Effect of inhibition of prostaglandin synthesis on the natriuresis induced by saline infusion in man

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(Received 23 March 1977; accepted 11 July 1977)

Summary

1. The effect of oral administration of an inhibitor of prostaglandin synthetase, indomethacin, on the natriuresis induced by the infusion of sodium chloride (saline) was studied in 11 healthy volunteers.

2. The administration of indomethacin did not alter sodium excretion before saline infusion, but it resulted in a significant increase of the natriuresis after saline infusion. This increase was not accompanied by any change in post-infusion urine flow rate or free water reabsorption.

3. It is suggested that intrarenal prostaglandins might suppress the natriuretic effect of saline infusion, probably by increasing sodium reabsorption in the distal nephron.

Key words: indomethacin, prostaglandins, sodium, volume expansion.

Introduction

Although prostaglandins were initially believed to be important natriuretic factors (Lee, 1974), recent experimental evidence has suggested that these biologically active substances may in fact function as an antinatriuretic hormone (Tobian & O'Donnell, 1976), this view arising from studies based on the use of inhibitors of prostaglandin synthetase (EC 1.14.99.1). Prostaglandin inhibition by either intrarenal infusion of indomethacin (Gill, Alexander, Halushka, Pisano & Keiser, 1975) or intravenous administration of meclofenamate or the new competitive inhibitor RO 20-572 (Kirschenbaum & Stein, 1976) has been found to increase sodium excretion in the conscious dog. But in other studies, no change at all or even a decrease in urinary sodium excretion has been noted during indomethacin administration in the anaesthetized dog (Bay & Ferris, 1975).

However, indomethacin has been reported to be effective in treating renal sodium wasting in Bartter's syndrome (Fichman, Zia, Speckart, Golub, Teller & Rude, 1976; Verberckmoes, van Damme, Clement, Amery & Michielsen, 1976) and to attenuate the natriuresis induced by frusemide in hypertensive subjects (Patak, Mookerjie, Bentzel, Hupert, Babej & Lee, 1975).

In view of this controversy, we have studied the effect of oral administration of indomethacin on the natriuresis induced by infusion of sodium chloride solution in healthy subjects. Our findings suggest that intrarenal prostaglandins exert an antinatriuretic action under certain circumstances.

Material and methods

Eleven healthy volunteer subjects, six men and five women aged 17–45 years, were studied. They were on a free sodium intake. Women were studied during the first half of their menstrual cycle and none of them was taking oral contraceptives. All subjects gave their informed consent. The protocol for the study was approved by the Director of the University Department.

Indomethacin, which has been shown to inhibit prostaglandin synthesis in man (Fichman et al.,
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1976) was administered in a dosage of 150 mg/day. Sodium chloride solution (150 mmol/l; saline) was infused intravenously, at a constant rate of 20 ml/min between 07.00 and 09.00 hours.

The experimental design was as follows: the first 2 days were control periods, and on the third day, saline was infused. Indomethacin was given daily from days 4 to 8, and on the last day of indomethacin administration, the saline infusion was repeated.

Body weight was recorded immediately before and after the experiment. Urine flow rate (V), endogenous creatinine clearance (C_cr), urinary sodium excretion rate (U_Na V), free water reabsorption (T^water_C) and mean arterial blood pressure were measured on the control periods, the fourth day of indomethacin administration and each of the 2 days on which saline was infused. In each period the urine was collected over 12 h (07.00–19.00 hours) without bladder catheterization. Fasting blood samples were taken 4 h after the start of urine collection. Serum and urine samples were analysed for endogenous creatinine (Hare, 1950), sodium concentration (flame photometer, Perkin–Elmer Coleman 51–Ca) and osmolality (osmometer, Osmette-Precision Systems). Free water reabsorption was calculated from the osmolar clearance (C_osm) and the urine flow rate according to the equation T^water_C = C_osm – V; mean blood pressure (MBP) was calculated from the diastolic (DBP) and systolic (SBP) blood pressure according to the equation MBP = (SBP + 2DBP)/3.

Comparisons were made by the unpaired t-test. Control values were taken as the mean of the two control periods.

Values are given as mean ± SEM.

Results

Saline infusion was followed by a statistically significant increase of V and U_Na V and by no significant change in C_cr, T^water_C and mean blood pressure both before and after indomethacin administration (Table 1). Indomethacin produced no significant change in either the pre-infusion values of the five variables measured or the post-infusion values of V, C_cr, T^water_C and mean blood pressure. Post-infusion U_Na V, however, increased significantly after indomethacin. The mean weight of the subjects (60.4 ± 4.1 kg) did not change significantly after indomethacin administration and salt loading (60.8 ± 4.0 kg).

Discussion

Oral administration of an inhibitor of prostaglandin synthetase, indomethacin, potentiated the natriuresis induced by the infusion of sodium chloride solution. Since less prostaglandin resulted in more natriuresis, it might be suggested that intrarenal prostaglandins, in saline infusion, function as an antinatriuretic hormone. This is in agreement with data from a similar experimental study in the conscious dog (Kirschenbaum & Stein, 1976). On the other hand, such a finding seems to be in

| Table 1. Pre-infusion and post-infusion values of urine flow rate, creatinine clearance, urinary sodium excretion rate, free water reabsorption and mean blood pressure before and after indomethacin administration in 11 healthy subjects |
|---------------------------------|-----------------|------------------|-----------------|
|                                | Before indomethacin | After indomethacin | P               |
| V(ml/min)                      | Pre-infusion | 0-74 ± 0-10     | 0-83 ± 0-13     | N.S.             |
|                                | Post-infusion | 1-69 ± 0-25     | 1-94 ± 0-18     | N.S.             |
|                                | P              | <0-01           | <0-001          |                 |
| C_cr(ml/min)                   | Pre-infusion | 138-5 ± 9-9     | 139-2 ± 8-7     | N.S.             |
|                                | Post-infusion | 127-6 ± 12-6    | 147-5 ± 14-6    | N.S.             |
|                                | P              | N.S.            | N.S.            |                 |
| U_Na V(μmol/min)               | Pre-infusion | 52-5 ± 8-3      | 54-0 ± 8-7      | N.S.             |
|                                | Post-infusion | 97-0 ± 14-3     | 139-0 ± 13-2    | <0-05            |
|                                | P              | <0-05           | <0-001          |                 |
| T^water_C(ml/min)              | Pre-infusion | 0-91 ± 0-19     | 0-90 ± 0-17     | N.S.             |
|                                | Post-infusion | 0-97 ± 0-30     | 1-31 ± 0-26     | N.S.             |
|                                | P              | N.S.            | N.S.            |                 |
| Mean blood pressure(mmHg)     | Pre-infusion | 91-7 ± 2-2      | 93-6 ± 2-7      | N.S.             |
|                                | Post-infusion | 94-5 ± 2-1      | 96-7 ± 2-0      | N.S.             |
|                                | P              | N.S.            | N.S.            |                 |
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marked contrast to the previous view that prostaglandins might decrease sodium reabsorption in the proximal tubule, and that, in this sense, they might mediate the natriuresis which follows the expansion of extracellular fluid volume (Lee, 1974).

It must be noted, however, that the possibility that endogenous prostaglandins may be important natriuretic factors has been largely entertained on evidence which has derived from the intrarenal or intravenous infusion of exogenous prostaglandins. The fact that increased sodium excretion occurs in response to exogenous prostaglandins (Lee, McGiff, Kaneglesir, Aykent, Mudd & Frawley, 1971; Martinez-Maldonado, Tsaparas, Eknoyan & Suki, 1972) does not necessarily mean that endogenous prostaglandins exert a local natriuretic action. It is possible that exogenous prostaglandins may affect renal sodium excretion by altering renal haemodynamics, and intrarenal prostaglandins may act directly on the tubular reabsorption of sodium (Anderson, Berl, McDonald & Schrier, 1976). This hypothesis is supported by the finding that locally applied prostaglandin E, increases active sodium transport across either the toad bladder (Lipson & Sharp, 1971) or the isolated short-circuited frog skin (Fassina, Carpenedo & Santi, 1968).

We found that inhibition of prostaglandin synthesis increased natriuresis only when saline was infused. Administration of indomethacin before saline infusion was not accompanied by any change in the sodium excretion rate, which implies that the antinatriuretic effect of intrarenal prostaglandins was rather specific for the state of saline loading. On the other hand, our finding that the increase of post-infusion natriuresis after indomethacin administration was not accompanied by any change in either urine flow rate or free water reabsorption could indicate that sodium reabsorption beyond the proximal tubule was diminished. This is compatible with the previous suggestion that prostaglandins exert their intrarenal action at the site of their synthesis in the renal medulla (McGiff & Iskovitz, 1973).

A number of studies has shown that saline loading inhibits sodium reabsorption in the proximal tubule (Dirks, Cirksena & Berliner, 1965; Cortney, Mylle, Lassiter & Gottschalk, 1965). The fact that the additional sodium which escapes reabsorption in the proximal tubule exceeds the amount excreted in the urine has led to the concept that there is actually an increase in the amount reabsorbed in more distal segments of the nephron (Landwehr, Klose & Giebisch, 1967). This assumption has been supported by several studies (Buchalew, Walker, Puschett & Goldberg, 1970; Bennett, 1973; Martinez-Maldonado, Eknoyan & Suki, 1974).

Saline loading has been found to increase the prostaglandins released into the renal venous blood (Papanicolaou, Safar, Hornych, Fontairan, Weiss, Bariety & Milliez, 1975). Thus the increase in sodium reabsorption in the distal tubule, which follows the increased sodium load emanating from the proximal tubule, might be mediated by prostaglandins released in the renal medulla. Inhibition of prostaglandin synthesis would then lead to an attenuation of distal sodium reabsorption, and, consequently, to a further increase in natriuresis induced by saline infusion.

References


