Prostaglandin-Induced Serotonin Release

Since serotonin[1,2] and prostaglandins[3,4] produce smooth muscle stimulation, possibly by facilitation of calcium influx[3,5], and gastric secretory depression, it has been suggested that prostaglandins (PG) might act via serotonin release[6]. We have shown that various doses of PGE_1 and PGE_2 did not significantly affect total mucosal serotonin levels in rat gastrointestinal mucosa[6]. It is possible, however, that, if the quantity of released amine was small, or the rate of its resynthesis rapid, no apparent releasing effect of PG might be seen in normal animals. Reported here are the effects of PGE_1 on gastrointestinal serotonin levels following amine depletion by *p*-chlorophenylalanine[7] and reserpine[8].

Animals. Adult male Sprague-Dawley rats weighing 200–310 g from the Charles River Laboratories Breeding Shed 1[9] were used. Details of cage housing and care have been presented previously[6]. *Drugs.* The preparation of PGE_1 and alcohol saline control solutions has been reported previously[6]. *P*-chlorophenylalanine (PCPA)[10] was prepared as follows: *PCPA 20 mg/ml.* Dissolve 2 g PCPA in 50.0 ml. D.D.W. add 5 drops Tween 80[11] and mix gently, without producing foam. Add 1.9 ml 10*N* NaOH and mix carefully. Add 10.0 ml 8.5 g/100 ml (w./v.) NaCl and 2.1 ml 10*N* HCl; mix carefully to avoid producing foam. Solution brought to final volume of 100 ml with D.D.W. pH is c. 1.8 at 22 °C. *PCPA control solution.* Add 5 drops Tween 80 to c. 25 ml D.D.W. and mix gently without producing foam. Add 10.0 ml 8.5 g/100 ml (w./v.) NaCl and 0.15 ml 10*N* HCl. Solution brought to final volume of 100 ml with D.D.W. pH is c. 1.8 at 22 °C.

Reserpine[12] 5.0 mg/kg (2.0 ml/kg) and 0.85 g/100 ml (w./v.) sodium chloride, 2.0 ml/kg were injected i.p. 4 h[8] prior to study. PCPA, 150.0 or 300.0 mg/kg (7.5 and 15.0 ml/kg) and 0.85 g/100 ml (w./v.) sodium chloride at pH 1.8, 15.0 ml/kg were injected i.p. 2 days prior to study. PGE_1 200.0 µg/kg (1.0 ml/kg) and alcohol saline, 1.0 ml/kg were injected either s.c. or i.v. (tail vein). Rats were killed by decapitation 30 min following s.c. injection and 1 min following i.v. injection.

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[11] Polyoxethylene sorbitol monoleate, Atlas Powder Co., Wilmington (Del., USA).
[12] Serpasil, Ciba Pharmaceuticals Ltd., Summit (New Jersey, USA).

Table I. Total mucosal serotonin 30 min following the s.c. injection of 200 µg/kg PGE_1 or alcohol saline in control and *p*-chlorophenylalanine (PCPA) pretreated rats. Data are presented as mean values ± S.E.M. The number of rats is indicated in brackets. There is no significant difference between data for each pair.

Groups	Tissues		
	Stomach fundus	Pyloric antrum	Mid-jejunum
Saline: alcohol saline	2.04 ± 0.29 (10)	12.27 ± 1.06 (10)	5.23 ± 0.18 (20)
Saline: PGE_1	2.35 ± 0.32 (10)	11.77 ± 1.24 (10)	4.83 ± 0.20 (20)
	n.s.	n.s.	n.s.
PCPA (150 mg/kg) alcohol saline	–	–	2.42 ± 0.65 (5)
PCPA (150 mg/kg) PGE_1	–	–	2.40 ± 0.42 (5)
			n.s.
PCPA (300 mg/kg) alcohol saline	1.46 ± 0.16 (10)	3.77 ± 0.23 (10)	2.26 ± 0.33 (10)
PCPA (300 mg/kg) PGE_1	1.07 ± 0.13 (10)	3.70 ± 0.51 (10)	2.36 ± 0.27 (10)
	n.s.	n.s.	n.s.

Table II. Total mid-jejunal mucosal serotonin 30 min following the s.c. injection of 200 µg/kg PGE_1 or alcohol saline in control and reserpinized rats. Data are presented as mean values ± S.E.M. The number of rats is indicated in brackets. *P* values are non-significant

Groups	Serotonin µg/g	*P* value
Saline: alcohol saline	4.46 ± 0.22 (13)	n.s.
Saline: PGE_1	4.49 ± 0.29 (11)	
Reserpine (5 mg/kg): alcohol saline	3.36 ± 0.16 (11)	n.s.
Reserpine (5 mg/kg): PGE_1	2.90 ± 0.15 (12)	

Table III. Total mid-jejunal serotonin 1 min following the i.v. injection of 200 µg/kg PGE_1 or alcohol saline in control and reserpinized rats. Data are presented as mean values ± S.E.M. The number of rats is indicated in brackets. *P* values are non-significant

Groups	Serotonin µg/g	*P* value
Saline: alcohol saline	4.20 ± 0.45 (6)	n.s.
Saline: PGE_1	4.32 ± 0.64 (6)	
Reserpine (5 mg/kg): alcohol saline	3.60 ± 0.64 (6)	n.s.
Reserpine (5 mg/kg): PGE_1	2.80 ± 0.31 (6)	

Serotonin analyses. Tissues analyzed were stomach fundus (SF), pyloric antrum (PA) and mid-jejunum (MJ). These were prepared as described previously[13] and serotonin assayed spectrophoto-fluorometrically[14]. Data in μg/g mucosa, wet weight, are presented as mean values ± S.E.M. Student's *t*-test was used to determine differences between groups.

Results. Serotonin was reduced approximately 50% in SF and MJ, and about 70% in PA following PCPA; no additional changes, however, were noticed after PGE_1 injection (Table I). In reserpinized rats no significant changes in total mucosal serotonin were noted following PGE_1 injected subcutaneously (Table II) or i.v. (Table III); reserpine reduced MJ serotonin stores about 20% (Tables II and III).

Discussion. The data presented confirm that PGE_1 apparently has no major releasing action on gastrointestinal serotonin. KOE[7] has indicated that PCPA reduces conversion of tryptophan to serotonin by inhibiting the activity of tryptophan hydroxylase, the rate limiting enzyme. The precise mode of action of reserpine is unknown, but it probably acts mainly by blocking amine re-uptake[15]. One might expect, therefore, that serotonin release, for example by PG, would be detectable in animals adequately pretreated with either PCPA or reserpine. Such was not the case, and data obtained following PG administration gave similar results when compared to control rats.

Gastrointestinal serotonin is mainly present in enterochromaffin cells[16] and enterochromaffin-like cells[17] with small quantities located in the myenteric plexus[18]. The cell of PG origin is not known but prostaglandins are liberated from the stomach and intestine[19–21] and recently they have been isolated from amine-peptide secreting tumours of the gut in man[22].

The close similarity between the actions of serotonin and prostaglandins may thus relate either to the liberation of undetectable quantities of serotonin by prostaglandins; the release of some third substance, for example a polypeptide, or the release or activation of prostaglandins by serotonin. This latter seems most likely since PG have been shown to interfere with the formation of cyclic AMP[23–25] and be intermediates in the action of hormones in a variety of tissues[26, 27].

Zusammenfassung. Bei Ratten wurde die Gesamtmenge von Serotonin in der Fundus- und Atriumschleimhaut sowie im mittleren Jejunum bestimmt. Prostaglandin E_1 (200 μg/kg, s.c. oder i.v.) reduzierte den Serotoninspiegel weder in den Kontrolltieren noch in mit *p*-Chlorophenylalanin (150 oder 300 mg/kg) oder mit Reserpin (5 mg/kg) vorbehandelten Tieren.

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Intrarenal Circulation in Mercuric Chloride-Induced Renal Failure

Intravenous or oral administration of suitable mercuric chloride doses brings about death due to acute anuria and consecutive uraemia. Because of the oligo-anuria the various parameters of renal function such as renal blood flow (RBF) etc. cannot be determined by the usual clearance technique. By applying some direct method RBF was found to be only slightly diminished, in moderate cases even renal hyperaemia could be observed (EPPINGER et al.[1], CONN et al.[2], BÁLINT[3]). SAPIRSTEIN's method[4] of ^{86}Rb fractionation (as modified by HÁRSING and PELLEY[5]) is suitable for the investigation of the intrarenal distribution of blood flow. In this study we aimed at the evaluation of total renal blood flow (RBF_{total}) by measuring directly the renal venous effluent and at the assessment of its intrarenal distribution by applying SAPIRSTEIN's method in mercuric chloride-induced renal failure.

The further aim of this study was to clarify the possible existence and role of renal vascular shunts in sublimate intoxication. According to the SAPIRSTEIN principle (based on fractional distribution of ^{86}Rb) only the blood flowing through capillaries (so-called nutrient flow: RBF_{nutr}) is to be determined. If the differences between simultaneously determined total and nutrient flow values

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