Lymphology 17 (1984) 43-45

REGULATION OF HUMAN LYMPH CONTRACTILITY BY PROSTAGLANDINS AND THROMBOXANE

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ABSTRACT:

Thromboxane A_2 (TXA_2), but not prostacyclin (PGI_2), plays an important role in human lymph vessel contraction. Paradoxically, whereas substantial amounts of PGI_2 are detectable in human lymphatics, TXA_2 is undetectable and probably derives from surrounding tissues.

Since the discovery of prostacyclin (PGI_2) this endogenously formed intermediate of arachidonic acid metabolism has been implicated as an important regulator of vascular tone and contractility (1). While information about prostaglandins (PG) in relation to lymphatics is limited, it is now known that human lymphatics generate significant amounts of PGI_2 (2,3). In a companion paper (4) we describe a clearer profile of prostaglandin synthesis in human lymphatics. However, thromboxane A_2, which reportedly contracts sheep and bovine lymph vessels (5), is undetectable. In this report we examine whether human lymph vessels resemble animal species in their response to arachidonic acid derivatives.

MATERIALS AND METHODS

We investigated 5 human lymphatics from 4 males and 1 female aged 15 to 47 years. The lymphatics were cut into rings with a circumference of about 5mm. Two wires were fixed via the lumen as described by Johnston and Gordon (5). The lower one was fixed to the bottom of a 5ml perfusion bath while the upper one was connected with an isometric transducer (Harvard Instruments) to a recorder (Pharmacia). The vessels were perfused with an oxygenated (95% O_2, 5% CO_2) Krebs-Ringer solution kept at a constant temperature of 37°C. The tension the vessels were placed under amounted to 0.5 g. PGH_2 was dissolved in the Krebs solution containing the lymph vessel. Thromboxane synthetase was inhibited by imidazole and a specific thromboxane synthetase inhibitor. Prostacyclin and PGE_1 were added to the Krebs-Ringer bath immediately prior to the experiment. Before beginning the experiment, the lymphatics were kept at a constant tension for at least 60 minutes in order to allow for "equilibration".

RESULTS

In the concentration range used little or no effect of PGI_2 or PGE_1 on lymphatic tone was detected (Fig. 1). In contrast, in the resting lymphatic vessel, PGH_2 exerted in a low nano-range concentration a sharp increase in tone. In the presence of imidazole this response was less prominent. Addition of phentolamine and methysergide in micro-range concentration failed to inhibit spontaneous rhythmic contraction of lymphatics.

DISCUSSION

Prostaglandins exert various effects on the vascular system. PGE_1 causes either contraction or relaxation (6) depending on site and dosage. PGI_2 also functions as a

contractile (7), biphasic (8,9), or relaxing agent (10,11). Results vary depending on vessels from different species, whether arteries or veins are examined and the site of testing (12-14). Johnston and Gordon (5) showed that TXA_2 and PGH_2 both contract lymphatics and extensive pharmacological testing confirms that these substances are important contractile stimulants for lymph vessels. In addition, these workers demonstrated that bovine and sheep lymph vessels in vitro convert PGH_2 to TXA_2 with a much stronger contractile effect. In contrast, examination of arachidonic acid metabolic profile more or less excludes an important synthesis and conversion to TXA_2 at least under in vitro conditions. On the other hand, as Fig. 1 demonstrates with inhibition of thromboxane synthetase or conversion of PGH_2 to TXA_2 by imidazole the contractile response of human lymphatics is partially suppressed. As various prostanoids are detectable in high concentrations in lymphatics (15), especially with inflammation, prostaglandins are likely an important modulator of lymphatic tone (16). Although Johnston and Gordon (5) demonstrated that important contractile stimulants to lymphatics are PGH_2 and TXA_2 and these findings are supported by lack of interference of lymphatic contractility in our study by the vasoactive drugs methysergide (serotonin antagonist) and phentolamine (adrenergic antagonist), the role of PGI_2 which is synthesized in substantial amounts in vessel walls (2,3) is less clear. Together these findings suggest key roles for both PGH_2 and TXA_2 in human lymphatic contractility, although the origin of TXA_2 is probably extralymphatic.

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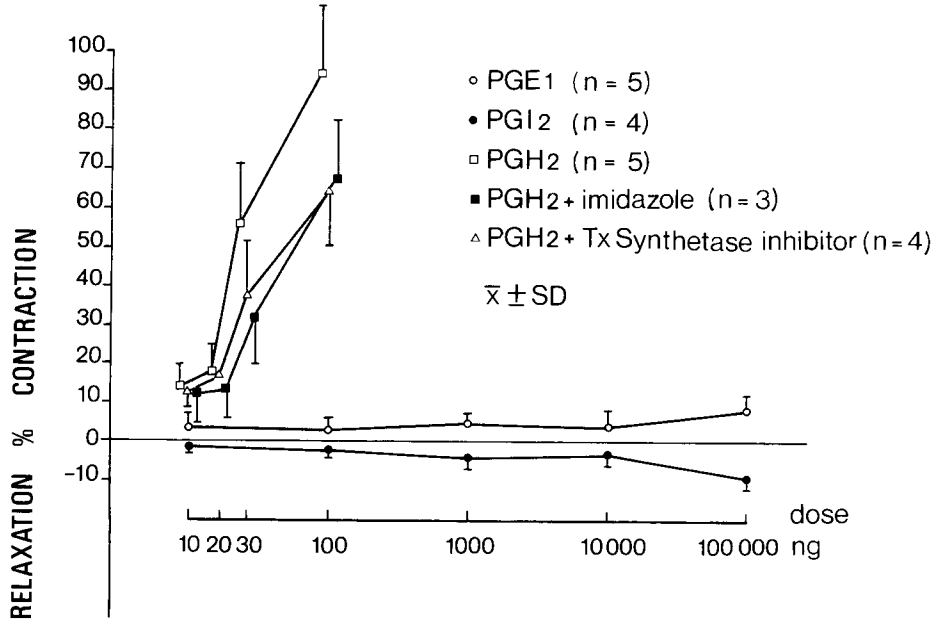

Figure 1: Effect of various prostaglandins in different doses on contractility of human lymph vessels. Below 0 line represents relaxation or "negative" contraction.

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