THE EFFECT OF METHYLERGONOVINE ON THE ENDOTHELIUM

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SUMMARY : The effect of methylergonovine on acetylcholine-induced relaxation was studied on the isolated rabbit aortic strips precontracted by phenylephrine. Acetylcholine produced a concentration-dependent relaxation and this relaxation was completely prevented after the removal of endothelium. Addition of methylergonovine to the medium significantly abolished the relaxing activity of acetylcholine. From these results it was concluded that the inhibition by methylergonovine of the vascular relaxing effect of acetylcholine is probably mediated through the endothelium. The pathogenesis of the thrombus induced by methylergonovine was discussed.

***Key Words** : Methylergonovine, Endothelium.*

INTRODUCTION

Ergonovine (E) and methylergonovine (ME) are administered to enhance postpartum uterus involution and to decrease bleeding. This effect is maintained by contracting both the uterus and the vascular bed of the uterus (Lemberger, 1978). Ergot alkaloids are also known to cause formation of emboli within the vascular bed (Williams, 1988).

Endothelial cells have been shown to release a substance which induces relaxation of the vascular smooth muscle and the substance was called endothelium-derived relaxing factor (EDRF) (Furchgott, 1983). Although the chemical structure of EDRF is not known, it is assumed to be nitric oxide (Palmer et al. 1987). ERDF has also been shown to inhibit platelet aggregation (Furlongi et al. 1987).

Previous studies have demonstrated that ß-adrenergic receptor blockers carteolol (Janczewski et al. 1987), propranolol (Ercan and Türker, 1988), and α_2-adrenergic blockers clonidin and guanfacine (Demirel et al. 1989) induce EDRF release.

The aim of this study was to investigate whether ME, which causes thromboembolism, similarly inhibits EDRF release within the vascular bed.

MATERIALS AND METHODS

Rabbits from both sexes weighing 1,5-2,5 kg were anaesthetized with 30 mg/kg intravenous sodium pentobarbital and aortic strips were prepared caring not to injure vascular endothelium. These strips were placed in Krebs solution at 37°C ventilated with 5 % CO_2+ 95 % O_2 and isotonic contractions were amplified 14 times and recorded. Following maximum 70 % precontraction by phenylephrine (10^{-7} M), concentration-dependent relaxation with acetylcholine was recorded. 10^{-6}M ME was then added to the medium and the same proce-

dures were repeated. The composition of Krebs solution in both medium was composed of (mM) : NaCl 112, KCl5, $NaHCO_3$ 25, NaH_2PO_4 1, $CaCl_2$ 2.5, $MgCl_2$ 0.5, dextrose 11.5.

Student's t-test was used for statistical analysis.

All the experimental procedures were performed at the Pharmacology Department of Faculty of Medicine, Gazi University.

RESULTS

Acetylcholine caused dose dependent relaxation in the aortic strips precontracted with 10^{-7}M phenylephrine. This relaxation was not recorded in strips of which the endothelium had been destructed. The relaxation disapppeared following the addition of 10^{-6}M ME (Fig 1). While pD_2 for acetylcholine was 6.08 ± 0.09, it fell to 2.43 ± 0.04 after ME instillation. This decrease was found to be statistically significant ($p<0.001$). The results are shown in fig 2. ME was ineffective on the rabbit aorta strips of which endothelium had been destructed. The baseline for the muscle precontracted with phenylephrine was unchanged with this dose of ME.

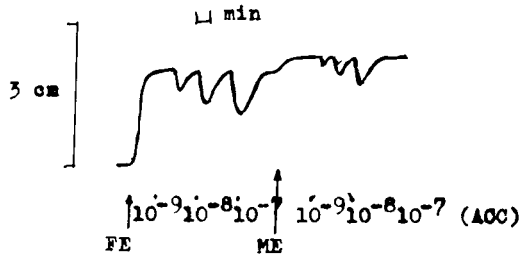

Fig 1 : Kymograph tracing of methylergonovine (ME) action on the relaxation effect of acetylcholine (ACC) on precontracted smooth muscle with phenylephrine (FE) (10^{-6}M).

DISCUSSION

Results of this study indicate that ME inhibits the relaxation effect of acetylcholine on rabbit aortic strips. Vascular endothelial cells are also known

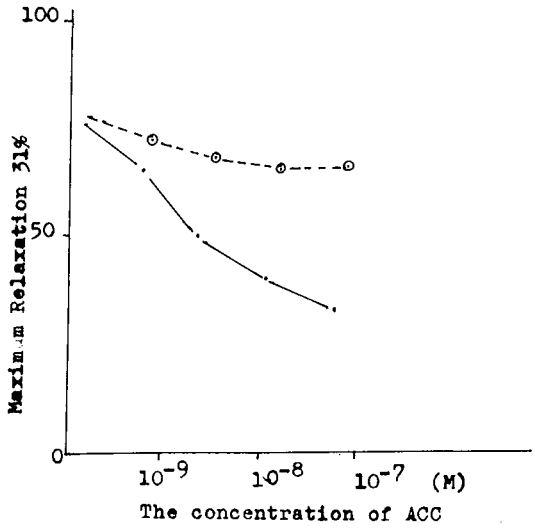

Fig 2 : Dose-dependent graphic illustrating relaxation by acetylcholine (ACC) (·---·), reduced in the presence of methylergonovine (ME) (^{0}---^{0}) on the submaximally contracted muscle with phenylephrine (FE).

to release prostacycline, which is a metabolite of the cyclooxygenase pathway (Vane, 1983). This mediator is the endogenous inhibitor of platelet aggregation (Sehillinger et al. 1986). Previous studies have shown that ME induces thrombus formation, but the mechanism is unknown (Williams, 1988). Our observation that ME inhibits the relaxation response caused by acetylcholine suggests that this effect might be due to an injury of the vascular endothelium. It is known that the relaxation response induced by acetylcholine is produced by EDRF released from endothelium (Furchgott, 1983). This relaxation response disappears following the mechanical destruction of the endothelium, too.

Both EDRF released by endothelium and prostacycline produced by the endothelium inhibit platelet aggregation (Furlongi et al. 1987; Sehillinger et al. 1986, Vane, 1983) ME may inhibit both EDRF and prostacycline production by destructing the endothelial cells and therefore leads to thrombus formation. Our results weigh in favor of the fact that ME has considerable risks when used in order to enhance involution of uterus and decrease postpartum bleeding.

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