It is well known that oxytocin, in addition to its uterotonic action, stimulates prostaglandin (PG) E and F release from pregnant uterus. In 1980, Williams and Tahir reported that the pre-incubation of pregnant uterine tissue with oxytocin caused a significant increase in the release of prostacyclin which was synthesized predominantly in rat uterus (1). We showed in the previous report that oxytocin caused a marked increase in PG (E and F) release in the uterus isolated from estrogen-treated rats (2). With these studies as a background there is yet little information available regarding whether oxytocin influences the prostacyclin release from ovariectomized and estrogen-treated rat uterus or not. We, therefore, examined the effect of oxytocin on the prostacyclin release by the uterus isolated from ovariectomized and estrogen-treated rats.

Female Wistar rats of about 6 weeks after birth, weighing approx. 120 g, were used. At a random estrous cycle, ovariectomy was performed in the same period via the bilateral dorso-lumbar approach using ether anesthesia. Ovariectomized rats were maintained for about 3 weeks. Ten μg of 17β-estradiol in 0.1 ml of sesame oil was injected s.c. to each ovariectomized rat. The rats were sacrificed by decapitation at 6, 12, 24 and 48 hr after estrogen injection and the isolated uterine tissues were used in two forms of slices and horns for the experiments of prostacyclin release. That is, the uterus was equally divided at the uterine cervix into left and right horns. The left horn was used as the oxytocin added group and the right horn as the control group. In the experiments using the uterine slices for prostacyclin release, each of the uterine slices was incubated in 0.5 ml of modified Locke-Ringer solution (m-LRS, pH 8.0) using a test tube. In the case of the uterine horns, each horn was mounted in an organ bath filled with m-LRS (2 ml) and kept stretched to a moderate extent by connecting it to a strain gauge (Nihon Kohden, SB-1T-H), but not so strongly as to prevent it from acquiring and maintaining a given tone. The incubation with oxytocin was carried out for 15 min at 20°C in m-LRS-containing oxytocin (10 mU/ml). In the determination of platelet aggregation, the blood was obtained from the abdominal aorta in anesthetized rats and collected into tubes containing 3.13% sodium citrate (9:1 v/v). Platelet-rich plasma (PRP) was prepared by centrifuging the blood for 15 min at 1100 rpm (Tomy Seiko Co., Ltd., CD-50SR), and platelet-poor plasma (PPP) was obtained by centrifuging the blood after PRP had been removed for 10 min at 3000 rpm. PRP was kept under 95% O₂–5% CO₂ (3). The amount of prostacyclin was estimated by a method similar to that of Williams et al. (4). Using 50 μl samples of PRP in the aggregometer cuvette (Rikadenki Kogyo Co., Ltd., RAM-21), the aggregation in response to 2–3 μM ADP (final concentration) was determined in each experiment. The incubation medium (0.01 ml) was added to
the cuvette 1 min before addition of ADP. The inhibition of aggregation was compared with that of authentic prostacyclin (kindly provided by Ono Pharmaceutical Co.) and expressed as ng/uterus.

The effects of oxytocin on the prostacyclin release from uterine slices before and after estrogen injection in ovariectomized rats were examined. As shown in Fig. 1, prostacyclin release into the medium from uterine slices of ovariectomized rats was significantly decreased at 12 and 24 hr after estradiol injection and restored to the level prior to estrogen treatment after 48 hr. Oxytocin exhibited no effect on prostacyclin release from uterine slices. Then, the examination using uterine horns was performed to measure the effects of oxytocin on prostacyclin release. Figure 2 shows the effect of oxytocin on prostacyclin release from estrogen-treated and non-treated uterine horns under the load condition (0, 250, and 500 mg) in ovariectomized rats. No influence of the load alone (without oxytocin) on prostacyclin release was observed in both estrogen-treated and non-treated rats. However, the inhibiting action of estrogen on prostacyclin release shown in Fig. 1 was recognized under all of the load conditions. On the other hand, the significant stimulatory action of oxytocin on prostacyclin release was recognized under 250 mg of load in the estrogen-treated group.

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**Fig. 1.** Effect of oxytocin and estrogen on PGI₂ release from uterine slices of ovariectomized rats. Each point shows the mean±S.E. of 5–11 rats. *P<0.05: Significantly different from the control (0 hr).

**Fig. 2.** Influence of load and oxytocin on PGI₂ release from estrogen-treated and non-treated uterine horns in ovariectomized rats. Each column shows the mean±S.E. of 6–10 rats. ■ without oxytocin, ▲ with oxytocin (10 mU/ml) *P<0.05: Significantly different from the control (load, 250 mg).
The effects of estrogen on PGE and F production in uterus have been investigated in ovariectomized rats (5-7). However, with respect to prostacyclin production, little is known except for the reports of Gimeno et al. and Thaler-Dao et al. (8, 9). Our results showed that prostacyclin release in both slices and horns of the uterus isolated from ovariectomized rats was significantly reduced by 17β-estradiol treatment. This is in good agreement with the results by Gimeno et al. using chopped uterine strips. On the other hand, it has been reported that oxytocin, as well as PGE and F, stimulates prostacyclin release from the late pregnant uterus which is highly sensitive to the uterotonic action of oxytocin (1), and non-pregnant uterus is not responsive to the PG releasing action of oxytocin (10). However, very little is known about the effect of oxytocin on the prostacyclin movement of the uterus isolated from ovariectomized and estrogen-treated rats. In the present paper, we found that the prostacyclin release from uterine horns reduced by estrogen was significantly increased by addition of oxytocin under the load condition of 250 mg in an organ bath, though this was not observed in uterine slices. Recently, it has been reported that human pregnant myometrium (11) and non-pregnant uterine cervix (12) increase PG synthesis in response to stretch. The release of PG from the cervix tended to be less under the higher load than under the lower load. Although no influence of the load alone in the present result was observed, it is suggested that suitable stretch conditions may result in the positive response of oxytocin to uterus. At present, the mode of action of oxytocin on PG release from rat uterus observed under the load is obscure. However, it is interesting that a report has shown that the enhancement of protein synthesis in rat diaphragm muscle is induced by mechanical stretch (13).

The present results indicate that estrogen reduces the release of prostacyclin in ovariectomized rat uterus and that the estrogen-treated uterus is responsive to the prostacyclin releasing action of oxytocin. In addition, they suggest that under the experimental conditions used, our method using uterine horns instead of slices may be more useful for the study of hormone or other drug actions in PGs production.

References

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