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Influence of niridazole and chloroquine on arterial and myometrial prostacyclin synthesis

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1 The effects of niridazole and chloroquine on rat arterial and myometrial prostacyclin (PGI_2) synthesis *in vitro* were investigated by use of a rat platelet antiaggregatory bioassay. Niridazole (233 μM) and chloroquine (97 μM) inhibited PGI_2 synthesis in both tissues.

2 Niridazole-induced inhibition in the myometrium was not reversed by exogenous arachidonic acid (33 μM) indicating a direct effect of the compound on PGI_2 synthesizing enzymes.

3 Chloroquine-induced inhibition in the myometrium was significantly reversed by exogenous arachidonic acid (33 μM) indicating a direct effect of the compound on arachidonic acid releasing enzymes (e.g. phospholipases A_2 and C).

4 Niridazole and chloroquine also inhibited prostaglandin E_2 synthesis in the myometrium.

5 Chloroquine- and niridazole-induced inhibition of prostaglandin synthesis may contribute towards a better understanding of some of their actions *in vivo*.

Introduction

The nitrocyclic compound niridazole exhibits an anti-inflammatory activity in some models of inflammation (Mahmoud & Warren, 1974; Delbarre, 1977) as well as its established schistosomicidal effects (Sneft & Hillman, 1973; Popiel & Erasmus, 1981). Similarly, the antimalarial drug chloroquine (McChesney & Fitch, 1984) exerts anti-inflammatory activity in some models of inflammation (Palmer & Weatherall, 1977; Tarayre *et al.*, 1982; Phadke *et al.*, 1982). Since shistosomal infections are accompanied by intestinal and urinary bladder inflammation, and prostacyclin (PGI_2) and other prostaglandins are known to mediate and/or potentiate inflammation (Ford-Hutchinson *et al.*, 1978; Kunkel *et al.*, 1981), it was thought of interest to examine the influences of the aforementioned drugs on PGI_2 synthesis by rat arterial and myometrial tissues. In addition the effect of the compounds on prostaglandin E_2 (PGE_2) synthesis by the myometrium was investigated.

Methods

Designation of day of pregnancy

Female Wistar rats (250 g) were caged separately with proven male rats over night. On the following morning the presence of a vaginal plug was taken as evidence of fertilization. This day was denoted as day 1 of pregnancy and the rats were then caged separately. On some occasions vaginal smears were taken in the morning and the day on which spermatozoa were found was denoted day 1 of pregnancy.

Preparation of myometrial tissues

On the selected day of pregnancy, rats were killed by decapitation. The abdomen was opened and the two uterine horns were exposed. The uteri were evacuated and the myometrium separated from the decidua as described previously (El Tahir & Williams, 1980).

Preparation of arterial tissues

Male Wistar rats (200 g) were killed by decapitation. The thorax was opened and the arterial vessel starting from the aortic arch (thoracic aorta) was located, covered with ice-cold Krebs solution (pH 8), cleared from adhering fat and tissues, cut longitudinally and transferred to a petri-dish containing ice-cold Krebs solution and stored over crushed-ice until required.

Incubation of the tissues

When required, arterial or myometrial tissues were blotted dry on filter paper and 20 mg pieces (in the case

of arterial tissue) and 100 mg (in the case of myometrial tissue) were cut out. Each piece was placed in a small plastic cuvette (0.7 × 3 cm) covered with 0.2 ml Krebs solution and incubated for 30 min at 37°C. The tissue was then chopped into small pieces and a siliconized stainless-steel stirrer added. Each tube was further incubated in an aggregometer chamber (H. Hupchurch and Co., U.K.) for 3 min at 37°C. The cuvette was removed and stored in crushed ice. The supernatant was aspirated with a microlitre syringe and aliquots were assayed for their PGI_2 content as indicated below. To examine the influences of niridazole and chloroquine on PGI_2 synthesis, the specified dose of the drug under investigation was added during the first 30 min incubation period at 37°C. Arachidonic acid was added to the tissue just before chopping. The procedure was then continued as above. Substances used to solubilize test drugs were added in the same concentrations to the incubation media of the control tissues. Due to the small quantity of arterial tissue provided by a single rat, each arterial tissue was divided into two portions one serving as a control and the other being treated with one dose of the test drug.

Estimation of prostacyclin in incubation media

Rat citrated platelet-rich plasma (PRP) was prepared as described previously (Ageel *et al.*, 1985). Aliquots (0.5 ml) of PRP were used in this study. Platelet aggregation was induced by addition of ADP in a dose that produces irreversible aggregation for at least 4 min (10 μM final concentration). The aggregation response was displayed on a MSE-recorder connected to H. Hupchurch-aggregometer. The PGI_2 content of aliquots of incubation media was estimated against authentic PGI_2 as described previously (El Tahir & Williams, 1980; Ageel *et al.*, 1985). In this bioassay system particular care was taken to ensure that all platelets were exposed to the same concentration of the drug that would be carried over when testing the antiaggregatory effect of an aliquot taken from an incubation medium of a treated tissue. For this purpose, the appropriate dose of the drug under investigation was added to the PRP 1 min before challenge with ADP. Such precautions were essential to allow for any effect that a particular drug will exert on the plateletes *per se*. PGI_2 synthesis was expressed as ng $PGI_2\,mg^{-1}$ wet tissue.

Thin layer chromatography (t.l.c.) of substances released into the incubation media of the arterial and myometrial tissues

In a separate series of experiments arterial tissue (200 mg) from 5 male rats and myometrial tissue (2 g) from two 18-day pregnant rats were incubated as outlined above. The incubation was terminated by acidification to pH 3 with citric acid and the media were extracted with diethyl ether. The ethereal extracts were evaporated under N_2 gas, the residues dissolved in ethanol and applied to silica gel plates (0.25 mm, E. Merck, F.R. of Germany). The plates were developed in the solvent system, chloroform: methanol: glacial acetic acid: water (90:8:1: 0.8 v/v/v/v/) (Nugteren & Hazelof, 1973). Authentic prostaglandins were applied on separate lanes. The resolved substances were revealed by exposure to iodine vapour.

Radioimmunoassay (RIA) of prostaglandin E_2 released by myometrial tissue

In some experiments myometrial tissues from 18-day pregnant rats were incubated in presence and absence of niridazole (233 μM) or chloroquine (97 μM) and the media were extracted and chromatographed as outlined above. Zones corresponding to PGE_2 were scraped, eluted in ethanol and the alcoholic layer separated by centrifugation. The alcohol was evaporated and the residue was dissolved in Krebs solution and the PGE_2 was estimated by RIA as described in the Amersham Kit procedure (Amersham).

Solubilization of the drugs used

Niridazole was initially dissolved in dimethyl sulphoxide (DMSO) to give 0.5% w/v. It was then diluted with Krebs solution to the desired strength. The maximum concentration of DMSO in the incubation medium was 0.01% v/v. Chloroquine diphosphate was dissolved in Krebs solution. Arachidonic acid was stored dissolved in ethanol (1% w/v). When required the desired quantity was taken, the alcohol was evaporated under N_2 and the residue was solubilized in Krebs solution after addition of an equivalent quantity of Na_2CO_3 (final pH 8). PGI_2 was stored as 0.1% w/v in 0.1 M Tris-hydroxide buffer, pH 9 and diluted in Krebs solution.

Composition of Krebs solution (mM) used was: NaCl 118.4, $NaHCO_3$ 25, NaH_2PO_4 1.13, $CaCl_2$ 1.8, KCl 4.7, $MgCl_2$ 1.3 and glucose 11. Drugs used were: niridazole (Ciba-Geigy, Basel, Switzerland), chloroquine diphosphate, arachidonic acid and adenosine diphosphate (Sigma, U.K.), PGI_2 (Wellcome Beckenham, U.K.), other prostaglandins (Upjohn, U.S.A).

Statistical significance was calculated by Student's *t* test.

Results

T.l.c. of the substances released into arterial and myometrial incubation media

The R_F values of the authentic prostaglandins (E_2, $F_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$) in the solvent system indicated above were 0.38, 0.13 and 0.19, respectively. T.l.c. of the arterial tissue extract revealed the presence of only one spot corresponding to 6-keto-$PGF_{1\alpha}$, the major metabolite of PGI_2. However, chromatography of the myometrial extract revealed the presence of two prostanoid spots: a major spot corresponding to 6-keto-$PGF_{1\alpha}$ and a minor spot corresponding to PGE_2.

Effect of niridazole on arterial prostacyclin synthesis

Platelet aggregation was induced by the addition of ADP (10 μM, final concentration). Pretreatment of the PRP for 1 min with niridazole (1.2–2 μM), doses equivalent to the amounts that would be carried over in the 3 or 4 μl test aliquots of the incubation media of niridazole (233 μM)-treated tissue, did not affect ADP-induced aggregation to any significant level. However, as a precaution niridazole (1.2 or 2 μM) was added to PRP 1 min before ADP in all cases except when testing the antiaggregatory effect of the aliquot from the treated tissue. Niridazole (233 μM) significantly decreased PGI_2 synthesis by the arterial tissue (mean ± s.e.mean) from 12.0 ± 0.4 (control) to 5.9 ± 0.2 ng $PGI_2\,mg^{-1}$ tissue ($P<0.01$, $n=6$). Similarly at a dose of 47 μM it significantly decreased the synthesis from 11.8 ± 0.8 (control) to 7.8 ± 0.3 ng $PGI_2\,mg^{-1}$ tissue ($P<0.01$, $n=6$). The mean % decreases in PGI_2 synthesis induced by the above effective doses are shown in Table 1. Niridazole (4.7 μM) had no significant effect on arterial PGI_2 synthesis.

Effect of niridazole on myometrial prostacyclin synthesis

Niridazole (47 and 233 μM) decreased PGI_2 synthesis by day-18 myometrial tissue from 2.30 ± 0.05 to 2.0 ± 0.2 and 1.5 ± 0.05 ng $PGI_2\,mg^{-1}$ tissue, respectively. The latter value was significantly smaller than control synthesis ($P<0.05$, $n=6$). The mean % decreases in PGI_2 synthesis induced by the above doses are shown in Table 1. Incubation of control tissue in the presence of exogenous arachidonic acid (33 μM) significantly increased PGI_2 synthesis from 2.3 ± 0.15 to 4.3 ± 0.2 ng $PGI_2\,mg^{-1}$ tissue ($P<0.01$, $n=6$). However, PGI_2 synthesis by niridazole (233 μM)-treated tissue in the presence of arachidonic acid (33 μM) was 2.50 ± 0.15 ng $PGI_2\,mg^{-1}$ tissue. This value was significantly smaller compared with PGI_2 synthesis by the non-treated tissue in the presence of arachidonic acid ($P<0.05$, $n=6$).

Effect of niridazole on myometrial prostaglandin E_2 synthesis

Pretreatment of myometrial tissues taken from 18-day pregnant rats with niridazole (233 μM) significantly decreased PGE_2 synthesis (mean ± s.e.mean) from 53.5 ± 4.8, to 17.4 ± 2.5 pg mg^{-1} tissue ($P<0.01$, $n=4$).

Effect of chloroquine on arterial prostacyclin synthesis

In these experiments when testing the antiaggregatory effect of aliquots of incubation media, an appropriate concentration of chloroquine was added to PRP 1 min before challenge with ADP so as to expose the platelets to the same concentration of chloroquine that would be carried over when testing the antiaggregatory effect of an aliquot taken from an incubation medium of chloroquine-treated tissues. Pretreatment of the tissue with chloroquine (97 μM) significantly decreased PGI_2 synthesis from 11.1 ± 0.6 (control) to 5.6 ± 0.2 ng $PGI_2\,mg^{-1}$ tissue ($P<0.01$, $n=6$). In other experiments chloroquine (19 μM) decreased PGI_2 synthesis from 11.8 ± 1.3 (control) to 9.3 ± 0.8 ng $PGI_2\,mg^{-1}$ tissue. However, this decrease was not significant ($P>0.05$, $n=6$). The mean % decreases in PGI_2 synthesis induced by the above two doses of chloroquine are shown in Table 1. Chloroquine (1.9 μM) had no significant effect on arterial PGI_2 synthesis.

Effect of chloroquine on myometrial prostacyclin synthesis

Chloroquine (19 and 97 μM) decreased PGI_2 synthesis

Table 1 Percentage decrease prostacyclin (PGI_2) synthesis by rat artery and myometrium induced by niridazole and chloroquine

Tissue	*% inhibition*			
	Niridazole		*Chloroquine*	
	(47 μM)	(233 μM)	(19 μM)	(97 μM)
Artery	33.8 ± 3.3*	51.1 ± 4.5*	20.8 ± 7.6	49.5 ± 3.1*
Myometrium	13.1 ± 4.3	35.0 ± 2.9*.	12.5 ± 3.1	62.4 ± 3.7*

Values are mean ± s.e.mean.
*$P<0.05$, $n=6$, compared with the corresponding control.

by day-12 myometrial tissue from 0.8 ± 0.05 (control) to 0.7 ± 0.08 and 0.3 ± 0.02 ng $PGI_2 mg^{-1}$ tissue, respectively. The latter value was significantly smaller compared with control synthesis ($P < 0.01$, $n = 6$). The mean % decreases in PGI_2 induced by the above 2 doses are shown in Table 1. Incubation of control tissue in the presence of arachidonic acid (33 μM) significantly elevated PGI_2 synthesis from 0.8 ± 0.05 to 1.3 ± 0.1 ng $PGI_2 mg^{-1}$ tissue ($P < 0.05$, $n = 6$). PGI_2 synthesis by chloroquine (97 μM)-treated tissue in the presence of arachidonic acid (33 μM) was 1.0 ± 0.1 ng $PGI_2 mg^{-1}$ tissue ($n = 6$). This value was not significantly different from basal synthesis or that observed in the non-treated tissue in the presence of exogenous arachidonic acid ($P > 0.05$, $n = 6$).

Effect of chloroquine on myometrial prostaglandin E_2 synthesis

Pretreatment of myometrial tissue taken from 18-day pregnant rats with chloroquine (97 μM) significantly decreased PGE_2 synthesis from 53.5 ± 4.8 to 24.6 ± 3.1 pg mg^{-1} tissue ($P < 0.01$, $n = 4$).

Discussion

The designation of the platelet antiaggregatory material released by the rat arterial and myometrial tissues as PGI_2 has been discussed previously (El Tahir & Williams, 1980; Ageel *et al.*, 1985). Interference from any other antiaggregatory prostaglandins released into the incubation medium was minimized by the use of rat platelets that are insensitive to the antiaggregatory effects of PGE_2 and PGD_2 (Silberbauer & Sinzinger, 1978).

Pretreatment of arterial and myometrial tissues of the rat with either niridazole or chloroquine inhibited PGI_2 synthesis. In addition, the compounds significantly inhibited PGE_2 synthesis by the myometrium. However, the compounds differed with regard to the mechanisms involved in the observed inhibitions. For instance, niridazole-induced PGI_2 inhibition was not reversed by exogenous arachidonic acid (AA), suggesting an action on the enzymes that convert AA to PGI_2, e.g. prostaglandin cyclo-oxygenase, peroxidase and/or PGI_2 synthetase. Niridazole may inhibit any of these enzymes by interacting with essential SH-groups. This conjecture is based on the ability of niridazole to complex with various thiol groups in mammalian and schistosomal proteins and the reversal of these interactions by free SH-group containing compounds (Varnes & Biaglow, 1982; Tracy *et al.*, 1983). A more likely enzyme is the prostaglandin cyclo-oxygenase that converts AA to the endoperoxide PGG_2. Indeed niridazole is shown to inhibit oxygen uptake and oxidative processes in some mammalian organs (Kheir Eldin *et al.*, 1976; Sharaf *et al.*, 1978).

The ability of AA to reverse chloroquine-induced inhibition of PGI_2 synthesis suggests that chloroquine acted via inhibition of AA release. Such a mechanism may involve inhibition of the enzymes phospolipase A_2 (PLA_2) and/or phospholipase C that evoke AA release (Newkirk & Waite, 1973; Bell *et al.*, 1979). Indeed chloroquine has been shown to inhibit various phospholipases (Matsuzawa & Hostetler, 1980; Kunze *et al.*, 1982; Hostetler & Reichman, 1982). Circumstantial evidence for chloroquine-induced inhibition of PLA_2 enzyme comes from its reported antagonism to oxytocin-induced uterine contractions (Chinyanga *et al.*, 1974; Okonkwo & Chukwudebelu, 1980) that partly involve activation of PLA_2 and release of prostaglandins (Vane & Williams, 1973; Williams & El Tahir, 1980).

Chloroquine-induced inhibition of the Ca^{2+}-dependent PLA_2 enzyme may involve a decrease in availability of free Ca^{2+} ions in the vicinity of the enzyme. Pertinent to this is the reversal of chloroquine-antagonism to oxytocin-induced uterine contractions by elevation of extracellular Ca^{2+} ion concentration (Chinyanga *et al.*, 1974).

Based on the evidence that PGI_2 and other prostaglandins mediate and/or potentiate inflammation (Ford-Hutchinson *et al.*, 1978; Kunkel *et al.*, 1981) it would be plausible to suggest that the effectiveness of niridazole against schistosomal infections may involve, besides the well-known direct effects on the schistosomes (Sneft *et al.*, 1973; Magzoub, 1973; Popiel & Erasmus, 1981), an inhibitory effect on schistosomal egg-induced inflammation in the urinary bladder and/or intestine. Indeed the eggs are shown to induce granulomas in some organs (Chensue *et al.*, 1983). It thus seems that an inherent ability of niridazole to inhibit the prostaglandin cyclo-oxygenase enzyme, as shown by inhibition of both PGI_2 and PGE_2 synthesis, underlies the general anti-inflammatory effect of the compound that has been observed in some inflammatory models (Mahmoud & Warren, 1974; Delbarre, 1977).

Similarly, the ability of chloroquine to inhibit arachidonic acid release with the concomitant inhibition of the prostaglandin cyclo-oxygenase- and lipoxygenase-derived arachidonic acid metabolites that are involved in inflammation (prostaglandins and leukotrienes) (Ford-Hutchinson *et al.*, 1978; Higgs *et al.*, 1979) may partly explain chloroquine-induced suppression of inflammation (Tarayre *et al.*, 1982; Phadke *et al.*, 1982). Furthermore, chloroquine-induced inhibition of the vasodilator prostaglandins (PGI_2 and PGE_2) may partly contribute towards better understanding of the biochemical mechanisms that underly chloroquine-induced retinopathy and nephrotoxicity (Datsis, 1972; Converse, 1982). Indeed, both retina

and kidney do accumulate the compound (McChesney & Fitch, 1984). This inference might be verified by direct examination of the effects of chloroquine on blood flow and PGI_2 synthesis in the organs.

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