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Stereoselective Differences in the Vasorelaxing Effects of S(+) and R(−) Ketamine on Rat Isolated Aorta

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Background: **S(+) ketamine, because of its higher anesthetic potency and lower risk of psychotomimetic reactions, has been suggested to be superior to presently available racemic ketamine. The racemate is a direct vasodilator *in vivo*, and thus the authors investigated the vasorelaxing effects of ketamine enantiomers on rat aorta.**

Methods: **Rat isolated aortic rings with and without endothelium were contracted with $3 \cdot 10^{-7}$ M norepinephrine. Then 10^{-5} to $3 \cdot 10^{-3}$ M S(+), R(−), or racemic ketamine were added cumulatively. Vascular responses to ketamine were further studied in rings pretreated with the nitric oxide synthase inhibitor N_{ω}-nitro-L-arginine (NNLA), the adenosine triphosphate-sensitive K^+ channel antagonist glibenclamide, and the L-type calcium channel blocking agent D888.**

Results: **Ketamine enantiomers and the racemate produced concentration-dependent vasorelaxation. The relaxing effect of S(+) ketamine was significantly weaker compared with R(−) ketamine and the racemate reflected by the half-maximum effective concentration (EC_{50}) values of $11.6 \cdot 10^{-4}$, $4.8 \cdot 10^{-4}$, and $6 \cdot 10^{-4}$ M, respectively. Removal of the endothelium and NNLA or glibenclamide pretreatment did not significantly alter the vasorelaxing effect of ketamine. In contrast, D888 pretreatment significantly shifted the concentration–effect curves of both S(+) and R(−) ketamine rightward (EC_{50} values of $18.9 \cdot 10^{-4}$ and $8.5 \cdot 10^{-4}$ M, respectively), whereas the difference between the isomers was not affected.**

Conclusions: **Vasorelaxation by ketamine enantiomers is quantitatively stereoselective: The effect of S(+)ketamine is significantly weaker compared with that of the racemate and R(−) ketamine. This stereoselective difference is not due to nitric oxide release, activation of adenosine triphosphate–sensitive potassium channels, or differential inhibition of L-type calcium channels. (Key words: Arteries; calcium channels; endothelium; intravenous anesthetics; potassium channels; nitric oxide; smooth muscle; stereoisomers.)**

THE intravenous anesthetic ketamine increases arterial blood pressure, mainly as a result of direct sympathetic stimulation.[1] However, ketamine is also a direct vasodilator *in vitro*.[2] Clinically relevant hypotension induced by ketamine may occur if sympathetic stimulation is prevented by other drugs or if the sympathetic nervous system is already maximally stimulated. Ketamine caused sustained hypotension during halothane and nitrous oxide anesthesia[3] and occasional decreases in blood pressure in critically ill and acutely traumatized patients.[4]

The commercially available ketamine is a racemic mixture of two isomers, S(+) and R(−) ketamine. Studies of the isolated enantiomers of ketamine in animals[5] and humans[6,7] revealed consistent results: The S(+)isomer was a more potent anesthetic (approximately three times) and caused less psychotomimetic side effects than did the R(−) form or the racemate. This might indicate an advantage of the S(+) ketamine over the racemate in terms of therapeutic efficacy.

The present study in rat isolated aortic rings was performed to determine whether the ketamine-induced vasorelaxation is characterized by quantitative stereoselective differences as well and also to investigate potential underlying mechanisms.

Materials and Methods

Preparation of Aortic Rings

Male Sprague-Dawley rats (250-350 g) were killed by cervical dislocation. The thoracic aorta was removed and carefully dissected from connective tissue. Four rings (approximately 3 mm wide) were cut off the vessel and suspended in a Schuler organ bath (20-ml chambers) filled with a modified Krebs-Henseleit solution

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composed of 118 mM NaCl, 4.7 mM KCl, 1.25 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 24.9 mM $NaHCO_3$, 5.5 mM glucose, and 10^{-5} M EDTA. The solution was continuously oxygenated with a 95% air and 5% carbon dioxide mixture and maintained at 37°C (*p*H 7.4). The aortic rings were set up on a resting tension of 10 mN (≈1 g). Preliminary experiments showed that this protocol gave tensions that were stable and reproducible. During the 60-min equilibration period, the bath solution was changed every 15 min, and the resting tension was periodically adjusted to 10 mN. Isometric tension was recorded with a force transducer (HSE $K30^R$, isometric quotient 133 μm/g; Hugo Sachs-Electronics, Hugstetten FRG). In some experiments, to define the role of NO, 10^{-4} M NNLA (N_ω-nitro-L-arginine), a specific inhibitor of nitric oxide (NO) synthase,[8] was added to the bath solution and aortic rings were incubated for another 20 min. When needed by protocol, the endothelium was removed by gently rubbing the intimal surface with a metal stick.

Experimental Design

Endothelium-intact (E+), endothelium-denuded (E−), and NNLA-treated endothelium-intact (NNLA) preparations were studied. After the equilibration period, submaximal (70–80%) contraction of the aortic rings was induced by $3 \cdot 10^{-7}$ M norepinephrine. Acetylcholine ($3 \cdot 10^{-7}$ M) was added to the bath to confirm endothelial integrity. Rings with more than 70% relaxation in response to acetylcholine were considered to possess intact endothelium (E+). In turn, no relaxation in denuded (E−) or NNLA-pretreated (NNLA) preparations indicated an effective removal of the endothelium (E−) or pharmacologic blockade of acetylcholine-induced NO release (NNLA), respectively. After washout and re-equilibration for 30 min, the following experiments were performed.

The aortic rings were again submaximally contracted with $3 \cdot 10^{-7}$ M norepinephrine, and the tension was allowed to reach a plateau, which was usually obtained within 20–30 min. Increasing concentrations (10^{-5} to $3 \cdot 10^{-3}$ M) of S(+), R(−), or racemic ketamine were added cumulatively to the bath chambers in half log-unit increments. Each new dose was added after the tension reached a steady state from the preceding dose, which was usually obtained within 10–20 min. One of the four rings always served as a vehicle control. In all experiments, the maximum volume added to the bath was 300 μl.

To define the role of ATP-sensitive K^+ channels (K_{ATP}), norepinephrine-contracted aortic rings were exposed to 10^{-7} M glibenclamide, a selective K_{ATP} antagonist,[9] and allowed to equilibrate for 15 min. Racemic ketamine was then cumulatively added to the organ bath chambers as described before.

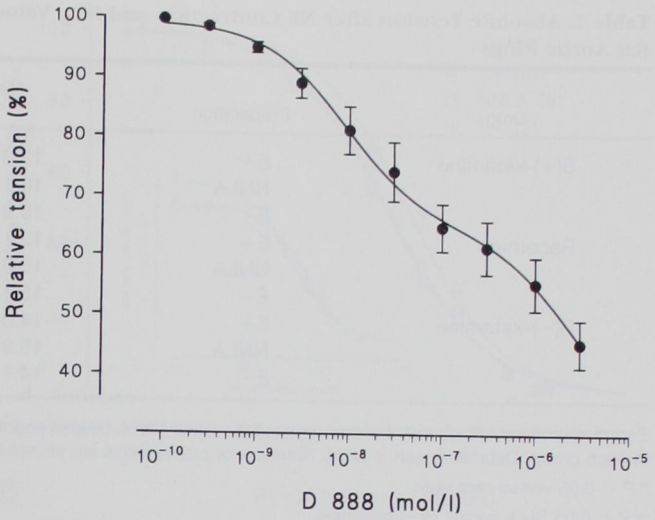

Fig. 1. The biphasic vasorelaxant effect of 10^{-10} to $3 \cdot 10^{-6}$ M D888 on $3 \cdot 10^{-7}$ M norepinephrine-contracted N_ω-nitro-L-arginine–pretreated rat aortic rings (n = 9). Hill analysis of the data yielded the following parameter values: The first segment of 10^{-10} to $3 \cdot 10^{-7}$ M lead to 34.4 ± 1.9% inhibition of initial tension at half-maximum effective concentration values of 8.09 ± 1.40 nM.

To study the role of effects independent of voltage-gated calcium channels in ketamine-induced vasorelaxation, norepinephrine-contracted aortic rings were exposed to the L-type calcium channel antagonist devapamil (D888, 10^{-7} M). Earlier it was shown that at the same concentration D888 selectively and completely inhibits L-type calcium channels in rat aorta;[10] in addition, there is evidence that D888 has no effect on intracellular calcium release or reuptake.[11] To verify this concentration in our setting, dose-finding experiments were performed in which D888 caused biphasic vasorelaxation (fig. 1). The first segment (10^{-10} to $3 \cdot 10^{-7}$ M, Hill coefficient n_H = 0.997) of the concentration–response curve depicted in figure 1 was considered to represent selective inhibition of L-type calcium channels. After equilibration of the aortic rings with 10^{-7} M D888 for 30 min, S(+) or R(−) ketamine were cumulatively added to the bath as described previously.

Calculations, Curve Fitting, and Statistical Analysis

The relaxation responses to increasing concentrations of the test compounds are expressed in absolute isomet-

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Table 1. Absolute Tension after NE Contraction and EC_{50} Values for Vasorelaxation by S(+)-, R(−)-, and Racemic Ketamine in Rat Aortic Rings

Drug	Preparation	Maximum Tension (mN)	EC_{50} (10^{-4} M)	n
S(+)-ketamine	E+	13.0 ± 0.51	11.6 ± 1.19*,†	14
	NNLA	16.1 ± 0.67‡	9.18 ± 0.83*,†	9
	E−	15.8 ± 0.74‡	8.49 ± 0.24*,†	4
Racemate	E+	12.1 ± 0.38	5.99 ± 0.77	11
	NNLA	15.6 ± 0.28‡	6.62 ± 0.24	7
	E−	15.1 ± 1.06‡	5.91 ± 0.19	3
R(−)-ketamine	E+	14.0 ± 0.88	4.83 ± 0.71	8
	NNLA	16.9 ± 0.78‡	3.92 ± 0.35*	9
	E−	14.7 ± 0.36	4.02 ± 0.36*	2

Endothelium-intact (E+), endothelium-denuded (E−), and NNLA-treated endothelium-intact (NNLA) preparations were studied. Complete relaxation was obtained in each group. Data are mean ± SEM. Numbers of preparations are shown in the last column.

* $P < 0.05$ *versus* racemate.

† $P < 0.05$ S(+)- *versus* R(−)-ketamine.

‡ $P < 0.05$ *versus* E+.

ric tension (mN) or as percentages of the maximum tension before ketamine administration. Concentration-effect curves were fitted individually for each ring according to the Hill equation after correction for time-related loss of tension in vehicle controls, which averaged 5-12%. Half-maximum effective concentrations (EC_{50}) obtained from these calculations as well as maximum contractile responses are expressed as means ± SEM. Curve fitting was performed by iterative nonlinear regression using the PC-based graphics software Fig. P version 6.0 (Biosoft, Cambridge, UK); this software was also used to draw the figures. Statistical analysis of EC_{50} and maximum contractile responses was performed using Kruskal-Wallis analysis of variance with post-tests according to Dunn's multiple comparison test. Differences were considered significant when $P < 0.05$.

Substances

Ketamine and its enantiomers were kindly provided by Gödecke Parke-Davis (Freiburg, Germany). D888 was kindly provided by Knoll AG (Ludwigshafen, Germany). All other compounds were purchased from Sigma Chemicals (Deisenhofen, Germany). All substances were dissolved in bidistilled water.

Results

Ketamine-induced Vasorelaxation in the Presence and Absence of Endothelium

Table 1 and figure 2 show the tension developed by the aortic rings after administration of $3 \cdot 10^{-7}$ M norepinephrine. Removal of the endothelium or NNLA pretreatment increased the absolute contractile response to norepinephrine by approximately 30%. This greater norepinephrine sensitivity can be explained by the elimination of NO release by removal of the endothelium[12] or inhibition of NO synthase.

Both S(+) and R(−) ketamine and the racemate caused concentration-dependent vasorelaxation of norepinephrine-contracted aortic rings to the baseline value (fig. 2). Removal of the endothelium or NNLA pretreatment did not influence the vasorelaxing action of ketamine: Comparison of EC_{50} values revealed no significant differences (fig. 2, table 1). Compared with the R(−)isomer and the racemate, the relaxing effect of S(+)ketamine was less pronounced, which is expressed by a rightward shift of its concentration-response curve (fig. 3) and reflected by a 2.4-fold and 1.9-fold increased EC_{50} value, respectively ($P < 0.05$; table 1).

Effect of Glibenclamide on Ketamine-induced Vasorelaxation

Addition of 10^{-7} M glibenclamide to norepinephrine-contracted aortic rings did not alter the contractile force. During these conditions, ketamine caused concentration-dependent relaxation to the baseline. The EC_{50} value of this action was $4.51 \pm 0.43 \cdot 10^{-4}$ M and thus not significantly different from that observed in rings without glibenclamide pretreatment. Therefore, stereoselective differences of the ketamine isomers

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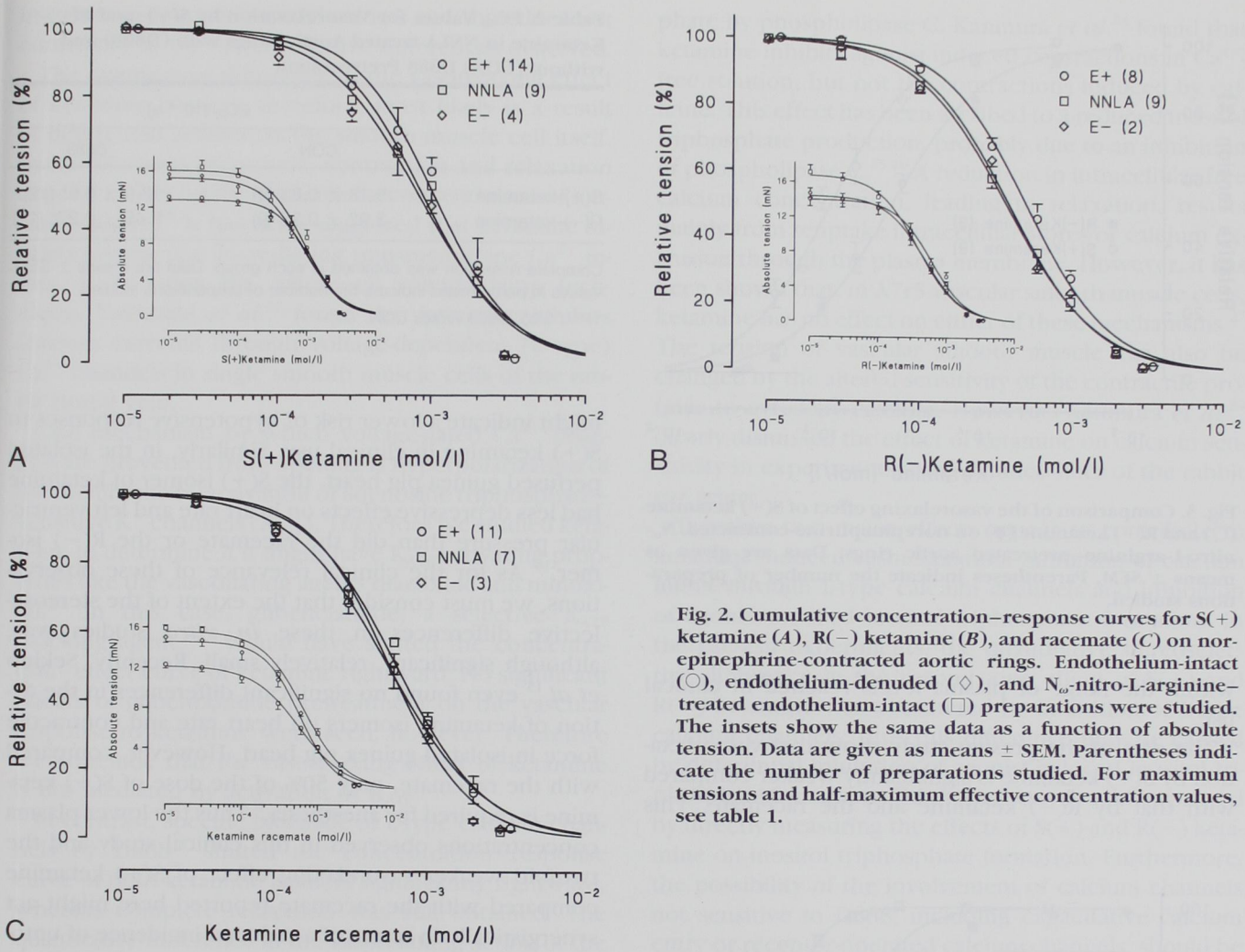

Fig. 2. Cumulative concentration–response curves for S(+) ketamine (*A*), R(−) ketamine (*B*), and racemate (*C*) on norepinephrine-contracted aortic rings. Endothelium-intact (○), endothelium-denuded (◇), and N_ω-nitro-L-arginine–treated endothelium-intact (□) preparations were studied. The insets show the same data as a function of absolute tension. Data are given as means ± SEM. Parentheses indicate the number of preparations studied. For maximum tensions and half-maximum effective concentration values, see table 1.

were not investigated in glibenclamide-pretreated aortic rings.

Effect of D888 on Vasorelaxation by Ketamine Stereoisomeres

As expected from the first series of experiments (fig. 1), D888 at a concentration of 10^{-7} M decreased the norepinephrine-induced contraction of the aortic rings by 30–35%. In the presence of D888, the concentration–effect curves of both S(+) and R(−) ketamine-induced vasorelaxation were shifted ($P < 0.05$) to the right 2.1 and 2.2 times at the EC_{50}, respectively. Complete relaxation, however, was still obtained (fig. 4). The stereoselective difference in the vasorelaxing action of the ketamine isomers was unaltered after D888 pretreatment (table 2).

Discussion

Because of its higher anesthetic potency and fewer psychotomimetic side effects, S(+) ketamine has been suggested to possess a better therapeutic efficacy compared with the racemic form currently available.[6,7] This led us to study the direct vasodilating effects of ketamine isomers and racemate in rat isolated aortic rings. Ketamine-induced vasorelaxation was observed in concentrations $>3 \cdot 10^{-5}$ M. Peak plasma concentrations of ketamine have been reported to reach a maximum of $>10^{-4}$ M in humans after intravenous administration of 2 mg/kg.[13] Although concentrations of *in vitro* models cannot be directly compared with *in vivo* conditions, these values indicate that concentrations of ketamine that induced relaxation of aortic rings in our setting are

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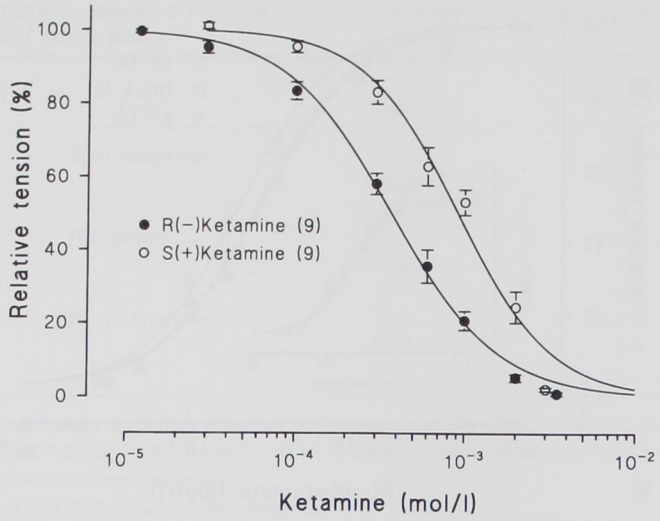

Fig. 3. Comparison of the vasorelaxing effect of S(+) ketamine (○) and R(−) ketamine (●) on norepinephrine-contracted, N_ω-nitro-L-arginine–pretreated aortic rings. Data are given as means ± SEM. Parentheses indicate the number of preparations studied.

within the range of plasma levels reached in clinical use.

The data of the present study show that vasorelaxation by S(+) ketamine is significantly weaker compared with that by R(−) ketamine and the racemate. This

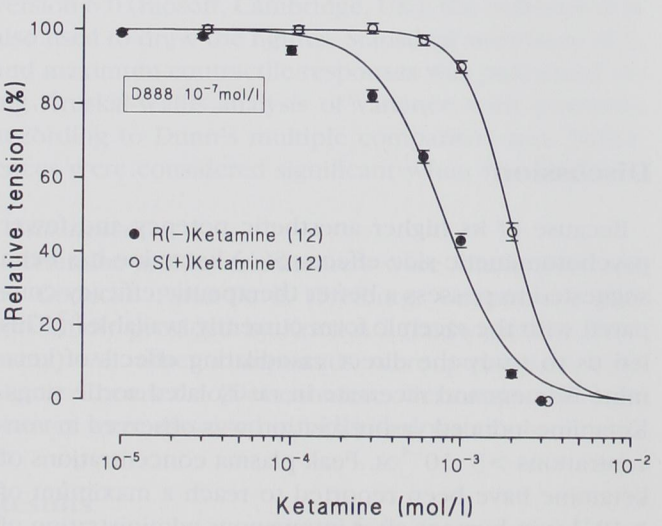

Fig. 4. The effect of L-type calcium channel blockade by 10^{-7} M D888 on the vasorelaxing effect of S(+) ketamine (○) and R(−) ketamine (●) on norepinephrine-contracted, N_ω-nitro-L-arginine–pretreated aortic rings. Data are given as means ± SEM. Parentheses indicate the number of preparations studied. For half-maximum effective concentration values, see table 2.

Table 2. EC_{50} Values for Vasorelaxation by S(+)- and R(−)-Ketamine in NNLA-treated Aortic Rings with (D888) and without (CON) D888 Pretreatment

	EC_{50} (10^{-4} M)	
	CON	D888
S(+)-ketamine	9.18 ± 0.83 (9)	18.9 ± 0.5* (12)
R(−)-ketamine	3.92 ± 0.35 (9)	8.45 ± 0.27* (12)

Complete relaxation was obtained in each group. Data are means ± SEM. Values in parentheses indicate the number of preparations studied.

* $P < 0.05$, D888 *versus* CON.

might indicate a lower risk of hypotensive responses to S(+) ketamine in clinical use. Similarly, in the isolated perfused guinea pig heart, the S(+) isomer of ketamine had less depressive effects on heart rate and left ventricular pressure than did the racemate or the R(−) isomer.[14] As for the clinical relevance of these observations, we must consider that the extent of the stereoselective differences in these *in vitro* studies was, although significant, relatively small. Recently, Sekino *et al.*[15] even found no significant differences in the action of ketamine isomers on heart rate and contractile force in isolated guinea pig heart. However, compared with the racemate, only 50% of the dose of S(+) ketamine is required for anesthesia.[6] Thus the lower plasma concentrations observed in this clinical study and the twofold weaker vasorelaxing effect of S(+) ketamine compared with the racemate reported here might act synergistically in terms of a reduced incidence of untoward hypotensive reactions.

The mechanisms of action of ketamine on the vascular smooth muscle cell might be responsible for the stereoselective differences in vasorelaxation observed among the isomers and the racemate. One possible site of action is the endothelium, which is essential for NO-mediated vasorelaxation.[12] However, our experiments showed that inhibition of NO synthase did not significantly alter the relaxing effect of the ketamine isomers. Recently, similar results were reported for racemic ketamine on isolated rabbit portal veins[16] and rabbit pulmonary arteries.[17] Besides NO, other mediators released by the endothelium, such as endothelium-derived hyperpolarization factor, prostacyclin, or endothelin, modify vascular tone.[18] However, in the present experiments, mechanical removal of the endothelium did not influence ketamine-induced vasorelaxation. Together these data suggest that the endothelium does not play a role

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in ketamine-induced vasorelaxation and thus does not contribute to the stereoselective differences observed.

The quantitative difference in the vasorelaxing effect of ketamine isomers, therefore, most likely is a result of differential actions on the smooth muscle cell itself. In vascular smooth muscle, contraction and relaxation depend mainly on the intracellular concentration of ionized calcium.[19] It has been suggested that ketamine inhibits contraction by reducing transmembrane Ca^{2+} influx.[2,20] By using the whole-cell voltage-clamp technique, Yamazaki *et al.*[21] found that ketamine inhibits calcium currents through voltage-dependent (L type) Ca^{2+} channels in single smooth muscle cells of the rabbit portal vein.

One mechanism by which voltage-gated Ca^{2+} channels are prevented from opening is hyperpolarization of the membrane by activation of adenosine triphosphate-sensitive K^+ channels (K_{ATP}). Therefore we studied ketamine to determine if it might have K_{ATP}-activating properties like the vasodilating agents diazoxide and minoxidil.[22] In this case, glibenclamide, a selective K_{ATP} blocking agent,[9,23] would have shifted the concentration-effect curve of ketamine rightward. No significant effects of glibenclamide pretreatment on the vascular response to ketamine were seen, however. Therefore we conclude that the vasorelaxing effect of ketamine is not mediated by activation of K_{ATP}.

In contrast, specific blockade of L-type calcium channels by D888[11] shifted the concentration-response curve of both ketamine isomers significantly rightward, whereas complete relaxation was still obtained. The quantitative difference in the vasorelaxing action of the ketamine enantiomers was not affected by D888 pretreatment. These data are consistent with the results of Sekino *et al.*[15]: Using the voltage-clamp technique, they showed that both ketamine isomers similarly suppressed the transsarcolemmal calcium influx through L-type calcium channels in the guinea pig heart. Two conclusions may be drawn from these observations: First, the stereoselective difference between the ketamine isomers is not due to differential inhibition of L-type calcium channels. Second, besides inhibition of transmembrane calcium influx through voltage-operated channels, additional mechanisms contributing to the vasorelaxing effect of ketamine can be assumed.

In vascular smooth muscle, another source of cytosolic free calcium is its release from the sarcoplasmic reticulum.[19] The mechanism responsible for calcium release from intracellular stores involves inositol triphosphate, which is produced from phosphoinositol diphosphate by phospholipase C. Kanmura *et al.*[24] found that ketamine inhibits agonist-induced contractions in Ca^{2+}-free solution, but not the contractions induced by caffeine. This effect has been ascribed to a reduced inositol triphosphate production, probably due to an inhibition of phospholipase C.[25,26] A reduction in intracellular free calcium concentration, leading to relaxation, results mainly from reuptake intracellular stores or calcium extrusion through the plasma membrane. However, it has been shown that, in A7r5 vascular smooth muscle cells, ketamine has no effect on either of these mechanisms.[27] The tension of vascular smooth muscle can also be changed by the altered sensitivity of the contractile proteins to cytosolic calcium. However, Kanmura *et al.*[24] clearly dismissed the effect of ketamine on calcium sensitivity in experiments using skinned fiber of the rabbit ear artery.

Together two major effects appear to contribute to ketamine-induced vasorelaxation: inhibition of calcium influx through L-type calcium channels and inhibition of agonist-induced inositol triphosphate formation. In the present experiments, the quantitative stereoselective difference in the vasorelaxing effect of S(+) and R(−) ketamine was not altered by inhibition of L-type calcium channels; thus this difference may be caused by differential inhibition of agonist-induced inositol triphosphate formation. This hypothesis should be proved by directly measuring the effects of S(+) and R(−) ketamine on inositol triphosphate formation. Furthermore, the possibility of the involvement of calcium channels not sensitive to D888, including capacitative calcium entry or receptor-operated calcium channels, should be addressed in future studies.

In conclusion, vasorelaxation by ketamine enantiomers in rat aorta is quantitatively stereoselective: The effect of S(+) ketamine is significantly weaker compared with the racemate and R(−) ketamine. This difference is not due to NO release, activation of ATP-sensitive potassium channels, or differential inhibition of L-type calcium channels. The clinical relevance of this observation may be increased by the higher anesthetic potency of S(+) ketamine. Studies in humans will be necessary to determine whether the use of S(+) ketamine is characterized by a lower risk for hypotension.

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