Effects of Glucagon-Like Peptide-1 Receptor Agonists on Hypothalamic-Pituitary-Adrenal Axis in Healthy Volunteers

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Context: Recent findings from animal and human studies indicate that glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) modulate stress response by activating the hypothalamic-pituitary-adrenal (HPA) axis, which may have relevant clinical implications.

Objective: To investigate the influence of GLP-1 RA treatment on HPA axis activity compared with placebo in healthy volunteers.

Design: Double-blind, randomized, crossover study.

Setting: University Hospital Basel, Switzerland.

Participants: Twenty healthy volunteers.

Intervention: Dulaglutide (Trulicity®) 1.5 mg and placebo (0.9% sodium chloride) were given subcutaneously once weekly for 3 weeks.

Main Outcome Measures: Twenty-four-hour urinary free cortisol, circadian rhythm of serum and salivary cortisol, cortisol after 1 mg dexamethasone suppression test, and cortisol levels before and after stimulation with ACTH.

Results: Urinary free cortisol levels were similar under dulaglutide [median (interquartile range) 240 nmol/L (164, 324)] vs placebo [188 nmol/L (133, 338), $P = 0.131$]. The circadian rhythm of serum and salivary cortisol were comparable in both groups as were cortisol levels after dexamethasone [dulaglutide 28 nmol/L (22, 47.5) vs placebo 26.5 nmol/L (15.8, 45.5), $P = 0.4$]. Serum cortisol levels in dulaglutide and placebo treated participants were 522 nmol (388, 710) and 530 nmol/L (394, 747), before ($P = 0.6$), and 658 nmol/L (604, 810) and 636 nmol/L (512, 910) after ACTH stimulation ($P = 0.87$).

Conclusion: Our results suggest that there is no activation of the HPA axis by long-term GLP-1 RA exposure, particularly dulaglutide, at the medically approved dosage of 1.5 mg once weekly. **(*J Clin Endocrinol Metab* 104: 202–208, 2019)**

The incretin hormone glucagon-like peptide 1 (GLP-1) is secreted from the enteroendocrine L cells and in the central nervous system by neurons of the ventrolateral medulla and the nucleus of the solitary tract of the hindbrain. GLP-1 is released in response to nutrition intake (1–6). It has a glucose-dependent insulinotropic effect on the pancreatic β cells, reduces glucagon release, and decelerates gastric emptying. Importantly, GLP-1

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Abbreviations: DST, dexamethasone suppression test; GLP-1, glucagon-like peptide-1; HPA, hypothalamic-pituitary-adrenal; IQR, interquartile range; RA, receptor agonist; VAS, visual analog scale.

also exerts central effects (*e.g.,* by promoting satiety) (1, 2, 7–9). Because of these properties, there is a widespread and continuously increasing use of GLP-1 receptor agonists (RAs) for the treatment of diabetes mellitus and obesity. It is therefore crucial to understand the various additional effects of these substances (10).

Recent findings point to a role of GLP-1 in stress response: GLP-1 immunoreactive fibers innervate the hypothalamic paraventricular nucleus directly connecting GLP-1 with CRH neurons (11, 12). In rodents, acute central and peripheral administration of GLP-1 and the more potent GLP-1 RA exendin-4 have been shown to activate the hypothalamic-pituitary-adrenal (HPA) axis by raising ACTH and cortisol levels in the blood (13). Likewise, plasma ACTH and cortisol levels were increased in humans after a single acute IV administration of GLP-1(14). Two recent studies showed that subchronic (7 to 14 days) treatment with the GLP-1 RA exendin-4 or liraglutide in rodents also induced a chronic stress–resembling state by rising cortisol levels, interrupting circadian cortisol secretion, and causing adrenal gland hypertrophy (13, 15). So far, the effects of prolonged exposure to GLP-1 RA on cortisol metabolism in humans are not known.

The aim of this study was therefore to explore HPA axis activity after a prolonged (*i.e.,* 3 week) treatment with the GLP-1 RA dulaglutide (Trulicity®) at a commonly used dosage compared with placebo in healthy volunteers.

Materials and Methods

Study design

This is a single-center, randomized, double-blind, placebo controlled, crossover trial with the objective to evaluate the effects of dulaglutide (Trulicity®) vs placebo on the HPA axis in healthy volunteers (NCT03141632). The trial was conducted at the University Hospital Basel, Switzerland, from October 2016 to May 2017. Twenty healthy volunteers were recruited. Inclusion criteria for study participants were age ≥18 years and ≤65 years and no regular drug intake, except for oral contraceptives. Exclusion criteria were history of pancreatitis and previous treatment with GLP-1 RAs within the last 3 months. The study protocol and study medication were approved by both the local ethic committee and the national agency for the authorization and supervision of therapeutic products (Swissmedic). Written informed consent was obtained from all study participants.

Study objective and outcomes

The objective of this study was to explore possible effects of dulaglutide vs placebo on HPA axis activity. HPA axis activity was assessed by different test methods and outcome measures: 24-hour free urinary cortisol levels, circadian rhythm of serum and salivary cortisol, serum cortisol after a 1-mg dexamethasone suppression test (DST), and serum cortisol values before and after ACTH stimulation.

Procedures

The procedures and timeline of the study are schematically explained in Fig. 1.

All study participants received a 3-week treatment with either dulaglutide (Trulicity®) 1.5 mg subcutaneously or placebo (0,9% sodium chloride) subcutaneously once weekly. In a second 3-week treatment phase, the study drugs were interchanged. Treatments (dulaglutide or placebo) were given in random order. The highest approved dosage of dulaglutide (1.5 mg once weekly) was used to detect any clinical relevant changes. The two treatment phases were separated by a washout period of 3 weeks. At the end of the second week during treatment, a 1-mg DST was performed. Serum cortisol levels were measured at 8:00 AM, 8 hours after intake (12:00 AM) of 1 mg dexamethasone. In the week after the third study drug injection, participants performed an overnight fast (no food and drinks) for 12 hours and were then observed at the study center during an 8-hour evaluation visit (8:00 AM to 4:00 PM). At patients' arrival, a catheter was placed in an antecubital vein. Blood for cortisol measurements was drawn at 8:00 AM, 12:00 PM, and 4:00 PM; at the same time, saliva was collected for the measurement of salivary cortisol. Twenty-four-hour urine collection was started at 8:00 AM for measurement of urinary cortisol. Standardized meals were served at fixed times and water *ad libitum* was available. Gastrointestinal symptoms (*e.g.,* nausea, abdominal pain) were assessed by a visual analog scale (VAS; *e.g.,* 1 = no nausea to 10 = maximal nausea). Before leaving the study center at 4:00 PM, participants were instructed to collect their urine until 8:00 AM the next day as well as saliva at 8:00 PM and 12:00 AM of the same day for later cortisol measurements. The day after, participants again presented at the study center at 8:00 AM and a 1 μg ACTH test (Synacthen®) was performed: blood samples were taken at 0 and 30 minutes (after injection of ACTH) to measure serum cortisol levels.

All serum, urinary, and salivary cortisol levels were determined with the Elecsys Cortisol Test 2010 (Roche Diagnostics GmbH, Mannheim, Germany), which is an electrochemiluminescence immunoassay with a limit of detection between 0.5 and 1750 nmol/L.

Statistical analysis

The full analysis set consisted of 20 participants. For all comparisons between dulaglutide and placebo, paired-samples Wilcoxon tests were performed. All variables are summarized in terms of their median and interquartile range (IQR). Analyses were performed using the statistic program R, version 3.4.3.

Results

Baseline characteristics

Twenty participants (60% female) aged 26.8 (±9.2) with the mean body mass index of 22.9 (±2.8) completed the study. Seven of the twelve female participants used combined hormonal contraceptives during the time of the study.

Baseline characteristics are presented in Table 1.

Effects on HPA axis

All outcome measures regarding HPA axis activity are summarized in Table 2.

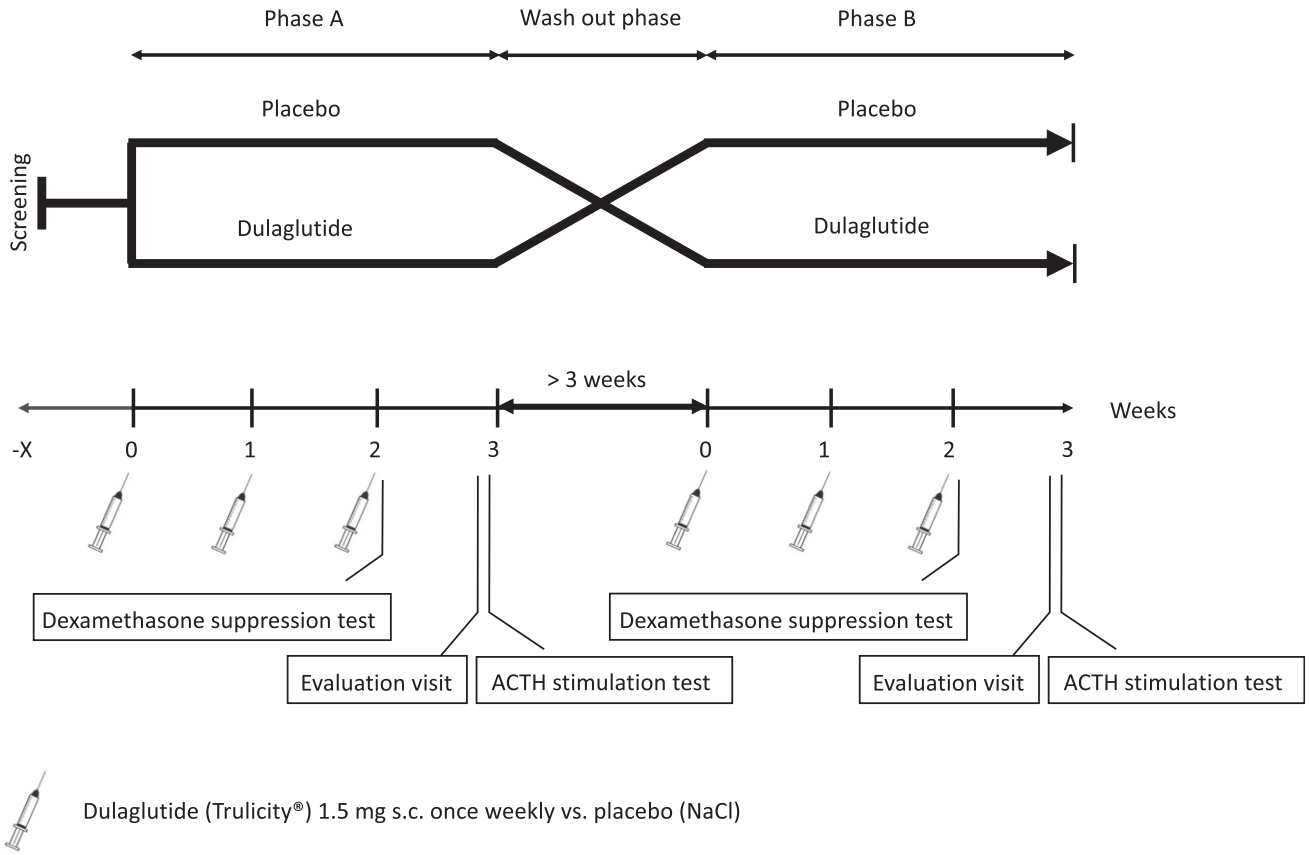

Figure 1. Study flow. s.c., subcutaneous.

Twenty-four-hour urinary free cortisol levels

The 24-hour urinary free cortisol levels were similar under dulaglutide and placebo [median (IQR) dulaglutide 240 nmol/L (164, 324) vs placebo 188 nmol/L (133, 338), $P = 0.13$] [Fig. 2(a)].

Circadian rhythm of serum and salivary cortisol

The circadian rhythm of serum cortisol levels was comparable under dulaglutide and placebo [Fig. 2(b)]. The same applied to salivary cortisol levels including midnight salivary cortisol levels, which were median (IQR) 5.1 nmol/L (2.65, 8.2) vs 5.9 nmol/L (4.4, 9.02) in dulaglutide and placebo-treated participants, $P = 0.24$ [Fig. 2(b)].

Serum cortisol after 1 mg DST

Serum cortisol levels after DST were higher under dulaglutide vs placebo [median (IQR) 34 nmol/L (24.5, 86) vs 31.5 nmol/L (17.5, 74.8), $P = 0.04$], as depicted in Fig. 2(c). This result was mainly influenced by four participants showing clearly elevated and outlying cortisol levels after dexamethasone suppression (>250 nmol/L) during dulaglutide treatment. Three suffered from gastrointestinal symptoms at the time point of the test in the dulaglutide phase, but not in the placebo phase (with adequate suppression of cortisol under placebo). One male patient showed high cortisol values (656 vs 298 nmol/L)

Table 1. Baseline Characteristics

	Mean (SD)
Sex, female/male	60% (12)/40% (8)
Age, y	26.8 (±9.2)
Body mass index, kg/m^2	22.9 (±2.8)
Systolic blood pressure, mm Hg	126.6 (±12.7)
Diastolic blood pressure, mm Hg	78.1 (±11.1)
Pulse, beats/min	71.2 (±10.7)
Weight, kg	70.4 (±12.4)

Table 2. Effects of GLP-1 RAs on HPA Axis Activity

	Dulaglutide	Placebo	
	Median [IQR]	Median [IQR]	*P*
24-h urine volume, mL	1250 [975, 2080]	1689 [1400, 2040]	0.04
24-h urinary free cortisol, nmol/24 h	240 [164, 324]	188 [133, 338]	0.13
Midnight salivary cortisol, nmol/L	5.1 [2.65, 8.2]	5.9 [4.4, 9.02]	0.24
Serum cortisol after DST, nmol/L[a]	28 [22, 47.5]	26.5 [15.8, 45.5]	0.4
Baseline serum cortisol, nmol/L[b]	522 [388, 710]	530 [394, 747]	0.6
Stimulated serum cortisol, nmol/L[b]	658 [604, 810]	636 [512, 910]	0.87

[a]Serum cortisol levels after 1 mg DST after exclusion of 4 participants with outliers.

[b]Serum cortisol levels before baseline serum cortisol and 30 min after ACTH stimulation.

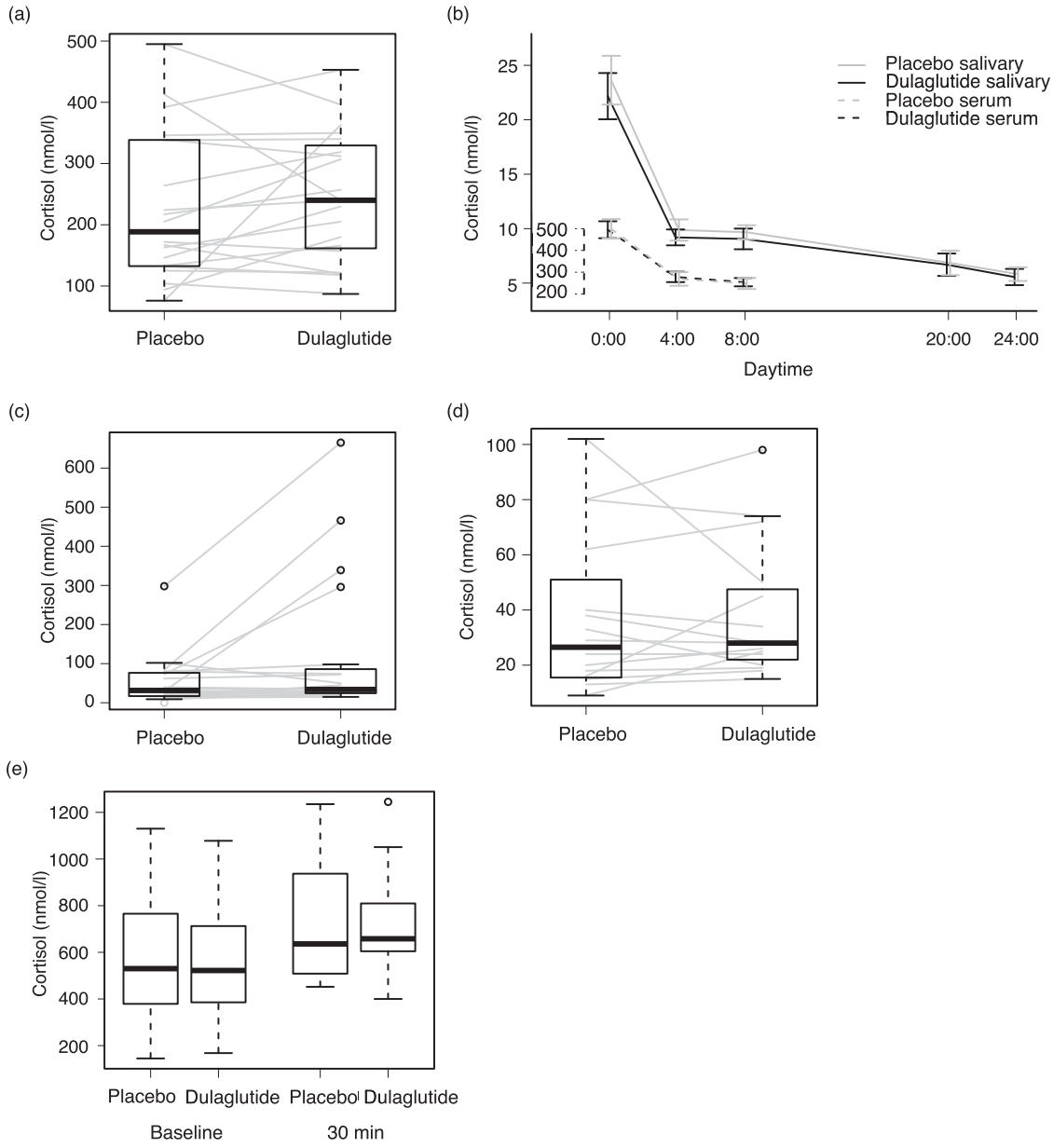

Figure 2. Effects of GLP-1 RAs on HPA axis activity. (a) Twenty-four-h urinary free cortisol under dulaglutide vs placebo. Thick line indicates the median; box indicates the IQR; whiskers include all points within the range of 1.5× the IQR. (b) Circadian rhythm of serum and salivary cortisol level. Solid lines show salivary cortisol for dulaglutide and placebo; dashed lines show blood plasma cortisol levels. Error bars contain two standard errors of the mean (one up, one down). (c) 1-mg DST. Serum cortisol levels under dulaglutide vs placebo. Thick line indicates the median; box indicates the IQR; whiskers include all points within the range of 1.5× IQR. (d) 1-mg DST (outliers omitted). Serum cortisol levels under dulaglutide vs placebo after exclusion of four participants with outliers. Thick line indicates the median; box indicates the IQR; whiskers include all points within the range of 1.5× the IQR. (e) Serum cortisol before and after ACTH stimulation for dulaglutide vs placebo. Thick line indicates the median; box indicates the IQR; whiskers include all points within the range of 1.5× the IQR. Times shown in military time.

both in the dulaglutide and placebo phase and was suspected to be noncompliant. After exclusion of these four participants, there was no statistical significance in cortisol levels under dulaglutide vs placebo [median (IQR) 28 nmol/L (22, 47.5) and 26.5 (15.8, 45.5), P = 0.4] [Fig. 2(d)].

Four female participants showed higher cortisol levels than expected (cortisol >50 nmol/L), both under dulaglutide and placebo. All four participants were treated with combined hormonal contraceptives.

In all previously mentioned participants with elevated cortisol levels after dexamethasone suppression (>50 nmol/L), Cushing syndrome could be excluded based on normal 24-hour urinary free cortisol and late night salivary cortisol levels.

Serum cortisol values before and after ACTH stimulation

Serum cortisol values before ACTH stimulation were similar under dulaglutide compared with placebo [median

(IQR) dulaglutide 522 nmol (388, 710) vs placebo 530 nmol/L (394, 747), $P = 0.6$]. After ACTH stimulation, they increased to 658 nmol/L (604, 810) and 636 nmol/L (512, 910) ($P = 0.87$), in dulaglutide- and placebo-treated participants, respectively. The resulting increase in serum cortisol levels from before to after ACTH stimulation did not differ between dulaglutide vs placebo [median (IQR) 160 nmol/L (84.5, 203) vs 132 nmol/L (83, 208), $P = 0.31$] [Fig. 2(e)].

Clinical effects

There was a significant weight effect during the dulaglutide treatment phase (−2.11 kg vs −0.29 kg during placebo, $P < 0.01$). Except for weight, no other body state parameter (blood pressure, heart rate) was significantly influenced by dulaglutide (data not shown).

Adverse events

Observed adverse events were mostly of a gastrointestinal nature (*i.e.,* nausea, abdominal pain, and diarrhea) (Table 3). Nausea was more common in the dulaglutide group, with 11 participants reporting some degree of nausea [median VAS (range) 4 (1-10)], especially in the early treatment phase. Two participants reported nausea during the evaluation visit, but at a very low score (VAS 1). On placebo, only a single nausea event (VAS 2) was reported, occurring during week 2.

Other gastrointestinal symptoms were also more common under dulaglutide (three events in week 1, one in week 2, and in week 3). In the placebo group, only one participant experienced abdominal pain in weeks 2 and 3).

Discussion

This study shows no effect of a 3-week treatment with the GLP-1 RA dulaglutide at 1.5 mg once weekly, on the HPA axis in healthy volunteers. Simulating the effect of a chronic treatment with GLP-1 RAs, these results do not support the idea that GLP-1 RAs cause a persistent activation of the HPA axis as suggested in previous studies (13, 15, 16). Gil-Lozano *et al.* (13, 14) and Krass *et al.* (15) showed in an animal model that singular acute and subchronic (7 to 14 days) administration of GLP-1 (7-36) amide and the GLP-1 RA exendin-4 and liraglutide induce elevated basal plasma cortisol levels compared with placebo. After the subchronic exposure, a chronic stress–resembling state with interrupted circadian cortisol secretion and adrenal gland hypertrophy was observed. In humans, acute IV administration of GLP-1 (7-36) amide increased plasma cortisol levels (14).

In contrast to the previous studies, our study focused on effects of a prolonged treatment duration, which is of higher clinical relevance because GLP-1 RAs are used in chronic diseases. Our finding of no effect on the HPA axis after a 3-week treatment stands in opposition to the observed acute effects in humans and rodents. Interestingly, the only test indicating higher cortisol levels in dulaglutide- vs placebo-treated participants was the DST, which was the earliest test performed (at the end of the second week). At that time point, many of dulaglutide-treated participants (11/20) reported gastrointestinal symptoms. This is in line with the literature showing that gastrointestinal adverse events peak in the early GLP-1 RA treatment period and then mostly resolve (17). We speculate that these initially pronounced gastrointestinal symptoms may be the reason for elevated cortisol levels in our and previous studies. Because the others were primarily animal studies, there was limited possibility to assess visceral illness. After a prolonged treatment period, subjects seem to adapt with regression of symptoms and normalization of cortisol secretion.

Furthermore, the finding that there is no prolonged effect on HPA axis activity in humans is strongly supported by recent outcome trials showing that chronic treatment with GLP RA (*e.g.,* liraglutide, semaglutide) is beneficial in terms of cardiovascular morbidity and mortality (18, 19).

The mechanism whereby circulating GLP-1 RAs may acutely activate the HPA axis remains unclear. In both animal model and in humans, elevated cortisol levels were preceded by a rise in ACTH, suggesting a central mechanism, likely mediated through CRH (3, 12–14). GLP-1 receptors are assumed to be expressed in the paraventricular nucleus of the hypothalamus, where CRH-producing neurons are located (20, 21). A direct activation of CRH via GLP-1 receptors seems plausible

Table 3. Gastrointestinal Symptoms Over the Study Period

	Baseline	Wk 1	Wk 2	Wk 3	Evaluation Visit	VAS Median (Range)
Nausea						
Dulaglutide	0	0	10	1	2	4 (1-10)
Placebo	0	0	1	0	0	2 (2)
Other gastrointestinal symptoms						
Dulaglutide	0	3	1	3	0	2 (2-3)
Placebo	0	0	1	1	0	1.5 (1-2)

VAS: 1 = minimal nausea/other gastrointestinal symptoms to 10 = maximal nausea/other gastrointestinal symptoms.

because small GLP-1 RA molecules [<400 to 500 daltons (*e.g.*, exenatide)] have been shown to cross the blood–brain barrier (22). However, how larger GLP-1 RA molecules (*e.g.*, dulaglutide, albiglutide) exert their central effects is a matter of debate. Their access to the central nervous system (passive diffusion, through fenestrated capillaries) might be hindered because of their large molecular size of >50 to 60 kilodaltons. Alternatively, a neural pathway influenced by peripherally active GLP-1 RAs is discussed. GLP-1 RAs may activate afferent sensory nerve fibers, whose signals stimulate neurons of the solitary tract nucleus, which in turn activates hypothalamic neurons (23, 24).

Besides CRH, other factors may contribute to the acutely elevated cortisol levels (12): GLP-1 RAs seem to activate the autonomic nervous system, leading to increased sympathetic innervation (25, 26), which in turn increases adrenocortical responsivity to ACTH (12, 27). A direct activation of the adrenal gland or the pituitary seems unlikely because these tissues do not express GLP-1 receptors (12, 28). Whatever the mechanism, it seems that this is a transient effect no longer present after prolonged treatment with GLP-1 RAs.

The following limitations have to be mentioned: first, the number of participants was limited to 20 subjects (and after the exclusion of four participants to 16 subjects when analyzing cortisol levels after dexamethasone suppression). Second, this study provides no information about acute GLP-1 effects on HPA-axis activity because we did not measure cortisol levels at baseline and after the first two subcutaneous injections of dulaglutide. Third, our assessment of the circadian rhythm might not have detected subtle changes given that the frequency of sampling was limited to five and three measurements per 24 hours for salivary and plasma cortisol levels, respectively. Fourth, we used dulaglutide as a study drug and are not able to transfer these results to other GLP-1 RAs. Given the large molecular size of dulaglutide, it is possible that it does not cross the blood–brain barrier and has less central activity compared with other GLP-1 RAs such as liraglutide, semaglutide, or exenatide, which are of smaller size (29). Finally, the cortisol metabolism and its interaction with GLP-1 RAs might be different in subjects with obesity or diabetes, who were excluded in this study, compared with healthy volunteers. Both conditions may alter the blood–brain barrier, leading to an easier central access and enhanced central activity of GLP-1 (30).

The strength of our study is its prospective, double-blind, placebo-controlled, randomized crossover design. The highest approved dosage of dulaglutide, 1.5 mg, was used in all participants. Moreover, we used a wide array of diagnostic tests to measure different physiological parameters of cortisol; therefore, we can provide high-sensitivity detection of any change in cortisol metabolism.

In summary, our data show that a 3-week treatment with the GLP-1 RA dulaglutide does not affect the HPA axis in the way a chronic stress-resembling state does. Our results encourage the concept that GLP-1 RAs are good options for a long-term treatment of chronic diseases such as diabetes mellitus 2 and obesity.

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