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Water-retention effect of suberogorgin was due to secretion of antidiuretic hormone in rat

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KEY WORDS suberogorgin; vasopressins; prostaglandins E; aldosterone; adrenalectomy; desoxycorticosterone; hypophysectomy; posterior pituitary hormones

ABSTRACT

AIM: To study the mechanism of antidiuretic effect of suberogorgin (Sub). **METHODS**: Conscious rat was given ig Sub 3.16 mg·kg^{-1} 20 min after water-loaded treatment and then urine was collected in metabolic cage. Ion excretion was determined in atomic emission spectrometry. Urinary prostaglandin E (PGE), plasma PGE, antidiuretic hormone (ADH), and aldosterone were measured with RIA. Sub *vs* pituitrin or DOCA effects were carried out in hypophysectomized or adrenalectomized rats. **RESULTS**: The urine volume and the excretions of urinary sodium and potassium were decreased, maximally by 91 %, 76 %, and 86 %, during the 24-h period after Sub. This antidiuretic effect possessed a progressive weakening with time. The concentrations of urinary PGE, plasma PGE, and ADH were increased by 25 %, 212 %, and 538 %, respectively, but plasma aldosterone was not significantly influenced, 2 h after Sub dosing. The response of urine-excretion of rat to Sub was almost resisted by hypophysectomy but not by adrenalectomy. **CONCLUSION**: Sub decreased the urine excretion by, at least in part, accelerating the secretion of ADH but neither by PGE nor by aldosterone.

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INTRODUCTION

Our previous studies demonstrated that suberogorgin (Sub) inhibited the activity of acetylcholinesterase (AChE)[1], but failed to directly affect the functions of α, β, H_1 receptors and Ca^{2+}, Na^+ channels[2,3]. Rat and cat experiments resulted in the antidiuretic effect of Sub[4], unlike other clinical AChE inhibitors such as neostigmine, physostigmine, and galanthamine, which indicated that Sub produced the water-retaining effect by an unknown means rather than the inhibition of AChE. The present study was engaged in initially elaborating this problem.

MATERIALS AND METHODS

Sub, spectrum pure, isolated by the Department of Chemistry, Sun Yat-Sen University, was dissolved in distilled water. Desoxycorticosterone (DOCA) and pituitrin (both injections) were manufactured by Shanghai Huaihai Pharmaceutical Factory.

Sprague-Dawley rats (n = 15, Grade Ⅱ, Certificate № 96A02) of either sex weighing 258 g ± s 10 g were bred in our laboratory. Rats were given ig Sub 3.16 mg·kg^{-1} 20 min after loading of water, and placed separately in stainless steel metabolism cages (20 - 22 ℃). Urine was collected and frozen for later analysis. The concentrations of urinary sodium and potassium were determined[4]. Urinary prostaglandin E (PGE), plasma PGE[5,6], antidiuretic hormone (ADH)[7,8], and aldosterone[9], which were sampled 2 and 4 h after Sub, were measured with RIA. Sub *vs* pituitrin or DOCA im effects were carried out in the rats (n = 10, 180 g ± s 5 g) which were hypophysectomized or adrenalectomized 72 h before medication.

Values were expressed as $\bar{x} \pm s$. Comparison between groups tested at the same time was made using paired t-test.

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RESULTS

Urine volume The cumulative urine volume of normal rat was decreased, maximally by 91 %, during 2 – 24 h after Sub dosing. This response displayed a time-dependent weakening tendency, while Sub still reduced the urine volume by 61 % 24 h after administration (Fig 1).

In the hypophysectomized rats, pituitrin 20 u · kg^{-1} im caused an obvious water-retention but Sub did not within 6 h after dosing. The latter only produced an insignificant effect except at 4 h (Fig 1).

The response of water excretion to Sub in adrenalectomized rat was similar to that in normal rats (Fig 1). Furthermore, Sub produced a stronger action compared with DOCA 50 mg·kg^{-1}.

Urinary ions and PGE The excretions of sodium and potassium were reduced within 24 h after Sub (Fig 2). These changes also displayed a time-dependence, like that in urine volume.

At 2 and 4 h after administration, Sub changed the cumulative excretion of urinary PGE from 144 ± 25 to 26 ± 5 and from 237 ± 41 to 68 ± 10 ng·kg^{-1} (all $P < 0.01$), although it increased the concentration of urinary PGE by 212 % and 153 %, respectively. (Tab 1)

Tab 1. Concentrations of urinary PGE and plasma PGE, ADH, and aldosterone in normal rats after administration of Sub. $n = 8 - 10$ samples. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* Sub 0 mg·kg^{-1}.

Time/ h	Sub/ mg·kg^{-1}	PGE/mg·L^{-1} Urine	PGE/mg·L^{-1} Plasma	ADH/ ng·L^{-1}	Aldosterone/ ng·L^{-1}
2	0	10.6 ± 2.4	34 ± 7	1.6 ± 0.3	26 ± 7
	3.16	21.3 ± 4.0^c	42 ± 8^b	10.2 ± 3.5^c	22 ± 6^a
4	0	9.7 ± 2.2	39 ± 8	1.8 ± 0.4	31 ± 8
	3.16	15.4 ± 3.1^c	46 ± 9^a	8.0 ± 3.1^c	28 ± 5^a

Plasma levels of PGE, ADH, and aldosterone At 2 and 4 h after Sub, increases of 25 % and 17 % in PGE, and of 538 % and 400 % in ADH were observed, respectively, but no obvious change in aldosterone was found. (Tab 1)

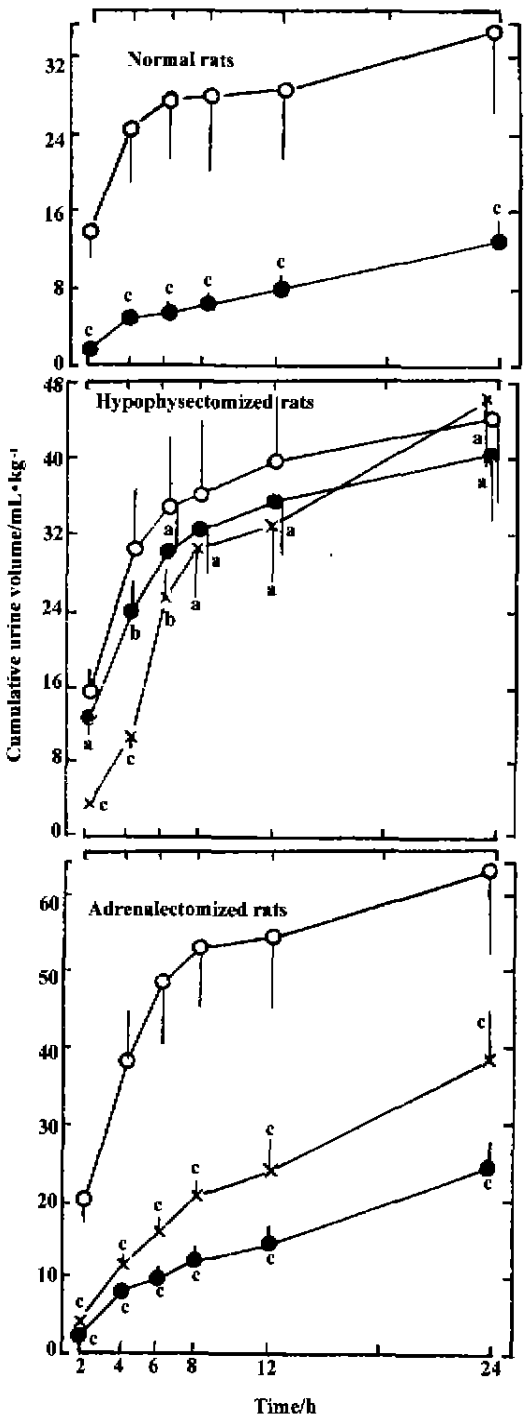

Fig 1. Effects of Sub on the cumulative urine volumes in normal-($n = 15$), hypophysectomized-($n = 10$), and adrenalectomized-($n = 10$) rats. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* Water. Water (○), Sub 3.16 mg·kg^{-1} (●), pituitrin 20 u · kg^{-1} (×) in hypophysectomized rats, and DOCA 50 mg · kg^{-1} (×) in adrenalectomized rats.

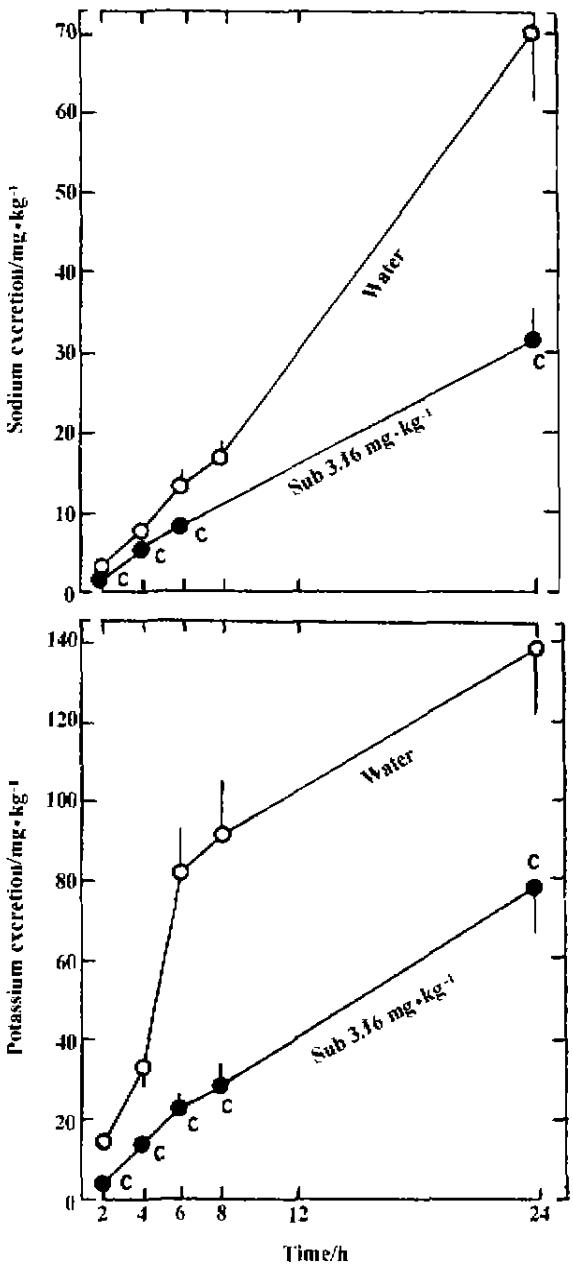

Fig 2. Effects of Sub on the cumulative excretions of urinary Na and K in normal rats. $n = 10$ rats. $\bar{x} \pm s$. $^cP < 0.01$ *vs* water.

DISCUSSION

Our previous study demonstrated that indometacin (Ind) partically or completely blocked the excitant action of Sub on isolated ileum[2], which suggested that Sub probably promote the prostaglandin (PG) synthesis. Present result of Sub-induced increase in plasma and urinary PGE provided a further evidence for such an inference. Up to now, several investigators have observed a decrease in urinary PGE after the administration of PG synthesis inhibitor. When animals or human beings were studied during Ind dosing, urinary PG, mainly of the E-type, excretion was markedly reduced, but frequently there was an insignificant change in urine volume[5]. Although the correlation between urine flow and renal PG excretion has not been clear, it can be believed that the increase of renal PG synthesis does not lead to an obvious response in water excretion. Thus it is not likely that the antidiuretic effect of Sub was due to the increase of PG synthesis.

ADH liberated by posterior pituitary caused an antidiuretic effect by increasing the water permeability in distal convoluted tubule and collecting duct. Water-retention induced by Sub, observed in previous[4] and present works, was almost but not completely dispelled after the rat was hypophysectomized, and furthermore, the plasma level of ADH in normal rats increased significantly after administration of Sub, so as to indicate that Sub produced the antidiuretic effect by means of, at least in part, accelerating ADH secretion.

In addition, present study demonstrated that there was no direct relationship between this response and the adrenal which secreted aldosterone to display an antidiuretic action. This conclusion resulted from the findings that the response of water excretion of rat to Sub was not weakened by adrenalectomia, and the plasma level of aldosterone in normal rat was not affected by Sub. The liberation of aldosterone has been believed to be unimportantly influenced by the function of hypophysis[10].

In summary, this study showed that Sub reduced the urine volume by accelerating the liberation of ADH but neither by PGE nor by aldosterone, although it did not address the question of whether Sub affected the ion excretions by the same line.

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柳珊瑚酸促进抗利尿激素释放而引起大鼠水潴留

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关键词 柳珊瑚酸；加压素；前列腺素 E；醛固酮；肾上腺切除术；脱氧皮质酮；垂体切除术；后垂体激素类

目的：了解柳珊瑚酸（suberogorgin，Sub）抗利尿作用的机制． **方法**：清醒大鼠给予水负荷后 ig Sub 3.16 mg·kg^{-1}，收集尿液，用原子发射光谱仪测定尿离子的总排出量；放射免疫法测尿 PGE 以及血浆 PGE、ADH 和醛固酮水平． **结果**：给药后 24 h 内，Sub 减少正常大鼠的累积尿量以及钠和钾的总排出量（最大值分别为 91 %，76 %和 86 %），此作用随时间逐渐减弱，并可因大鼠去垂体而几乎完全消失，但不受去肾上腺影响． 给药后 2 h，Sub 使尿 PGE 以及血浆 PGE 和 ADH 浓度分别提高 25 %，212 %和 538 %，但不影响醛固酮水平． **结论**：Sub 的水潴留作用缘于它促进抗利尿激素的释放，而与 PGE 和醛固酮无关．

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