Effect of Maternal Paraquat Administration on the Fetal Ductus Arteriosus in the Rat

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Abstract. The ductus arteriosus (DA) in the fetal rat was calibrated using a whole-body freezing method, 3 hr after maternal treatment with paraquat at a dose of 25 mg/kg of body weight on days 19–21 of gestation. On days 20 and 21, the DA was significantly constricted. The DA was also significantly constricted on day 19 2/3 but not on day 19 1/2. It is concluded that paraquat has a constrictive effect on the DA and that the onset of this effect occurs in the first half of day 19 of gestation.—Key Words: ductus arteriosus, fetal rat, paraquat.


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 [11, 16] as well as in man [2]. The toxicity is especially marked in the lung, characterized by initial development of pulmonary edema and damage to the alveolar epithelium. The mechanism of pulmonary injury is believed to be related to the intracellular generation of free radicals of oxygen by the cyclic reduction and oxidation of paraquat leading to lipid peroxidation of cell membranes as a type of oxidant-induced injuries [19]. On the other hand, since paraquat can cross the placenta to reach the fetus, it is likely that paraquat has also a fetal toxicity, though the degree of its toxicity may be low because of its low concentrations in fetuses compared with maternal tissues [3]. Consequently, a working hypothesis can be settled in such a manner that paraquat exerts some effect, probably constrictive, on the fetal ductus arteriosus (DA) which is closely related to the fetal pulmonary circulation. The present study was undertaken to test whether the foregoing working hypothesis could be supported.

Female Wistar rats, 12–15 weeks old at the time of mating, were used. They were maintained on 12-hr on- and 12-hr off-light cycle with food (Labo-MR Breeder) and water both \textit{ad libitum} at room temperature of 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, and the pregnant rats were caged individually thereafter.

Pregnant rats were killed at 1 p.m. (day 19 1/2) and 4 p.m. (day 19 2/3) on day 19, and 1 p.m. on days 20 and 21. They had been given subcutaneously 25 mg/kg paraquat 3 hr prior to sacrifice. This interval (3 hr) was chosen referring to our previous report [11]. As controls, other rats had been given the vehicle, physiological saline 3 hr prior to sacrifice. At autopsy of caesarean section, each male fetus was rapidly immersed in an acetone-dry ice mixture. Only male fetuses were used for observation in order to exclude possible sex differences in caliber of the DA and in manner of its response to exogenous agents. The frozen fetuses were weighed individually, and 4 fetuses of similar weight were then 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 by a method described previously [11]. Briefly, the chest of the frozen fetus was shaved from the back toward the ventral side to expose the exact site where the DA was separated from the aorta. At this site, the DA was calibrated with an ocular micrometer set in a dissecting microscope.

Data were analyzed statistically with Student’s \textit{t} test, and \textit{p} value less than 0.01 was considered statistically significant.

From day 19 1/2 to day 21 1/2, the DAs of control fetuses were gradually dilated. The difference in caliber of the DA between control and experimental fetuses was significant in all groups except on day 19 1/2, at which time the DA was not constricted (Fig. 1).

This observation constitutes a new line of evidence that paraquat, when given to the pregnant rat during the late gestational period, can induce a significant constriction of the fetal DA. In detail, paraquat at the dosage used in the present study caused a constriction of the DA from day 19 2/3 onwards, but failed to induce the constriction on day 19 1/2. Therefore, the present working hypothesis can be fully supported.

![Graph](image_url)

\textbf{Fig. 1.} Changes in caliber of the fetal DA at different times of gestation, 3 hr after maternal treatment with paraquat (25 mg/kg). Open columns show controls, hatched columns paraquat-treated fetuses. Each column represents mean ± SEM of 12 determinations from 3 litters. * \textit{p}<0.01: significantly different from control.
It is well known that the dilation of the DA is maintained by prostaglandins (PGs) [6, 7, 14, 17, 20]. On the other hand, glucocorticoids cause the DA to be constricted [15, 21], the effect being due to their inhibition of PG biosynthesis [12, 13]. In our previous study [1], similar results were obtained by indomethacin, a synthetic compound having a nature similar to that of glucocorticoids. Constriction of the fetal DA induced by indomethacin was not observed on day 19 1/2, but was observed from day 19 2/3. Considering these facts, it can be speculated that the onset of the susceptibility of the DA to exogenous agents occurs in the first half of day 19 of gestation.

The lung, a target for paraquat toxicity, has been demonstrated to contain a large amount of PGs and to have a considerable capacity to synthesize and metabolize PGs [5, 10]. According to Giri et al. [9], the plasma concentration of PGE₂ is increased in response to paraquat (45 mg/kg, i.p.) in rats. On the other hand, the same investigators reported decreased plasma PGE₂ levels in dogs and decreased PGE₂ synthesis in guinea pig lung after treatment with paraquat [4, 8]. Therefore, it seems that there is a species difference in the action of paraquat on PGs. However, the mechanism leading to the constriction of the fetal DA in the present study cannot be fully explained. If the patency of the DA is maintained only by prostaglandins, it likely follows that a medium, but toxic [18], dose of paraquat (25 mg/kg, s.c.) has a kind of inhibitory actions on PGs, resulting in the constriction of the fetal DA.

It is concluded that paraquat has a constrictive effect on the fetal DA and that the onset of the susceptibility of the DA to paraquat occurs in the first half of day 19 of gestation in the rat.

REFERENCES