Prostaglandin E_2 Receptor EP4 Inhibition Constricts the Rat Ductus Arteriosus

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Toshiki Sakuma, Toru Akaike, and Susumu Minamisawa

Keywords
Ductus arteriosus · Prostaglandin · EP4 antagonist

Patent ductus arteriosus (PDA) often occurs in premature infants [1]. At present, the cyclooxygenase inhibitor indomethacin is used to treat patients with PDA by inhibiting prostaglandin E_2 synthesis. However, its efficiency is frequently limited [2] and adverse effects are problematic [3]. We have demonstrated that the prostaglandin E_2 receptor EP4 specifically expresses in the rat ductus arteriosus (DA) [4]. Therefore, we hypothesized that EP4 inhibition promoted closure of the DA with fewer side effects.

We first examined the effect of the EP4 antagonist RQ-15986 (CJ-042794) on isometric tension of the ex vivo DA at embryonic day 19 (e19) and 21 (e21). RQ-15986 at a dose of $10{-}^4$ M significantly increased the isometric tension of the DA up to 57 ± 14% and 78 ± 11% of 120mM KCl contraction at e19 and e21, respectively. The constrictive effect of RQ-15986 was greater on the DA than on the aorta. Second, we tested the effect of RQ-15986 on in vivo DA. RQ-15986 was intraperitoneally injected into fetuses at e19 and e21. We measured the inner diameter of the vessels by a rapid whole-body freezing method. RQ-15986 constricted the DA but not the aorta in a dose-dependent manner. The contraction percentage was greater at e21 than at e19. Finally, RQ-15986 did not constrict the marginal artery of the colon.

T. Sakuma
The Jikei University School of Medicine, Minato, Tokyo, Japan

T. Akaike · S. Minamisawa (✉)
Department of Cell Physiology, The Jikei University School of Medicine, Minato, Tokyo, Japan
e-mail: sminamis@jikei.ac.jp

T. Nakanishi et al. (eds.), *Molecular Mechanism of Congenital Heart Disease and Pulmonary Hypertension*, https://doi.org/10.1007/978-981-15-1185-1_42

We demonstrated that RQ-15986 constricted the DA with fewer side effects. We concluded that EP4 inhibition would be a promising alternative strategy to treat a patient with PDA.

Acknowledgment This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (T.A., S.M.), MEXT-Supported Program for the Strategic Research Foundation at Private Universities (S.M.), the Vehicle Racing Commemorative Foundation (S.M.), The Jikei University Graduate Research Fund (S.M.), and the Miyata Cardiology Research Promotion Foundation (S.M.).

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