Regulation of myometrial contraction by ATP-sensitive potassium (K\textsubscript{ATP}) channel via activation of SUR2B and Kir 6.2 in mouse

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ABSTRACT. ATP-sensitive potassium (K\textsubscript{ATP}) channels are well characterized in cardiac, pancreatic and many other muscle cells. In the present study, functional expression of the K\textsubscript{ATP} channel was examined in non-pregnant murine longitudinal myometrium. Isometric contraction measurements and Western blot were used. K\textsubscript{ATP} channel openers (KCOs), such as pinacidil, cromakalim, diazoxide and nicorandil, inhibited spontaneous myometrial contractions in a reversible and glibenclamide-sensitive manner. KCOs inhibited oxytocin (OXT)- and prostaglandin F\textsubscript{2α} (PGF\textsubscript{2α})-induced phasic contractions in a glibenclamide-sensitive manner. SUR2B and Kir6.2 were detected by Western blot, whereas SUR1, SUR2A and Kir6.1 were not. These results show that pinacidil, cromakalim, diazoxide and nicorandil-sensitive K\textsubscript{ATP} channel openers are involved in the regulation of myometrial contractility in non-pregnant and pregnant mice [10]. In non-pregnant and pregnant myometria [10, 13–15, 23]. Recently, we also reported functional upregulation of TASK-2 channels in pregnant than that in non-pregnant mice [10]. Interestingly, K\textsubscript{ATP} channels are also key contributors to labor at term [7]. However, the existence subtypes and role of K\textsubscript{ATP} channels in myometrium is still not well defined. Therefore, we characterized the molecular isoforms and physiological functions of K\textsubscript{ATP} channels in murine myometrium in this study.
MATERIALS AND METHODS

Tissue preparation for isometric contraction: All experiments were performed in accordance with the guidelines for animal care and use approved by Chungbuk National University and The Physiological Society of Shanghai Jiaotong University. Female non-pregnant ICR (age, 10–12 weeks) mice were anesthetized with fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether (Sevoflurane; Maruishi Pharma., Osaka, Japan) and killed by cervical dislocation [10]. The uteri were cut open from the neck to the end of the uterine horns, rinsed in Krebs-Ringer bicarbonate (KRB) solution and pinned on a Sylgard plate [10]. Longitudinal muscle strips (1 × 5 mm) were mounted on vertical chambers in an isometric contractile measuring system. One end of the tissue was tied to a fixed holder, and the other side was linked to a force transducer (Harvard Instruments, Holliston, MA, U.S.A.). The PowerLab-Data Acquisition System and a personal computer running Charter v5.5 software (ADinstruments, Colorado Springs, CO, U.S.A.) were used. Each strip was stretched passively to resting tension for 1–2 hr after a 1.5 hr equilibration [10]. Contractile responses of the strip to high K+ (50 mM) were repeated two times.

Solution and drugs: KRB solution (CO₂/bicarbonate-buffered Tyrode) contained (in mM): NaCl 122, KCl 4.7, MgCl₂ 1, CaCl₂ 2, NaHCO₃ 15, KH₂PO₄ 0.93 and glucose 11 (pH 7.3–7.4, bubbled with 5% CO₂/95% O₂). Equimolar concentration of Na⁺ was replaced by K⁺ to make high K⁺ (50 mM) solution. The external solution was changed by solutions which had previously been incubated (bubbled with 5% CO₂/95% O₂, 36°C) in water bath before the application. Pretreatment of various blockers was applied for 12–15 min before the application of K⁺ ions. All drugs used in this study were purchased from Sigma (St. Louis, MO, U.S.A.).

Western blot: Tissues were fresh-frozen in liquid nitrogen and were homogenized in homogenation buffer containing 0.01% (v/v) protease inhibitor cocktail. Tissue homogenates were then centrifuged for 10 min, and proteins were measured by a Bradford protein assay using BSA as the standard. Equal amounts (20–40 µg) of soluble proteins were separated using 8% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE) at 100V for 90 min and transferred to a PVDF membrane. The PVDF membranes were blocked with 5% skim-milk in TBS buffer solution, followed by incubation with Kir 6.1, Kir 6.2, SUR1, SUR2A and SUR2B (Santa Cruz (Dallas, TX, U.S.A.); Millipore (Darmstadt, Germany); and StressMarq (Victoria, Canada); 1:500–1:200) antibodies. The membranes were incubated with secondary antibody
Glibenclamide 20 µM

![](image)

1 g
5 min

Cromakalim 5 µM

Oxytocin 10 nM

Glibenclamide 20 µM

0.5 g
3 min

Cromakalim 20 µM

Fig. 2. Inhibition of murine myometrial contractions by cromakalim. (A) Cromakalim (5 µM) completely inhibited spontaneous contractions of murine myometrium in a glibenclamide-sensitive manner. (B) Cromakalim (20 µM) completely inhibited OXT (10 nM)-induced phasic contractions in a glibenclamide-sensitive manner. Data are summarized in (C) and (D).

Statistics: Data were expressed as means ± standard errors of the mean (means ± SEM). The ANOVA and Student’s t-test were used to measure the statistical significance. P-values less than 0.05 were regarded as statistically significant.

RESULTS

Inhibition of isometric contractions in murine myometrium by pinacidil: Spontaneous isometric contractions of 1.9 ± 0.4 g and 3 ± 2.1 cycles/min were recorded (n=60) (Figs. 1A, 2A, 2B and 4A). High K+ produced 0.4 ± 0.07 g contractions (n=60; data not shown). Pinacidil (5 µM), which opens KATP channels (KCOs), inhibited spontaneous myometrial contractions in a glibenclamide-sensitive manner (Fig. 1A). Pinacidil (5, 10 and 20 µM) inhibited phasic contractions of murine longitudinal myometrium to 14 ± 12.1%, 8 ± 8.3% and 0% of the control (n=8, 6 and 4, respectively; P<0.05; Fig. 1C). Glibenclamide, which blocks KATP channels, reversed the inhibition of spontaneous isometric contractions by pinacidil (5 µM) to 63 ± 12% of the control (n=6; P<0.05; Fig. 1C). Oxytocin (OXT, 10 nM) produced tri-phasic contractions that included initial contractions, followed by tonic contractions overlapped with phasic contractions (Fig. 1B). The phasic contractions produced by OXT (10 nM) were inhibited by pinacidil (20, 50 and 100 µM) to 26 ± 25.8%, 19 ± 12.5% and 18 ± 11.9% of the control (n=4, 7 and 5, respectively; P<0.05; Fig. 1D). Glibenclamide reversed the inhibition of spontaneous isometric contractions by pinacidil (50 µM) to 86 ± 26.5% of the control (n=5; P<0.05; Fig. 1D).

Inhibition of isometric contractions in murine myometrium by cromakalim: Cromakalim inhibited spontaneous contractions completely in a glibenclamide-sensitive manner. Cromakalim (5 µM) inhibited spontaneous contractions, which were recovered by glibenclamide (Fig. 2A and 2C). Cromakalim (1, 5 and 10 µM) inhibited phasic contractions to 34 ± 21.1%, 20.1 ± 20.0% and 0% of the control (n=5, respectively; P<0.05; Fig. 2C). Glibenclamide reversed the
inhibition of spontaneous isometric contractions caused by cromakalim (5 µM) to 84 ± 1.5% of the control (n=5; P<0.05; Fig. 2C). Cromakalim (20 and 100 µM) also inhibited OXT (10 nM)-induced phasic contractions to 34 ± 21.4% and 14 ± 12.6% of the control (n=6 and 4, respectively; P<0.05; Fig. 2B and 2D). Glibenclamide reversed the inhibition of spontaneous isometric contractions by cromakalim (100 µM) to 79 ± 3.5% of the control (n=4; P<0.05; Fig. 2D). As shown in Fig. 2B, tonic contraction by OXT was also suppressed by cromakalim in a glibenclamide-sensitive manner.

Inhibition of isometric contractions in murine myometrium by nicorandil: Nicorandil (20–100 µM) inhibited spontaneous myometrial contractions in a glibenclamide-sensitive manner (Fig. 3A). Nicorandil (20, 50, 100 and 300 µM) inhibited spontaneous myometrial contractions to 34 ± 21.4% and 14 ± 12.6% of the control (n=6, 12, 12 and 1, respectively; P<0.05; Fig. 3C). OXT (10 nM)-induced phasic contractions were also inhibited by nicorandil (100–500 µM) in a glibenclamide-sensitive manner (Fig. 3B). OXT (10 nM)-induced phasic contractions were inhibited by nicorandil (100 and 500 µM) to 65 ± 15.7% and 40 ± 19.7% of the control (n=11 and 8, respectively; P<0.05; Fig. 3D). Glibenclamide reversed the inhibition of spontaneous and OXT-induced phasic contractions caused by nicorandil (100 µM and 500 µM) to 71 ± 8.6% and 113 ± 2.9% of the control (n=10 and 5, respectively; P<0.05; Fig. 3C and 3D).

Inhibition of prostaglandin F\(_2\alpha\) (PGF\(_2\alpha\))-induced phasic contractions in murine myometrium by KCOs: PGF\(_2\alpha\) produced tri-phasic contractions, such as initial contractions, followed by tonic contractions overlapped with phasic contractions in murine uterine smooth muscle (Fig. 4A–4D). All KCOs completely inhibited acetylcholine (ACh)-induced contractions in a glibenclamide-sensitive manner too (data not shown; see discussion).

Identity of the K\(_{ATP}\) channel subunits in murine myometrium: The identity of the K\(_{ATP}\) channel in murine myometrium...
was studied. SUR1, SUR2A and Kir6.1 were not detected by Western blot. However, proteins compatible with SUR2B (58K) and Kir6.2 (55K), which were composed of K\(_{\text{ATP}}\) channels, were detected in murine myometrium (Fig. 5A and 5B). The density of each SUR2B/β-actin and Kir6.2/β-actin was 383 ± 112.4 and 236 ± 58.8 (n=5 and 7, respectively).

**DISCUSSION**

This is the first report that K\(_{\text{ATP}}\) channels composed or SUR2B and Kir6.2 produced relaxation of various contractions by diverse KCOs of murine myometrium.

Regulation of smooth muscle function via K\(_{\text{ATP}}\) channels is dependent on these types of Kir and/or SUR isoforms [3, 22]. K\(_{\text{ATP}}\) channels are octomeric proteins formed with inwardly rectifying potassium (Kir) channel subunits along with SUR receptor subunits, and there are several types of K\(_{\text{ATP}}\) channel combinations [2, 3]. In structure, Kir is a pore forming structure, and SUR provides binding sites for ATP and KCOs [2, 3]. The combination of Kir6.1/SUR2B (and/or Kir6.2/SUR2B) in vascular smooth muscle [3] and Kir6.2/SUR2B in guinea-pig stomach was identified [22]. K\(_{\text{ATP}}\) channels in atrial and ventricular myocytes are composed differently, as atrial and ventricular myocytes have the same Kir 6.2 subunit but different SUR subtypes called SUR1 and SUR2A, respectively [3]. The physiological functions of K\(_{\text{ATP}}\) channels are diverse in various tissues, including regulation of resting membrane potential modulation of calcium influx, and regulating the force and frequency of gastrointestinal tract contractions [3, 22]. Therefore, their function cannot be determined without isolating the isoforms from each tissue.

In myometrium, Kir6.1, Ki6.2, SUR1 and SUR2B isoforms have been identified in human myometrium [7]. Recently, expression of SUR2A subtype was also reported [9]. However, isoforms of Kir6.1 and SUR2B only have been identified as functional K\(_{\text{ATP}}\) channel in rat and human [9, 20]. In our study, as shown in results, we detected Kir6.2 and SUR2B subtypes in murine myometrium by Western blot. At this moment, unfortunately, we cannot explain the different expression of K\(_{\text{ATP}}\) channels in each myometrium. Functionally, pinacidil and diazoxide are representative activators of K\(_{\text{ATP}}\) channels in mammals by relaxing human uterine arterial and human pregnant uterine smooth muscle [17, 20]. As shown in Figs. 1 and 4A, pinacidil relaxed murine longitudinal uterine muscle. Although data not shown, diazoxide (100, 200 and 300 µM) inhibited spontaneous contractions to 63 ± 11.1%, 26 ± 16.3% and 0% of the control (n=9, 5 and 4, respectively; P<0.05) in
a glibenclamide-sensitive manner (recovered to 56 ± 7.1% of the control; \( P<0.05 \); Fig. 2C). Diazoxide (100 and 300 \( \mu M \)) also inhibited OXT-induced phasic contractions to 51 ± 15.0% and 14 ± 13.5% of the control (\( n=12 \) and 6, respectively; \( P<0.05 \)) in a glibenclamide-sensitive manner (recovered to 40 ± 18.4% of the control; \( P<0.05 \)). It also inhibited \( \text{PGF}_{2\alpha} \)-induced contraction (Fig. 4B). In addition, cromakalim and nicorandil suppressed metmyometrial contractions in a reversible and glibenclamide-sensitive manner (Figs. 2, 3, 4C and 4D). Nicorandil and diazoxide have been used to treat ischemic heart disease and hypertension [11]. Nicorandil was as effective as nifedipine for tocolysis during preterm labor in a randomized-controlled study [11]. We found every four KCOs produced glibenclamide-sensitive relaxation of diverse isometric contractions of murine myometrium. Therefore, we believed that combination of Kir6.2 and SUR2B in murine myometrium might be target for every four KCOs and play a crucial role for myometrial relaxation.

\( K_{\text{ATP}} \) channel expression levels in myometrium may be associated with the stage of pregnancy [9], and \( K_{\text{ATP}} \) channels in myometrium are down regulated during late pregnancy. It has been suggested that decreased \( K_{\text{ATP}} \) channel expression at term of pregnancy is responsible for enhanced myometrial contractility at labor. It has also been suggested that upregulation of \( K_{\text{ATP}} \) channels in parturients >35-year-of-age might be responsible for the increased rate of birth complication in these women [9]. As strong contractions are produced from several hours to even days during labor, energy metabolism is very complex at this time. In addition, we found that substituting D-mannitol for glucose inhibited the frequency of \( \text{PGF}_{2\alpha} \)-induced contractions from 1.8 ± 0.17 to 0.5 ± 0.14 (\( n=2; \) data not shown). Thus, \( K_{\text{ATP}} \) channels may be one of a target for regulation of myometrial contractions. At molecular level, Kir6.2 is required for protection against myocardiac ischemia/reperfusion (I/R) injury and skeletal muscle weakness [8, 12]. In addition, it was also reported that vasodilation by metabolic inhibition, such as oxygen glucose deprivation (OGD)-mediated inhibition, was attenuated in SUR2 null arteries [1].

Uterine smooth muscle spasms via vascular contracture and/or local contraction of vessels [17] through production of \( \text{PGF}_{2\alpha} \) might be responsible for dysmenorrhea. Unfortunately, no medications can effectively reduce myometrial spasms factory. We only found the molecular and physiological functions of \( K_{\text{ATP}} \) channels in this study, and activation of \( K_{\text{ATP}} \) channels (Kir6.2/SUR2B) in the murine uterus produced reversible relaxation (Fig. 5). \( K_{\text{ATP}} \) channel regulator agents modulate contractility of human and rat smooth muscle. We also observed that KCOs inhibited \( \text{PGF}_{2\alpha} \)-induced contraction in murine myometrium in a reversible- and glibenclamide-sensitive manner (Fig. 4). Generally, the regulation of myometrial contraction is modulated by many endogenous factors [26]. Finally, pinacilid (10 \( \mu M \)) inhibited ACh-induced phasic contractions to 17% of the control (\( n=11; \) \( P<0.05 \)) in a glibenclamide-sensitive manner (recovered to 73% of the control; \( n=8; \) \( P<0.05 \)). Diazoxide (100 \( \mu M \)), cromakalim (10 \( \mu M \)) and nicorandil (100 \( \mu M \)) also inhibited it to 43%, 8.6% and 40% of the control in a glibenclamide-sensitive manner (\( n=6; 5 \) and 8, respectively; \( P<0.05 \); data not shown).

Therefore, \( K_{\text{ATP}} \) channels may be a key factor in menstrual pain, which needs to be studied in the future.

CONFLICTS OF INTERESTS

No conflicts of interest exist for this study.

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