

# Ketamine Stereoselectively Affects Vasorelaxation Mediated by ATP-sensitive $K^+$ Channels in the Rat Aorta

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**Background:** The effect of ketamine on vasodilation mediated by adenosine triphosphate (ATP)-sensitive  $K^+$  channels has not been studied. The present study was designed to determine whether ketamine might stereoselectively affect vasorelaxation induced by an ATP-sensitive  $K^+$  channel opener in the isolated rat aorta.

**Methods:** Rings of the rat aorta with or without endothelium were suspended for isometric force recording. During contraction to phenylephrine ( $3 \times 10^{-7}$  M), vasorelaxation in response to an ATP-sensitive  $K^+$  channel opener levromakalim ( $10^{-8}$  to  $10^{-5}$  M) or a nitric oxide donor sodium nitroprusside ( $10^{-10}$  to  $10^{-5}$  M) was obtained. Glibenclamide ( $10^{-5}$  M), S(+) ketamine ( $10^{-4}$  M), or ketamine racemate ( $10^{-5}$  to  $10^{-4}$  M) was applied 15 min before addition of phenylephrine.

**Results:** Vasorelaxation induced by levromakalim was completely abolished by an ATP-sensitive  $K^+$  channel antagonist glibenclamide ( $10^{-5}$  M) in the aorta with or without endothelium. Ketamine racemate ( $3 \times 10^{-5}$  to  $10^{-4}$  M) significantly inhibited this vasorelaxation in a concentration-dependent fashion, whereas S(+) ketamine did not affect the relaxation. However, the highest concentration of ketamine racemate and S(+) ketamine used in the present study did not alter vasorelaxation in response to sodium nitroprusside in the aorta without endothelium.

**Conclusion:** In the isolated rat aorta, clinically relevant concentrations of ketamine racemate can inhibit relaxation induced by an ATP-sensitive  $K^+$  channel opener, whereas S(+) ketamine did not produce any inhibitory effect on this vasorelaxation. These results suggest that ketamine stereoselectively alters vasodilation *via* ATP-sensitive  $K^+$  channels in the conduit artery.

It is well known that the commercially available ketamine is a racemic mixture of two isomers, S(+) and R(-) ketamine. The S(+) isomer reportedly has a more potent anesthetic effect and fewer psychotomimetic side effects compared with the R(-) isomer or the racemate.<sup>1,2</sup> These appear to be reasons for the expectation that in the near future S(+) ketamine, rather than ketamine racemate, should be available for clinical use as an intravenous anesthetic or a *N*-methyl-D-aspartate receptor antagonist.

A recent study in cardiac myocytes has demonstrated that ketamine racemate inhibits the activity of sarcolemmal adenosine triphosphate (ATP)-sensitive  $K^+$  channels.<sup>3</sup> In addition, more recent studies in the isolated rat heart and the *in vivo* model of rabbit have demonstrated that ketamine racemate and R(-) ketamine, but not S(+) ketamine, are capable of attenuating the ischemic preconditioning of heart, indicating that R(-) ketamine inhibits the activity of mitochondrial ATP-sensitive  $K^+$  channels in these preparations.<sup>4,5</sup> These results suggest that ketamine may stereoselectively reduce the activity of these channels in cardiac myocytes.

Cumulative findings from recent studies have indicated that ATP-sensitive  $K^+$  channels play a crucial role in physiologic and pathophysiologic vasodilation.<sup>6-8</sup> In contrast to above findings in cardiac myocytes, the effect of ketamine on vasorelaxation mediated by ATP-sensitive  $K^+$  channels has not been studied. In addition, the subtype of ATP-sensitive  $K^+$  channels in vascular smooth muscle cells is distinct from other subtypes, including those expressed in cardiac sarcolemma.<sup>9</sup> Therefore, the present study was designed to investigate whether clinically relevant concentrations of ketamine alter vasorelaxation induced by an ATP-sensitive  $K^+$  channel opener in the isolated rat aorta, and whether this effect of ketamine is stereoselective.

## Materials and Methods

The institutional animal care and use committee approved this study. Male Wistar rats (250–350 g) were anesthetized with inhalation of 3% halothane. During this anesthetic condition, the rats were killed by exsanguination, and their thoracic aortas were harvested. Thoracic aortic rings of 2.5-mm length were studied in modified Krebs-Ringer's bicarbonate solution (control solution) of the following composition: NaCl 119, mM; KCl 4.7, mM;  $CaCl_2$ , 2.5 mM;  $MgSO_4$ , 1.17 mM;  $KH_2PO_4$ , 1.18 mM;  $NaHCO_3$ , 25 mM; and glucose, 11 mM. In some rings, the endothelium was removed mechanically. Endothelial removal or intact endothelial function was confirmed by the absence and the presence of the relaxation in response to acetylcholine ( $10^{-5}$  M), respectively. Several rings cut from same artery were studied in parallel. Each ring was connected to an isometric force transducer and suspended in an organ chamber filled with 10 ml of control solution (37°C, pH 7.4) bubbled with 95%  $O_2$  and 5%  $CO_2$ . The artery was gradually stretched to the optimal point of its length-tension curve as determined by

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the contraction to phenylephrine ( $3 \times 10^{-7}$  M). In most of studied arteries, optimal tension was achieved approximately at 1.5 g. Preparations were equilibrated for 90 min. During submaximal contraction to phenylephrine, the concentration–response curve to levcromakalim ( $10^{-8}$  to  $10^{-5}$  M) or sodium nitroprusside ( $10^{-10}$  to  $10^{-5}$  M) was obtained. Some rings were pretreated with glibenclamide ( $10^{-5}$  M), S(+) ketamine ( $10^{-4}$  M), or ketamine racemate ( $10^{-5}$  to  $10^{-4}$  M), which was given 15 min before addition of phenylephrine ( $3 \times 10^{-7}$  M). The vasorelaxation was expressed as a percentage of the maximal relaxation in response to papaverine ( $3 \times 10^{-4}$  M), which was added at the end of experiments to produce the maximal relaxation (100%) of arteries.

### Drugs

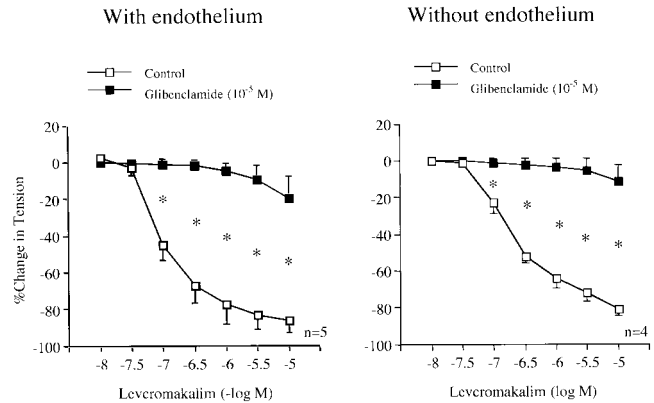
The following pharmacologic agents were used: dimethyl sulfoxide (DMSO), glibenclamide, S(+) ketamine, ketamine racemate, phenylephrine, and sodium nitroprusside (Sigma, St. Louis, MO). Levcromakalim was a generous gift from GlaxoSmithKline plc (Greenford, UK). Drugs were dissolved in distilled water such that volumes of less than 60  $\mu$ l are added to the organ chambers. Stock solutions of levcromakalim ( $10^{-5}$  M) and glibenclamide ( $10^{-5}$  M) were prepared in DMSO ( $3 \times 10^{-4}$  M). The vehicle (DMSO) of glibenclamide itself did not affect the vasorelaxation in response to levcromakalim (data not shown). The concentrations of drugs are expressed as final molar (M) concentration.

### Statistical Analysis

The data are expressed as means  $\pm$  SD; n refers to the number of rats from which the aorta was taken. Statistical analysis was performed using repeated measures analysis of variance (ANOVA), followed by Scheffé F test for multiple comparisons. Differences were considered to be statistically significant when *P* was less than 0.05.

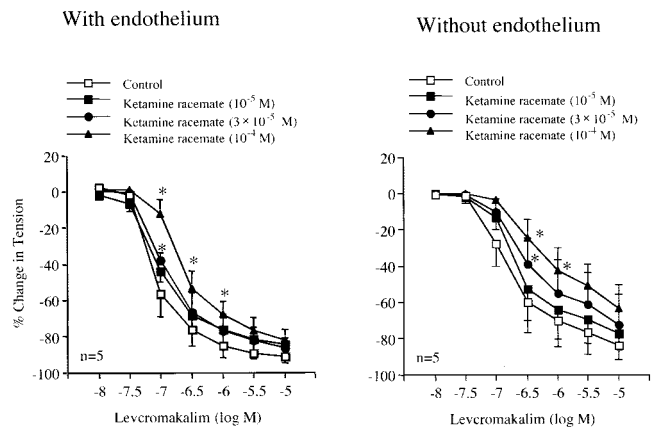
## Results

During submaximal contraction to phenylephrine ( $3 \times 10^{-7}$  M), a selective ATP-sensitive K<sup>+</sup> channel opener levcromakalim ( $10^{-8}$  to  $10^{-5}$  M) produced vasorelaxation of the rat aorta with or without endothelium in a concentration-dependent fashion (fig. 1). This relaxation induced by levcromakalim was completely abolished by a selective ATP-sensitive K<sup>+</sup> channel antagonist glibenclamide ( $10^{-5}$  M; fig. 1). Ketamine racemate ( $3 \times 10^{-5}$  to  $10^{-4}$  M) significantly inhibited vasorelaxation in response to levcromakalim in a concentration-dependent fashion (fig. 2), whereas S(+) ketamine ( $10^{-4}$  M) did not affect the relaxation (fig. 3). In contrast, ketamine racemate ( $10^{-4}$  M) and S(+) ketamine ( $10^{-4}$  M) did not alter vasorelaxation in response to a nitric oxide donor sodium nitroprusside ( $10^{-10}$  to  $10^{-5}$  M) in the aorta with-

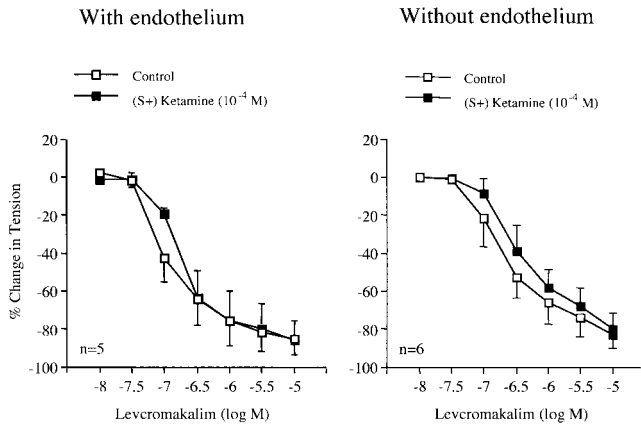


**Fig. 1.** Concentration–response curves to levcromakalim ( $10^{-8}$  to  $10^{-5}$  M) in the absence and in the presence of glibenclamide ( $10^{-5}$  M), obtained in the rat thoracic aorta with or without endothelium. Data are shown as means  $\pm$  SD and expressed as percent of maximal relaxation induced by papaverine ( $3 \times 10^{-4}$  M; 100% =  $1,060 \pm 134$  mg [*n* = 5] and  $1,020 \pm 305$  mg [*n* = 5] for control rings with endothelium or rings treated with glibenclamide, 100% =  $1,045 \pm 91$  mg [*n* = 4] and  $1,030 \pm 289$  mg [*n* = 4] for control rings without endothelium or rings treated with glibenclamide, respectively). \*Difference between control rings and rings treated with glibenclamide is statistically significant (*P* < 0.05).

out endothelium (fig. 4). Ketamine racemate ( $10^{-5}$  to  $10^{-4}$  M) and S(+) ketamine ( $10^{-5}$  to  $10^{-4}$  M) produced only slight vasorelaxation in the endothelium-denuded aorta contracted by phenylephrine ( $3 \times 10^{-7}$  M), and the relaxations produced by these compounds were not different (fig. 5). In addition, neither ketamine racemate nor S(+) ketamine affected contraction in response to



**Fig. 2.** Concentration–response curves to levcromakalim in the absence or in the presence of ketamine racemate ( $10^{-5}$ ,  $3 \times 10^{-5}$ ,  $10^{-4}$  M), obtained in the rat thoracic aorta with or without endothelium. Data are shown as means  $\pm$  SD and expressed as percent of maximal relaxation induced by papaverine ( $3 \times 10^{-4}$  M; 100% =  $1,160 \pm 221$  mg [*n* = 5],  $1,032 \pm 267$  mg [*n* = 5],  $976 \pm 54$  mg [*n* = 5], and  $1,008 \pm 270$  mg [*n* = 5], for control rings with endothelium and rings treated with ketamine racemate [ $10^{-5}$ ,  $3 \times 10^{-5}$ , or  $10^{-4}$  M], 100% =  $1,060 \pm 86$  mg [*n* = 5],  $936 \pm 43$  mg [*n* = 5],  $956 \pm 120$  mg [*n* = 5], and  $944 \pm 100$  mg [*n* = 5], for control rings without endothelium and rings treated with ketamine racemate [ $10^{-5}$ ,  $3 \times 10^{-5}$ , or  $10^{-4}$  M], respectively). \*Difference between control rings and rings treated with ketamine racemate ( $3 \times 10^{-5}$ ,  $10^{-4}$  M) is statistically significant (*P* < 0.05).

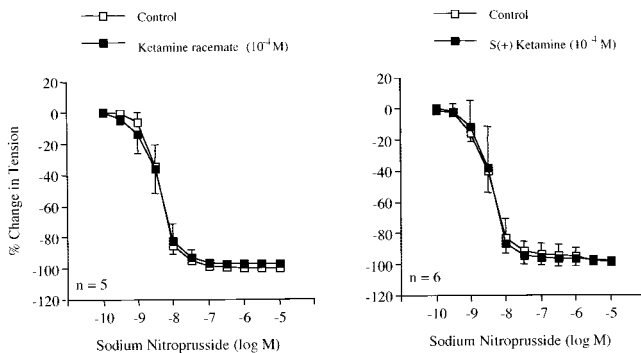


**Fig. 3.** Concentration–response curves to levcromakalim in the absence or in the presence of S(+) ketamine ( $10^{-4}$  M) obtained in the rat thoracic aorta with or without endothelium. Data are shown as means  $\pm$  SD and expressed as percent of maximal relaxation induced by papaverine ( $3 \times 10^{-4}$  M; 100% =  $1,216 \pm 278$  mg [ $n = 5$ ] and  $1,072 \pm 195$  mg [ $n = 5$ ], for control rings with endothelium and rings treated with S(+) ketamine [ $10^{-4}$  M], 100% =  $1,180 \pm 155$  mg [ $n = 6$ ] and  $1,083 \pm 154$  mg [ $n = 6$ ], for control rings without endothelium and rings treated with S(+) ketamine [ $10^{-4}$  M], respectively).

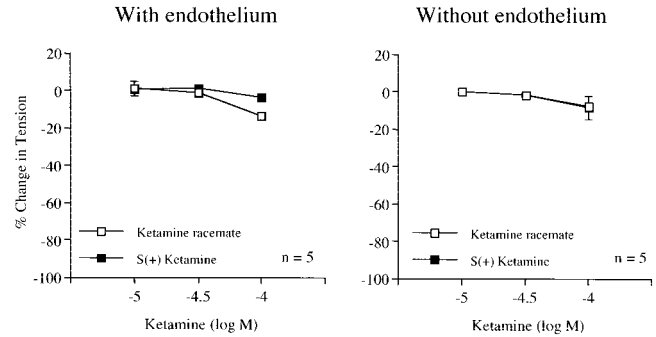
phenylephrine ( $3 \times 10^{-7}$  M) (data not shown) and maximal relaxation induced by papaverine ( $3 \times 10^{-4}$  M) (see figure legends).

## Discussion

This is the first study demonstrating that in the isolated rat aorta, ketamine racemate inhibits vasorelaxation induced by an ATP-sensitive  $K^+$  channel opener, whereas S(+) ketamine did not produce any inhibitory effect on this relaxation. These results suggest that ketamine enantiomers may differentially alter vasodilation *via* ATP-sensitive  $K^+$  channels.



**Fig. 4.** Concentration–response curves to sodium nitroprusside ( $10^{-10}$  to  $10^{-5}$  M) in the absence or in the presence of ketamine racemate or S(+) ketamine ( $10^{-4}$  M), obtained in the rat thoracic aorta without endothelium. Data are shown as means  $\pm$  SD and expressed as percent of maximal relaxation induced by papaverine ( $3 \times 10^{-4}$  M; 100% =  $784 \pm 215$  mg [ $n = 5$ ] and  $788 \pm 228$  mg [ $n = 5$ ] for control rings or rings treated with ketamine racemate [ $10^{-4}$  M],  $903 \pm 158$  mg [ $n = 6$ ] and  $900 \pm 204$  mg [ $n = 6$ ] for control rings or rings treated with S(+) ketamine [ $10^{-4}$  M], respectively).



**Fig. 5.** Concentration–response curves to ketamine racemate or S(+) ketamine ( $10^{-5}$  to  $10^{-4}$  M) obtained in the rat thoracic aorta with or without endothelium. Data are shown as means  $\pm$  SD and expressed as percent of maximal relaxation induced by papaverine ( $3 \times 10^{-4}$  M; 100% =  $1,044 \pm 67$  mg [ $n = 5$ ] and  $1,024 \pm 243$  mg [ $n = 5$ ] for rings with endothelium treated with ketamine racemate or S(+) ketamine, 100% =  $1,224 \pm 100$  mg [ $n = 5$ ] and  $1,204 \pm 179$  mg [ $n = 5$ ] for rings without endothelium treated with ketamine racemate or S(+) ketamine, respectively).

Our previous studies demonstrated that levcromakalim is a selective ATP-sensitive  $K^+$  channel opener in the rat aorta, suggesting that this preparation is one of the established models by which we can evaluate the role of ATP-sensitive  $K^+$  channels in a conduit artery.<sup>8,10</sup> Indeed, in the present study and in our previous studies, a selective ATP-sensitive  $K^+$  channel antagonist glibenclamide abolished vasorelaxation in response to levcromakalim, also indicating the selectivity of levcromakalim on ATP-sensitive  $K^+$  channels in blood vessels.<sup>8,10–12</sup> In addition, our previous finding that glibenclamide does not alter vasorelaxation in response to nitric oxide donors in the rat aorta reinforces the selectivity of glibenclamide on ATP-sensitive  $K^+$  channels in this preparation.<sup>13</sup>

In the rat aorta, ketamine racemate inhibited vasorelaxation induced by levcromakalim in a concentration-dependent fashion, and this inhibitory effect was unchanged even in the presence of endothelium. These results support the conclusion that ketamine racemate may modulate ATP-sensitive  $K^+$  channels on vascular smooth muscle, although a previous study demonstrated that rat aorta endothelial cells express ATP-sensitive  $K^+$  channels.<sup>14</sup> Our finding is also in agreement with a recent study documenting that the same concentrations of ketamine racemate as used in the present study inhibit the activity of sarcolemmal ATP-sensitive  $K^+$  channels in cardiac myocytes.<sup>3</sup> Therefore, ketamine racemate appears to similarly reduce the activity of two different subtypes of ATP-sensitive  $K^+$  channels expressed in vascular smooth muscle cells and cardiac myocytes.<sup>9</sup> Additionally, in the rat aorta, ketamine racemate did not alter vasorelaxation induced by sodium nitroprusside. Our results suggest that this intravenous anesthetic agent may selectively affect ATP-sensitive  $K^+$  channels and that a nitric oxide donor may be capable of offsetting the

inhibitory effect of ketamine racemate on vasodilation mediated by these channels.

In the blood vessels, the effects of ketamine on K<sup>+</sup> channels, other than those of ATP-sensitive, have not been well studied. A recent study on canine pulmonary artery has demonstrated that ketamine racemate inhibits vasorelaxation induced by endothelium-derived hyperpolarizing factor, which can produce relaxation mediated by Ca<sup>2+</sup>-dependent K<sup>+</sup> channels.<sup>15</sup> However, in this study, Murray *et al.*<sup>15</sup> documented that ketamine decreases Ca<sup>2+</sup> levels in the cultured endothelial cells, suggesting that ketamine racemate may impair vasorelaxation mediated by the hyperpolarizing factor *via* the inhibition of increase in endothelial Ca<sup>2+</sup>, which can induce production of this factor. Therefore, even considering these previous studies, it is unclear whether ketamine racemate can produce the inhibition of Ca<sup>2+</sup>-dependent K<sup>+</sup> channels in vascular smooth muscle cells.

In contrast to the results with ketamine racemate, S(+) ketamine did not produce any inhibitory effect on vasorelaxation mediated by ATP-sensitive K<sup>+</sup> channels. Because ketamine racemate is the mixture of S(+) and R(-) ketamine stereoisomers, our results suggest that R(-) ketamine can solely produce the impairment of vasodilation mediated by ATP-sensitive K<sup>+</sup> channels. The ATP-sensitive K<sup>+</sup> channel is a complex of two proteins: the sulfonylurea receptor, which is a member of the ATP-binding cassette transporter family, and Kir6.1 or 6.2, which belongs to the inward rectifier K<sup>+</sup> channel family.<sup>9</sup> As recent biochemical studies have revealed that the sulfonylurea receptor of ATP-sensitive K<sup>+</sup> channel is a primary target of the openers of this channel, R(-) ketamine appears to alter vasorelaxation in response to an ATP-sensitive K<sup>+</sup> channel opener *via* the effect on the sulfonylurea receptor of these channels.<sup>16</sup> In the isolated rat heart and in the *in vivo* model of rabbit, ketamine racemate and R(-) ketamine, but not S(+) ketamine, were capable of attenuating the ischemic preconditioning of heart, indicating that R(-) ketamine may inhibit the activity of mitochondrial ATP-sensitive K<sup>+</sup> channels in cardiac myocytes.<sup>4,5</sup> In contrast to the subtype of smooth muscle ATP-sensitive K<sup>+</sup> channels, that of mitochondrial ATP-sensitive K<sup>+</sup> channels has not been cloned, and, therefore, it is still unclear whether R(-) ketamine can similarly affect the channel compartments like the sulfonylurea receptor expressed in cardiac myocytes and vascular smooth muscle cells, resulting in the inhibition of these ATP-sensitive K<sup>+</sup> channels.<sup>17</sup> However, these studies, including ours, strongly support the conclusion that ketamine stereoselectively reduces the activity of ATP-sensitive K<sup>+</sup> channels in these preparations.

Less than 10<sup>-4</sup> M of ketamine racemate and S(+) ketamine itself similarly produced only slight vasorelaxation in the aorta contracted by phenylephrine. As already

reported in the rat aorta, ketamine enantiomers, including S(+) ketamine and ketamine racemate, seem to be capable of inducing only slight vasodilator effect in these concentration ranges.<sup>18</sup> Previous studies in pulmonary and mesenteric arteries also demonstrated that ketamine racemate, within the concentration ranges similar to the present study, can produce only slight vasorelaxation in arteries contracted with an  $\alpha$ -agonist norepinephrine.<sup>19,20</sup> In addition, in the present study, neither ketamine racemate nor S(+) ketamine affected contraction in response to phenylephrine. Therefore, it is unlikely that the effect of ketamine racemate on vasorelaxation mediated by ATP-sensitive K<sup>+</sup> channels are modified by its vasoconstrictor and vasodilator effect on the aorta.

It was reported that 5 min after induction of anesthesia with 2 mg/kg of ketamine racemate, the plasma concentration reaches 6 × 10<sup>-5</sup> M.<sup>21</sup> As about 20% of ketamine are bound to plasma proteins, concentrations of ketamine used in the present study are clinically relevant.<sup>22</sup> Therefore, our results suggest that in clinical situations, ketamine racemate impairs vasodilation mediated by ATP-sensitive K<sup>+</sup> channels, whereas the same concentrations of S(+) ketamine do not alter the vasodilation.

During hypoxia, acidosis, and ischemia, ATP-sensitive K<sup>+</sup> channels are activated, resulting in arterial dilation or increased tolerance of tissues to ischemia.<sup>7,23,24</sup> In addition, several available ATP-sensitive K<sup>+</sup> channel openers are expected to manage cardiovascular disorders, including hypertension and ischemic heart disease.<sup>25-27</sup> Therefore, during pathophysiologic situations, ketamine racemate and R(-) ketamine, but not S(+) ketamine, may impair vasodilator effects induced by activation of ATP-sensitive K<sup>+</sup> channels, which play an important role in regulation of circulation. A recent *in vivo* study on the rat demonstrated that high doses of S(+) ketamine, but not R(-) ketamine, significantly reduce neuronal cell damage in the cerebral cortex after global forebrain ischemia.<sup>28</sup> These results, in addition to our own, may indicate the possibility that ketamine stereoselectively modulates ATP-sensitive K<sup>+</sup> channels or N-methyl-D-aspartate receptors, resulting in changes of outcome after cerebral ischemia. Because the same subtype of ATP-sensitive K<sup>+</sup> channels appears to be expressed in conduit and resistance arteries, our results obtained from a conduit artery may have relevance to vasodilation in resistance blood vessels, such as cerebral arterioles.

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