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Evidence of the role of the vagal nerves as a monitor in the gastrointestinal-renal axis of natriuresis in human: Effects of vagotomy

Constantinos E. Alifieris[a,b,*], Dimitrios T. Trafalis[a], Aris D. Efstratopoulos[c], Emmanuel K. Alifieris[d,e,f]

[a] Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[b] Department of Surgery, Agia Olga Hospital, Athens, Greece
[c] Third Internal Medicine and Hypertension Unit, General Hospital of Athens, National and Kapodistrian University of Athens, Athens, Greece
[d] Medical School, National and Kapodistrian University of Athens, Athens, Greece
[e] Second Surgery Department, General Hospital of Chania "Agios Georgios", Chania, Greece
[f] Second Surgery Department, Piraeus General Hospital "Agios Pandeleimon", Piraeus, Greece

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ABSTRACT

This study aimed to investigate the mechanism of gastrointestinal regulation of natriuresis. Sixteen subjects without (group I) and sixteen subjects with a truncal vagotomy (group II), were given a daily diet of 18 mmol of sodium for 5 days (D1–D5). The sodium deficit for this period was calculated for each subject and on the morning of day-6 (D6), their cumulative deficit (E) was given as 3% NaCl. In both groups the subjects were divided to receive the hypertonic saline either orally (Ior, IIor) or intravenously (Iiv, IIiv). During the period of low sodium diet when compared to group II subjects of group I (1) had a greater weight loss ($p < 0.005$), (2) demonstrated a larger drop in pulse pressure ($p < 0.005$), (3) achieved a positive sodium equilibrium later (D5 vs D4) and (4) developed a greater sodium deficit ($p < 0.005$). During the two 12 h periods of D6, both Ior and Iiv exhibited greater natriuresis during the first 12 h period ($p < 0.0001$) whereas both IIor and IIiv did so during the second 12 h period ($p < 0.0001$). On D6 Ior excreted the greatest percentage of E (E%; 35.63% ± 3.12%, $p < 0.0001$) compared to Iiv (17.06% ± 1.78%), IIor (16.03% ± 3.54%) and IIiv (15.39% ± 2.77%) whereas E% was not different between the other subgroups. These results indicate that the differential natriuresis between oral and intravenous sodium loading in previously sodium deprived subjects, is due to a mechanism in which the vagal nerves play a significant role as part of neural reflex or via a natriuretic hormone.

1. Introduction

1.1. Background

Renal sodium excretion depends on the sodium intake, on hormonal factors (e.g. aldosterone) and on local factors including hemodynamic effects (e.g. renal artery perfusion pressure) which regulate the glomerular filtration rate (GFR) and the tubular reabsorption of sodium. Sodium balance is linked to the control of extracellular fluid volume through venous or arterial pressure and volume receptors (Wadei and Textor, 2012). Earlier evidence has demonstrated that in human subjects once they were sodium depleted, oral intake of sodium is followed by a greater diuresis of sodium than is with intravenous sodium intake (Lennane et al., 1975). The difference in natriuresis was specific to sodium since this phenomenon was not observed when the loading was in the form of hypertonic glucose or NH_4Cl. In a later study, it was suggested that in man (Carey, 1978), this differentiated natriuresis is not regulated by a mechanism that depends on aldosterone which was against earlier suggestions (Lennane et al., 1975). Sodium excretion seems to be regulated by a series of sensors and effectors. The potential sensors of the changes in sodium intake, total body sodium and extracellular fluid volume along with the potential effectors of sodium excretion can be divided into physical, hormonal and neural (Reinhardt and Seeliger, 2000). Recent research however postulated that a gastrointestinal-renal axis that regulates natriuresis does not exist (Preston et al., 2012) and furthermore, that earlier suggestions of a role of a guanylin-family peptide in the differential natriuresis cannot be proven (Michell et al., 2008). In the investigation of neural factors as part of this regulation, bilateral cervical vagotomy in dogs was associated with an antidiuretic effect and increased natriuresis

* Corresponding author at: Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, 75 Mikras Asias, 115-27 Goudi, Athens, Greece.
E-mail address: kalifier@med.uoa.gr (C.E. Alifieris).

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(Schrier et al., 1972) whereas bilateral subdiaphragmatic vagotomy in rats impeded natriuresis and caused retention of sodium and hypertension (Reyes et al., 1992).

1.2. Objectives

The purpose of this study was to investigate further the mechanism of splanchnic regulation of natriuresis, and in particular the significance of the subdiaphragmatic vagal nerves as part of this mechanism in man. In this randomized physiological clinical trial, we aimed to determine total, cumulative and mean hourly renal sodium excretion following an oral versus an intravenous hypertonic saline loading in sodium-depleted volunteers versus in sodium-depleted subjects who had undergone truncal vagotomy. The hypothesis was that if a vagal mechanism that affects natriuresis existed, it would have been abolished in the vagotomized subjects whereas it would be intact in the non-vagotomized. Thus, natriuresis following oral sodium loading would be greater than that following intravenous loading in those with intact vagal nerves, but this difference would not be observed in those with severed vagal nerves.

2. Methods

2.1. Eligibility criteria

In this study, inclusion criteria demanded subjects older than 18 years who had previously undergone truncal vagotomy with antrectomy or pyloroplasty for (1) emergent or elective use in patients intolerant, non-compliant or resistant to medical therapy, (2) complicated peptic ulcer disease in patients expected to have high recurrence rates or (3) other surgical or medical indications including medication allergies and patient preference. Truncal vagotomy was performed just below the diaphragm by a complete division of the left and right vagal nerves (also known as anterior and posterior) above the gastroesophageal junction and above the hepatic, celiac or any other variable or accessory branches at this level. Sections of these trunks were sent to the pathologist for microscopic evidence that the vagal nerves had been truly divided. Those pathology reports were necessary for patient inclusion to this study. For the control group, subjects with a history of duodenal ulcers without any previous surgery for peptic ulcer were selected. Subjects were excluded from the study if history or medical examination or basal laboratory measurements revealed any signs or symptoms of renal disease, diabetes, anemia, active infection, hematuria, cerebrovascular disease, or coronary artery disease and its complications. Subjects on any kind of chronic medical treatment would be excluded and any subjects would have a delayed entry to the study for at least 15 days post-use of any kind of short-term medical treatment (such as antibiotics). A 7-day window period was also applied for cessation of habitual use of smoking and alcohol intake. Subjects were also not allowed to exercise or consume caffeine or tea 48 h prior to- and during the experiment. Subjects were withdrawn if they demonstrated non-compliance to the study protocol. Prior to the study initiation, a careful medical and surgical history was taken and a full medical exam was performed.

2.2. Subjects

A total of 32 volunteers were studied. They were divided into two groups: Group I was composed of 16 Caucasian subjects with history of ulcers of the duodenal bulb. These were fourteen men and two women, of ages ranging from 31 to 67 years (mean 46.1 years), weighing 48–85.4 kg (61.74 ± 2.94; mean ± S.E.M.) with a body mass index (B.M.I.) of 18.36–27.26 kg m^{-2} (21.95 ± 0.81) and a body surface area (B.S.A., DuBois) of 1.49–2.02 m^2 (1.70 ± 0.04). Group II was composed of 16 Caucasian men of ages ranging 33–57 years (mean 46.6) who had undergone subdiaphragmatic bilateral vagotomy for the treatment of duodenal ulcers 1–36 months before the study (mean 7.2 months), weighing 53–81.8 kg (64.56 ± 2.06) with a BMI of 19–26.64 kg m^{-2} (22.5 ± 0.55) and a BSA of 1.56–2 m^2 (1.74 ± 0.07). Vagotomy with antrectomy was performed in 13 subjects and vagotomy with pyloroplasty was performed in 3 subjects. All of the subjects were volunteers and had given written informed consent. The study was approved by the local ethics committee and was in full compliance with the World Medical Association Declaration of Helsinki regarding the ethical principles for medical research involving human subjects.

2.3. Experimental protocol

The experiments were performed on a continuous 7-day period and included two phases. The first phase comprised of a control-day of no intervention with habitual diet (day 0 or D0) followed by a continuous 5-day period (day 1 or D1 to day 5 or D5) of a controlled sodium diet to create a sodium deficit based on previous experience (Carey, 1978); the second phase was the day of delivery of a calculated amount of the created sodium deficit (D6). D6 was divided in two 12-h periods, the first further divided into three 4-h fractions (Q1 to Q3) and the second period divided into two 6-h fractions (Q4 and Q5).

A 24-h urine sample from 07:00 of D0 to 07:00 of D1 as well as a basic metabolic panel was required to measure renal function and natriuresis. Baseline height (Marsden H-268, Marsden Weighing Machine Group Ltd., Rotherham, UK) and weight (Seca 755, Sigma Med Co, Spata, Greece) measurements were taken. The subjects from D1 and onwards were allowed to drink only distilled water as needed. The rest of the daily diet included 300 g of unsalted bread, 150 g of unsalted spaghetti, 300 g lean chicken, 2 medium-sized eggs, 200 ml of fresh milk and 400 g of cauliflower. The diet was divided in 3 separate meals at 07:30, 13:30 and 19:30. This low-sodium diet provided only 18 mmol sodium, 130 mmol of potassium and 2019 kcal per day. On each day the subject would be awakened at 06:45 emptied their bladder at 07:00 and then would be weighed, examined and have blood sampled. During examination the blood pressure was measured first in the reclining and then in the standing position. Then blood samples were drawn from an antecubital vein. The patient would continue the low-sodium diet and was instructed to maintain a reclined position throughout the day with minimal exercise as possible and was allowed to stand up for micturition and eating.

On the morning of D6 at 07:00 after examination and urine and blood sampling, the quantity of sodium deficit was calculated and given to each patient in the form of 3%NaCl solution over 30 min. All the subjects continued with the same diet. The sodium replenishment was given orally to eight subjects of group I (subgroup Ior) and eight subjects of group II (Subgroup IIor) while the remaining half of subjects in each group (subgroup Iiv and subgroup IIiv) received intravenous sodium loading via an intravenous antecubital catheter from the contralateral arm to the one that blood samples were taken. The choice of subjects for each subgroup was randomized by coin toss and the two females were equally distributed between Ior and Iiv. The quantity of sodium given to cover their deficit was calculated as following: the low-sodium diet provided only 18 mmol Na per 24 h. This was subtracted from the amount of sodium excreted in urine per 24 h. To the sodium deficit for the 5-day period, 25 mmol (5 mmol per day) was added for extra-renal loss (National Research Council, 1989). The sum was regarded as the patient's total sodium deficit.

24-h urine output was measured daily for sodium, potassium and creatinine and creatinine clearance was normalized to BSA (DuBois and DuBois, 1989). Arterial systolic (SBP) and diastolic (DBP) pressures were measured using a previously calibrated mercury sphygmomanometer (Focal Corporation FC-113, Kashiwa, Japan). In each patient the pulse pressure (PP) was calculated (PP = SBP − DBP) and the mean arterial pressure (MAP) was estimated (MAP = DBP + PP/3). On the morning of D0 to D5, measurements were made of amounts of