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Short communication

INDOMETHACIN AND PARACETAMOL: INTERACTION WITH PROSTAGLANDIN SYNTHESIS IN THE RAT STOMACH

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Using ex vivo incubation of mucosal strips the production of prostaglandins (I_2- and E-like PGs) in the rat stomach was demonstrated by bioassay. Indomethacin inhibited this PG synthesis 1 and 4 h after oral drug administration. Paracetamol stimulated the production of PGs when given by itself but could not prevent the inhibitory action of indomethacin. Protection of the stomach by paracetamol against the injuring effect of indomethacin is therefore not due to preservation of the production of protective PGs.

Paracetamol Indomethacin Prostaglandins Stomach

1. Introduction

Paracetamol has been shown to reduce the gastric injuring side-effect of indomethacin (Van Kolfschoten et al., 1982). This protective effect occurred after both oral and subcutaneous administration of paracetamol. Moreover, protection was seen against gastric erosions induced with indomethacin administered either orally or subcutaneously. It was therefore concluded that the protective effect of paracetamol against indomethacin-induced erosions resulted from a pharmacodynamic action on the mucosal cells rather than from a physicochemical interaction between the two drugs.

It has also been demonstrated that, under certain circumstances in vitro, paracetamol stimulates the synthesis of E-type PGs in bovine seminal vesicles (Robak et al., 1978; McDonald-Gibson and Collier, 1979). As several PGs protect the gastric wall against the damaging effect of indomethacin (Robert, 1976), we proposed the hypothesis that paracetamol protects the stomach against indomethacin by stimulating the inhibited local biosynthesis of protective PGs (Van Kolfschoten et al., 1982). This hypothesis has also been proposed for the protective effect of paracetamol against gastric injury induced by aspirin but it has been shown that paracetamol cannot stimulate the PG synthesis which is inhibited by aspirin (Van Kolfschoten, 1981). The erosive activity of indomethacin differs from that of aspirin (Van Kolfschoten et al., 1982). Moreover the inhibition of PG synthesizing enzymes by indomethacin is reversible while it is not in the case of aspirin (Stanford et al., 1977).

In the present study the interaction of indomethacin and paracetamol with regard to the ex vivo biosynthesis of PGs by the rat gastric mucosa, during 1 and 4 h, was analysed.

2. Materials and methods

Male Wistar rats (CPB, TNO, Zeist, The Netherlands) were fasted for 24 h with free access

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to water. Experiments were started with the oral administration of indomethacin 8 mg · kg^{-1}, paracetamol 250 mg · kg^{-1} or the combination of both drugs. Drugs were suspended in a 4% solution of Tween 80 which was also given to control rats (5 ml · kg^{-1}). The rats were killed by decapitation 1 or 4 h after drug administration and the stomachs were then removed.

Drug dosages and sampling times were the same as before (Van Kolfschoten et al., 1982). Indomethacin (8 mg · kg^{-1}) caused significant gastric damage 1 h after administration, and more damage at 4 h; paracetamol reduced this damage significantly. Gastric mucosal tissue was prepared for generation of PGs using the method described by Whittle (1978).

The anti-aggregatory activity of PGI_2 was used to determine its concentration in the supernatants. Blood was obtained from an anaesthetized rabbit and mixed with sodium citrate (9:1). Platelet-rich plasma (PRP) was prepared by centrifugation at 200 × g for 20 min at room temperature. PRP was aggregated reversibly at 37°C with adenosine diphosphate (ADP) (5–10 μM). Aliquots of sample or standard were added to the PRP one min before ADP and the percentage inhibition of aggregation was measured. Aliquots of the supernatant were tested after boiling for PGE-like activity on the oil-immersion superfused rat stomach strip. Standard curves were made using authentic PGI_2 and PGE_2.

After analysis of variance of the data, the differences between treatment groups were assumed to be real if F-tests revealed probability levels of less than 0.05.

3. Results

Gastric mucosal tissue of control rats generated both I_2-like and E-like PGs. Indomethacin decreased the formation of PGI_2 to levels which could not be detected by the method used (< 5 ng/g tissue) both 1 h and 4 h after administration. PGE_2 production was also diminished at both times; the decrease seemed to be less at 4 h but the influence of time on the effect of indomethacin was not significant. Paracetamol itself caused a three-fold increase in PGI_2 formation at both times. PGE_2 production was also enhanced by paracetamol alone, especially at 4 h. The influence of the combination of the two drugs was not different from that of indomethacin by itself: a decrease of both PGI_2 and PGE_2 production, below the detection limit in the case of PGI_2.

TABLE 1

Effects of indomethacin (8 mg·kg^{-1}), paracetamol (250 mg·kg^{-1}) and the combination of the two drugs on the production of PGs by the gastric mucosa. Mean production in nanogram ± S.E.M. (n) per g of tissue weight.

Treatment	Hours after administration	
	1	4
PGI_2		
Vehicle (control)	60 ± 18 (7)	44 ± 6 (8)
Indomethacin	< 5 * (7)	< 5 * (8)
Paracetamol	180 ± 44 * (7)	152 ± 26 * (8)
Indomethacin + paracetamol	< 5 (7)	< 5 * (8)
PGE_2		
Vehicle (control)	94 ± 19 (6)	107 ± 16 (7)
Indomethacin	46 ± 13 * (6)	88 ± 29 * (7)
Paracetamol	133 ± 20 * (6)	226 ± 33 * (7)
Indomethacin + paracetamol	47 ± 15 * (6)	67 ± 17 * (7)

* Significantly different from control value; $P < 0.05$; F-test.

4. Discussion

Indomethacin markedly inhibited PGI_2 synthesis in the rat stomach thus confirming earlier observations of Whittle (1978). In contrast to the latter author we found production of considerable amounts of PGE_2 which was also inhibited by indomethacin. Similarly Konturek et al. (1981) and Van Kolfschoten et al. (1981) observed production of both PGI_2 and PGE_2 which could be inhibited by aspirin.

Co-administration of paracetamol with indomethacin resulted in the same inhibition of PG synthesis as after indomethacin alone: the suspected stimulation of the inhibited PG synthesis by paracetamol did not occur. Paracetamol how-

ever was found to stimulate PG synthesis when administered without indomethacin. This is in agreement with the observations of Van Kolfschoten et al. (1981) who used the ex vivo gastric mucosa, and of Robak et al. (1978) and McDonald-Gibson and Collier (1979) who used bovine seminal vesicles in vitro. The latter authors stated that paracetamol renders the elevated PG synthesis more vulnerable to inhibition by aspirin and indomethacin, resulting in potentiation of the inhibitory effect. Our results with mucosal tissue and the results of Brune and Peskar (1980), obtained with measurement of PG synthesis in macrophages, do not support such a potentiation ex vivo.

The stimulation of the generation of PGI_2 and PGE_2 by paracetamol could originate from two possible mechanisms. Firstly, paracetamol could act as a phenolic cofactor resulting in an increased formation of PGs (Robak et al., 1978). Secondly, the radical scavenging properties of paracetamol could lead to deactivation of noxious free hydroxyl radicals which are genrated during PG biosynthesis and which can destroy PG synthesizing enzymes, especially PGI_2 synthetase. Thus paracetamol could prevent enzyme destruction and, at the same time, stimulate the step in PG synthesis in which the radicals are formed by decreasing product inhibition (Kuehl et al., 1979). Our results do not allow us to discriminate between these two possible mechanisms of action.

As stimulation of PG biosynthesis is unlikely to be the mechanism of action explaining the protection provided by paracetamol against the gastric damaging effect of indomethacin and aspirin (Van Kolfschoten et al., 1981) other possibilities should be considered. Paracetamol might directly activate protective factors in the gastric mucosa e.g. mucus and bicarbonate secretions.

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