Exenatide Enhances Kaliuresis under Conditions of Hyperkalemia

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Experiments on Wistar rats showed that exenatide (0.015-0.5 nmol per 100 g body weight) somewhat increased renal excretion of potassium from 7±1 to 16±1 μmol/h/100 g body weight ($p<0.05$) in animals with normal serum concentration of glucose (4.6±0.4 mM) and potassium (4.3±0.1 mM). Exenatide dramatically enhanced excretion of potassium under conditions of hyperkalemia (11.4±0.4 mM) produced by intraperitoneal injection of 1.25% KCl solution (5 ml per 100 g body weight). During the first postinjection hour, potassium excretion increased 2-fold and attained 97±11 μmol/h/100 g body weight in comparison with potassium load alone (47±9 μmol/h/100 g body weight, $p<0.05$). The data attest to a possible role of peptide regulators in normalization of potassium balance via renal mechanisms.

Key Words: *homeostasis; potassium excretion; kidney; exenatide*

Maintenance of stable potassium concentration in blood plasma is an obligatory condition of stable work of the cells in various organs and systems (the concentration of potassium ions in the cytoplasm is almost 30-fold higher than that in the extracellular fluid) [3]. Hypo- and hyperkalemia are well recognized as the symptoms of certain pathologies [2]. Changes of potassium concentration in the blood serum lead to severe functional disturbances in cardiomyocytes and neurons [7,9]. During consumption and digestion of vegetable food, large quantity of potassium is absorbed in the intestine and enters the blood. Under these conditions, stability of K^+ concentration in the blood plasma could be disturbed unless the consorted counteracting work of the system providing potassium homeostasis in the blood. The experiments with administration of potassium salines in the stomach revealed transient elevation of potassium concentration in the blood followed by rapid excretion of K^+ by the kidneys [1,8,10]. The mechanism of potassium homeostasis in the blood suggests involvement of insulin known to help potassium entry into the cells in the company with glucose [4]. In its turn, secretion of insulin is stimulated by glucagon-like peptide 1 and its synthetic analog exenatide, which was observed during hyperglycemia [6]. Thus, it is instructive to reveal the individual role of exenatide-like factors in potassium homeostasis during administration of extra potassium salts into organism under normoglicemia, which is not accompanied with up-regulation of insulin secretion [5].

This work was designed to examine the effect of exenatide on renal kaliuretic function in animals not administered with glucose, but injected intraperitoneally with KCl.

MATERIALS AND METHODS

The experiments were carried out on female Wistar rats weighing 180-240 g. All protocols have been approved by IEPB animal care committee. Exenatide was dissolved in 0.9% NaCl saline to concentrations of 0.05, 0.15, 0.5, 1.5 or 5 μM and injected intramuscularly in a dose of 0.1 ml per 100 g body weight (n=10 in each series). Potassium load (PL) was produced by intraperitoneal injection of 1.25% KCl (5 ml/100 g body weight). PL was accompanied with injection of

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physiological saline in control group (n=8) or exenatide (0.15 nmol per 100 g body weight) in the experimental group (n=10).

The rats were placed in the individual tight boxes with a wire floor. Spontaneous urinary excretion was recorded for 4 h. The experimental rats were injected with exenatide (n=6), potassium (n=8) or their combination (n=8). On postinjection hour 1, blood was drawn under nembutal-chloralose narcosis (nembutal, 0.75%; chloralose, 0.37%; dose 0.6 ml/100 body weight).

Osmolarity of blood serum and urine was measured by cryoscopy on a 3300 Micro-Osmometer (Advanced Instruments Inc.). Creatinine was assayed with kinetic method by the Jaffe reaction using an EOS Bravo W automatic biochemical analyzer. Sodium and potassium concentrations were measured using a Corning-410 Flame Photometer under air-propane flame. Concentration of glucose was determined in the capillary blood with the help of test strips using an Accu-Chek Go (Roche) glucometer. Diuresis, electrolyte excretion, rate of glomerular filtration was calculated per 100 g body weight. Exenatide was synthesized in Chair of Natural Compounds Chemistry in Department of Chemistry of St. Petersburg State University under the guidance of Prof. M. I. Titov.

The data were analyzed statistically using Statistica 6.0 software and presented as $M\pm m$. Significance was assessed at $p<0.05$ by ANOVA test and the Newman–Keuls test for multiple comparisons.

RESULTS

Exenatide injection did not change potassium level in blood serum (Table 1). The peptide slightly increased renal potassium secretion, the increase was the same despite the applied doses ranged from 0.015 to 0.5 nmol per 100 g body weight.

To examine the renotropic effect of exenatide under positive potassium balance, the rats were injected intraperitoneally with 1.25% KCl (5 ml/100 g body weight). This concentration of potassium ions is isosmotic to the blood serum and does not provoke the response of osmoregulatory system. PL dramatically (3-fold) enhanced the concentration of potassium ions in blood serum (Table 1). Under these conditions, the blood serum osmolarity remained normal due to the balance of univalent cations manifested by the decrease in concentration of sodium ions (Table 1). PL increased renal excretion of K^+, which grew up persistently and attained maximum in 2.5 h postinjection (Fig. 2).

In the experiments with PL, exenatide (0.15 nmol/100 g) dramatically accelerated renal excretion of potassium ions (Fig. 2). A pronounced elevation of this excretion (more than 2-fold) was observed as early as 30-40 min postinjection (Table 2, Fig. 2). Thus, exenatide promoted a rapid excretion of injected potassium ions.

The comparative study of renal excretion of sodium and potassium ions over 1 h after PL attests to a highly specific renal reaction. Individual injection of

TABLE 1. Effect of Exenatide (0.15 nM/100 g) and PL on Physicochemical Parameters of Rat Blood Serum 1 h Postinjection

Injection	n	P_{Osm}, mosmol/liter	P_{Na}, mM	P_K, mM
Control	17	291±1	135±1	4.3±0.1
PL	8	293±2	122±1*	13.0±0.8*
Exenatide	6	286±1*	130±1*	4.5±0.1
PL+exenatide	8	292±2	123±1*	11.4±0.4*

Note. *$p<0.05$ compared to the control.

TABLE 2. Effect of Exenatide (0.15 nM/100 g) and PL on Na^+ and K^+ Renal Excretion during the First Hour Postinjection

Injection	n	$U_{Na}V$, μmol/h	EF_{Na},%	U_KV, μmol/h	EF_K,%
Control	10	22±3	0.9±0.1	7±1	9±1
PL	8	8±2*	0.5±0.1*	47±9*	29±4*
Exenatide	20	343±18*	14.2±1.0*	16±1*	19±2*
PL+exenatide	10	84±12*°	5.1±0.9*°	97±11*°	58±7*°

Note. $p<0.05$ compared to the *control, °PL. All indices were calculated by 100 g body weight.

exenatide (0.15 nmol/100 g) to rats greatly elevated excretion of Na^+ by 15.6 times and increased excretion of K^+ by "merely" 2.3 times. Different renal behavior was observed during combined administration of PL and exenatide, *i.e.*, under conditions characterized with positive balance of potassium ions in the organism and the acute need to restore the initial level of potassium in the blood. Under conditions of hyperkalemia, injection of exenatide (0.15 nmol/100 g) enhanced renal excretion of Na^+ and K^+ ions, respectively, by 3.8 and 13.9 times in comparison with the control values. Thus, exenatide 2-fold increased potassium excretion during PL (Table 2). Calculation of the excreted fractions of filtered sodium and potassium (EF_{Na} and EF_K, Table 2) convincingly demonstrates the role of renal tubular cells in these effects, which moderate reabsorption of Na^+ ions and dramatically elevate secretion of K^+ with enhancement of EF_K by 6 times. Evidently, the reaction of the renal control system depends on the ionic balance: under positive balance of K^+ ions, sodium excretion changes to a lesser degree than potassium excretion. What mechanisms underlie this reasonable behavior?

The data obtained demonstrate the role of peptides that are similar to glucagon-like peptide 1 (exenatide is one of such mimetics) in the maintenance of potassium balance in the organism. It is important that exenatide exerted its effect under conditions of normoglicemia: serum concentrations of glucose were 4.6±0.4 mM in control and 4.5±0.3 mM after injection of the drug. In other words, the effect of exenatide did not depend on re-distribution of K^+ ions related to changes in glucose level. According to current views, involvement of kidneys in potassium balance depends on mineralocorticoids [3], although other endocrine factors were not analyzed in this respect in the literature. It is noteworthy that restoration of potassium balance under the action of exenatide is a selective process triggered by the need to excrete a surplus of potassium ions from the organism. Thus, the data obtained indicate the possible role of the peptide regulators in that scope of renal functions, which are directed to maintain and normalize potassium balance.

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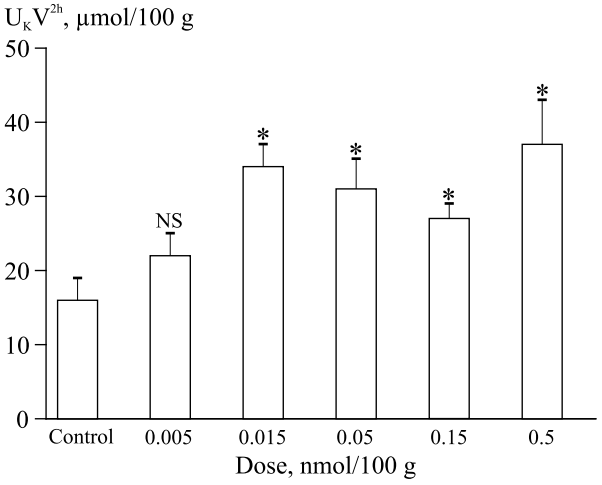

Fig. 1. Dependence of renal potassium excretion on exenatide dose. Ordinate: total excretion of K^+ during 2 h postinjection. *p<0.05 in comparison with the control.

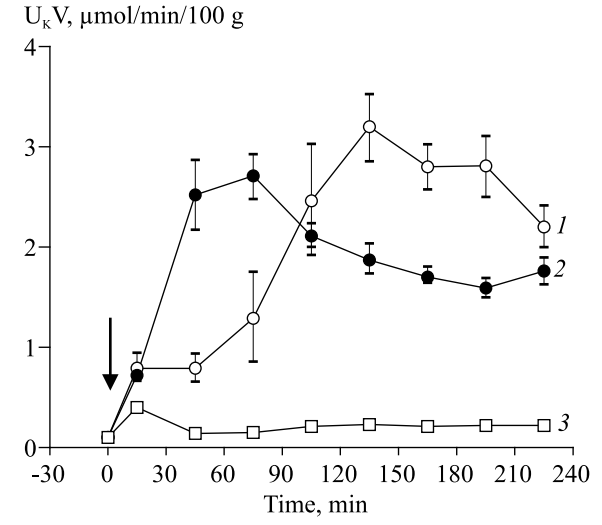

Fig. 2. Effect of exenatide on renal potassium excretion U_KV after PL. Arrow marks injection of: PL (*1*), PL+exenatide (*2*), and exenatide (*3*).

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