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Short Review Open Access

Role of Ion Channels in Ductus Arteriosus Closure

Toru Akaike and Susumu Minamisawa*

Department of Cell Physiology, Jikei University School of Medicine, Tokyo, Japan

Abstract

The Ductus Arteriosus (DA) is a normal and essential fetal structure that connects the main pulmonary artery and the descending aorta. The DA constriction which occurs immediately after birth is triggered by: (a) an increase in oxygen tension, (b) a dramatic decline in circulating PGE_2 and a promotion of its degradation in the lung, (c) a decrease in the expression of PGE receptors in the DA wall and (d) a decrease in blood pressure within the DA. Ion channels play an essential role in this acute response that is known as functional DA closure. Oxygenation from fetal to neonatal circulation inhibits several potassium channels (voltage-dependent and ATP-dependent), which then leads to membrane depolarization. This depolarization triggers the activation of voltage-dependent calcium channels, and extracellular calcium then enters into the cytosol of smooth muscle cells of the DA. Calcium is also released from the sarcoplasmic reticulum, with a consequent supply provided through store-operated calcium channels. An increase in cytosolic calcium induces DA constriction. Ion channels also play a role in vascular remodeling of the DA, although this has not yet been extensively investigated. Voltage-dependent L- and T-type calcium channels promote formation of intimal thickening through an increase in proliferation and migration of DA smooth muscle cells. Current medical treatment for patients with persistent patent DA is limited to cyclooxygenase inhibitors such as indomethacin and ibuprofen. A better understanding of the role of ion channels in vasoconstriction and vascular remodeling of the DA may encourage the design and development of novel pharmacological treatments for patients with patent DA. In this review, we focus on current knowledge on the roles of ion channels in the DA.

Keywords: Ion channels; Calcium; Potassium; Oxygen; Vascular remodeling; Contraction; Ductus Arteriosus (DA)

Clinical Background of Patent Ductus Arteriosus

The ductus arteriosus (DA), an essential fetal artery that connects the main pulmonary artery and the descending aorta, closes spontaneously within a few days after birth. The primary driving force behind DA closure is an increase in oxygen tension and a decline in circulating prostaglandin E_2 (PGE_2) [1-3]. When the DA remains open after the first 3 days of life, the resulting condition is known as patent ductus arteriosus (PDA). The incidence of PDA unaccompanied by any other cardiovascular abnormality has been estimated to be 0.06% of term infants [4]. Nevertheless, the incidence sharply increases in premature infants. Symptomatic PDA cases have been found in 28% of very-low-birth-weight infants (<1500g) and 55% of extremely-low-birth-weight infants (<1000g) [5,6]. The presence of PDA significantly increases life-threatening risks in preterm infants, such as pulmonary edema and deterioration of respiratory status, which further decreases oxygen tension in these infants and keeps the DA open. Although oxygen is a potent vasoconstrictor of the DA, a high concentration of oxygen inhalation is prohibited in low-birth-weight infants because of the risk of oxygen-mediated tissue injury such as retinopathy. Pharmacological treatment of PDA has been limited to cyclooxygenases (COX) inhibitors such as indomethacin and ibuprofen.

Overview of the Mechanism of DA Closure

Mammalian DA closure, including that in humans, is thought to occur due to a combination of two different mechanisms. One is an acute response of smooth muscle constriction within the first several hours of life, known as functional closure of the DA. The other is a relatively chronic response of structural change in the DA during the prenatal period, known as anatomical closure of the lumen [7-9]. Progression of neointimal thickening represents a significant structural change during late gestation and the first several days of life. After shutting down blood flow, progressive apoptosis and fibrotic changes occur in the DA, resulting in permanent DA closure and a remnant structure known as the *ligamentum arteriosum*. Although this process is similar among mammalian DA, the time course of the two mechanisms varies between species. The DA constriction immediately after birth is triggered by: (a) an increase in oxygen tension, (b) a dramatic decline in circulating PGE_2 and a promotion of its degradation in the lung, (c) a decrease in the expression of PGE receptors in the DA wall, and (d) a decrease in blood pressure within the DA [7,8]. Endothelin-1, nitric oxide (NO), norepinephrine, acetylcholine, thromboxane A2, and bradykinin have been proposed as potential vasoreactive agents, in addition to oxygen and PGE [10-19].

Anatomical closure of the DA is associated with the distinct differentiation of the vessel wall. Intimal thickening is the most prominent phenotypic change and involves several processes: (a) an area of subendothelial deposition of an extracellular matrix, (b) the disassembly of the internal elastic lamina and the loss of elastic fiber in the medial layer, and (c) the migration of undifferentiated medial smooth muscle cells (SMCs) into the subendothelial space. Finally, the DA permanently closes, and the remnant of the DA is known as the *ligamentum arteriosum* in adults [7].

Pharmacological Treatment of PDA

In terms of medical treatment for patients with PDA, nonselective COX inhibitors such as indomethacin and ibuprofen, which inhibit

***Corresponding author:** Susumu Minamisawa, Department of Cell Physiology, Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan, Tel: +81-(0)3-3433-1111; Fax: +81-(0)3-3433-1279; E-mail: sminamis@jikei.ac.jp

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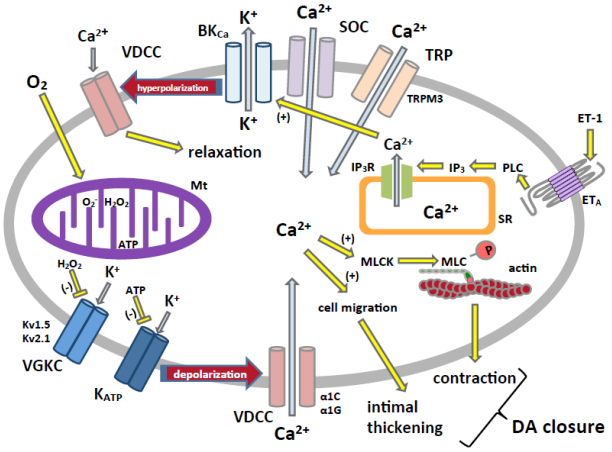
PGE_2 synthesis, are the only available pharmacological agents at present. Since the discovery of this effect more than 35 years ago, no medication for PDA has been developed [20,21]. The efficiency of COX inhibitors depends on gestational age. Although indomethacin is an effective treatment for term infants with symptomatic PDA, it is less effective in preterm infants because of inadequate DA contraction [20-22]. Recently, it has been suggested that one of the causes of such low efficiency is undeveloped intimal cushion formation [9]. Chronic activation of the PGE_2 receptor EP4 promotes the production of hyaluronic acid, an extracellular matrix, which induces SMC migration into the subendothelial layer [9]. In fact, COX-1/2 double knockout mice exhibit persistent PDA [23]. No less important is the fact that COX inhibitors have critical adverse effects, in addition to their low efficiency. It has been reported that premature infants with symptomatic PDA are at risk for necrotizing enterocolitis, renal failure, chronic lung disease, pulmonary hemorrhage, and intraventricular hemorrhage [24]. The postnatal use of the COX inhibitors may also increase the risk of intestinal perforation and renal failure [25-28]. Therefore, a new therapeutic agent for preterm infants with PDA is needed. To develop a new strategy of medical treatment in patients with PDA, it is extremely important to first understand the precise molecular mechanisms underlying both functional and anatomical DA closure. Although the modulation of anatomical DA closure should be considered in future therapeutic strategies for PDA, controlling the vascular tone of the DA could feasibly aid in the discovery of a new strategy for treatment of PDA at present, because the fundamental mechanism of functional closure of the DA has been intensively investigated. At birth, functional closure of the DA is mainly initiated by an oxygen-induced vasoconstrictor mechanism. Although endothelium-derived relaxing and constricting factors such as prostaglandins and endothelin are known to play an important role in regulating DA tone, oxygen constricts the DA in the absence of endothelium, suggesting that the core of the oxygen-sensing mechanism largely depends on the intrinsic character of DA SMCs [10,29,30]. It has been known that specific ion channels in the sarcolemma work as oxygen sensors or effectors. Therefore, in the present review, we will focus on the ion channels involved in functional closure of the DA, and especially on their oxygen-sensing mechanisms.

Oxygen-Induced Contraction and Ion Channels

It has been proposed that an increase in oxygen tension is the most potent vasoconstrictive factor of the DA after birth. The lumen of the DA is perfused by blood with a PO_2 of about 18 mmHg in the fetal lamb [31]. Arterial PO_2 rapidly increases to 90-100 mmHg after birth. Kennedy and Clark were the first to demonstrate that the DA is constricted by oxygen [32]. Although most vascular smooth muscles contract in response to an increase in oxygen tension, the response of the DA to oxygen is much greater in magnitude [31]. This response is due to the DA having developed a specialized oxygen-sensing system. Interestingly, this high sensitivity of the DA to oxygen is related to development in mammalian fetus and chick embryos [33,34]. The premature DA did not constrict even when PO_2 was raised to over 500 mmHg in lambs at less than 80 days' gestation (full term gestation in the lamb is around 150 days). The intrinsic maturation of DA SMCs, including the functional development of a certain ion channel, is required for the oxygen sensing mechanism. Importantly, Roulet and Coburn demonstrated that the oxygen-induced contraction of the guinea pig DA was associated with SMC depolarization [35]. Furthermore, an increase in oxygen tension inhibits the entire cell potassium current, suggesting that potassium channels play an important role in the high sensitivity of the DA to oxygen. Most studies suggest that voltage-dependent potassium channels (Kv channels) are responsible for



K^+: potassium ion, Ca^{2+}: calcium ion, O_2 oxygen, O_2^- : superoxide anion, H_2O_2: hydrogen peroxide, ATP: Adenosine Triphosphate, ET-1: Endothelin-1, ET-A: Endothelin A receptor, PLC: Phospholipase C, IP3: Inositol Triphosphate, IP3R: IP3 receptor, MLCK: Myosin Light Chain Kinase, MLC: Myosin Light Chain, Kv: Voltage gated potassium channel, K_{ATP}: ATP-sensitive potassium channel, BK[Ca]: Large-conductance voltage–dependent and calcium-activated potassium channels, VDCC: Voltage-dependent calcium channel, SOC: Store-operated calcium channel, TRP: Transient receptor potential channel, Mt: mitochondria, SR: sarcoplasmic reticulum

Figure 1: A schematic model of DA closure via ion channels.

oxygen's effect on membrane depolarization [30,36,37]. Interestingly, in SMCs of the resistant pulmonary arteries, hypoxia inhibits the potassium current and depolarizes the cell membrane, resulting in calcium entry via voltage-dependent L-type calcium channels, which is the same process seen in oxygen-induced contraction of the DA [38]. The precise mechanism behind these two tissue types oppositely sensing oxygen and then making use of similar effectors has not been fully understood (Figure 1).

ATP-sensitive potassium channels (K_{ATP} channels) have also been implicated as oxygen sensors [39]. Inhibition of the potassium current causes membrane depolarization, resulting in an activation of voltage-dependent L-type/T-type calcium channels and a subsequent increase in intracellular calcium [2].

Intracellular calcium is also increased by calcium release from the sarcoplasmic reticulum (SR) via the phospholipase C (PLC)-inositol triphosphate (IP3) signal pathway in DA SMCs. Furthermore, the release of calcium from the IP3-sensitive store in the SR due to oxygen promotes calcium entry through store-operated calcium channels in the sarcolemma [40]. Accordingly, many channels and transporters in DA SMCs are believed to be involved in oxygen-induced DA constriction.

Intracellular calcium conjugates calmodulin activates myosin light chain kinase (MLCK), which is a specialized calcium-calmodulin dependent kinase II. Phosphorylated myosin light chain (MLC) by MLCK causes an actin-myosin interaction, resulting in ATP-dependent muscle contraction. MLC phosphatase then dephosphorylates the phosphorylated MLC and releases the actin-myosin interaction, resulting in relaxation. Intracellular calcium is excluded from the cell through the sodium-calcium exchanger in the plasma membrane and is also loaded into the SR though the SR calcium pumps (SERCA) [41-43]. Finally, the effect of the rise in cytosolic calcium is amplified by enhanced calcium sensitivity of the actin-myosin interaction in the DA. Rho-kinase is believed to play

a critical role in higher calcium sensitivity in the DA [44], which is, unfortunately, beyond the scope of this review.

Channels

Voltage gated potassium channel (Kv1.5, Kv2.1)

Several studies have demonstrated that 4-aminopyridine (4-AP)-sensitive, voltage gated potassium channels (Kv) play a central role in oxygen-induced constriction in the DA [30,45,46]. At the molecular level, potassium channels are composed of pore-forming α-subunits which co-assemble with cytoplasmic regulatory/auxiliary -subunits. Both Kv -subunits (Kv1.2, Kv1.5, Kv2.1, Kv3.1, Kv4.2, Kv4.3, and Kv9.3) and Kv -subunits have been shown to possess oxygen sensing capabilities [47]. Among them, Kv1.2, Kv1.5, and Kv2.1 are the predominant Kvα-subunit in the human DA, and Kvγ1.2 is a predominant Kvβ-subunit in the pig DA [37,48,49]. Michelakis et al. demonstrated that rotenone and antimycin, mitochondrial electron transport chain inhibitors, decreased diffusible redox-mediator (H_2O_2) production and increased potassium current through Kv channels, resulting in relaxation of oxygen-induced constriction of the DA [48]. They also demonstrated that H_2O_2, like oxygen, inhibited potassium currents and depolarized DA SMCs. They then concluded that oxygen increases the production of H_2O_2 through activating the mitochondrial electron transport chain complexes I or III and then inhibiting Kv channel activity in the DA [45,46,48-50].

In contrast with the full term DA, the immature DA is less likely to constrict in response to oxygen at a physiological concentration [49,51,52]. Waleh et al. demonstrated that Kv channels appear to be the only potassium channels that oppose ductus tension in the mature DA [53]. The poor response of the DA to oxygen could be related to ionic immaturity, i.e., reduced expression and function of oxygen- and 4-AP-sensitive Kv channels. In humans, the expression levels of Kv1.2 and Kv2.1 proteins are lower in preterm than in term foetuses [49]. Importantly, *in vivo* transfer of the gene for Kv1.5 or Kv2.1 partially restores the contractive capabilities of oxygen in the DA of the preterm rabbit [51]. These results suggest that modulating the vascular tone through the oxygen-sensitive Kv channels offers a novel therapeutic target in preterm infants.

Recently, Fan et al. demonstrated that PGE_2 increased the potassium current through the PGE_2-specific receptor EP4, which led to vasorelaxation in the preterm rabbit DA [49]. This result indicates that the PGE_2-EP4 signal promotes vasorelaxation not only by activation of MLC phosphatase but also by an increase in potassium current .

ATP-sensitive potassium channels (K_{ATP})

ATP-sensitive potassium channels play an important role in maintaining membrane resting potential. After birth, an increase in oxygen tension produces intracellular ATP more through oxidative phosphorylation in mitochondria, which closes ATP-sensitive potassium channels and then induces membrane depolarization in the DA. Nakanishi et al. demonstrated that glibenclamide, a second generation sulfonylurea that inhibits ATP-sensitive potassium channels, contracted the isolated rabbit DA exposed to fetal oxygen tension. In addition, cromakalim, an ATP-sensitive potassium channel activator, relaxed the oxygen-induced DA contraction [39]. Waleh et al. suggested that ATP-sensitive potassium channels play a role in only the immature DA, but not in the mature DA in sheep fetuses [53]. Nevertheless, maternal administration of tolbutamide and chlorpropamide, which are first generation sulfonylureas that can pass through placenta, contracted the full term rat DA up to 50% (personal communication with Dr. Kazuo Momma). On the contrary, Ågren et al. demonstrated that glibenclamide had no effect on the chick DA at any developmental stage [33]. Therefore, the role of ATP-sensitive potassium channels may differ among species. In humans, the role of ATP-sensitive potassium channels has not yet been investigated. Recently, a gene mutation of SUR2 has been identified to cause Cantu syndrome, which exhibits a PDA phenotype at a low frequency [54,55]. Although the effect of the SUR2 gene mutation has not been demonstrated in the DA, mutations in SUR2 attenuate the inhibitory effect of ATP-sensitive potassium channel currents, resulting in channel opening [54]. This genetic data implicates that the K_{ATP} channel plays a role in the closure of the human DA. Also, it is reported that PGE_2 and endothelin-1 (ET-1) is associated with the ATP-sensitive potassium channel. Glibenclamide inhibits the fetal lamb DA relaxation induced by M&B-28767, which is a PGE_2 receptor EP3 agonist, although the expression of EP3 in the DA is not abundant [56]. ET-1 and PKC activators, such as phorbol-12, 13-dibutyrate and 1-olelyl-2-acetyl-sn-glycerol, reduce the ATP-sensitive potassium channel current in pulmonary artery (PA) SMCs [57]. Nevertheless, further studies are needed to understand whether these regulatory factors of ATP-sensitive potassium channels play a role in DA closure.

Large-conductance voltage-dependent and calcium-activated potassium channels (BK[Ca])

In addition to Kv and K_{ATP} channels, several recent studies have demonstrated that large-conductance voltage-dependent and calcium-activated potassium channels (BK[Ca]) may regulate the vascular tone of the DA. BK[Ca] channels are known to be abundantly expressed in vascular SMCs, including the premature rat DA [58]. Although several studies have indicated that BK[Ca] channels respond to oxygen, BK[Ca] is unlikely to be involved in oxygen-induced ductal constriction [48,58-60]. Alternatively, activation of BK[Ca] channels may play a role in countering relaxation for the oxygen-induced contraction after birth or hypercarbic acidosis-induced relaxation [58,61].

Voltage-dependent L-type calcium channels (L-type VDCC)

Calcium entry through voltage-dependent calcium channels increases intracellular calcium, resulting in vessel contraction by phosphorylation of MLC. Oxygen activates voltage-dependent L-type calcium channels, leading to DA constriction in term rabbit DA [30,36]. Takizawa et al. demonstrated that the L-type VDCC blocker verapamil inhibits the spontaneous closure of the DA in newborn rats [62]. Cav1.2 is a predominant isoform of voltage-dependent L-type calcium channels, and Cav1.2 is also expressed in the rat DA [63]. Thebaud et al. suggested that the immaturity of oxygen sensitivity in L-type calcium channels contributes to impaired oxygen-induced DA constriction in preterm rabbit DA [36]. Maturity of voltage-dependent L-type calcium channels is required for oxygen induced DA constriction. In this regard, our previous study demonstrated that maternal administration of vitamin A significantly increased the expression levels of Cav1.2 and Cav3.1 mRNAs in the rat DA [63]. In addition to the role of voltage-dependent L-type calcium channels in the regulation of

vascular tone, we found that both L-type and T-type calcium channels promoted SMC proliferation in the DA, which may be involved in the formation of intimal thickening in the DA [63].

Voltage-dependent T-type calcium channels (T-type VDCC)

We, and other investigators, previously reported that calcium influx through voltage-dependent T-type calcium channels also promotes oxygen-induced DA closure [39,64]. We also found that oxygen-induced activation of voltage dependent T-type calcium channels,

especially Cav3.1, promotes not only vascular constriction but also neointimal thickening via an increase in SMC migration in the DA [64]. Importantly, α1G, a Cav3.1 subunit, is predominantly expressed in the rat neonatal DA, and is significantly up-regulated in oxygenated rat DA tissues and SMCs [64]. These data imply that the regulation of T-type calcium channels is an alternative therapeutic target to selectively constrict the DA.

Voltage-dependent sodium channels

At present, there is no report demonstrating that voltage-dependent sodium channels are involved in DA closure. Instead, Clyman et al. have demonstrated that calcium influx and efflux through the sodium-calcium exchanger regulates DA constriction [65,66].

Store-operated calcium (SOC) channels and transient receptor potential (TRP) channels

Although calcium entry through voltage-dependent calcium channels plays a major role in oxygen-induced DA constriction after birth, intracellular calcium is also increased by the release of calcium from the IP3-sensitive store in the SR [67]. Hong et al. also found that significant normoxic contraction of the rabbit DA occurred in the presence of the K_V channel blocker 4-AP and the BK[Ca] blocker TEA [40]. This depolarization-independent DA constriction is caused by the release of calcium from the IP3-sensitive store in the SR and subsequent calcium entry through store-operated calcium (SOC) channels [40]. The SOC current is thought to pass through transient receptor potential (TRP) channels [68]. In the sheep DA, inhibition of SR calcium-ATPase activates store-operated calcium channels in the presence of the L-type calcium channel blocker nifedipine, and then calcium influx from the extracellular space occurs, which contributes to DA constriction [65]. Lu et al. reported that TRPC1, TRPC4, and TRPC6 channels are abundant in pulmonary artery SMCs and are involved in store-operated calcium entry in response to hypoxia [69]. Hong et al. reported that TRPC1 and TRPC4 were identified in the DA by RT-PCR and Western blot analysis [40]. The role of TRPC1 and TRPC4 in oxygen-induced DA constriction requires further investigation.

Closing Remarks

Closure of DA occurs in two phases. During the first, several hours after birth in term neonates, there is a functional closure as a result of smooth muscle contraction of the DA via an increase in oxygen tension and a decline in circulating PGE_2. Ion channels, especially several potassium channels, play an essential role in this acute response that is known as functional DA closure. Oxygen inhibits potassium channels such as Kv1.5, Kv2.1, and K_{ATP}, resulting in membrane depolarization. Calcium entry through calcium channels such as L- and T-type voltage-dependent calcium channels and store-operated calcium channels increase intracellular calcium, which induces DA constriction. In addition, ion channels also play a role in vascular remodeling of the DA. Voltage-dependent L- and T-type calcium channels promote formation of intimal thickening through an increase in proliferation and migration of DA SMCs. A better understanding of the role of ion channels in vasoconstriction and vascular remodeling of the DA should provide an opportunity to design and develop novel pharmacological treatments for patients with PDA.

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