Propranolol Inhibits the Spontaneous Closure of the Ductus Arteriosus in Newborn Rats

Kazuyoshi ARISHIMA, Tatsuya TAKIZAWA, Takashi ODA, Masako YAMAMOTO, Hirofumi TOGASHI, Hiroaki SOMIYA, and Yasunobu EGUCHI

Departments of Anatomy II and Developmental Biotechnology, Azabu University School of Veterinary Medicine, Fuchinobe, Sagamihara-shi, Kanagawa 229, Japan
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ABSTRACT. Newborn rats delivered by cesarean section were given subcutaneously propranolol (PRO), a β-adrenergic blocker, (1) immediately or (2) 180 min after delivery. The diameter of the ductus arteriosus (DA) of the newborn pups was calibrated at 30, 60 and 90 min after the PRO-administration. The results were as follows: (1) The DA calibers of the pups given 0.2, 1.0, 5.0 mg/kg PRO immediately after cesarean delivery remained significantly larger than those of controls in a dose-dependent manner for 30 min after treatment. In the 5 mg/kg group, the enlargement of the DA was prolonged for 90 min after treatment. (2) In untreated pups, the DA completely closed by 180 min after cesarean delivery. The DA was not affected by the administration of 5 mg/kg PRO at 3 hr after delivery. It was concluded that, PRO inhibits the spontaneous constriction of the DA, suggesting an important role of β-adrenergic stimulation on the spontaneous closure of the DA in newborn rats. — KEY WORDS: ductus arteriosus, propranolol, rat (newborn).


The sympathoadrenal system is activated in the human fetus during uncomplicated delivery [5, 11]. In lambs, catecholamine concentration abruptly rises to a very high level at birth [15, 16] and a similar increase was observed in newborn rats under anoxic stress [12]. Such catecholamine surge during or after delivery suggests its functional importance in neonatal adaptation in that it improves aeration of the lungs by enhancing airway liquid absorption [6], increasing cardiac performance [4], and mobilizing glucose and free fatty acids [10, 15]. These reports suggest that the surge of catecholamine may play a significant role in the spontaneous closure of the ductus arteriosus (DA), which is necessary to adapt to neonatal gaseous exchange in the lungs from fetal gaseous exchange in the placenta. Accordingly, the present study was conducted to examine whether a β-adrenergic blocker, propranolol, directly affects the spontaneous constriction of the DA in newborn rats.

Female Wistar rats, 12–15 weeks old at the time of mating, were used in this study. They were maintained on a commercial diet (CE-2, Clea Japan, Tokyo) and tap water ad libitum and kept in a room at a temperature of 22 ± 3°C and a relative humidity of 55 ± 10%. Female rats were placed with a male overnight and examined the next morning for the presence of sperm in the vaginal smear. The day on which sperm was found was designated day 0 of gestation, and the females were caged individually thereafter. Pregnant rats were killed by decapitation at 1 p.m. on day 21 of gestation, and the pups were immediately taken out by cesarean section. Only male pups were examined in this study to eliminate possible differences due to gender.

In the first series of experiments, newborn pups were divided into the following groups and given each treatment regimen immediately after birth: Group 1 was given a subcutaneous injection of 0.2 mg/kg of propranolol hydrochloride (PRO, Sigma, St. Louis): Group 2 was given 1 mg/kg PRO: Group 3 was given 5 mg/kg PRO: and Group 4 was given saline alone and served as the control. PRO was dissolved in physiological saline so that 50 ml of solution be given to each pup. During the experiments, the pups were placed in a humid chamber which was maintained at 37°C.

In the second series of experiments, newborn pups were placed in a chamber maintained at 37°C for 180 min after cesarean delivery, at which time the DA should be completely closed under normal conditions [8, 19]. Then, the pups were subcutaneously injected with either 5 mg/kg PRO or saline alone, and their DAs were calibrated at intervals after PRO injection.

In both the first and second series of experiments, each pup was rapidly frozen in an acetone-dry ice mixture at intervals and stored for a few days at -20°C until DA calibration. Their DAs were calibrated by the whole-body freezing and shaving method described elsewhere [1, 2]. Statistical analyses of the data were performed using Student’s t test. A p value less than 0.05 was considered to be significant.

Table 1 shows the results of the first series of experiments. The calibers of the DA of control pups were decreased to less than 30% of the initial value in 30 min and 6% in 90 min after cesarean delivery. In all the groups treated with PRO (Groups 1, 2 and 3), a significant enlargement of the DA was induced compared with controls and the effect was dose-dependent at least for 30 min after treatment. Thereafter this enlargement became not obvious except in the pups receiving the highest dose. In the 5 mg/kg group, the enlargement of the DA was prolonged for 90 min after treatment.

In the second series of experiments, in untreated pups, the DA was completely closed by 180 min after cesarean delivery. The DA was not affected by 5 mg/kg PRO when it was given at 3 hr after delivery.

Such drugs as indomethacin [1, 17] and ethanol [2] cause
Table 1. Changes in the caliber of the Ductus Arteriosus in newborn rats following propranolol injection immediately after cesarean delivery

<table>
<thead>
<tr>
<th>Dose of propranolol (mg/kg)</th>
<th>Caliber of the Ductus Arteriosus (μm): mean ± SEM</th>
<th>Time after treatment (min)</th>
<th>Initial</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (saline)</td>
<td>757 ± 22 (7)</td>
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<tr>
<td>0.2</td>
<td>622 ± 123 (8)*</td>
<td></td>
<td>108 ± 15 (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>643 ± 102 (7)**</td>
<td></td>
<td>104 ± 18 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>700 ± 98 (8)**</td>
<td></td>
<td>136 ± 20 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The figures in parentheses are the numbers of animals obtained from 4-7 litters. *: Significantly different from the control (**: p<0.05, ***: p<0.01).

premature constriction of the fetal DA if these chemicals are given transplacentally late in pregnancy probably because they inhibit the biosynthesis of prostaglandins (PGs).

The results of the present study revealed that a relatively low dose of propranolol, when given to newborn rats, can inhibit and delay the spontaneous constriction of the DA. The effect on the newborn DA was dose-dependent, but it appeared of rather short duration because the inhibitory effect was not obvious after 30 min. When injected in 180 min after cesarean delivery, the drug exerted no re-opening action on the once-constricted DA.

Catecholamine has been shown to produce the ductus constriction, although the effect is evident only at concentrations well above the physiologic level [3]. As mentioned above, a surge of catecholamine during or after delivery has been demonstrated [5, 11, 12, 15, 16] and catecholamine level in the umbilical artery of nonasphyxiated newborn infants is about 10-fold higher than that in the mother during delivery [12]. Considering these reports, the present study supports the hypothesis that β-adrenergic stimulation plays a significant role in the spontaneous closure of the DA after delivery, although some other humoral and neural factors may also contribute [3].

According to a review by Clyman [3], the patency of the DA is regulated by a balance of opposing actions by PGE2 and oxygen. The patency of the DA after PRO treatment may be mediated through the actions of PGs. PRO had no dilating effect on the once-constricted DA in the present study, whereas, administration of PGE1 or PGE2 has been reported to induce a re-opening of the DA in humans [7, 13, 14] and rats [9, 18]. Therefore, the patency of the DA induced by PRO in neonatal rats may occur through a different mechanism than that induced by PGs.

It was concluded that, PRO inhibits the spontaneous constriction of the DA, suggesting an important role of β-adrenergic stimulation on the spontaneous closure of the DA in newborn rats.

REFERENCES