New Insights on How to Treat Patent Ductus Arteriosus

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Abstract

The ductus arteriosus (DA) must be closed after birth for the establishment of adult circulation. Extremely preterm infants, however, frequently have patent ductus arteriosus (PDA), which associates with significant morbidity and mortality. At birth, the separation of the fetus from its maternal environment constitutes a dramatic change for the infant. Initiation of respiration changes serum composition and oxygen tension resulting in the closure of the DA. We found that serum osmolality was significantly decreased early after birth in rats, and that the hypo-osmolality sensor transient receptor potential melastatin (TRPM) 3 had increased expression in the rat DA compared to the aorta. Our data suggest that a decrease

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in serum osmolality promotes DA closure via TRPM3 and that an increase in osmolality dilates the DA. For extremely preterm infants, recent recommendations include immediate amino acid supplementation. We examined plasma amino acid composition and found an association between low glutamate concentration and PDA. Our data suggest that glutamate induces DA contraction through the AMPA receptor GluR-mediated noradrenaline production. Based on these data, maintaining proper levels of serum osmolality and amino acid composition may improve the therapeutic outcome of PDA in extremely preterm infants.

Keywords

Ductus arteriosus · Smooth muscle · TRP channel · AMPA receptor

37.1 Introduction

In the fetus, the ductus arteriosus (DA) diverts ventricular output away from the high-resistance pulmonary vascular bed into the systemic circulation. Although its patency is essential for fetal circulation, once pulmonary circulation is established, the DA must be closed.

Despite considerable progress in medical management for preterm infants, 25% of PDA in extremely preterm infants is still resistant to pharmacological therapies, i.e., cyclooxygenase inhibitors, which have been the only pharmacological therapeutic strategy since the mid-1970s [1–3]. Therefore, novel strategies for PDA in extremely preterm infants are required.

At birth, dynamic changes occur in serum components. A previous study demonstrated that serum osmolality decreased transiently after birth, but recovered over the next few days in full-term human neonates [4]. However, the significance of this transient decrease in osmolality has never been addressed. Amino acid composition is also changed after birth. Amino acid administration beginning immediately after birth has recently been suggested [5]. However, the role of amino acids on DA regulation has not been reported. Therefore, we investigated the roles of serum osmolality and amino acid composition in DA closure.

37.2 Novel Mechanisms Regulating DA Closure

37.2.1 Decreased Serum Osmolality Promotes DA Contraction

Under physiological conditions, body-fluid osmolality is tightly regulated to near 300 mOsm/kg through the intake or excretion of water and salt [6]. Hypotonicity is sensed, partly, by the transient receptor potential (TRP) channels, such as TRP vanilloid 4 (TRPV4) [7] or TRP melastatin 3 (TRPM3) [8, 9], which acts as a Ca^{2+} channel. Because changes in intracellular Ca^{2+} are associated with DA contraction [10–12], we focused on TRP channels.

Fig. 37.1 Proposed diagram for the role of serum osmolality after birth. Transient decrease in serum osmolality induces DA contraction via TRPM3. [Ca]_i: intracellular Ca²⁺

We found that rats exhibited a similar transient hypo-osmolality after birth as in humans. Hypotonic stimulation induced constriction of DA rings and increased Ca²⁺ transient in DA smooth muscle cells. TRPM3 was highly expressed in the rat DA, and TRPM3-targeted siRNA abolished the Ca²⁺ response to hypo-osmolality. The TRPM3 stimulator, pregnenolone sulfate, induced rat DA constriction *ex vivo* and *in vivo*. Contrary to these findings, intra-peritoneal hypertonic fluid administration impaired rat DA closure.

In humans, neonatal serum hypo-osmolality was observed in relatively mature preterm infants (≥ 28 weeks). In extremely preterm infants (< 28 weeks), however, this hypo-osmolality was not observed. Instead, a rapid increase in osmolality occurred after birth in extremely preterm infants. The degree of osmolar increase was greater in patients with PDA.

These data suggest that a transient decrease in serum osmolality may promote DA closure during the first few days of life (Fig. 37.1) [13].

37.2.2 Glutamic Acid Contributes to DA Closure

First, we analyzed amino acid composition in human neonates. Aminogram results in human neonates at day 2 revealed that the plasma glutamate concentration was significantly lower in extremely preterm infants (< 28 weeks gestation) with PDA than in those without PDA and relatively mature preterm infants (28–29 weeks gestation).

It has been shown that glutamate stimulates noradrenaline release [14, 15]. Many adrenergic nerve terminals were shown in the muscular walls of the human DA, and fluorometric results revealed the presence of noradrenaline in the human DA [16]. A previous report demonstrated that noradrenaline induced significant constriction of the DA even in the 20-week human fetus [16]. Moreover, a recent study demonstrated that glutamate induces noradrenaline release through glutamate ionotropic receptor α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) type subunit 1 (GluR1) [17]. As a result, we investigated the role of glutamate in DA closure.

In the rat, GluR1 mRNA was highly expressed in the DA compared to the aorta on gestational day 19 (preterm) and gestational day 21 (term). GluR1 proteins were co-localized with tyrosine hydroxylase-positive autonomic nerve terminals in the rat and human DA. Intraperitoneal administration of glutamate promoted

Fig. 37.2 Proposed diagram for the role of glutamate in the DA. Glutamate stimulates autonomic nerve terminals of the DA, resulting in noradrenaline release. This noradrenaline promotes DA contraction via $\alpha 1$ adrenergic receptor ($\alpha 1$ AR)

noradrenaline production in the rat DA. Glutamate administration induced DA contraction in both preterm (gestational day 20) and term rat fetuses *in vivo*. Glutamate-induced DA contraction was attenuated by the Ca^{2+} -sensitive GluR receptor antagonist NASPM or the adrenergic receptor $\alpha 1$ blocker, prazosin.

These data suggest that glutamate induces DA contraction through GluR-mediated noradrenaline production (Fig. 37.2) [18].

37.3 Future Direction and Clinical Implications

PDA often causes serious problems in very premature infants, depending on the degree of left-to-right shunting. It has been reported that more than 50% of infants with birth weights <1000 g receive pharmacological therapy consisting of cyclo-oxygenase (COX) inhibitors or surgical ligation of the DA. Because the current pharmacological and surgical therapies for treating PDA are not always ideal, it is highly desirable to find a relatively simple and noninvasive strategy that would prevent PDA from occurring.

Our study demonstrated that serum osmolality is transiently decreased after birth, and this decrease may be a physiological mechanism to facilitate DA contraction. The significance of this transient decrease in serum osmolality has been largely overlooked. It may be time to reconsider the importance of serum osmolality. Keeping their serum osmolality at the proper, but not elevated, level may be important among preterm infants at risk for PDA.

Our data also suggest that glutamate promoted DA contraction in preterm infants. The composition of amino acid mixtures varies between commercially available solutions. Of note, glutamate concentration is markedly different compared to the other components among commercially available amino acid solutions (0.8–10.0 g/L). Supplementation of glutamate might help to prevent PDA in extremely preterm infants, and the importance of amino acid composition, *i.e.*, glutamate, may need to be considered in postnatal circulatory adaptation.

Acknowledgments The authors are grateful to Yuka Sawada for technical assistance. This study was funded by MEXT/JSPS KAKENHI (U.Y., JP17K19403, JP16H05358, JP15H05761; S.I., JP17K16276; J.S., JP16H07107; Y.I., JPH1605300), and the Yokohama Foundation for the Advancement of Medical Science (J.S.), the Japan Agency for Medical Research and Development (AMED) (Y.I., 66890007, 56689113), and the Kitsuen Research Foundation (Y.I., 71890005).

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