Protective Effects of Prostaglandin E₂ on the Paraquat-Induced Constriction of the Fetal Ductus Arteriosus in the Rat

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Abstract. Pregnant rats on day 21 of gestation received a subcutaneous injection of paraquat (25 mg/kg). Two hr later, some fetuses of these rats received a subcutaneous injection of prostaglandin E₂ (PGE₂). The caliber of the ductus arteriosus (DA) of fetuses was measured 1 hr later. The DA of fetuses of paraquat-treated pregnant rats was significantly constricted compared with that of fetuses of control pregnant rats given physiological saline. However, the DA of PGE₂-treated fetuses of paraquat-treated pregnant rats had a caliber comparable to that of control rats. The maternal plasma PGE₂ level decreased following paraquat treatment. These results suggest that the decrease of maternal PGE₂ level results in a constriction of the DA of fetuses.

Key words: ductus arteriosus, paraquat, prostaglandin E₂


Paraquat (1,1'-dimethyl-4,4'-bipyridylidium) was originally developed in England in 1955 as a bipyridylidum herbicide. This chemical is widely used in agriculture, but its high toxicity has been reported in animals [6, 9] as well as in humans [2]. The toxicity is especially marked in the lung, and is characterized by development of pulmonary edema and damage to the alveolar epithelium. The mechanism of such pulmonary injuries is believed to be related to the intracellular generation of free oxygen radicals by the cyclic reduction and oxidation of paraquat leading to lipid peroxidation of cell membranes as a type of oxidant-induced injuries [12]. However, since paraquat can cross the placenta to reach the fetus, it is possible that paraquat is toxic to the fetus as well, although the degree of its toxicity may be low because of its low concentrations in fetuses compared with maternal tissues [3]. Our previous study, however, revealed that paraquat treatment of rats during late stages of gestation induced a constriction of the DA of their fetuses [11]. It has been also shown that PGE₂ maintains the fetal DA patent [4, 5, 8, 10, 13]. The present study was undertaken to clarify the mechanism of paraquat-induced constriction of the fetal DA. Thus, pregnant rats were treated with paraquat, and their fetuses of these rats were treated with PGE₂. Changes in the caliber of the fetal DA and in the maternal plasma PGE₂ level were examined.

Female Wistar rats 12-15 weeks old at the time of mating were used. They were maintained on a 12-hr on- and 12-hr off-light cycle with food (Labo-MR Breeder) and water available ad libitum at 22±3°C and humidity of 55±10%. They were housed with males overnight and examined the next morning for the presence of sperm in the vaginal smear. The day on which sperm was found was designated as day 0 of gestation after which the females were placed in individual cages.

In the first series of experiments, paraquat was given to each pregnant rat at a dose of 25 mg/kg, and 2 hr later, the rat underwent ether anesthesia and a midventral laparotomy. Several fetuses in each litter were given a subcutaneous injection of 4 μg PGE₂ (Sigma) through the uterine wall and autopsied 1 hr later. Cesarean section was performed at the time of 13:00 on day 21 of gestation at which time each fetus was rapidly immersed in an acetone-dry ice mixture. The frozen fetuses were weighed individually, and 4 fetuses having similar weight were selected from each litter and stored for several days at -20°C prior to observation. At the time of observation, the caliber of the DA was determined as described previously [1]. In the second series of experiments, rats on day 21 of gestation were subcutaneously given paraquat (25 mg/kg). Three hr later, blood was sampled from the abdominal aorta of these rats under ether anesthesia. Plasma PGE₂ levels were determined by radioimmunoassay. Antisera and [125I]PGE₂ analogue tracer (NEN; DuPont) were obtained.

The obtained data were analyzed by Student's t test, and a p value less than 0.01 was considered to be significant.

The DA of fetuses of paraquat-treated rats was significantly constricted compared with that of fetuses of pregnant rats treated with physiological saline. However, the caliber of the DA of PGE₂-treated fetuses of paraquat-treated rats was significantly greater than that of non-treated fetuses of the same litter, comparable to that of fetuses of physiological saline-treated rats (Fig. 1). The maternal plasma PGE₂ levels at 3 hr after paraquat treatment, was significantly lower than that in controls (Fig. 2).

We previously found that 25 mg/kg paraquat treatment of pregnant rats in late stages of gestation induced a constriction of the DA of their fetuses, and that the constriction reached its highest degree 3 hr later [7]. Consequently, in the present study, fetuses were examined 3 hr after maternal paraquat administration, and some of these fetuses were given PGE₂ 1 hr before examination. As a result, the fetal DA which had been once constricted by paraquat, became patent again by PGE₂. The plasma PGE₂ level of pregnant rats treated with paraquat (25 mg/kg) was significantly decreased 3 hr later coincidentally with the highest degree of the DA constriction. It is speculated that a decreased amount of...
maternal plasma PGE$_2$ results in a reduction of transplacental transfer of PGE$_2$ to fetuses. It is also known that the ability of fetuses to synthesize PGE$_2$ is lower than that of adults. It is, therefore, likely that following maternal paraquat treatment, the PGE$_2$ level in fetuses is severely reduced.

Our results indicate that paraquat induces a constriction of the fetal DA by interfering with PGE$_2$ activities.

REFERENCES