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GLP-1 receptor agonists do not affect sodium intake: Exploratory analyses from two randomized clinical trials

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ABSTRACT

Objectives: Excessive sodium intake, despite current dietary advice, remains a global issue with cardiovascular and renal consequences. The aim of this study was to determine whether glucagon-like peptide receptor agonists (GLP-1 RAs), used as antihyperglycemic agents for type 2 diabetes (T2DM) management, may reduce salt cravings as they are known to reduce hedonic feeding behavior and are involved in sodium homeostasis by increasing renal sodium excretion.

Methods: We performed exploratory analyses using data from two randomized, clinical crossover trials, which primarily aimed to assess the effects of GLP-1 RAs on central satiety and reward circuits and subsequent related feeding behavior. In study A, healthy, obese individuals and patients with T2DM were randomly assigned to receive intravenous administration of placebo or GLP-1 RA exenatide with or without concurrent GLP-1 receptor blockade, on separate testing days. In study B, individuals with T2DM randomly received GLP-1 RA liraglutide (titrated up to 1.8 mg daily) or titrated insulin glargine for 12 wk. In both studies, participants received an ad libitum mixed meal that served to calculate sodium intake. Moreover, salt craving was scored using a Likert scale.

Results: In study A, acute exenatide, parallel to reduced total food intake, reduced sodium intake in all studied groups by up to 30%. In study B, prolonged liraglutide treatment did not affect sodium or total caloric intake. Neither acute exenatide nor prolonged liraglutide treatment affected salt craving as measured by the Likert scale.

Conclusion: Acute exenatide reduced sodium intake in light of a generalized reduction in food ingestion, while prolonged intervention with liraglutide did not lower sodium intake. Neither intervention affected salt craving. Given the known effects of these drugs on renal sodium excretion, blood pressure, and renal and cardiovascular outcome, it seems plausible to perform dedicated mechanistic studies in humans to assess the effects of GLP-1 RA administration on sodium balance.

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Introduction

Worldwide, excessive sodium intake represents a public health problem, especially in patients with type 2 diabetes mellitus (T2DM). Although traditionally the human body has been primed to store sodium for times of scarcity, in the current era of sodium abundance, this function has been associated with hypertension, cardiovascular disease, and chronic kidney disease [1]. Large epidemiologic trials have demonstrated that sodium restriction is associated with improvements in renal and cardiovascular outcome in patients with T2DM [2]. However, although clinicians counsel patients on sodium restriction, in clinical practice, advice frequently is not adhered to. In addition to the low availability of low-

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sodium food, one possible explanation is that sodium intake is well embedded in habitual preferences and cultural behavior. Moreover, physiologically, the regulation of sodium intake is complex and involves many factors, including several hormones (e.g., angiotensin II and aldosterone), baroreceptor input, and sodium content in the cerebrospinal fluid [3]. Pharmacologic compounds modulating these processes could be beneficial for sodium restriction.

Glucagon-like peptide (GLP)-1 receptor agonists (GLP-1 RAs) are injectable glucose-lowering drugs now widely used as second- or third-line therapy in T2DM in clinical practice. Apart from their glucose-lowering properties, GLP-1 RAs have several extra-glycemic effects [4]. Importantly, GLP-1 RAs reduce food intake through stimulation of satiety and by decreasing hedonic feeding behaviors [5]. These drugs target the insula, putamen, and amygdala [6], areas that are interestingly also involved in salt craving [7]. Moreover, we know that GLP-1 RAs affect sodium homeostasis, as they increase renal sodium excretion in several studies [8–10]. Combined, we hypothesized that GLP-1 RAs may reduce sodium intake. Such an effect could be an explanation for the recent observation that GLP-1 RAs reduce cardiovascular risk beyond glycemic control [11].

Methods

We performed exploratory analyses in two clinical intervention trials in which sodium intake was monitored using similar methodology. The trials were primarily designed to assess the effects of GLP-1 RA on central satiety and reward circuits and subsequent related feeding behaviors in acute (study A) and prolonged (study B) settings. Both studies were performed at the Amsterdam University Medical Center, location VUmc, were registered at clinicaltrials.gov, were approved by the local ethics review board, and were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization on Good Clinical Practice. All participants provided written informed consent before any trial-related activities.

Study A

Study A was a randomized, placebo-controlled, crossover study that assessed the acute effects of the GLP-1 RA exenatide on feeding behavior in humans using functional magnetic resonance imaging (fMRI) techniques. The full study methods were published previously [12]. Sixteen healthy lean individuals, 16 obese normoglycemic individuals, and 16 obese patients with T2DM were included. All were matched for age and sex. Additionally, the obese participants with and without diabetes were matched for body mass index (BMI).

Participants underwent three visits in random order with a washout period of ≥1 wk. During the visits, participants received intravenous infusion of exenatide (targeting therapeutic plasma levels [12], exenatide combined with a GLP-1 receptor blocker (exendin 9-39); or placebo (saline 0.9%). Patients, but not study physicians, were blinded to the interventions. All interventions were performed during a somatostatin pancreatic-pituitary clamp, to diminish any interfering effects of pancreatic hormones. During the testing day, an ad libitum lunch buffet was administered to measure sodium intake. Moreover, questionnaires were used to measure salt craving.

Patients arrived at the study center after an overnight fast. At that point, a food questionnaire was completed. The clamp procedure was started and followed by the study intervention after 60 min. After 90 min of exenatide or placebo infusion (during which the fMRI scans were performed), the lunch buffet was given (see below), and a food questionnaire was completed. All infusions were discontinued after the meal.

Study B

This was a randomized, crossover, intervention study, as published previously [6]. The aim of this study was to assess the effects of prolonged intervention with a GLP-1 RA on feeding behavior. Twenty overweight or obese patients with T2DM were included (mean ± SD, age 59.7 ± 4.2 y, BMI 32.1 ± 4.7 kg/m^2, hemoglobin A1c, 54 ± 9 mmol/mol (7.2 ± 0.9%), diabetes duration 7.1 ± 5.4 y).

In randomized order, patients were treated for 12 wk with liraglutide once daily (titrated ≤1.8 mg subcutaneously) or insulin glargine (predetermined treat-to-target algorithm to achieve similar glycemic control compared with the liraglutide-arm). During each intervention period, participants had three study visits: at baseline, after 10 d, and after 12 wk of treatment. Endpoint measurements at each visit included questionnaires and an ad libitum lunch buffet.

Patients arrived at the study center after an overnight fast. Upon arrival, a food questionnaire was completed. Then, fMRI scans were performed. During one of these scans, participants received a standardized liquid meal (300 mL, 450 kcal [carbohydrate 56.1 g, fat 17.4 g, and protein 18 g] and 270 mg sodium). The ad libitum lunch and a second food questionnaire followed 3.5 h after the liquid meal.

Ad libitum lunch buffet

Participants were advised to eat as much as they wanted, and were not made aware that their choices and food intake were being monitored. The buffet included well-known salty products (cheese, bread) and non-salty products (sugar, peanut butter). Other products included margarine, mayonnaise, chicken filet, ham, lettuce, tomatoes, yogurt, jam, fresh juice, coffee/tea, apple, banana, muffins or cake. After 30 min, the buffet was taken away. The amount of consumed sodium and kcal were calculated by weighing the remains.

Questionnaires

At the beginning of each study visit, and immediately before the lunch buffet, participants were asked to use a 10-point Likert scale to rate their hunger and the desire to eat something salty.

Statistical analysis

For the acute intervention study (study A), analysis of variance (ANOVA) was used to compare baseline intake between the groups. Treatment-induced effects were analyzed by paired *t* tests. Differences between the studied groups (lean control, obese control, and T2DM) were analyzed by performing an ANOVA on the differences between interventions (exenatide and exendin-9) and placebo. Statistical analyses for the prolonged study (study B) were performed using linear mixed models. In the within-group analyses, only time was added as independent variable, and analyses were performed separately for the two interventions. For the treatment effects over time, both intervention and time were included as independent variables.

Results

Baseline characteristics for both studies are described in Table 1.

Study A

During placebo infusion, sodium intake (mean ± SD) was 1000 ± 380 mg during the 30 min of observation time, which was similar between controls (908 ± 445 mg), obese individuals without diabetes (1062 ± 386 mg), and patients with T2DM (1032 ± 303 mg; $P = 0.488$). During exenatide infusion, sodium intake was decreased among all groups (lean controls −325 ± 313 mg, $P = 0.001$; obese controls −268 ± 419 mg, $P = 0.022$; T2DM −188 ± 321 mg, $P = 0.033$), without statistical difference between the groups (Fig. 1A). Sodium intake did not differ from placebo during exenatide/exendin 9-39 infusion. Exenatide infusion significantly reduced kcal intake in all studied groups. When corrected for the decrease in kcal, exenatide did not independently reduce sodium intake. Salt craving, as measured on the Likert scale and assessed immediately before the ad libitum lunch buffet, did not differ between placebo, exenatide, and the combination of exenatide/exendin 9-39 over the three studied populations.

Study B

Baseline sodium intake was 884 ± 82 mg in all patients. Liraglutide had no significant effect on sodium intake (mean change from baseline to day 10: −60.3 ± 61.7 mg, $P = 0.336$; mean change from baseline to week 12: −15.5 ± 61.7 mg, $P = 0.803$), or any of the other tested nutrients (Fig. 1B). Similarly, insulin glargine did not affect sodium intake (mean change from baseline to day 10: −17.6 ± 653.2 mg, $P = 0.743$; mean change from baseline to week 12: −14.5± 52.7, $P = 0.785$). No statistically significant differences between treatment groups was found. Kcal intake was not affected by either treatment and no between-group difference was observed. Salt craving,

Table 1
Baseline characteristics

Parameter	Study A (acute)			Study B (prolonged)
	Healthy lean	Healthy obese	T2DM	
Age (y)	57.8 ± 1.9	58 ± 2.1	61.4 ± 1.5	60.1 ± 4.1
Male/Female	8/8	8/8	8/8	11/9
BMI (kg/m^2)	23.2 ± 0.4	32.6 ± 0.7	34 ± 0.9	31.6 ± 4.5
HbA1c				
%	5.5 ± 0.03	5.5 ± 0.07	6.9 ± 0.22	7.2 ± 0.9
mmol/mol	37.4 ± 0.3	37.5 ± 0.08	51.6 ± 2.4	54.6 ± 9.3
Medication				
Diuretics	0	0	5	5
RAAS-inhibitors	0	0	10	8

BMI, body mass index; Hb, hemoglobin; RAAS, renin-angiotensin-aldosterone system; T2DM, type 2 diabetes mellitus.

as measured by the Likert scales, was not affected by either treatment, nor were there any between-group differences.

Discussion

In the current analysis, we retrospectively used data from two randomized controlled trials by our group to study our hypothesis that GLP-1 RA could reduce sodium intake. In the acute setting, exenatide reduced sodium intake by ~200 to 300 mg compared with placebo-infusion (≤30%). However, this reduction was likely part of the generalized reduction in food intake, and not an effect on salt craving per se. This was reflected by the lack of reduction in salt craving using food questionnaires. Prolonged intervention with liraglutide did not affect sodium intake (nor caloric intake) nor questionnaire-reported salt craving.

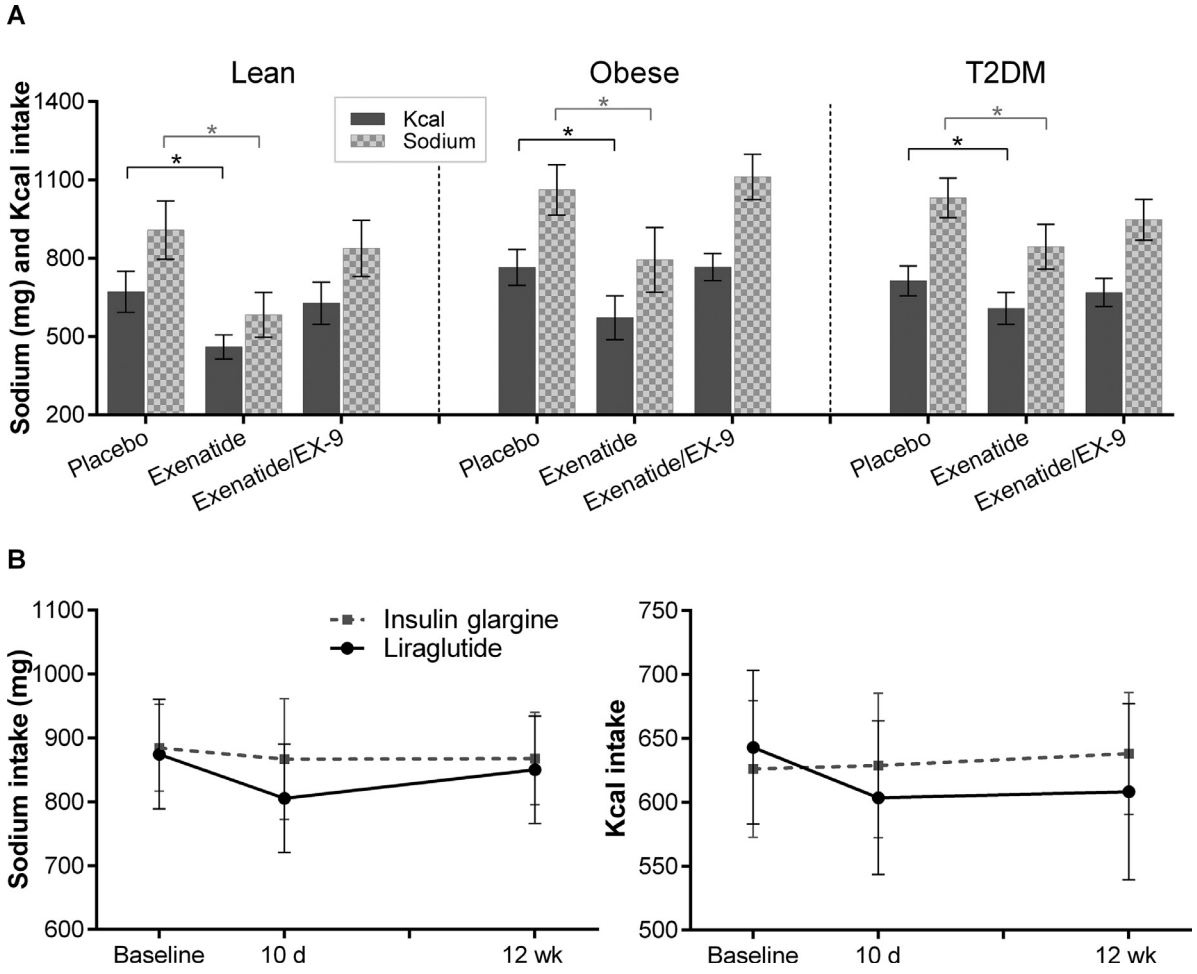

Fig. 1. Effect of GLP-1 RA exenatide (with/without concomitant EX-9-39) versus placebo in lean, obese, and T2DM patients (study A), and GLP-1 RA liraglutide versus titrated insulin glargine in T2DM patients (study B) on sodium and caloric intake. (**A**) Effects of placebo, exenatide, and the combination of exenatide/EX 9-39 on sodium intake (in mg) and caloric intake (in kcal) during an ad libitum lunch buffet, divided by the three studied groups (lean, obese, and type 2 diabetes patients). *Significant treatment effect ($P < 0.05$). Effects of liraglutide and insulin glargine on (**B**) sodium intake in mg and caloric intake in kcal. EX, exendin; GLP-1 RA, glucagon-like peptide 1 receptor agonists; T2DM, type 2 diabetes mellitus.

A drug-induced decrease in sodium intake could have many beneficial health effects, as high sodium intake has been associated with hypertension, cardiovascular, and renal disease. Fascinatingly, large cardiovascular outcome trials have demonstrated that GLP-1 RA improve these specific disorders [13-15]. At this point, it is thought that these effects are not caused by improved glycemic control, and an effect on sodium homeostasis could well be involved. As indicated, we had several arguments to hypothesize an effect of GLP-1 RA on sodium intake. First, GLP-1 RAs reduce food intake by reducing hedonic feeding behaviors. The brain areas affected by GLP-1 RAs, including the insula, putamen, and amygdala, are also involved in salt cravings [6,7]. However, studies focusing on effects of GLP-1 RAs on central nervous system activation so far use caloric food cues to trigger responses for fMRI, and as such likely may not be generalized to salt cravings. Thus, to answer whether GLP-1 RAs affect brain areas in sodium intake, specific fMRI studies with sodium cues should be performed.

Second, GLP-1 reduces levels of and post-receptor messaging of angiotensin II and aldosterone, which are considered major activators of salt cravings. For example, in healthy volunteers, single-shot liraglutide reduced angiotensin II levels by ~20%. However, we and others have been unable to reproduce such effects (as reviewed elsewhere [10]). Finally, preclinical data suggest that exenatide may increase vasopressin levels [16], another hormone that increases salt appetite. However, clinical data for vasopressin are lacking. Unfortunately, the present studies did not measure these mechanisms, which contribute to sodium intake.

Although our data appears to be suggesting that GLP-1 RAs do not affect sodium intake, there are in fact two points that need further consideration. First, although acute exenatide decreased sodium intake, albeit due to a generalized reduction in food intake, prolonged intervention with liraglutide had no such effect. This could be explained by differences in pharmacokinetics. Exenatide is considered to be a short-acting GLP-RA, whereas liraglutide is a long-acting agent. The long-acting agents demonstrate tachyphylaxis on several of their effects, the most recognized being gastric emptying (which could also affect total food intake) [17]. As such, it can be suggested that a prolonged study with short-acting agents (e.g., exenatide or lixisenatide) could yield different results.

Second, as indicated, GLP-1 RAs increase renal sodium excretion [10]. Physiologically, this should trigger salt cravings, as long as the osmotic setpoint has not been altered [18]. In our prolonged intervention study, liraglutide did not increase sodium intake. Unfortunately, we did not measure renal sodium excretion. Nevertheless, the hypothesis that GLP-1 RAs increase sodium excretion without compensatory increasing sodium intake needs further study.

This study had several limitations. The data were derived from two studies that were not primarily designed to assess our hypothesis. Nevertheless, both trials used an identical ad libitum lunch buffet, and sodium intake was recorded using the same methodology. A single lunch might not be representative for 24-h sodium intake. Participants in both studies did not adhere to a strictly regulated sodium diet before the testing days. Finally, in this analysis, we only focused on sodium intake, yet as discussed, sodium balance involves many factors that could be measured to better understand the effects of GLP-1 RA treatment on sodium intake.

We feel that the current study can best be considered as hypothesis generating, and we propose future studies using validated methods to measure sodium balances, such as weighted food diaries combined with 24-h urinary sodium excretion, complemented by measurements of hormones and/or fMRI studies, to understand how GLP-1 RAs affect sodium homeostasis in humans.

Conclusion

In the acute setting, GLP-1 RAs reduce sodium intake by a generalized reduction in food intake, but after prolonged intervention, no effect on sodium intake can be found. Given the beneficial effects of GL-1 RAs on cardiovascular outcomes beyond glycemic control, it seems it would be useful to further study whether an effect on sodium intake could be involved.

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