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Venous prostaglandin-like activity in diarrhoeal states

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SUMMARY Prostaglandin E_2-like activity was determined in peripheral venous blood of control subjects and in patients with acute gastroenteritis and active ulcerative colitis, using a bioassay method. No significant diurnal variations of prostaglandin levels were detected in the control group, while significantly raised venous plasma prostaglandin-like activity was detected in acute gastroenteritis and in active ulcerative colitis.

Administered prostaglandin (PGs) can produce diarrhoea (Misiewicz *et al.*, 1969; Karim and Filshie, 1970; Karim, 1971) and PGs have been implicated in certain pathological conditions where diarrhoea is present (Sandler *et al.*, 1968; Williams *et al.*, 1968). PGs are also believed to be involved in inflammation (Willis, 1969; Giroud and Willoughby, 1970; Greaves *et al.*, 1971) and the production of pain (Ferreira, 1972). The present investigations were to examine PG release in intestinal inflammatory disorders where diarrhoea or disturbed motility are prominent symptoms.

Methods

Peripheral venous blood (10 ml) was removed from patients undergoing outpatient assessment of active ulcerative colitis, from patients with acute gastroenteritis, and from bed-rested patients in an orthopaedic ward who showed no signs of gastrointestinal or inflammatory disease (control group). None of the control subjects was undergoing treatment with non-steroidal anti-inflammatory drugs. Blood was withdrawn by disposable plastic syringe, transferred to chilled lithium heparin tubes, and centrifuged immediately. PGs were extracted from plasma using Amberlite XAD-2 resin in columns 10 cm × 0·7 cm diameter as described by Keirse and Turnbull (1973). Experiments performed after the addition of known amounts of tritiated PGs to blood samples gave recoveries from the columns consistently in the range 79-83%. PG-like activity was assayed using a rat stomach fundic strip (Vane, 1957) using pure PGE_2 as standard (UpJohn Company Ltd). The preparation was perfused with Krebs solution (37°C) made more specific for PGs by the addition of antagonists (hyoscine, methysergide, mepyramine all at 0·2 μg/ml: pronethanol and indomethacin at 1 μg/ml) and gassed with 95% O_2 + 5% CO_2. Presence of specific PGs was confirmed by thin layer chromatography (Green and Samuelsson, 1964). Results were analysed statistically using Student's *t* test.

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Results

VENOUS PROSTAGLANDIN LEVELS IN CONTROL GROUP

The plasma PGE_2-like activity in peripheral venous blood taken from 42 control subjects at three times during the day is shown in Table 1. These subjects were bed-rested patients recovering from minor orthopaedic surgery and had no detected inflammatory or gastrointestinal diseases. The differences in PGE_2-like activity seen throughout the day in each of the three groups (male, female, and combined) were not statistically significant ($P > 0·1$). The differences in activity between groups, at corresponding collection times, were not statistically significant ($P > 0·1$). The control venous plasma concentration was 0·68 ± 0·08 (SEM) ng; PGE_2 equivalents/ml (n = 119).

Table 1 *Venous plasma levels of prostaglandin-like activity at 08.30, 12.00, and 16.30 hours*

	Time		
	08.30	*12.00*	*16.30*
Males	0·81 ± 0·20 (23)	0·55 ± 0·17 (22)	0·45 ± 0·26 (20)
Females	0·74 ± 0·18 (19)	0·52 ± 0·13 (19)	1·1 ± 0·28 (16)
Males and females	0·78 ± 0·13 (42)	0·53 ± 0·11 (41)	0·73 ± 0·20 (36)

Figures are ng PGE_2-equivalents/ml plasma ± 1 SEM. The numbers of measurements are given in parentheses.

PLASMA PROSTAGLANDIN E_2-LIKE ACTIVITY IN ACUTE GASTROENTERITIS AND ULCERATIVE COLITIS

The plasma PGE_2-like activity in peripheral venous blood from nine patients admitted to hospital with acute gastroenteritis was 5·3 ± 1·3 (SEM) ng; PGE_2 equivalents/ml (Table 2). This was significantly greater than the control value ($P < 0.01$). Plasma PGE_2-like activity in six patients with active ulcerative colitis was 6·5 ± 1·2 (SEM) ng/ml, significantly greater than the control value ($P < 0.01$).

Table 2 *PGE_2-like activity in peripheral venous plasma*

Subjects	*Number*	*PGE_2-like activity* (ng/ml plasma)*
Control	119	0·68 ± 0·08
Acute gastroenteritis	9	5·3 ± 1·3
Active ulcerative colitis	6	6·5 ± 1·2

*Figures are mean ± 1 SEM.

Discussion

The occurrence of high levels of PGE-like activity in the peripheral venous circulation is surprising, as PGs are thought to be rapidly removed by passage through the lungs (Piper *et al.*, 1970). The results may indicate survival of PGs in the lungs, or, more likely, the activity (in the bioassay system) of PG metabolites. An endogenous inhibitor of PG synthetase (EIPS) in human plasma has recently been described (Saeed *et al.*, 1977). These workers suggest the possibility that EIPS may control PG synthesis. In patients with acute ulcerative colitis deficiency of such a mechanism could lead to increased PG synthesis.

The control venous plasma PG-like material value is rather high and may represent PG formation during handling, as no PG synthetase inhibitor was added to blood samples after collection. Nevertheless, a statistically significant difference exists between values obtained from patients and controls.

There is indirect evidence that the diarrhoeagenic action of cholera exotoxin may involve PG production; pretreatment of animals with non-steroidal anti-inflammatory agents which inhibit PG synthetase reduces intestinal fluid secretion (Finck and Katz, 1972; Jacoby and Marshall, 1972). The diarrhoea associated with gastroenteritis and ulcerative colitis probably results from large amounts of PGs produced within the inflamed intestinal mucosa. We present here evidence for increased levels of PGE-like material in extracts of peripheral venous blood from patients with acute infective gastroenteritis and active ulcerative colitis. It is proposed that PGs play a role in the pathophysiology of inflammatory bowel diseases and may be responsible for production of diarrhoea in these conditions. It is still unclear whether increased PG production is a primary cause or a result of inflammation.

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