for this difference in cortisol baseline concentrations (all $P > .48$ for Treatment × Time). Adjusting cortisol and ACTH concentrations for age, BMI and HOMA-IR did not yield essentially different results ($P > .8$ for Treatment × Time). Plasma non-esterified fatty acid (NEFA) concentrations decreased postprandially and were comparable between conditions ($P > .05$ for all comparisons; Figure 3C). Lactate concentrations, which increased postprandially with a peak approximately 2 hours after the oGTT ($P < .001$ for Time), were not affected by oxytocin ($P > .05$ for all comparisons; Figure 3D).

3.3 | Energy expenditure and cardiovascular measures

Oxytocin did not affect resting energy expenditure (REE) assessed by indirect calorimetry ($F(1,24) = 0.785$, $P > .38$ for Treatment × Time). Thus, REE was comparable between the oxytocin and placebo conditions during baseline (2142.96 ± 51.21 vs. 2110.28 ± 61.83 kcal/day) and the postprandial state (2172.56 ± 49.91 vs. 2163.64 ± 52.80 kcal/day; $P > .32$ for single time-point comparisons; $P = .058$ for Time). The respiratory quotient decreased postprandially compared with baseline ($P < .01$ for Time), but was comparable between the oxytocin and placebo conditions in the fasted (0.93 ± 0.02 vs. 0.91 ± 0.02) and the postprandial state (0.78 ± 0.01 vs. 0.79 ± 0.02; $P > .25$ for all comparisons). In terms of changes between the preprandial and the very early postprandial state, this pattern is comparable with related findings after glucose ingestion.[21] Heart rate was reduced in the oxytocin compared with the placebo condition, averaging 65.28 ± 1.45 versus 68.80 ± 1.53 bpm ($P < .01$) at 120 minutes and 64.12 ± 1.79 versus 68.24 ± 2.00 bpm ($P < .05$) at 180 minutes postadministration ($F(1,24) = 4.8$; $P = .038$ for Treatment across the experimental period; Figure 4A). Blood pressure was generally comparable between conditions throughout the experimental period both in terms of systolic and diastolic values (all $P > .23$; Figure 4B,C; see Figure S2 for cardiovascular variables in the participants with obesity or normal weight of our previous studies[8,16]). Body fat content and lean body mass assessed at the start of each experimental session did not differ between conditions (all $P > .4$; see Table 1 for results at screening).

3.4 | Psychological variables

VAS ratings of hunger, thirst and the desire to eat increased, whereas those of satiety decreased throughout the experimental period (all $P < .05$ for Time); oxytocin generally did not modulate these ratings ($P > .05$ for all comparisons; data not shown). Ratings of happiness, anxiousness and stress were not affected by oxytocin compared with placebo (all $P > .05$), while tiredness was increased in the oxytocin versus placebo condition ($F(3,80) = 3.68$; $P = .012$ for Treatment × Time; this effect vanished after adjustment for age and BMI; $P > .69$). Subjective well-being according to the categories good/bad mood, alertness/sleepiness and calmness/agitation was not affected by oxytocin compared with placebo (all $P > .2$). Awareness of neuroglycopenic and autonomic symptoms was not affected by oxytocin versus placebo (all $P > .1$). In interviews at the end of the study, participants were unable to correctly indicate whether they had received oxytocin or placebo ($\chi^2 = 2$, $P = .16$).

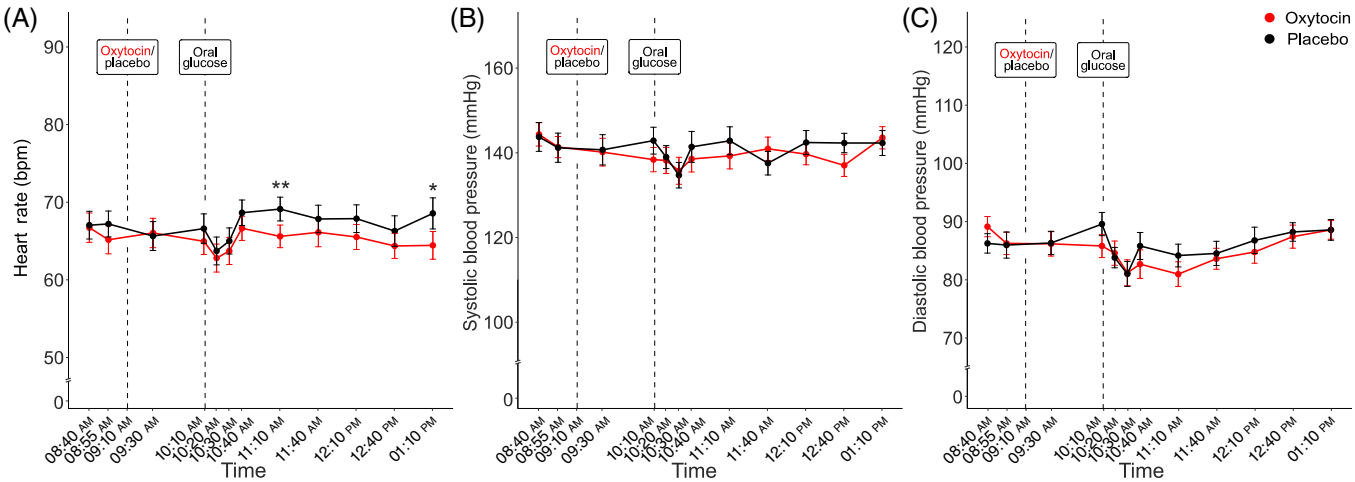

FIGURE 4 Cardiovascular measures. Mean values ± SEM of A, Heart rate, B, Systolic blood pressure, and C, Diastolic blood pressure in men with T2D at baseline and after administration of 24 IU oxytocin (red) or placebo (black) at 09:10 AM followed by the oGTT after the blood collection at 10:10 AM. $N = 25$; $^*P \leq .05$; $^{**}P < .01$ for comparisons between conditions (paired t-tests). oGTT, oral glucose tolerance test; SEM, standard error of the mean; T2D, type 2 diabetes.

4 | DISCUSSION

We show that acute oxytocin administration to male patients with well-controlled T2D does not induce the improving effect on glucose homeostasis previously observed in healthy men.[8] Intranasal delivery of oxytocin before an oGTT did not alter key variables of glucose metabolism in men with T2D, although the increase in circulating oxytocin concentrations and the decrease in heart rate elicited by exogenous oxytocin indicate its efficacy in this sample of participants. The absence of acute glucoregulatory effects of oxytocin in T2D is in line with the negative outcome in men with obesity[16] and indicates that peripheral insulin resistance hampers the impact of oxytocin on glucose metabolism.

The robust increase in plasma oxytocin concentrations in the oxytocin compared with the placebo condition confirms the efficacy of intranasal oxytocin administration. The slight, but significant, reduction in heart rate by oxytocin compared with placebo ties in with findings that intravenous oxytocin administration decreases the heart rate in spontaneously hypertensive rats by reducing arterial blood pressure.[22] Decreasing effects of subcutaneous oxytocin on blood pressure have been found to be restricted to male hypertensive rats,[23] but were observed in both female and male normotensive rats[24]; interestingly, the opposite effects were found after intraperitoneal oxytocin delivery to male mice, possibly as a result of vasopressin receptor engagement.[25] Also, in our previous experiments, oxytocin did not alter the heart rate in participants with normal weight[8] or obesity,[16] so that oxytocin's cardiovascular impact—and cardioprotective potential, for example, in the treatment of diabetic cardiomyopathy[26]—should receive greater attention. Future studies should also address potential anti-inflammatory effects, inasmuch chronic infusion of oxytocin has been shown to reduce markers of systemic and adipose tissue inflammation in an animal model of obesity and diabetes.[27]

In our previous study in healthy men,[8] oxytocin administered according to the same paradigm as in the current experiments attenuated the peak excursion of plasma glucose and augmented the early increases in insulin and C-peptide concentrations in response to the oGTT, while blunting insulin and C-peptide peaks. Our subsequent results indicated that oxytocin loses some or all of its glucoregulatory effect in individuals with obesity and insulin resistance,[16] but left open the question to what extent insulin resistance and associated glucose intolerance in the absence of strongly elevated body fat mass compromises the oxytocin effect. The current results were obtained in patients with full-blown T2D who were only mildly overweight. Their comparison with the results in men with normal weight and those with obesity show that impaired insulin sensitivity per se, as reflected by the attenuation of NEFA-insulin sensitivity index (ISI) values[28] in T2D, and of ISI according to Matsuda values both in T2D and obesity, abolishes the acute glucoregulatory effect of oxytocin. As expected, insulin secretion according to the insulinogenic index was reduced in T2D and increased in obesity, but did not differentially affect the oxytocin effect. With a mean age of approximately 63 years, the patients with T2D were older than the previous participants with normal weight or obesity, who were approximately aged 25 years. Age-associated decreases in insulin sensitivity[29] might have contributed to the observed pattern, which, however, was not altered by statistical adjustment for age or disease duration. All patients with T2D were taking metformin, which reduces hepatic glucose output and improves muscular insulin sensitivity.[30] With a mean HbA1c of approximately 6.9%, their resulting glycaemic control was good in clinical terms, which, arguably, might have hampered the detection of additional subtle oxytocin effects; on the other hand, an interfering or masking effect of glucotoxicity on oxytocin's impact is unlikely.

The mechanisms behind the improving effect of oxytocin on glucose homeostasis in normal-weight, healthy individuals are still under investigation.[2] Recent experiments point to a hypothalamus-β cell circuit that regulates insulin secretion and includes oxytocinergic neurons in the hypothalamic paraventricular nucleus.[31] Furthermore, oxytocin neurons in the supraoptic nucleus of the hypothalamus act as glucose sensors.[2] Considering the increase in circulating oxytocin concentrations after intranasal delivery of the peptide and the fact that islets of Langerhans harbour oxytocin receptors,[9] peripheral contributions are probable. The current findings do not allow insights into the (neuro)physiological mechanisms that hamper oxytocin's effect on glucose homeostasis in individuals with insulin resistance. Notably, the lack of glucoregulatory oxytocin effects in T2D and obesity contrasts with the preserved attenuating impact of oxytocin on food intake in men with obesity.[6,7] These diverging patterns suggest that brain mediators of oxytocin's hypophagic effect, which involve regions that convey cognitive control,[32] are oxytocin-sensitive in individuals with metabolic impairments, whereas glucoregulatory networks, in which peripheral effectors may be more relevant,[12,33] do not adequately respond to oxytocin in states of insulin resistance. In a rigorous recent clinical trial, 8 weeks of 4×24 IU/day of intranasal oxytocin reduced calorie intake in adults with obesity at week 6, but did not decrease body weight,[34] underlining the need for additional long-term investigations. They should also address the role of brain insulin resistance[35] and assess oxytocin effects on mood, which might affect appetite and food intake.[36]

The differences in body weight and composition between the participants of our studies raise questions on the dosing of oxytocin and on endogenous oxytocin signalling in relation to metabolic status.[2] Studies on dose–response relationships in humans relying on intranasal oxytocin administration indicate that body weight does not modulate the impact of exogenous oxytocin[37] and even suggest non-linear oxytocin effects, that is, greater efficacy at lower to medium doses (8-24 IU), albeit in terms of neurobehavioural rather than metabolic effects.[38] The dose of 24 IU of intranasal oxytocin applied here and previously[5–8,16,32] has been most widely used in human studies.[39] However, in light of earlier experiments in healthy men showing that intravenous oxytocin infusion at a dose of 6 IU but not 3 IU increases insulin secretion in response to intravenous glucose,[40] it remains to be seen if higher doses or different concentrations of oxytocin, or the use of oxytocin analogues with a more selective receptor binding profile,[25] are also able to improve glucose homeostasis in patients with T2D. Endogenous oxytocin concentrations have been found to be proportional to body weight,[41,42] but there are also reports of

decreased concentrations in obese Zucker rats,[43] individuals with obesity[44,45] and, notably, patients with diabetes.[44,46] Because of the complexity of analysing oxytocin concentrations, which impedes direct comparisons between individual studies,[33,38] we refrained from respective comparisons between the current and our previous studies.[8,16] We did not find acute oxytocin effects on energy expenditure as measured by indirect calorimetry, which is mostly in line with previous experiments in individuals without diabetes, regardless of body weight status,[5,6,8,16] although acute oxytocin-induced attenuations of the respiratory quotient have been reported.[7]

To the best of our knowledge, this is the first study to investigate the acute effect of oxytocin on glucose homeostasis in patients with T2D with state-of-the-art methodology, which also enabled us to compare the current results with those in healthy individuals and those with obesity. Still, it has some limitations that will need to be addressed in future research. We did not include female patients and did not systematically investigate potential interactions with antidiabetic medication. As outlined above, it might also be argued that different or intensified oxytocin dose regimens could improve glucose homeostasis in patients with T2D, but the current proof-of-principle study was laid out to investigate the effect of oxytocin at the dose known to be efficient in healthy participants.[8] Likewise, potentially beneficial long-term effects as observed in animal models[15] were beyond the scope of this investigation. While further work on the translational potential of oxytocin administration in metabolic disorders is needed,[46] the demonstration that T2D is associated with decreased sensitivity to oxytocin's acute glucoregulatory impact is a necessary and relevant step in this direction.

AUTHOR CONTRIBUTIONS

MH and AF designed the study, with the support of HP, TG and CG-C. NM, KK and LF enrolled patients and carried out experiments for the study; RJ-vS provided technical support. NR, NM and MH analysed the data. All the authors discussed the results. NR and MH wrote the manuscript; NM, HP and AF contributed to the writing; all the authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

No potential conflicts of interest relevant to this article are reported.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request. No applicable resources were generated or analyzed during the current study.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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