ISSN 0362-1197, Human Physiology, 2019, Vol. 45, No. 6, pp. 685–692. © Pleiades Publishing, Inc., 2019.
Russian Text © The Author(s), 2019, published in Fiziologiya Cheloveka, 2019, Vol. 45, No. 6, pp. 116–123.

Effect of the Glucagon-like Peptide-1 Mimetic on Ion- and Osmoregulating Renal Functions in Normoglycemia and Hyperglycemia

A. V. Kutina[a], *, E. V. Balbotkina[a], T. A. Karavashkina[a], and E. I. Shakhmatova[a]

[a] *Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg, Russia*

**e-mail: kutina_anna@mail.ru*

Received October 5, 2018; revised January 9, 2019; accepted April 3, 2019

Abstract—Incretins are hormones with a wide range of biological activity. We studied the ratio of the glycemic effect of the glucagon-like peptide-1 mimetic and its effect on the renal excretion of sodium and water. It was found that both effects depend on the initial blood concentration of glucose. In normoglycemia, exenatide had no effect on blood sugar level, but it significantly increased urinary sodium excretion and reabsorption of solute-free water. In hyperglycemia the blood glucose concentration was normalized by exenatide, while the excretion of sodium by the kidneys and the reabsorption of solute-free water were increased to a small extent. This pattern was found both in patients with type 2 diabetes mellitus and in rats with hyperglycemia induced by intraperitoneal injection of glucose.

Keywords: hyperglycemia, glucagon-like peptide-1, sodium, solute-free water, kidney, diabetes mellitus, exenatide

DOI: 10.1134/S036211971904008X

Incretins are intestinal tract hormones involved in the regulation of carbohydrate metabolism. Their effects were discovered in the early 20th century, and the term incretin was proposed by La Barre in 1932 to designate the activity of the intestinal mucosa extract whose injection caused the blood glucose level to decrease [1]. The main incretins are glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) whose structures were identified in 1973 and 1985 [1]. Postprandial insulin secretion (50–70%) by pancreatic β-cells depends on GLP-1 [2]. In addition, GLP-1 acts as a metabolic signal for glucose-dependent suppression of glucagon by α-cells, delayed emptying of the stomach, and suppression of appetite [3]. Incretin-based medications have been developed for the treatment of type 2 diabetes mellitus (incretin mimetics, gliptins) [3–5]. Animal experiment and the experience of the clinical use of GLP-1 mimetics show that the spectrum of incretin functions is considerably wider than regulation of carbohydrate metabolism [6]. The GLP-1 receptors have been found to be located not only in β- and α-cells of the pancreas, but also in the liver, heart, brain, and kidneys. Animal experiments confirmed the involvement of GLP-1 in the regulation of water and salt homeostasis [7]. The natriuretic effect of GLP-1 and incretin mimetics has been described [8], as well as the influence on the excretion of other ions and water [7, 9].

The question of integration of a specific regulatory process into the general system of regulations in the whole organism, of the mechanisms of interaction between various hormones and biologically active substances is a fundamental physiological problem. Earlier, it was shown that, in the regulation of water–salt metabolism, the effect of incretins is superimposed on the action of other hormones, which provided for restoration of homeostasis even in differently directed shifts in the internal environment parameters. Incretins accelerate sodium excretion and reabsorption of water in hyperosmia, chlorides in hyperchloremia, water in hypoosmia and hyperhydration, etc. [9]. Hyperglycemia may lead to shifts in the blood electrolyte composition [10] and change the direction and/or intensity of the effect of incretin mimetics on the kidney [11]. It was of interest to assess the ratio of the hypoglycemic effect of incretin to its influence on the excretion of ions and water by the kidney. We carried out the study of the effect of the incretin mimetic exenatide on the renal function at different blood levels of glucose. Patients with type 2 diabetes mellitus and normal rats with hyperglycemia induced by parenteral administration of glucose were examined.

METHODS

Twenty women with type 2 diabetes mellitus were enrolled in the study. The ages of the patients varied

between 34 and 66 years; the disease duration was in the range of 1–30 years. The subjects were treated in the Leningrad Regional Clinical Hospital on an inpatient basis. The basic therapy of type 2 diabetes mellitus included diet and sugar-lowering drugs in all patients. None of them received incretin mimetics earlier.

On the examination day, the patients did not take medications, nor did they have breakfast to avoid stimulation of GLP-1 secretion. The urine was sampled before and after exenatide injections with voluntary voiding; the time over which each urine sample was accumulated, as well as its volume, was recorded. Immediately after collecting the first morning urine sample (approximately in the period from 8:00 to 8:30 a.m.), which was used for assessing the initial parameters of the renal function in each specific patient, they had their blood from the cubital vein for biochemical tests withdrawn, the glucose level in capillary blood measured, and exenatide (Baeta, AstraZeneca, United Kingdom) injected subcutaneously at a 5 μg once-daily dose. After exenatide injection, the urine was sampled for 2 h, and the glucose level was measured repeatedly at the end of the observation period.

Experiments were performed on 40 female Wistar rats with a body mass of 180–230 g. The rats were maintained in plastic cages with wood-particle bedding (five rats in a cage). They were fed on the standard granulated feed (OOO Laboratorkorm, Russia) and drank water ad libitum. In the evening before the experiment, the feed was taken away, but the animals had easy access to water. At the end of each experiment, the animals were returned into the vivarium cages and used in the subsequent experiments not earlier than in a week's time.

In order to model hyperglycemia in rats, intraperitoneal injection of 0.15 g of *D*-glucose (Ekros, Russia) per 100 g of body weight (b. w.) in the form of 50% solution [12] was used. Exenatide was injected intramuscularly at a dose of 0.2 μg in 0.1 mL per 100 g b. m., for which purpose the Baeta preparation was diluted 120-fold with saline. Capillary blood from the tails of the animals was sampled before and 15, 30, and 60 min after intraperitoneal injection of glucose solution to analyze the dynamics of glycemia on exposure to exenatide; exenatide or vehicle was injected 15 min prior to the load test. In order to study the kidney function on exposure to the incretin mimetic, intact animals were injected exenatide or simultaneously an intraperitoneal injection of glucose. Diuresis was recorded with spontaneous voiding for 4 h, for which purpose the animals were placed in individual cages with a wire floor, a funnel, and a measuring tube. In order to analyze osmolality and the serum composition of electrolytes, the blood was sampled from the common carotid artery under Zoletil anesthesia (5 mg intramuscularly per 100 g b. m. of Zoletil, Virbac, France) in individual experiments before and after intraperitoneal glucose load at 5 and 30 min. The number of animals in each series was ten.

Osmolality in the serum and urine samples was determined by the cryoscopic method using a 3300 microosmometer (Advanced Instruments, United States); the sodium and potassium concentration, a Sherwood-420 flame photometer (Sherwood Scientific, United Kingdom) and an Erba XL-200 automatic biochemical analyzer ion-selective unit (Erba Lachema, Czech Republic). The urine and serum creatinine measurements were made using the kinetic method by Jaffe reaction; the serum glucose measurements, using the glucose oxidase test on an automatic biochemical analyzer. The capillary blood concentration of glucose was measured using an Accu-Chek Performa glucose meter (Roche Diagnostics, Germany). The level of glycated hemoglobin was determined using a D-10 analyzer (BIO-RAD, United States).

The following parameters characterizing the functional capacities of the kidneys were used: $U_{Na}V$, sodium ion excretion; C_{Osm}, solute clearance; C_{Na}, sodium ion clearance; $T^{C}_{H_2O}$, reabsorption of solute-free water. Below are the equations for the calculation of the clearance of solutes, sodium ions, and reabsorption of solute-free water: $C_{Osm} = (U_{Osm}/P_{Osm})V$, $C_{Na} = (U_{Na}/P_{Na})V$, $T^{C}_{H_2O} = (U_{Osm}/P_{Osm})V - V$, where U_{Osm} is urine osmolality; P_{Osm} is serum osmolality; U_{Na} is urinary sodium concentration; P_{Na} is serum sodium concentration; V is diuresis. In rats, all the kidney function parameter values were calculated per 100 g b. w.; in human subjects, per 1.73 m^2 of the body surface area.

The statistical processing data are represented as $M \pm m$; for comparison and the assessment of significance, paired and unpaired Student's t tests with Bonferroni correction were used; the difference was considered to be statistically significant at $p < 0.05$.

RESULTS

All the patients enrolled in the study were divided into two groups according to the fasting blood glucose level on the examination day: below 6.2 mM (normoglycemia) and above 6.2 mM (hyperglycemia). The clinical characteristic of patients included in the study groups is represented in Table 1. The patients from the two groups did not differ in age, duration of diabetes mellitus, the complication rate, and concomitant diseases. In twelve patients, the course of diabetes mellitus was complicated by the development of diabetic nephropathy (in all at the microalbuminuria stage); in five, by diabetic retinopathy and/or polyneuropathy. Arterial hypertension, dyslipidemia, chronic gastroduodenitis, and cholelithiasis were among concomitant pathologies. The creatinine level in all the patients corresponded to normal values and did not differ in two experimental groups. The level of glycated hemo-

Table 1. Characteristic of examined patients with type 2 diabetes mellitus

Parameter	Normoglycemia ($n = 10$)	Hyperglycemia ($n = 10$)
Age, years	56 ± 3	53 ± 2
Duration of diabetes mellitus, years	1–30	1–20
Incidence of diabetic nephropathy, %	60	60
Glycated hemoglobin, %	6.6 ± 0.3	9.5 ± 0.8*
BMI	34.4 ± 1.8	33.9 ± 1.6
Incidence of AH, %	70	70
SBP, mmHg	136 ± 6	128 ± 4
DBP, mmHg	78 ± 2	78 ± 2
Blood osmolality, mOsm/kg H_2O	301 ± 2	300 ± 2
Blood sodium, mM	147 ± 2	140 ± 2*
Blood potassium, mM	5.0 ± 0.1	4.4 ± 0.2*
Creatinine, μM	69 ± 7	65 ± 7

* Statistically significant intergroup differences (t test, $p < 0.05$). BMI denotes body mass index; AH, arterial hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

globin was shown to be significantly higher in the group of patients with fasting hyperglycemia at the moment of examination (Table 1). Thus, despite the administered therapy, long-term control of the blood sugar level in these patients was worse. All the patients were overweight: four patients had pre-obesity; nine, grade 1 obesity; four, grade 2 obesity; three, grade 3 obesity. The body mass index and the arterial pressure level on the examination day did not differ significantly in the two experimental groups (Table 1). As revealed, patients with hyperglycemia had a lower blood level of sodium and potassium (but within normal range). Note that blood osmolalities in the two groups did not differ (Table 1).

The injection of exenatide into hyperglycemic patients was shown to significantly decrease the blood glucose concentration 2 h after the moment of injection (Fig. 1). In patients with fasting normoglycemia, the injection of exenatide did not influence the blood glucose concentration. These data agree with the glucose-dependent character of the insulinotropic effect of incretin mimetics [3–5]. Analysis of the kidney function in those examined showed that the injection of exenatide statistically significantly increased the excretion of sodium ions and reabsorption of solute-free water. This effect was more pronounced in normoglycemic patients (Fig. 2).

In order to test the hypothesis that the character of the action of exenatide on the renal function depends on the level of glycemia, animal experiments were performed. Hyperglycemia in normal Wistar rats was induced by the performance of the intraperitoneal glucose tolerance test. Unlike oral, intraperitoneal injection of glucose does not stimulate incretin secretion, owing to which an increase in the blood insulin concentration and normalization of the glycemic level occur slowly [5, 6].

As soon as 5 min after intraperitoneal injection of 50% glucose, the rat blood glucose level and osmolality were shown to increase by 11.7 ± 1.1 mM and by 9 ± 1 mOsm/kg H_2O, respectively; after 30 min of the experiment, hyperglycemia persisted, but the sodium ion concentration decreased; serum osmolality virtually returned to the initial value (Table 2). Analysis of

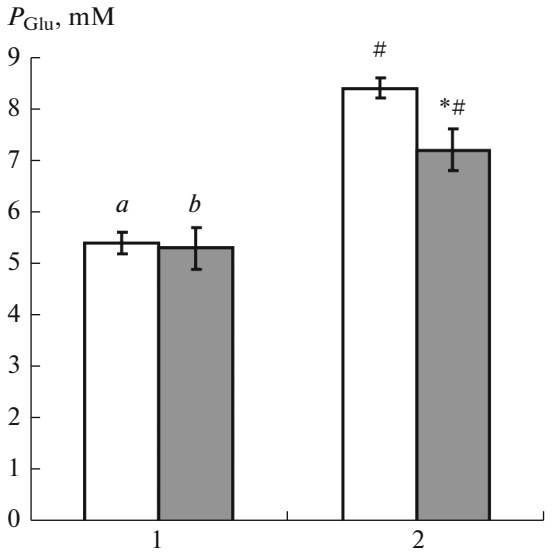

Fig. 1. Effect of a single injection of exenatide on the blood glucose concentration (P_{Glu}) in patients with type 2 diabetes mellitus with a different initial glycemic levels. Groups of patients: 1, with the initial normoglycemia; 2, with the initial hyperglycemia; the parameters: *a*, before and *b*, 2 h after exenatide injection. Statistically significant differences in the groups: * before and after exenatide injection (paired t-test, $p < 0.05$); # between the groups of patients with the initial normoglycemia and hyperglycemia (t test, $p < 0.05$).

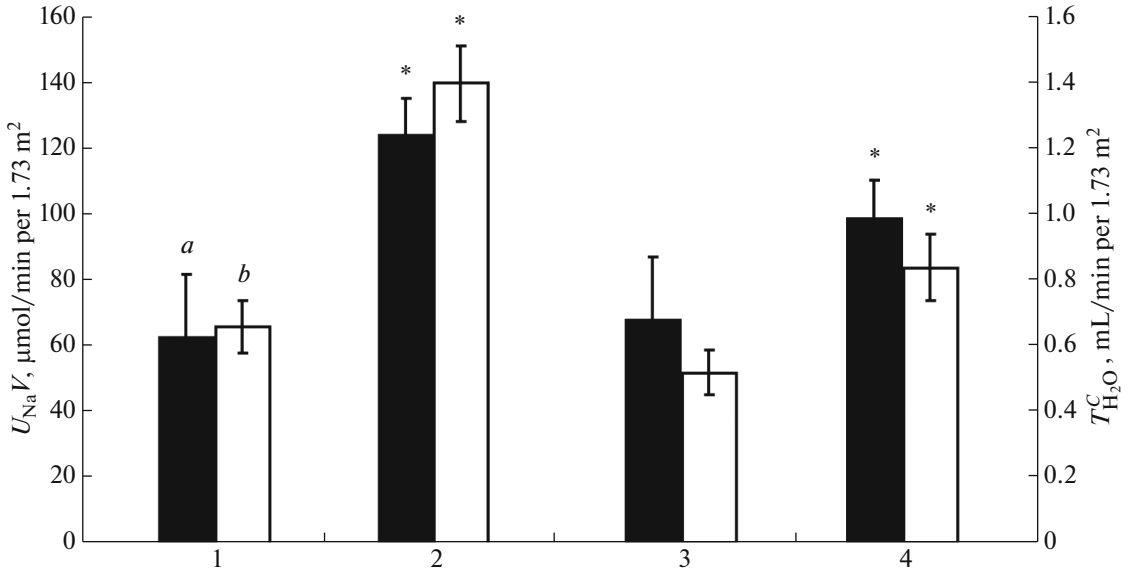

Fig. 2. Effect of exenatide on sodium ion excretion ($U_{Na}V$) and reabsorption of solute-free water $\left(T^C_{H_2O}\right)$ in patients with type 2 diabetes mellitus at different initial glycemic levels. Groups of patients: 1 and 2, with initial normoglycemia (2 h before and after exenatide injection, respectively); 3 and 4, with initial hyperglycemia (2 h before and after exenatide injection, respectively); parameters: *a*, $U_{Na}V$; *b*, $T^C_{H_2O}$. * Statistically significant difference in the groups before and after exenatide injection (paired *t* test, $p < 0.05$).

the sodium and glucose dependence of blood osmolality showed that 5 min after the load test, the rise in osmolality was determined by a sharp increase in the blood glucose concentration (Fig. 3). Reversal of blood osmolality to normal values after 30 min occurred due to both the glucose and sodium concentration decrease. At 30 min after the load sample, an inverse relationship between the level of glucose and sodium ions was revealed in rat blood ($r = -0.74$, $p < 0.05$) (Fig. 3).

In hyperglycemia induced by intraperitoneal injection of glucose, the sodium ion excretion by the rat kidneys decreased (from 5.88 ± 1.17 to 0.22 ± 0.04 μmol per 100 g b. m. within 2 h) as did the clearance of solutes and sodium and reabsorption of solute-free water (Fig. 4) compared with intact animals. The injection of exenatide against this background normalized the blood glucose level (Fig. 5) and stimulated reabsorption of water in the kidneys (Fig. 4); the sodium ion excretion was retained at a level (0.80 ± 0.25 μmol per 100 g b. m. within 2 h), which was significantly lower than in the control animals without glucose injection. Exenatide induced in normoglycemic rats a marked increase in the solute clearance, primarily due to the excretion of sodium ions, as well as increased reabsorption of solute-free water (Fig. 4).

DISCUSSION

The results of examination of diabetic patients with various levels of glycemia at the time of exenatide injection showed distinctions in the level of the effect on the excretion of sodium and reabsorption of water. Similar shifts were shown in normal animals whose hyperglycemia was induced by intraperitoneal injection of glucose. In this study, the excreted sodium fraction in response to the injection of exenatide varied in rats between 0.02 ± 0.01 and 6.5 ± 0.6% at dif-

Table 2. Rat serum osmolality and concentrations of glucose and sodium and potassium ions at different times after intraperitoneal load with glucose solution

Blood serum parameters	0 min ($n = 10$)	5 min ($n = 10$)	30 min ($n = 10$)
Glucose, mM	6.1 ± 0.2	17.8 ± 1.4*	12.2 ± 0.9*
Osmolality, mOsm/kg water	295 ± 1	304 ± 1*	298 ± 2*
Sodium, mM	143 ± 1	142 ± 1	132 ± 1*
Potassium, mM	4.0 ± 0.1	4.1 ± 0.1	4.8 ± 0.1*

* Statistically significant differences between the parameter values at 0 min (*t*-test with Bonferroni correction, $p < 0.05$).

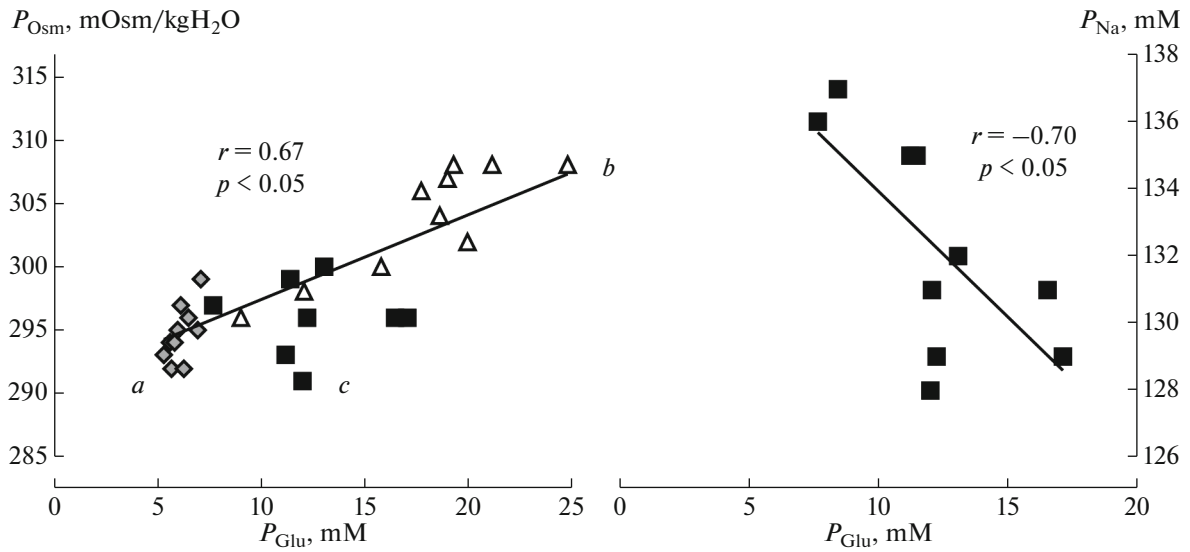

Fig. 3. Dependence of serum osmolality (P_{Osm}) and the serum sodium concentration (P_{Na}) on the glycemic level (P_{Glu}) after intraperitoneal injection of glucose solution. Values: *a*, 0 min, *b*, 5 min; *c*, 30 min after the beginning of the experiment. *r* is Pearson correlation coefficient.

ferent initial blood levels of glucose. The results of this study allow us to explain the inconsistency of the data on the acute effects of incretin mimetics in humans available in the literature. In most studies carried out during examination of patients with type 2 diabetes mellitus, statistically significant but small changes in sodium ion excretion were found [13, 14]; no influence of the drugs on the glomerular filtration rate or the renal hemodynamics parameters was revealed [13–16]. At the same time, examination of overweight patients without carbohydrate metabolism disorder demonstrated an increase in the excreted sodium fraction to 2.45%, a rise of the glomerular filtration rate (by 20%), intraglomerular pressure and effective renal plasma flow, and lower resistance of an afferent arteriole influenced by exenatide [17].

Earlier, the data on the relationship between the direction and degree of the effects of incretins on the excretion of water and salts by the kidneys and the current state of the water–salt balance were obtained in the animal experiments [7]. It was established that the incretin GLP-1 and its mimetics depressed proximal sodium reabsorption [8, 18, 19], and the sodium ion excretion value observed under certain conditions depends, among other things, on the influences of other hormones and biologically active substances on the processes of distal sodium reabsorption (vasopressin, mineralocorticoids, prostaglandins, etc.) [7, 9]. This study showed that acute hyperglycemia in rats contributes to a significant suppression of sodium excretion by the kidneys and interferes with the natriuretic action of exenatide. This effect may be determined by a hyperglycemia-induced decrease in the blood level of sodium and by a response-induced increase in the ion reabsorption by the renal tubules. Long-term hyperglycemia in humans may also lower the blood sodium concentration [20]; this effect is aimed at normalizing its osmolality and maintaining osmotic homeostasis. Several studies showed that the effect of diuretics and natriuretics was substantially less salient during hyperglycemia [21–23]. Another mechanism of antinatriuretic effect of hyperglycemia in rats and humans may be linked to insulin secretion. It was shown earlier that insulin increased sodium reabsorption in a nephron [24] and the functional activity of sodium cotransporters (Na/K/2Cl [25], Na/Cl [26]), as well as the number of distal epithelial Na-channels [27], which may require to prevent postprandial renal sodium losses [28].

Incretins are involved in both regulation of carbohydrate metabolism and maintenance of water–salt homeostasis. The results of this study show an essential role of the physiological background against which the realization of the effects of an individual biologically active substance occurs. The increase in the blood glucose level leads to a number of changes in the internal environment of the body necessitating the maintenance of a stable level of solutes, shifts in osmolality and the blood concentration of the main ions. The maintenance of homeostasis under hyperglycemic conditions requires the functional systems of the body to change both the utilization of glucose by the cells and the ion and water transport by the kidneys. These processes are reflected by increased reabsorption of solute-free water and limited sodium excretion characteristic of hyperglycemia. Under these conditions, GLP-1 mimetic aids in normalization of the blood concentration of glucose and retention of water

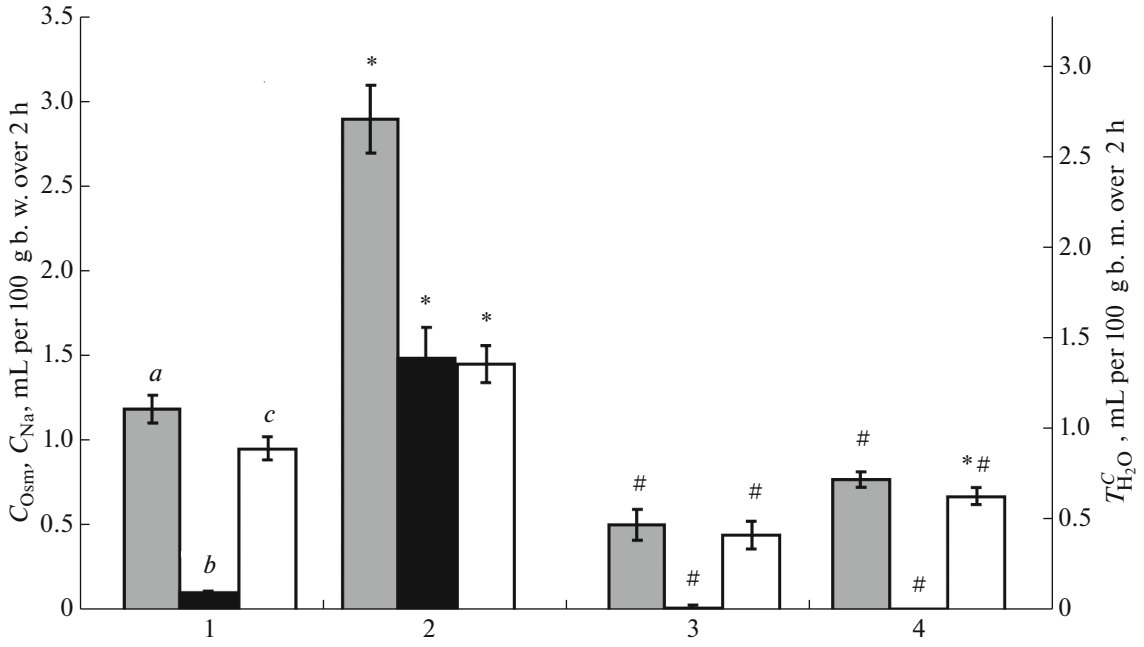

Fig. 4. Effect of exenatide on the reabsorption solute-free water $\left(T^{C}_{H_2O}\right)$, clearance of osmotically active substances (C_{Osm}) and sodium ions (C_{Na}) in rats against the background of hyperglycemia induced by intraperitoneal glucose load. Groups of animals: 1, control; 2, exenatide; 3, glucose load; 4, glucose load + exenatid ; parameters: *a*, C_{Osm}; *b*, C_{Na}; *c*, $T^{C}_{H_2O}$. Statistically significant differences: * with the corresponding control (*t* test with Bonferroni correction, $p < 0.05$); # with a similar group without glucose load (*t* test with Bonferroni correction, $p < 0.05$).

in the body; an increase in sodium excretion occurs to a lesser degree than on exposure to exenatide in normoglycemic humans and animals.

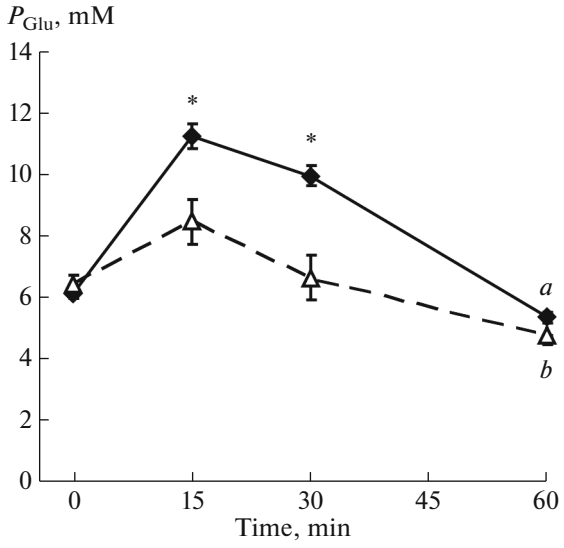

Fig. 5. Influence of exenatide on the glycemic level (P_{Glu}) after intraperitoneal glucose load in rats. Groups of animals: *a*, glucose load; *b*, glucose load + exenatide. * Statistically significant differences with the group without exenatide injection (*t* test with Bonferroni correction, $p < 0.05$).

CONCLUSIONS

The results demonstrate the relationship between the influence of GLP-1 mimetics on the excretion of sodium and water by the kidneys and the tendencies of shifts in the physicochemical parameters of the internal environment. Both the hypoglycemic effect of exenatide and its influence on the kidney functions in patients with type 2 diabetes mellitus and rats with hyperglycemia induced by intraperitoneal injection of glucose have been shown to depend on the initial blood sugar level. The results of the study give evidence of the homeostatic significance of the system of incretins and emphasize the necessity of integrative physiological investigations in the whole body for understanding the role of individual humoral factors in the general system of regulations.

FUNDING

This study was carried out in the framework of the state contract of the Federal Agency for Scientific Organizations of Russia (state registration no. AAAA-A18-118012290371-3) and supported in part by the Russian Foundation for Fundamental Research, project no. 17-04-01216.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest connected with the publication of this article.

Statement on the welfare of animals. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in studies involving human participants were in accordance with the biomedical ethics principles formulated in the 1964 Helsinki Declaration and its later amendments and approved by the bioethics commission of the Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences (St. Petersburg). Informed consent was obtained from all individual participants involved in the study after their being explained the potential risks and advantages, as well as the essence of the future study.

REFERENCES

1. Shestakova, M.V. and Vikulova, O.K., Modern pharmacotherapy of type 2 diabetes using analogues of glucagon-like peptide-1 (GLP-1), *Sakharnyi Diabet*, 2007, no. 1, p. 9.
2. Holst, J.J., Deacon, C.F., Vilsboll, T., et al., Glucagon-like peptide-1, glucose homeostasis and diabetes, *Trends Mol. Med*., 2008, vol. 14, no. 4, p. 161.
3. Galstyan, G.R., Karataeva, E.A., and Yudovich, E.A., Evolution of glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes, *Sakharnyi Diabet*, 2017, vol. 20, no. 4, p. 286.
4. Biryukova, E.V. and Yakubova, T.R., Byetta: past, present, and future, *Eff. Farmakoter.*, 2015, no. 11, p. 34.
5. Gallwitz, B., Novel therapeutic approaches in diabetes, *Endocrinol. Dev.*, 2016, vol. 31, p. 43.
6. Nauck, M.A. and Meier, J.J., Incretin hormones: their role in health and disease, *Diabetes Obes. Metab*., 2018, vol. 20, suppl. 1, p. 5.
7. Natochin, Yu.V., Marina, A.S., and Kutina, A.V., The role of incretin as an integrator of sodium and water balance regulation, *Dokl. Biol. Sci.*, 2014, vol. 458, no. 1, p. 271.
8. Crajoinas, R.O., Oricchio, F.T., Pessoa, T.D., et al., Mechanisms mediating the diuretic and natriuretic actions of the incretin hormone glucagon-like peptide-1, *Am. J. Physiol. Renal Physiol.*, 2011, vol. 301, no. 2, p. F355.
9. Kutina, A.V., Golosova, D.V., Marina, A.S., et al., Role of Vasopressin in the regulation of renal sodium excretion: interaction with glucagon-like peptide-1, *J. Neuroendocrinol.*, 2016, vol. 28, no. 4. https://doi.org/10.1111/jne.12367
10. Shutskaya, Zh.V., Shakhmatova, E.I., Kuznetsova, A.A., and Natochin, Yu.V., The role of the kidneys in the regulation of osmolality and concentrations of cations in the blood serum in hyperglycemia, *Hum. Physiol.*, 2008, vol. 34, no. 5, p. 601.
11. Shakhmatova, E.I., Pimenova, E.V., and Shutskaya, Zh.V., The influence of Byetta (Exenatide) on the osmoregulatory function of the kidneys in humans with diabetes mellitus, *Eksp. Klin. Farmakol.*, 2014, vol. 77, no. 3, p. 24.
12. De Vogel-van den Bosch, J., Hoeks, J., Timmers, S., et al., The effects of long- or medium-chain fat diets on glucose tolerance and myocellular content of lipid intermediates in rats, *Obesity*, 2011, vol. 19, no. 4, p. 792.
13. Tonneijck, L., Smits, M.M., Muskiet, M.H., et al., Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomized, double-blind, placebo-controlled trial, *Diabetologia*, 2016, vol. 59, no. 7, p. 1412.
14. Tonneijck, L., Smits, M.M., Muskiet, M.H., et al., Renal effects of DPP-4 inhibitor sitagliptin or GLP-1 receptor agonist liraglutide in overweight patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled trial, *Diabetes Care*, 2016, vol. 39, no. 11, p. 2042.
15. von Scholten, B.J., Hansen, T.W., Goetze, J.P., et al., Glucagon-like peptide 1 receptor agonist (GLP-1 RA): long-term effect on kidney function in patients with type 2 diabetes, *J. Diabetes Complications*, 2015, vol. 29, no. 5, p. 670.
16. Skov, J., Pedersen, M., Holst, J.J., et al., Short-term effects of liraglutide on kidney function and vasoactive hormones in type 2 diabetes: a randomized clinical trial, *Diabetes Obes. Metab.*, 2016, vol. 18, no. 6, p. 581.
17. Muskiet, M.H., Tonneijck, L., Smits, M.M., et al., Acute renal haemodynamic effects of glucagon-like peptide-1 receptor agonist exenatide in healthy overweight men, *Diabetes Obes. Metab.*, 2016, vol. 18, no. 2, p. 178.
18. Schlatter, P., Beglinger, C., Drewe, J., and Gutmann, H., Glucagon-like peptide 1 receptor expression in primary porcine proximal tubular cells, *Regul. Pept.*, 2007, vol. 141, no. 1–3, p. 120.
19. Thomson, S.C., Kashkouli, A., and Singh, P., Glucagon-like peptide-1 receptor stimulation increases GFR and suppresses proximal reabsorption in the rat, *Am. J. Physiol. Renal Physiol.*, 2013, vol. 304, no. 2, p. F137.
20. Roscoe, J.M., Halperin, M.L., Rolleston, F.S., and Goldstein, M.B., Hyperglycemia-induced hyponatremia: metabolic considerations in calculation of serum sodium depression, *Can. Med. Assoc. J.*, 1975, vol. 112, no. 4, p. 452.
21. Mozaffari, M.S. and Schaffer, S.W., Impaired saline-stimulated diuresis and natriuresis in the conscious hypertensive glucose-intolerant rat, *Am. J. Hypertens.*, 2002, vol. 15, no. 1, p. 58.
22. Marwaha, A. and Lokhandwala, M.F., Diminished natriuretic response to dopamine D1 receptor agonist, SKF-38393 in obese Zucker rats, *Clin. Exp. Hypertens.*, 2003, vol. 25, no. 8, p. 509.
23. Arumugam, S., Sreedhar, R., Miyashita, S., et al., Comparative evaluation of torasemide and furosemide on rats with streptozotocin-induced diabetic nephropathy, *Exp. Mol. Pathol.*, 2014, vol. 97, no. 1, p. 137.
24. Brands, M.W. and Manhiani, M.M., Sodium-retaining effect of insulin in diabetes, *Am. J. Physiol.-Regul. Integr. Comp. Physiol.*, 2012, vol. 303, no. 11, p. R1101.
25. Ueda-Nishimura, T., Niisato, N., Miyazaki, H., et al., Synergic action of insulin and genistein on

$Na^+/K^+/2Cl^-$ cotransporter in renal epithelium, *Biochem. Biophys. Res. Commun.*, 2005, vol. 332, no. 4, p. 1042.

26. Chavez-Canales, M., Arroyo, J.P., Ko, B., et al., Insulin increases the functional activity of the renal NaCl cotransporter, *J. Hypertens.*, 2013, vol. 31, no. 2, p. 303.

27. Blazer-Yost, B.L., Esterman, M.A., and Vlahos, C.J., Insulin-stimulated trafficking of ENaC in renal cells requires PI3-kinase activity, *Am. J. Physiol., Cell. Physiol.*, 2003, vol. 284, p. C1645.

28. Irsik, D.L., Blazer-Yost, B.L., Staruschenko, A., and Brands, M.W., The normal increase in insulin after a meal may be required to prevent postprandial renal sodium and volume losses, *Am. J. Physiol.-Regul. Integr. Comp. Physiol.*, 2017, vol. 312, no. 6, p. R965.

Translated by E. Babchenko