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Blockade of Myocardial ATP-sensitive Potassium Channels by Ketamine

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Background: **The adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel underlies the increase in potassium permeability during hypoxia and ischemia. The increased outward potassium current during ischemia may be an endogenous cardioprotective mechanism. This study was designed to determine the effects of ketamine on K_{ATP} channel in rat hearts.**

Methods: **Inside-out and cell-attached configurations of patch-clamp techniques and 3 M potassium chloride-filled conventional microelectrodes were used to investigate the effect of ketamine on K_{ATP} channel currents in single rat ventricular myocytes and on the action potential duration of rat papillary muscles, respectively.**

Results: **Ketamine inhibited K_{ATP} channel activity in rat ventricular myocytes in a concentration-dependent manner. In the inside-out patches, the concentration of ketamine for half-maximal inhibition and the Hill coefficient were 62.9 μM and 0.54, respectively. In a concentration-dependent manner, ketamine inhibited pinacidil- and 2,4-dinitrophenol–activated K_{ATP} channels in cell-attached patches. The application of ketamine to the intracellular side of membrane patches did not affect the conduction of single-channel currents of K_{ATP} channels. Ketamine increased the action potential duration, which was then shortened by pinacidil in a concentration-dependent manner.**

Conclusions: **Ketamine inhibited K_{ATP} channel activity in a concentration-dependent manner. These results suggest that ketamine may attenuate the cardioprotective effects of the K_{ATP} channel during ischemia and reperfusion in the rat myocardium. (Key words: Anesthetics, intravenous: ketamine. Channels: K_{ATP} channel. Heart: action potential duration. Measurement techniques: patch clamp.)**

This article is accompanied by a highlight. Please see this issue of ANESTHESIOLOGY, page 26A.

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ADENOSINE triphosphate (ATP)-sensitive potassium (K_{ATP}) channels represent a family of potassium channels inhibited by intracellular ATP ($[ATP]_i$).[1–3] Since the first description of the K_{ATP} channels in cardiac myocytes,[1] K_{ATP} channels were discovered in various tissues, including pancreatic β cells,[2–4] skeletal muscle,[5] smooth muscle,[6] and the central and peripheral nervous systems.[7,8] Because K_{ATP} channels are gated by intracellular ATP, these channels are believed to link cellular metabolism with membrane excitability. K_{ATP} channels have been associated with diverse cellular functions such as shortening of cardiac action potentials,[9] myocardial ischemic preconditioning,[10] hormone secretion (for example, insulin, growth hormone),[3,11] skeletal muscle excitability,[5] vasodilation,[12–13] and neurotransmitter release.[14]

In heart cells, the K_{ATP} channel is activated during conditions of ischemia,[15] hypoxia,[16] or metabolic stress.[17] Activation of the K_{ATP} channel leads to a shortened cardiac action potential, which results in a decrease in Ca^{2+} influx.[18] In contrast, K_{ATP} channel blockade may prevent action potential shortening, which typically occurs during periods of metabolic stress when ATP stores are reduced. The maintenance of increased Ca^{2+} entry contributes to metabolic deterioration and ischemic damage in the absence of K_{ATP} channel activation.

Because ketamine has been advocated for patients

whose cardiac performance must be maintained or increased, we examined the effects of ketamine on K_{ATP} channel activity in the rat myocardium.

Materials and Methods

Our investigation conformed with the *Guiding Principles in the Care and Use of Animals* as approved by the Council of the American Physiology Society.

Single-Channel Recording

Cell Isolation. Single rat ventricular myocytes were prepared by enzymatic digestion, as described previously.[19] Male Sprague-Dawley rats (weight, 250–300 g) were stunned with a blow on the neck and killed by spinal cord dislocation. After opening the chest cavity, hearts were quickly excised and immersed in Krebs-Henseleit (KH) buffer solution (*p*H 7.35). Excised hearts were perfused in a retrograde manner *via* the aorta in a Langendorff apparatus with KH solution saturated with a 95% oxygen and 5% carbon dioxide gas mixture for 5 min to clear visible blood. Isolated hearts were perfused with Ca^{2+}-free KH solution until they stopped beating, and then they were perfused with Ca^{2+}-free KH solution containing 0.075% collagenase (CLS 2; Worthington Biomedical Co., Freehold, NJ) for about 30 min. After enzymatic digestion, ventricular muscle was removed mainly from the lower left ventricular wall near the ventricular septum. The muscle was cut into small pieces and then mechanically dissociated into single cells by gentle agitation in Ca^{2+}-free KH solution containing 1% bovine serum albumin. The cells were allowed to settle at the bottom of the container by gravity and the supernatant of the cell suspension was removed by replacing it with Ca^{2+}-free KH solution containing 1% bovine serum albumin. All cells used for the experiments were rod-shaped and had clear striations. Krebs-Henseleit solution contained 118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 10 mM HEPES, 25 mM $NaHCO_3$, 10 mM pyruvate, 11 mM dextrose, and 1 mM $CaCl_2$.

Current Recording and Data Analysis. Gigaseals were formed with Sylgard-coated pipettes (borosilicate, Kimax-51, Kimble Glass Inc., Owens, IL) with 4 or 5 MΩ resistance. Single-channel currents were recorded using the inside-out and cell-attached configurations of the patch-clamp method described by Hamil *et al.*[20] Channel currents were recorded with an Axopatch 1D patch-clamp amplifier (Axon Instruments, Foster, CA) and stored on video tapes *via* pulse code modulator (PCM-501ES; Sony, Tokyo, Japan) for subsequent computer analysis. Electric signals were converted into digits and stored on a hard disk of a personal computer (486 DX4; Hyundai, Seoul, Korea) at a sampling rate of 330 kHz with an analog-to-digital converter (Digidata 1200; Axon Instruments). pClamp software (Version 5.7.2; Axon Instruments) was used for data acquisition and analysis. The 50% threshold method was used to detect events. The open probability (P_o) was calculated using an equation derived from Spruce *et al.*[21]:

$$P_o = \left(\sum_{j=1}^{N} t_j \cdot j \right) / T_d N$$

where t_j is the time spent at current levels corresponding to $j = 0,1,2,\ldots,N$ channels in the open state; T_d is the duration of the recording; and N is the number of the channels active in the patch. Recordings of 30–60 s were analyzed to determine P_o. The channel activity was expressed as $N \cdot P_o$. Changes of channel activity in the presence of drugs were calculated as the relative ratio of the channel activity between the values obtained before and after drug treatment. All experiments were done at 22 ± 2°C. The standard bath and pipette solutions contained 140 mM KCl, 2 mM $MgCl_2$, 5 mM EGTA, and 10 mM HEPES (*p*H 7.2).

Action Potential Recording from Rat Papillary Muscle

The rat hearts were rapidly excised and transferred to a dissection bath filled with Tyrode's solution oxygenated with a 97% oxygen and 3% carbon dioxide mixture. Papillary muscles were carefully dissected free from the right ventricular wall, mounted horizontally in a narrow channel of a tissue chamber, and continuously superfused with oxygenated Tyrode's solution at 36°C or 37°C. The size of dissected papillary muscles ranged from 0.5–1 mm in width and was 2 or 3 mm in length. The mural end of the muscle was fixed by an insect pin to the bottom of the chamber coated with Sylgard. The portion of the muscle adjacent to the insect pin was pressed against the floor by stimulating electrodes, which were used to elicit action potentials and contractions. The action potentials were elicited by stimulating the cardiac cells with square pulses (1 Hz, lasting 1 ms, 20–30% above threshold voltage) by a stimulator *via* a stimulus isolation unit (WPI, Sarasota, FL). Action potentials were recorded with a 3-M KCl-filled microelectrode (10–20 MΩ) connected to an amplifier (KS-700; WPI) and were displayed on an oscilloscope (dual-beam stor-

age 5113; Tektronix, Beaverton, OR). Tracings on the oscilloscope screen were photographed using 35-mm film and also recorded on a chart recorder (RS 3400; Gould, Cleveland, OH). Rat papillary muscle was superfused with Tyrode's solution at a constant rate (5 ml/min). Tyrode's solution contained 137 mM NaCl, 5.4 mM KCl, 1.05 mM $MgCl_2$, 0.45 mM NaH_2PO_4, 11.9 mM $NaHCO_3$, 1.8 mM $CaCl_2$, and 5 mM dextrose.

Drugs

The following compounds were used: ketamine hydrochloride (Yuhan, Seoul, Korea), 2,4-dinitrophenol (Sigma Chemical Co., St. Louis, MO), pinacidil monohydrate (Leo Pharmaceutical, Copenhagen, Denmark), glibenclamide (RBI, Natick, MA), and ATP (Sigma Chemical Co.).

Statistics

All data were presented as means ± SD. Repeated-measures analysis of variance, followed by Scheffé's multiple-range test, was applied to identify significant differences among the effects observed with different concentrations of ketamine. Paired statistical comparisons were made using paired *t* tests. In all comparisons, $P < 0.05$ was considered significant.

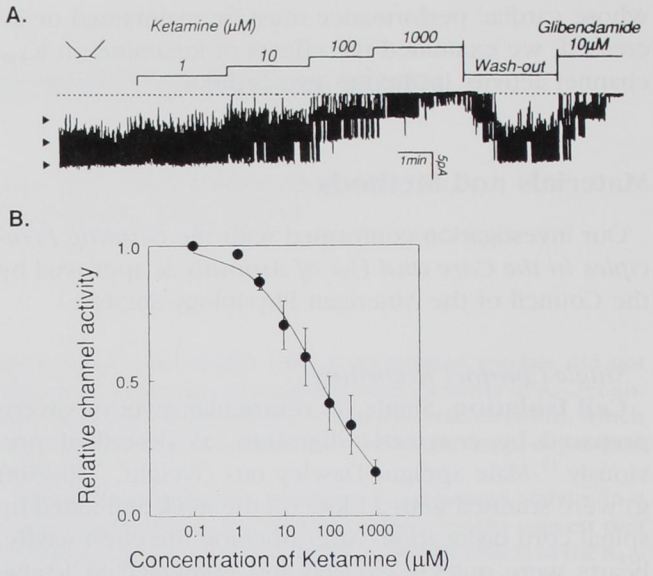

Fig. 1. Effect of ketamine in the bath solution on the K_{ATP} channel activity of inside-out patches. The membrane potential was held at −60 mV. (*A*) A representative tracing for the inhibitory effects of ketamine on the K_{ATP} channel activity. The dotted line indicates the zero current level. (*B*) The relation between relative channel activity of the K_{ATP} channel and concentrations of ketamine. Each data point with the vertical bar denotes means ± SD from 12 separate patches and normalized to the channel activity immediately before ketamine treatment. The continuous line in the graph was fitted to the Hill equation (see text).

Results

Effects of Ketamine on K_{ATP} Channel Activity in Inside-Out Patches

To evaluate the inhibitory effect of ketamine on K_{ATP} channels, the effect of ketamine on K_{ATP} channel activity in single rat ventricular myocytes was examined using the inside-out and cell-attached configurations of the patch-clamp techniques. Activation of the K_{ATP} channels observed in inside-out patches was inhibited by 1 mM ATP or 10 μM glibenclamide and showed a unitary conductance of 65–70 pS. These channel properties were consistent with K_{ATP} channel currents recorded previously.[22]

When inside-out patches were formed in an ATP-free bath solution, maximal K_{ATP} channel activities were observed. Ketamine inhibited K_{ATP} channel activity at a concentration as low as 1 μM and produced a concentration-dependent inhibition of K_{ATP} channel activity. K_{ATP} channel activity was almost completely inhibited by 10^{-3} M ketamine. Washout of ketamine resulted in more than 80% recovery of the channel activity, and glibenclamide completely blocked the channel activity (fig. 1A). On formation of inside-out patches in the ATP-free bath solution, K_{ATP} channel activity gradually decreased with time. This phenomenon is known as "run-down."[4] Therefore, data obtained from such experiments, as shown in figure 1A, may not represent an accurate ketamine-K_{ATP} channel activity relation. To minimize the time-dependent decrease of the channel activity (*i.e.*, the run-down phenomenon) and to obtain an accurate ketamine-K_{ATP} channel activity relation, we determined the effect of a single concentration of ketamine from each inside-out patch within 3 min of patch excision. Under these conditions, the average percent recovery of K_{ATP} channel activities after ketamine washout was 94 ± 5% of $N \cdot P_0$ before ketamine treatment (n = 96). The plot of relative channel activities as a function of ketamine concentration was fitted to the Hill equation using the least-squares method[23] (fig. 1B):

$$y = 1 / 1 + ([D]/K_i)^H$$

where y is the relative $N \cdot P_o$, [D] is the concentration of ketamine, K_i is the ketamine concentration at which half-maximal inhibition of the channels occurs, and H

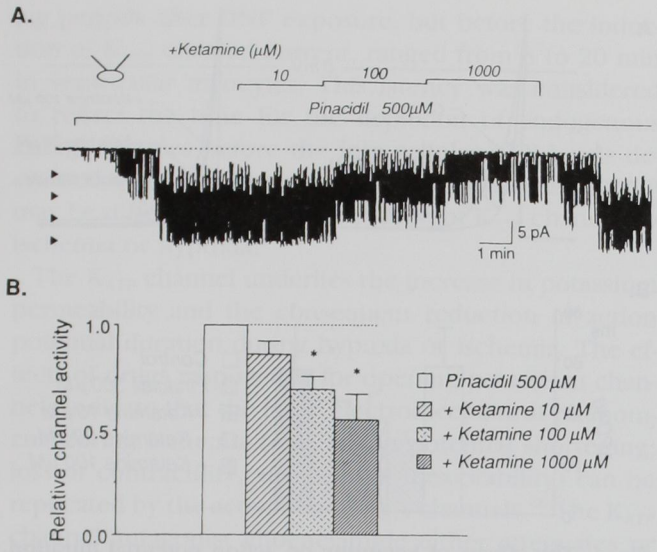

Fig. 2. Effect of ketamine on pinacidil-induced opening of K_{ATP} channels in cell-attached patches. Pinacidil in the bath solution activated K_{ATP} channel activity, and ketamine inhibited this effect of pinacidil in a concentration-dependent manner. (*A*) A representative tracing in which the inhibitory effect of ketamine on the pinacidil-induced K_{ATP} channel activity. (*B*) The averaged relative channel activity from 12 observations obtained under the same experimental conditions as in panel *A*. Results are presented as means ± SD. *Significantly different from control ($P < 0.05$). Other information is the same as in figure 1.

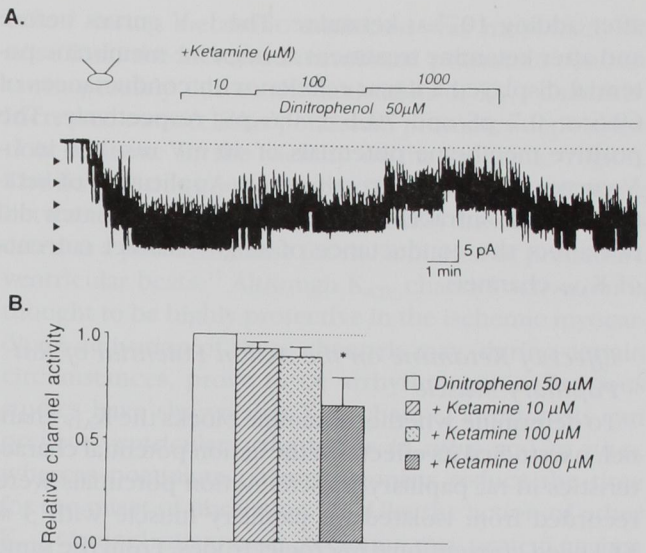

Fig. 3. Influence of ketamine on 2,4-dinitrophenol (DNP)-induced opening of K_{ATP} channels in cell-attached patches. DNP in the bath solution activated K_{ATP} channels, and ketamine inhibited the DNP-induced effect in a concentration-dependent manner. (*A*) A representative tracing in which ketamine inhibits the DNP-induced opening of K_{ATP} channels. (*B*) The averaged relative channel activity from 12 observations obtained under the same experimental conditions as in figure 3A. Results are presented as means ± SD. *Significantly different from control ($P < 0.05$). Other information is the same as in figure 1.

is the Hill coefficient. The K_i and Hill coefficient for ketamine were 62.9 μM and 0.54, respectively.

Effects of Ketamine on Pinacidil- or 2,4-Dinitrophenol-Induced Activation of K_{ATP} Channels

To observe the effect of ketamine on K_{ATP} channel activity in intact ventricular myocytes, we next examined the effect of ketamine on pinacidil- or 2,4-dinitrophenol (DNP)-induced openings of K_{ATP} channels in cell-attached patches (figs. 2 and 3).

No channel openings were observed in the absence of pinacidil or DNP in cell-attached patches. Pinacidil (5×10^{-4} M) increased K_{ATP} channel activity, which was inhibited by ketamine in a concentration-dependent manner (fig. 2). Removal of ketamine from the bath solution resulted in more than 80% recovery of K_{ATP} channel activity. An inhibitor of mitochondrial ATP synthesis, DNP (5×10^{-5} M), opened K_{ATP} channels in cell-attached patches. This opening of K_{ATP} channels was also inhibited by ketamine in a concentration-dependent manner (fig. 3). These results indicate that ketamine inhibits K_{ATP} channel activity in intact myocardial cells.

The Effect of Ketamine on the Conductance of K_{ATP} Channel

Figure 4 shows the current-voltage (I–V) relation obtained in four inside-out membrane patches before and

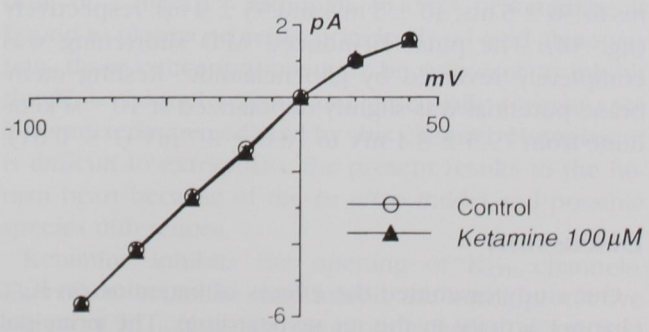

Fig. 4. Current-voltage (I–V) relation before and after ketamine (10^{-4} M) treatment in inside-out patches containing only one active K_{ATP} channel. Each data point with the vertical bar denotes the means ± SD from four observations.

after adding 10^{-4} M ketamine. The I-V curves before and after ketamine treatment at negative membrane potential displayed a linear relation with conductances of 69.6 ± 0.7 pS and 70.1 ± 0.6 pS, respectively. The positive membrane potentials of 40 mV resulted in I-V curves with inward rectification. Application of ketamine to the intracellular side of membrane patch did not affect the conductance of single-channel currents of K_{ATP} channels.

Effect of Ketamine on the Action Potential of Rat Papillary Muscle

To determine whether ketamine blocks the K_{ATP} channel, we studied its effects on the action potential characteristics in rat papillary muscle. Action potentials were recorded from isolated rat papillary muscle with 3 M KCl-filled conventional microelectrodes. From the same papillary muscle preparations stimulated at 1 Hz, the resting membrane potential was −79.1 ± 2.4 mV (n = 6), and the action potential duration at 100% repolarization was 142.4 ± 17.5 ms. The maximum effect of ketamine on action potentials was observed about 5 min after exposure to the drug, and the ketamine effect was readily reversible. The action potential duration at 90% repolarization (APD_{90}) was increased by 10^{-5} M, 3×10^{-5} M, and 10^{-4} M of ketamine from 65 ± 11 ms to 66 ± 11 ms, 71 ± 12 ms, and 89 ± 14 ms, respectively. Glibenclamide (10^{-5} M) had no effect on normal action potentials. The effects of ketamine on action potential duration were also examined using pinacidil. Papillary muscles were superfused with a solution containing 3×10^{-4} M pinacidil, followed by 10^{-5} M, 3×10^{-5} M, and 10^{-4} M ketamine or 10^{-5} M glibenclamide. Pinacidil shortened the APD_{90} from 55 ± 17 ms to 28 ± 4 ms (fig. 5A). The pinacidil-induced APD_{90} was increased by 10^{-5} M, 3×10^{-5} M, and 10^{-4} M ketamine from 28 ± 4 ms to 36 ± 5 ms, 40 ± 5 ms, and 55 ± 9 ms, respectively (fig. 5B). The pinacidil-induced APD shortening was completely reversed by glibenclamide. Resting membrane potential was slightly depolarized at 10^{-4} M ketamine from 79.5 ± 3.1 mV to 76.8 ± 2.7 mV ($P < 0.01$).

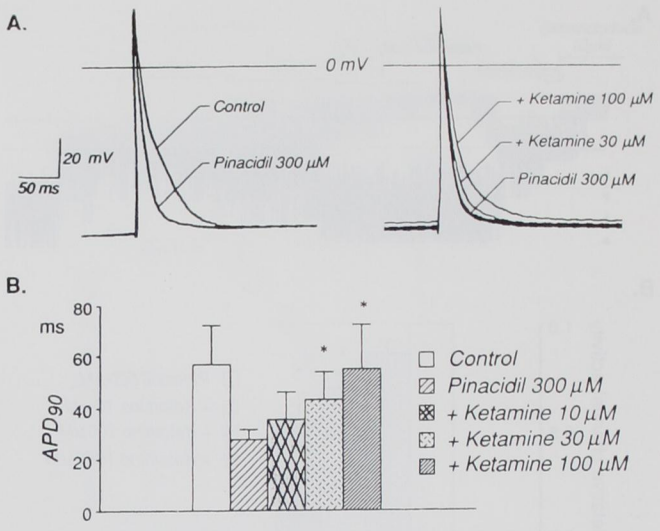

Fig. 5. The effects of ketamine on action potential duration, which was shortened by pinacidil. (*A*) A representative action potential profile of rat papillary muscle. The effects of ketamine on pinacidil-treated action potentials were recorded at a stimulation rate of 1 Hz. The horizontal line indicates 0 mV. (*B*) The averaged increases of action potential duration are shown for six observations obtained under the same experimental conditions as in figure 5A. Results are presented as means ± SD. *Significantly different from control ($P < 0.05$).

Discussion

Our study examined the effects of ketamine on K_{ATP} channel activity in the rat myocardium. The principal findings are that ketamine inhibits K_{ATP} channel activity and increases action potential duration.

The K_{ATP} channel is only activated at low ATP concentrations, with half-maximal inhibition of channel opening at 20-100 μM,[1,24] whereas the normal intracellular ATP concentration is much higher (5-10 mM). However, the measured $[ATP]_i$ at the time of action potential shortening (or in metabolic blockade of ischemia) is in the millimolar range, which is close to normal level.[25] The role of the K_{ATP} channel in response to myocardial ischemia, therefore, has been questioned. In contrast, several recent studies have shown that because of the high density of cardiac K_{ATP} channels, only a small increase in the open state probability (less than 1%) was sufficient to shorten action potential duration during ischemia.[26,27] Production of ATP is expected to decrease during hypoxic or ischemic conditions, and the levels of other metabolites (*e.g.*, ADP, lactate, and protons) that affect channel activities may increase. The dose-response curve resulting from the cellular metabolite that affects the channel activities shifts to the right, causing the amount of ATP required to hold all of the channels closed to increase. From these considerations, K_{ATP} channels may play a role in shortening action potential duration, even if $[ATP]_i$ does not fall substantially below the normal intracellular level. In our study, we used DNP, an inhibitor of oxidative phosphorylation in mitochondria, to induce the K_{ATP} channel current. The

lag periods after DNP exposure, but before the induction of K_{ATP} channel current, ranged from 3 to 20 min in ventricular myocytes. This latency was considered to reflect the time for the depletion of endogenous energy sources before the intracellular ATP levels decreased. However, the opening of K_{ATP} channel by DNP may be different from the activation of K_{ATP} channel by ischemia or hypoxia.

The K_{ATP} channel underlies the increase in potassium permeability and the consequent reduction in action potential duration during hypoxia or ischemia. The effects of drugs responsible for opening potassium channels indicate that the basic electromechanical phenomena during ischemia (*e.g.*, action potential shortening, loss of contractility, and cellular inexcitability) can be replicated by the activation of K_{ATP} channels.[28] The K_{ATP} channel antagonist glibenclamide either attenuates or abolishes hypoxia-induced action potential shortening.[10] In our findings, pinacidil-induced reduction of action potential duration was abolished by ketamine in a dose-dependent manner, and the pinacidil-induced shortening of APD was completely reversed by glibenclamide. These results indicate that the target for ketamine-induced action potential prolongation is the same K_{ATP} channel; that is, a target for glibenclamide.

During ischemia or hypoxia, K_{ATP} channels open to induce several protective responses in the heart. With reperfusion or reoxygenation, oxygen free radicals are generated, which could trigger a chain of damaging chemical reactions, resulting in "reperfusion injury." The free radical-induced injury can be attenuated by potassium channel openers acting on K_{ATP} channels.[29] In addition, the K_{ATP} channels may also be involved in "ischemic preconditioning," a cardioprotective phenomenon wherein brief ischemia increases the tolerance of myocytes to subsequent prolonged ischemic insults.[30] During ischemia, opening of K_{ATP} channels benefits the heart, possibly by reducing Ca^{2+} influx through voltage-operated calcium channels, thus slowing ATP depletion and decreasing calcium-induced toxicity. Gross and Auchampach[31] reported that glibenclamide, a K_{ATP} channel blocker, abolished the effects of preconditioning. In our study, ketamine inhibited K_{ATP} channel activities in inside-out and cell-attached patches. These results suggest that inhibition of the K_{ATP} channel by ketamine may aggravate ischemia-reperfusion injury and attenuate ischemic preconditioning.

Extracellular potassium concentration increases rapidly during myocardial ischemia because of increased potassium efflux. Weiss *et al.*[32] reported that potassium efflux during metabolic inhibition was most likely to arise from the increased membrane potassium conductance possibly due to the activation of K_{ATP} channels. Increased extracellular potassium promotes depolarization of tissue in the vicinity of the ischemic region. The flow of this injury current (*i.e.*, the current flowing between ischemic and normal cells) has been implicated as a potential cause for the initiation of premature ventricular beats.[33] Although K_{ATP} channel activation is thought to be highly protective in the ischemic myocardium, activation of these channels may, during certain circumstances, prove to be arrhythmogenic. Previous studies have shown that K_{ATP} channel antagonists can prevent ventricular arrhythmias *in vitro* and *in vivo*, whereas potassium channel agonists reduce the time for the onset of fibrillation.[34,35] Like the action of other K_{ATP} channel antagonists, ketamine may protect against arrhythmia formation during myocardial ischemia.

The effects of ketamine on the other potassium channels have been reported. Kulkarni *et al.*[36] reported that ketamine reduced the maximal conductance of Kv2.1 in the mammalian brain. They suggested that the inhibition of potassium currents leads to increased neuronal excitability. Endou *et al.*[37] reported that ketamine inhibited the Ca^{2+}-insensitive transient outward potassium current, resulting in prolonged action potential duration in rat hearts. In the present study, ketamine increased action potential duration in rat papillary muscle. Ketamine increased action potential duration more remarkably in the presence of pinacidil, which markedly shortens the action potential duration in rat papillary muscle. These results indicate that ketamine inhibits transient outward potassium channels and K_{ATP} channels in rat ventricular myocytes.

In humans, the peak plasma concentration of ketamine is 3-60 μM during anesthesia with an intravenous dose of 2 mg/kg.[38] Although 45-50% of ketamine is bound to plasma proteins, principally α1-acid glycoprotein, these concentrations may be sufficient to inhibit the K_{ATP} channel activity and potentially reverse antiischemic effects mediated by this channel. However, it is difficult to extrapolate the present results to the human heart because of the *in vitro* model and possible species differences.

Ketamine inhibits the opening of K_{ATP} channels. Therefore, ketamine may inhibit the cardioprotective effects of K_{ATP} channels, promote ischemic injury, and produce irreversible damage. Further studies are needed to characterize the clinical significance of these findings in the human heart.

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