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Vasopressin Inhibits Sarcolemmal ATP-Sensitive K^+ Channels via V_1 Receptors Activation in the Guinea Pig Heart

Masago Tsuchiya, MD; Kunihiko Tsuchiya, MD; Rumi Maruyama, MD; Genzou Takemura, MD; Shinya Minatoguchi, MD; Hisayoshi Fujiwara, MD

To examine the effect of vasopressin on the sarcolemmal ATP-sensitive K (K_{ATP}) channel, cell-attached, inside-out and open-cell-attached methods of patch clamp techniques were used in isolated guinea pig ventricular myocytes. Suppressing both glycolytic and oxidative ATP production attained K_{ATP} channel activation. In the cell-attached mode, vasopressin inhibited K_{ATP} channels in a concentration-dependent manner with an IC_{50} of 15.1±1.8 nmol/L. In the inside-out configuration, vasopressin failed to block K_{ATP} channels. In the cell-attached mode, manning compound (1 μmol/L), a V_1 receptor-selective antagonist, blocked the inhibitory action of vasopressin, although OPC-31260 (1 μmol/L), a V_2 receptor-selective antagonist could not affect the action of vasopressin. In addition, vasopressin lost its inhibitory action on K_{ATP} channels when the channel was activated by pinacidil, a K channel opener and in the open-cell-attached mode effected by streptolysin-O. Thus, the inhibitory action of vasopressin K_{ATP} channels may occur via V_1 receptor related mechanism. (*Circ J* 2002; **66:** 277–282)

Key Words: Sarcolemmal K_{ATP} channels; V_1 receptor; Vasopressin

Vasopressin is one of the physiologically active peptides that regulate humoral immunity by promoting reabsorption of water in the kidney and simultaneously having a potent vasoconstrictive action on vascular smooth muscle by increasing the production of inositol 1,4,5-triphosphate (IP3) and 1,2-diacylglycerol (DG) and activating the voltage-dependent Ca channel, which results in elevation of the intracellular Ca concentration[1,2]

Recently, it has been reported that secretion of vasopressin increases in pathophysiological conditions such as angina pectoris, acute myocardial infarction and chronic heart failure[3] During such conditions of metabolic inhibition, activation of the sarcolemmal K_{ATP} channel[4] is known to regulate Ca^{2+} entry and myocardial contractility in order to lessen the myocardial damage[5,6] Moreover, activation of this channel minimizes the infarct area in animal models[7] and elicits a cardioprotective action in dogs with pacing-induced heart failure[8] On the other hand, its activation has been reported to shorten the action potential duration, thereby in part acting arrhythmogenically in acute ischemia[9,10] Moreover, Martin et al[2] reported that vasopressin inhibited the sarcolemmal K_{ATP} channels and activated the voltage-dependent Ca channel, thereby regulating insulin secretion in rat pancreatic β-cells. Wakatsuki et al[11] reported that vasopressin activated Ca-activated K channels and simultaneously controlled vascular tone by suppressing sarcolemmal K_{ATP} channels in porcine coronary vascular smooth muscle cells in the cell-attached configuration. More recently, it has been reported that the vasopressin V_1 receptor couples to protein kinase C via activation of phospholipase C and that vasopressin V_2 receptor links to G protein coupled protein kinase including adenylate cyclase[12–15] In the central nervous system, Easaw[16] showed that vasopressin-inhibited the voltage-dependent outward current via the V_1 receptor, and it activated the same current via the V_2 receptor.

Therefore vasopressin regulates excitation of neurons in a diagonal band of the rat. However, the action of vasopressin in the heart still remains controversial. The present study aimed to examine the physiological implication of vasopressin's effects on sarcolemmal K_{ATP} channel in enzymatically isolated guinea pig ventricular myocytes using both cell-attached and inside-out configurations.

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Second Department of Internal Medicine, Faculty of Medicine, Gifu University, Gifu, Japan

Mailing address: Hisayoshi Fujiwara, MD, PhD, Division of Cardiac Electrophysiology, The Second Department of Internal Medicine, Faculty of Medicine, Gifu University, Tsukasamati, Gifu, Gifu 500-8705, Japan. E-mail: ryoujun@pa3.so-net.ne.jp

Methods

Preparation of Single Ventricular Cardiomyocytes

Adult male guinea pigs of 250–300 g were anesthetized with pentobarbital sodium (40–50 mg/kg ip) and isolated ventricular cells were obtained using the collagenase perfusion method[17] In brief, the chest was briefly opened under artificial ventilation, the aorta cannulated and the heart quickly dissected. Using a Langendorff apparatus, the heart was retrogradedly perfused with normal Tyrode's solution for about 5 min to wash out the blood in the vessels, followed by nominally Ca^{2+}-free Tyrode's solution for about 3 min at 36°C. The heart was then switched to nominally Ca^{2+}-free Tyrode's solution containing 0.4 mg/ml of collagenase (type I; Sigma, St Louis, MN, USA) for 13 min and rinsed with a high K^+, low Ca^{2+} 'KB solution' (in mmol/L): L-glutamic acid 70, KCl 25, taurine 20, KH_2PO_4 10, $MgCl_2$ 3, EGTA 0.5, glucose 11 and HEPES 10 (pH 7.3 with KOH) for 5 min. The composition of Tyrode's solution was (in mmol/L): 143 NaCl, 0.3 NaH_2PO_4, 5.4 KCl, 0.5 $MgCl_2$, 1.8 $CaCl_2$ and 5 HEPES-NaOH (pH = 7.4 adjusted by NaOH).

The left ventricle was cut into small pieces in KB solu-

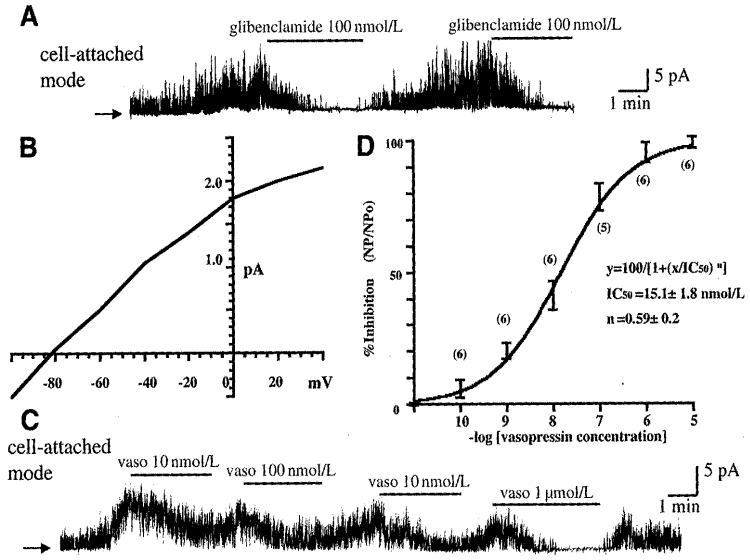

Fig 1. Effect of vasopressin on KATP channel currents. (A) Chart recording of KATP currents activated by metabolic poisoning with 5.5 mmol/L 2-deoxyglucose and 1 mmol/L CN^- at a holding potential of 0 mV. The horizontal arrow on the left of the trace shows the zero current level. The bars above the trace indicate the application of various test solutions. Single channel currents activated by metabolic poisoning were reversibly inhibited by 1 mmol/L glibenclamide. (B) Unitary current-potential relationships. (C) Inhibitory action of vasopressin (10 nmol/L–1 mmol/L) on KATP currents. Vasopressin suppressed KATP currents in a concentration-dependent fashion. (Çc) Concentration–inhibition relation between [vasopressin] and NP/NPo of KATP channels. Horizontal bars indicate SEM values. Numbers in parentheses indicate the number of observations. The data were fitted to the Hill equation: $NP/NP_o = 1/\{1+([\text{vasopressin}]/IC_{50})^n\}$; where is the half maximal vasopressin concentration to block the channel activity and n is the Hill coefficient.

tion at room temperature. The cell suspension was passed through 105-mm mesh filter and single cells were obtained after centrifuged at 400 rpm for 3 min and pre-incubated at 36°C for 60 min in KB solution containing the metabolic inhibitor, 2-deoxy-glucose (5.5 mmol/L; Sigma) to suppress glycolytic ATP production.

Electrophysiology

Under all experimental conditions, normal Tyrode's medium was used as the pipette solution. Single-channel activities were recorded by a patch-clamp amplifier (AXOPATCH 200A, AXON Instruments, USA) with simultaneous backup on videotape via a pulse coded modulation converter system (NF RP880 Japan) for later off-line analysis. KATP channels were activated by glucose-free, K^+ rich external solution containing 1 mmol/L NaCN (in the cell-attached method) and without 1 mmol/L NaCN (inside-out and cell-attached conditions). The composition of the external solution was (in mmol/L) 150 KCl, 2 $MgCl_2$ 0.5 EGTA, and 5 HEPES-KOH (pH=7.4 adjusted by KOH). In this solution, the transmembrane potential was virtually eliminated.

Borosilicate glass pipettes (Hilgenberg, Malsfeld, Germany) were pulled at a resistance of 3–5 MΩ for experiments.

Drugs

Vasopressin (Sigma), des-Gly^9-[β-Mercapto-β, β-cyclopentamethylene-propionyl^1, O-Et-Tyr^2-Val^4-Arg^8]-vasopressin (Sigma), which has both potent V_1 receptor antagonism and weak V_2-receptor-antagonism;[18] manning compound (Sigma), a V_1 receptor-antagonist;[19] and OPC-31260 (Otsuka, Pharmaceutical Co Ltd), a V_2 receptor-antagonist[20] were prepared as stock solutions by dissolving in distilled water and in 0.1% dimethylsulphoxide (DMSO) and were further diluted by test extracellular solutions prior to use. Stock solutions for glibenclamide (1 μmol/L; Hoechst Frankfurt Germany) and pinacidil (1 μmol/L; Sigma) were prepared by dissolving in DMSO 1 mmol/L. DMSO alone did not affect membrane currents. Streptolysin-O (Sigma) was prepared at the concentration of 0.08 U/ml for the open-cell attached configuration.[21] All other reagents were purchased from Sigma Co Ltd. The cell-attached and open-cell-attached experiments were conducted at 35–37°C and the inside-out experiment was performed at room temperature.

Data Analyses

The mean patch current ($I=NP_oi$) was measured as the average difference between baseline currents (no channel open) and open channel currents. The unitary amplitude of open channel currents (i) was estimated using an analysis of the amplitude distribution on a NEC personal computer at a Bessel type cut-off frequency of 0.5 kHz at a sample frequency of 1 kHz.

The mean number of open channels (NP) was given by the product of the number of available channels in the patch (N) and the probability of their being open (P). NP was estimated from the mean patch currents ($I=NPi$) as I/i.

Percent inhibition in the presence of various concentrations of vasopressin [$\%(Np_o-NP/NP_o)$] were calculated with the normalization by NP_o obtained in the absence of vasopressin ($=NP_o$) and are plotted against vasopressin concentrations. The relation was then fitted to the Hill equation with the Marquardt-Levenberg algorithm:

$$\%(Np_o-NP/NP_o) = 100\times(1+([\text{vasopressin}]/IC_{50})^n)^{-1} \quad \text{eqn (1)},$$

where IC_{50} indicates the half maximal concentration for inhibition of vasopressin, and n the Hill coefficient.

Results

Dose-Dependent Inhibition of KATP Channels by Vasopressin in the Cell-Attached Experiments

Fig 1 illustrates the action of vasopressin on KATP currents in the cell-attached mode. In this experiment, exposure of ventricular myocytes pre-treated with 2-deoxy-glucose to glucose-free 150 mmol/L K^+ solution containing 1 mmol/L CN^- usually produced an outward single channel current at 0 mV holding potential within 10–15 min.

Fig 1A shows the reversible inhibitory action of glibenclamide (100 nmol/L) applied outside the patch membrane on the currents induced by metabolic poisoning, and Fig 1B shows the unitary current-membrane potential relationships obtained from 8 different experiments. The I–V curve shows a weak inward rectification as expected. The single channel conductance was calculated 21.6±1.8 pS and rever-

sal potential was –83.5±3.3 mV, which is close to the equilibrium potential for K^+ under the present recording conditions. The experimental data in Fig 1A, B identify the KATP channel activities and correspond closely with those of a previous report[22]

Fig 1C shows the strong inhibitory action of a low concentration of vasopressin (10 nmol/L – 1 μmol/L) on KATP currents activated in the same conditions as before. Vasopressin suppressed KATP currents in a concentration-dependent fashion and the reason why the KATP channel was inhibited by a second application of vasopressin (10 nmol/L) more strongly than with the first application (100 nmol/L) might be related to a decrease in maximal channel activities (decline in channel activity).

Fig 1D summarizes the concentration–inhibition relationship of vasopressin. In a total of 30 myocytes, relative open probabilities were obtained by normalizing mean patch currents in the presence of selected concentrations of vasopressin to the control, and data are plotted as the function of vasopressin concentration. Each plot represents the mean values and SEM (vertical bars).

The inhibitory effects of vasopressin appeared to become saturated at concentrations greater than 10 mmol/L. The smooth curve in the graph is the best fit to eqn (1) with an IC_{50} of 15.1±1.8 nmol/L (Hill coefficient = 0.59±0.20).

These findings strongly suggested that vasopressin could block KATP currents activated in the cell-attached mode.

Vasopressin Failed to Inhibit KATP Channels in the Inside-Out Experiments

Fig 2 shows the inside-out recordings. In this mode, after the excision of the cell-attached patch in the standard 150 mmol/L K^+-solution without ATP and CN^-, the KATP channel showed sudden activation. After the channel activity attained a steady state, as shown in Fig 2, vasopressin (1–10 μmol/L) lost its inhibitory action in 21 of 23 preparations. However, glibenclamide completely inhibited the KATP channel. Therefore, these findings suggest that vasopressin acts on KATP channels from outside the cell membrane via a receptor-mediated signaling pathway.

Vasopressin Acts on KATP Channels Through the V1 Receptor

The data shown in Fig 3A, B were recorded in the cell-attached mode. Two types of vasopressin receptors are known to couple to various signal transduction pathways[3,7,12–15]

We examined which type of receptor is involved in the vasopressin-induced inhibition on KATP channels using des-Gly^9-[β-Mercapto-β, β-cyclopentamethylene-propionyl^1, O-Et-Tyr^2-Val^4-Arg^8]-vasopressin (1 μmol/L), which has potent V1 receptor antagonism and weak V2 receptor antagonism, manning compound (1 μmol/L), a V1 receptor-selective antagonist, and OPC-31260, a V2 receptor-selective antagonist[20] These compounds used alone did not change the channel activity induced by metabolic stress.

Application of des-Gly^9-[β-Mercapto-β, β-cyclopentamethylene-propionyl^1, O-Et-Tyr^2-Val^4-Arg^8]-vasopressin (1 μmol/L) blocked the inhibitory action of vasopressin on single KATP channels. After washing out this compound, the same concentration of vasopressin, however, closed the channels (Fig 3A). In contrast, OPC-31260 (1 μmol/L) failed to affect the inhibitory effect of vasopressin (Fig 3B).

To verify the receptor specificity, manning compound was used in the next experiment and it completely blocked the suppressive action of vasopressin on KATP channels activated in the cell-attached mode (Fig 3C).

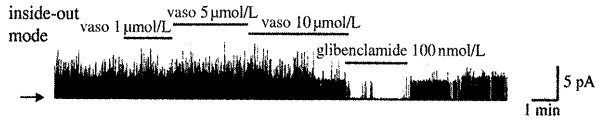

Fig 2. Effect of vasopressin in the inside-out mode on the KATP channel current in the standard 150 mmol/L K^+-solution without metabolic inhibition. Vasopressin failed to inhibit KATP channel activity in the inside-out mode, whereas glibenclamide completely shut it down.

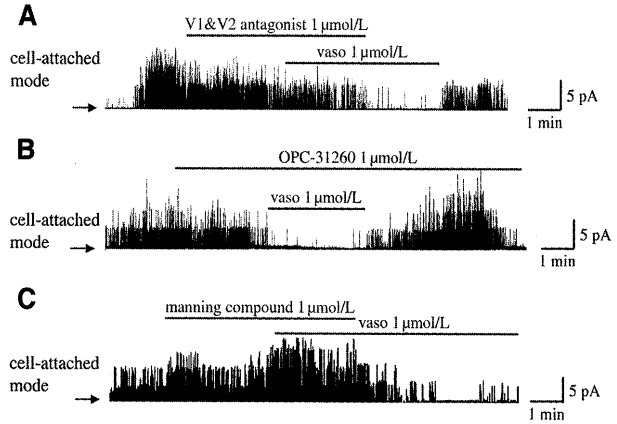

Fig 3. Effects of vasopressin on KATP channels in the presence of the vasopressin V1 and V2 receptor antagonists. The experimental conditions shown in Fig 3A, B were reproduced in the cell-attached mode. (A) Application of V1 and V2 antagonist (1 μmol/L) blocked the inhibitory action of vasopressin on single KATP channels. After washing out the antagonist, the same concentration of vasopressin closed the channels. (B) OPC31260 (1 μmol/L) failed to affect the inhibitory action of vasopressin. (C) Manning compound (1 μmol/L) completely blocked the suppressive action of vasopressin on KATP channels activated in the cell-attached mode. Bars indicate applications of agents to the outside of the pipette.

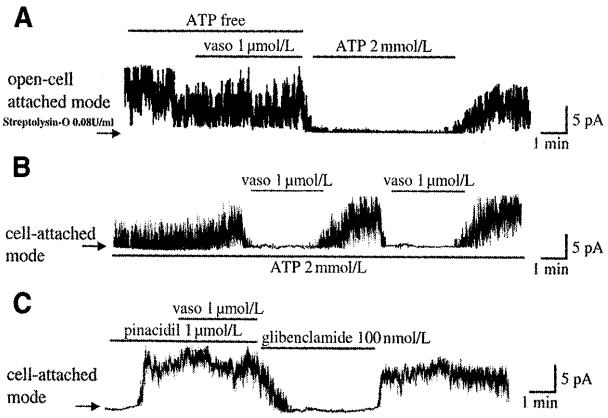

Fig 4. Vasopressin lost its inhibitory action on KATP channel in the open-cell-attached mode and K channel opener experiments. (A) In the open-cell-attached mode, vasopressin lost its inhibitory effects on KATP channel currents activated by lowering ATP concentration. However ATP (2 mmol/L) blocked this activity. (B) In the cell-attached mode, extracellular application of ATP could not affect vasopressin action on KATP channel openings. Subsequent application of vasopressin (1 μmol/L) shut it down. (C) In the cell-attached mode, pinacidil (1 μmol/L) abolished the inhibitory action of vasopressin on the KATP channel.

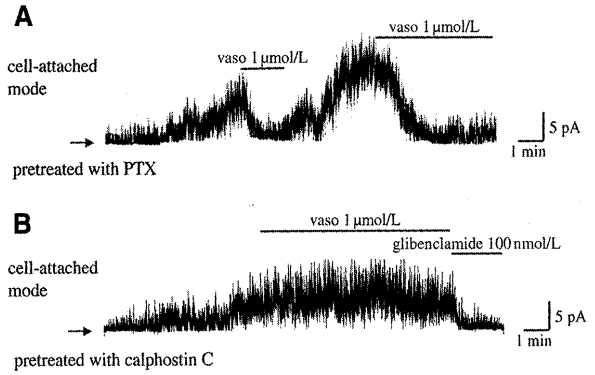

Fig 5. Inhibitory action of vasopressin on KATP channel really derives from PLC-PKC pathway not from adenylate cyclase-PKA pathway. (A) Pretreatment with PTX did not change the action of vasopressin. (B) Pretreatment with calphostin C antagonized the inhibitory action of vasopressin.

Inability to Inhibit KATP Channels by Vasopressin in the Open-Cell Attached Patch and Channels Activated by K Channel Openers

In order to examine the signal transduction pathway of this vasopressin-dependent inhibition on KATP channels more precisely, the open-cell attached mode was employed. The recording configuration was achieved by a brief (3–5 min) application of the bathing solution (150 KCl, 10 HEPES, 1 ATP, and 1 EGTA) containing streptolysin-O (0.08 U/ml) after completion of the cell-attached formation.

As illustrated in Fig 4A, a low ATP concentration, obtained by ATP free bathing solution, produced the typical KATP channel openings. Subsequent application of vasopressin (1 μmol/L) outside the pipette was no longer effective. Raising the ATP concentration to 2 mmol/L outside the pipette blocked the channel activation. In contrast, when the channel was activated in the cell-attached mode (Fig 4B), ATP (2 mmol/L) applied outside the pipette did not alter the channel activity. However, extracellular application of vasopressin (1 μmol/L) inhibited the channel activities even in the presence of extracellular ATP.

Thus, a change in intracellular ATP concentration may be involved during vasopressin-mediated inhibition on KATP channels, because vasopressin lost its inhibitory action when the intracellular ATP concentration was clamped by the outer solution in the open-cell attached mode.

To demonstrate that vasopressin-mediated inhibition on KATP channels requires a change in the intracellular ATP concentration, we examined the action of vasopressin on KATP channels activated by pinacidil, which can open the KATP channel without a change in intracellular ATP concentration or a loss of signaling substrate (almost intact cell membrane) (Fig 4C).

KATP channel activation produced by pinacidil (1 μmol/L) in the absence of metabolic inhibition could not be suppressed by vasopressin (1 μmol/L), suggesting that in fact vasopressin needs a change in intracellular ATP to be effective on KATP channels. A similar finding was observed in 5 other myocytes.

The inhibitory action of vasopressin on the KATP channel was not observed when we used a low dose of pinacidil to activate the channel because a low concentration of pinacidil does not reliably activate KATP channels (data not shown).

Several investigators have reported ATP-dependent regulation of this channel activity during metabolic inhibition of myocytes. Schackow and Ten Eick[23] showed that the opening of KATP channels is accelerated by β-adrenoceptor stimulation via an increase in ATP consumption in adult cat ventricular myocytes. The mechanism of this β-adrenoceptor-mediated stimulatory action was attributed to the depletion of endogenous ATP by the activation of adenylate cyclase via G_s beneath the membrane. In this way, activation and inhibition of KATP channels could be regulated in a reciprocal fashion by a change in intracellular ATP concentration that is caused by receptor-mediated stimulation. Thus, the level of subsarcolemmal ATP concentration may change during vasopressin-mediated inhibition on KATP channels.

Although intracellular ATP is involved in the second messenger pathway mediating the inhibition of KATP channels, the actual link between the vasopressin receptors and intracellular ATP remains unknown. Because the V_1 receptor has been shown to couple to protein kinase C via phospholipase C, and the V_2 receptor links to adenylate cyclase via pertussis toxin (PTX)-sensitive G-proteins in the heart[12,13,15] we examined which type of G-proteins were linked to vasopressin-mediated inhibition of KATP channels.

According to these experiments, we treated the myocytes with PTX for 60 min before the experiments. Even after exposure to PTX, vasopressin (1 μmol/L) completely blocked the KATP channel openings activated by metabolic inhibition (Fig 5A). On the other hand, when the myocytes were pretreated with calphostin C, a selective protein kinase C (PKC) blocker, the inhibitory action of vasopressin on KATP channels disappeared.

Subsequent extracellular application of glibenclamide (100 nmol/L) suppressed KATP channel (Fig 5B), which was a finding consistently observed in 5 other cells, suggesting that the PKC pathway participates in the blocking action of vasopressin on KATP channels.

Discussion

Recently, it was reported that mitochondrial KATP channel activation is more relevant to cardioprotection than sarcolemmal KATP channel enhancement in ischemic preconditioned myocardium[24–27] Sato et al[24–27] demonstrated that diazoxide, a selective mitochondrial KATP channel opener, resulted in cardioprotection in a rabbit ventricular cell model of ischemia.

In contrast, using a dog heart model of ischemia, Toller et al[28] showed that both the mitochondrial KATP channel and sarcolemmal KATP channel are involved in ischemic preconditioning. Additionally, in an ischemic preconditioning model of the canine heart, Kitakaze et al[29] reported that both channels independently play an important role. Therefore, in the present study, we focused on the action of vasopressin on sarcolemmal KATP channels.

A previous study[11] demonstrated that vasopressin could suppress the KATP channel in vascular smooth muscle cells, but its action in the heart has not been fully reported. In our experiments, isolated guinea pig ventricular myocytes were preincubated with 2-deoxyglucose, a glycolytic production inhibitor, and single KATP channel activation was obtained by extracellular application of cyanide, an oxidative production inhibitor. In the cell-attached configuration, vasopressin dose-dependently suppressed the KATP channel currents via a V_1 receptor related mechanism. On the other hand, another researcher[30] reported that this inhibition was not brought about by receptor-mediated action but de-

pended on a change in membrane potential. However, in the present study, a change in membrane potential was observed in only a few experiments (data not shown). Furthermore, the KATP channel activity induced in the open-cell-attached mode was not blocked by vasopressin and was inhibited only by extracellular application of ATP. In addition, KATP channel activity produced by the K channel opener under normal intracellular ATP concentration could not be suppressed by vasopressin.

In the open-cell-attached mode, utilizing the tiny membrane holes, intracellular ATP can be clamped at the desired level by bathing the preparation in extracellular solutions containing a given ATP concentration. An increase in subsarcolemmal ATP may be involved in the vasopressin-induced inhibition of KATP channels, because vasopressin lost its inhibitory action when the intracellular ATP concentration was controlled by exogenous ATP (open-cell-attached mode) or when these channels were activated by pinacidil without intracellular ATP depletion. These findings strongly suggest that a change in intracellular ATP concentration is the final determining element that initiates the inhibitory action of vasopressin on the KATP channel.

Therefore, vasopressin modulates intracellular ATP concentration via a receptor-mediated signaling pathway and, moreover, this inhibitory action on the KATP channel is antagonized by a V1 receptor antagonist but not by a V2 receptor antagonist.

In general, vasopressin stimulation facilitates membrane phosphoinositide hydrolysis by phospholipase C (PLC), thereby generating inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DG), and resulting in PKC activation. Recently, the PKC-dependent modulation of KATP channel activity was reported in both human and rabbit cardiocytes[31–33] Using the excised inside-out patch method with rabbit ventricular myocytes, Light et al[33] showed that PKC inhibits KATP channels at low cytoplasmic ATP concentration, but activates them at the physiological (mmol/L) level of ATP, and thereby alters the sensitivity of the channel to ATP.

To rule out which pathway is involved in vasopressin-mediated suppression of the KATP channel, myocyte were preincubated with a PKC inhibitor, calphostin C, which abolished the inhibitory action of vasopressin. Therefore, the Ca concentration-mediated PKC pathway is related with this blocking action of vasopressin, but in our study, the extracellular Ca concentration was fully chelated by 0.5 mmol/L EGTA, so the change in intracellular Ca density alone could modulate PKC activity through activation of phosphoinositide breakdown[5]

During metabolic stress, ATP beneath the cell membrane is usually depleted, but intracellular ATP spared and compensated for by an increase in mitochondrial ATP synthesis. Therefore sarcolemmal ATP is less than net ATP. Under such conditions, PKC activation by vasopressin induced the inhibition of ATP consumption and this ATP increase finally blocked KATP channel activity. This hypthesis is supported by reports that PKC suppressed KATP channel under the condition of lower intracellular ATP concentration[32,33] Thus, it is likely that vasopressin suppresses the KATP channel when intracellular ATP is depleted by metabolic stress.

It has been reported that vasopressin is harmful during myocardial ischemia[32,33] such as with angina pectoris, because of its potent vasoconstrictive action on vascular smooth muscles, including those of the coronary artery, which can be explained by PKC activated voltage-dependent Ca channel enhancement secondary to KATP channel inhibition. In addition, in heart failure and severe myocardial ischemia, activation of the sympathetic nervous system generally elevates the secretory level of hormones such as renin, angiotensin, aldosterone, vasopressin, and so on. In an ovine model of myocardial infarction, Charles et al[34] reported a significant increase in plasma vasopressin levels, which exacerbated the myocardial injury.

These findings raise the question of whether an increase in vasopressin secretion may occur to compensate such cardiac imbalance and therefore clinical usage of vasopressin receptor antagonists for treatment of heart failure and myocardial ischemia would be expected. In a vasopressin receptor-mediated study of rat myocardial infarction, Fujita et al[35] demonstrated that OPC-31260, a vasopressin V2 receptor antagonist, improved left ventricular end-diastolic pressure more effectively than OPC-21268, a vasopressin V1 receptor antagonist. Therefore, the effect of V1 receptor and V2 receptor antagonists on KATP channel inhibition by vasopressin was also examined by us.

Clinical Implications of Vasopressin

The clinical serum level of vasopressin of the healthy human ranges from 0.4 to 4 pmol/L[3] but there was a large discrepancy between the clinical vasopressin concentration and that which inhibited the KATP channel in the cell-attached mode of the present study. We explain this difference as follows. In myocardial ischemia or heart failure, there is no reason why the local vasopressin concentration would be higher than the normal systemic serum level. There is more concern about the vasopressin receptors, because during cardiac ischemia and heart failure, V1 receptor-mediated vasoconstriction of vascular smooth muscle cells may cause further myocardial damage, and in addition, V2 receptor-mediated reabsorption of water causes volume overload and aggravates heart failure and myocardial ischemia when renal blood flow is decreased as a result of left ventricular dysfunction.

In order to prevent this harmful action of vasopressin, the clinical use of each vasopressin receptor antagonist is required. The V1 receptor antagonist has a cardioprotective action in the myocardium by antagonizing the inhibitory action of vasopressin, which can sometimes be cardiotoxic during ischemia.

However, vasopressin is a physiologically active peptide that maintains homeostasis, so it remains a concern that prophylactic oral application of an antagonist may create a humoral imbalance in reverse. Therefore, it would be better to administer a vasopressin receptor antagonist temporarily and intravenously during the acute stage of myocardial infarction or heart failure.

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