Inhibitory Effect of 2,5-Dimethylpyrazine on Oxytocic Agent-induced Uterine Hypercontraction of Normal or Pregnant Female Rats

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Intraperitoneal administration of 2,5-dimethylpyrazine (2,5-DMP) was found to inhibit oxytocin- and prostaglandin F$_2$α-induced tetanic uterine contractions in normal or pregnant female rats. This suggests that 2,5-DMP may be used as a counteraction agent or relaxant for preventing oxytocic agent-induced medical accidents including uterine rupture or pressure death of the fetus due to uterine contractions.

**KEY WORDS** 2,5-Dimethylpyrazine; Rat uterus; Contraction; Oxytocin; Prostaglandin F$_2$α

2,5-Dimethylpyrazine (2,5-DMP), an alkylpyrazine, has been isolated from roasted or fermented food products, such as roasted coffee beans, brown tea, Bacillus subtilis natto etc. 1-3) It is also detected in rodent and human urine and is considered to be an endogenous product originating from the adrenal gland. 4) 2,5-DMP is known to have an inhibiting effect on weight increase of the uterus and prostate or seminal vesicles in female and male rats when administered intraperitoneally.5-6)

Our previous work demonstrated that intraperitoneal administration of 2,5-DMP neither affected plasma estradiol levels nor inhibited estradiol uptake by the uterus in rats.7)

In the present study, we examined the direct effect of intraperitoneally administered 2,5-DMP on spontaneous or pregnant oxytocin-induced uterine hypercontraction. The possible use of 2,5-DMP relaxation during oxytocin agent-induced hypercontraction of the uterus is also discussed.

2,5-DMP purchased from Aldrich Chemical Company Inc. (Wisconsin USA), oxytocin (Atonin O, 5 unit/ampule) from Teikoku Zoki Pharm. Co. Ltd., and prostaglandinF$_2$α (Prostalmon F, 0.1mg/ml) from Ono Yakuhin Pharm. Co. Ltd. were used. Ten week-old Wistar strain female rats were used. Pregnants rat were used 7 days after observation of a vaginal plug. After administration of nembutal 40mg/kg, i.p., the right uterine horn was exposed by a low abdominal incision of 1 cm, and the midpoint of the horn was gripped with a small metal clip. The clip was joined by means of a string to a force-displacement transducer which recorded uterine contractions isometrically on a polygraph (Nihon Kohden). An initial force of 2 g was applied to the string and normal uterine contractions was observed for 15-20 min. Then, oxytocin or prostaglandinf$_2$α was administered and 2,5-DMP was injected intraperitoneally 15-20 min later. Oxytocin 0.5 unit i.p. was administered and 2,5-DMP at doses of 70, 150, and 250 mg/kg. Observations were made for about 20 min after 2,5-DMP injection.
Fig. 1. Effect of 2,5-DMP on spontaneous movement of rat uterus

Estrous cycle: estrous

As shown in Fig. 1, 2,5-DMP reduced spontaneous uterine contractions in nembutal-anesthetized rats. The countercontraction effect of 2,5-DMP on oxytocin- or prostaglandin F$_2$α-induced strong uterine contractions was observed when the dose was greater than 150 mg/kg (Fig. 2). The mode of the countercontractile effect of 2,5-DMP was the same as that of ritodrine (Uterine, a $\beta$-agonist) or diltiazem (Ca-antagonist). Fig. 3 shows the effect of 2,5-DMP (250 mg/kg) on pregnant uterine contractions. 2,5-DMP showed a clear countercontractile effect.

Fig. 2. Effect of 2,5-DMP on oxytocic agent-induced rat uterine movement
Recently, in clinical obstetrics, the number of reports on accident caused by acute or sustained uterine contractions has increased, such as fetal distress from hypoxia due to hyper contraction and uterine rupture due to the use of oxytocic agents. In most cases, \( \beta \)-stimulants and Ca-antagonists are used for treatment of such oxytocin- or prostaglandin- induced uterine hyper contraction. However, these drugs cause serious side effects such as lowering of blood pressure and accelerating or retarding effects on cardiac functions including atrioventricular block etc. 

2,5-DMP has an LD\(_{50}\) value higher than 1000 mg/kg and has much less effect on blood pressure and heart beat rate. Therefore, 2,5-DMP with its efficient anti-uterine contraction effect and weaker side effects may be a more useful agent for treatment of oxytocic agent-induced uterine hypercontractions.

References

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