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SEX-RELATED DIFFERENCE IN THE EFFECT OF ASPIRIN ON PROSTAGLANDIN METABOLISM IN RAT PLATELET AND AORTA

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SUMMARY

The effect of aspirin on the production of the arterial prostacyclin (PGI_2)-like substance and platelet malondialdehyde (MDA) was investigated in rats of both sexes. No significant sex difference observed with the arterial PGI_2-like substance. But, following the aspirin treatment, the production of the PGI_2-like substance was significantly decreased in male rats. There was significant sex difference in the production of platelet MDA before the aspirin treatment. And after the aspirin treatment, platelets of both sexes produced significantly less MDA. It is possible that sex difference in the effect of aspirin is related to the quantitative difference of cyclooxygenase activity between platelets and vasal wall.

INTRODUCTION

Aspirin has been reported to be an effective antithrombotic agent in a number of recent clinical trials (1-4), and was found to be effective in preventing strokes in the patients of transient ischemic attacks (3), and in decreasing the incidence of venous thrombosis in the patients undergoing hip surgery (4). But the antithrombotic effects of aspirin were limited to male patients.

The antithrombotic effect of aspirin is attributed to its ability to acetylate cyclooxygenase, the initial enzyme in the metabolic pathway of arachidonic acid, and to block the production of prostaglandins (PGs) and thromboxanes (TXs) (7, 8).

Recently, it has been suggested that the balence between prostacyclin (PGI_2) produced by vasal wall and TXA_2 produced by

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platelets plays an important role in thrombus formation and cardiovascular diseases (9). In this study, the effect of aspirin on the production of the arterial PGI_2-like substance and platelet malondialdehyde (MDA) was investigated in rats. And the results with male and female rats were compared.

MATERIALS AND METHODS

Animals - Wistar rats of both sexes weighing 200 to 240 g were used. Animals were housed in wire-bottlon cages in a temperature controlled room with a fixed lighting schedule, and allowed free acess to standard laboratory food (Oriental Co. MF) and water. Rats were fasted for 1 hr before drug administration.
Drug - Aspirin was suspended in 0.5 % carboxymethylcellulose sodium salt for p.o. administration. The administered dose of aspirin were 20, 50, 100 mg/kg.
PGI_2-like substance determination - The animals were sacrified by a blow on the head and the abdominal aortae were used for study. The abdominal aortae were quickly isolated, and raised with Krebs-Ringer Phosphate (KRP), pH 7.4. After each of 2 cm sample taken from the abdominal aortae was stretched longitudinally, it was incubated in 1 ml of KRP at 37°C for 10 min. The content of the PGI_2-like substance was immediately bioassayed according to the cascade suspension technique of Vane et al. (10). The amount of the PGI_2-like substance formed was expressed as ng PGI_2/mg weight of dry tissue per minute, using the synthetic PGI_2 as the standards (kindly supplied by Ono-Yakuhin Co. Ltd.).
MDA determination - The platelet-rich plasma (PRP) was obtained by the differential centrifugation technique reported by Okuma et al. (11). MDA production was determined according to Yagi's spectrofluorometrical method using thiobarbituric acid (12). Thrombin (5 U/ml) was used as a stimulator of MDA production. The results of the samples were expressed as μmoles MDA/3×10^8 platelets determined from a standard curve derived by measuring the fluorescent intensity of the known amounts of hydrolized (1,1,3,3)-tetraethoxypropane.

RESULTS AND DISCUSSION

The effect of aspirin on the production of the arterial PGI_2-like substance is shown in Fig. 1. The production was significantly decreased in aspirin-treated rats as compared to control ($p<0.05$), but this aspirin effect was not apparent in female rats. Sex difference was evidently observed in the effect of aspirin.

Platelets obtained from male and female rats were stimulated by thrombin. There was significant sex difference in the produc-

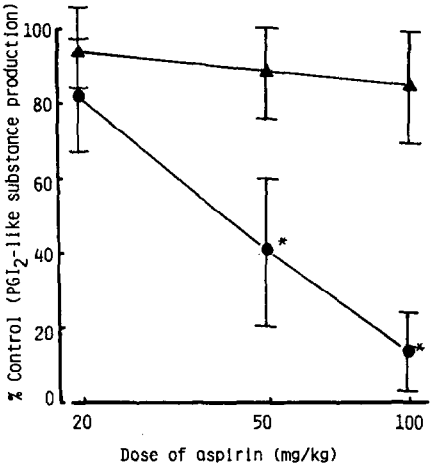

Fig. 1 The effect of aspirin on the production of the arterial PGI_2-like substance in male and female rats.

Abdominal aortae were obtained from rats 1 hr after treatment with aspirin (100 mg/kg). PGI_2-like substance was determined after stretched-stimulating by the cascade superfusion technique. Mean±S.D. (n=8) —●— ; male, -▲- ; female, * $p<0.05$

tion of platelet MDA before the aspirin treatment. And the MDA production was measured 1 hr after treatment with 100 mg/kg of aspirin. The platelet fraction of both sexes produced significantly less MDA following the aspirin treatment.

Table 1. The effect of aspirin on malondialdehyde production in rat platelets

	MDA production(nmol/3 10^8platelets)	
	Before treatment	After treatment
Male	0.033±0.006	0.012±0.005*
Female	0.022±0.004	0.014±0.003*

Platelets were obtained from rats 1hr after treatment with 100 mg/kg aspirin. MDA production was determined to spectrofluorometrical method using thiobarbituric acid. Thrombin (5U/ml) was used as a stimulator of MDA production.
Mean±S.D. (n=6), $p<0.05$

These data show that cyclooxygenase of arterial wall is more active in males than in females. There was significant sex difference in the production of platelet MDA before the aspirin treatment. But the difference was found in the inhibitory effect of aspirin on the production of platelet MDA by male and female rats that were exposed to the equal dose of aspirin *in vivo*.

Perton and his co-workers noticed that cyclooxygenase of vasal wall *in vitro* and *in vivo* is less sensitive to aspirin than that of platelets. There is also evidence that vascular tissue recovers from the aspirin inhibition within 24 hr by regeneration of its cyclooxygenase.

The platelets of both male and female rats have different sensitivity to aggregating agents (14, 15). And it has also been noted that experimentally induced arterial thrombosis was greater in males than in females (16. 17). Our data support this phenomenon.

The interaction of aspirin-treated platelets with vasal wall may be different according to sex. The sex difference in antithrombotic effect of aspirin may be related to the quantitative difference of the cyclooxygenase activity between platelets and vasal wall.

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