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Interactions of Ketamine with Vasoactive Amines at Normothermia and Hypothermia in the Isolated Rabbit Heart

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Ketamine has been demonstrated to inhibit norepinephrine uptake in the adrenergic neuronal membrane, an action similar to that of cocaine. This study evaluated possible potentiation of five vasoactive amines, norepinephrine, epinephrine, tyramine, dopamine, and isoproterenol, by ketamine in the isolated rabbit heart at 35, 30, 25 and 20 C. The hearts were perfused with one of the vasoactive amines alone, ketamine (500 μg/ml) alone, and combinations of ketamine with the amines, in random order. Heart rate, left ventricular dP/dt, and left ventricular systolic, diastolic, and mean pressures were recorded.

Heart rate was decreased by ketamine alone; this effect became less significant with increasing hypothermia. No significant change from control was observed at 25 or 20 C. Heart rate increased significantly during perfusion with ketamine plus norepinephrine, epinephrine, or tyramine compared with control, and during perfusion with these amines alone at 35 C. The potentiation of heart rate caused by ketamine plus norepinephrine compared with norepinephrine alone was not affected by cooling to any temperature, while the difference between extents of potentiation by epinephrine or tyramine with and without ketamine decreased with cooling, becoming insignificant at 25 C or less.

Dopamine and isoproterenol produced greater increases of heart rate alone than when perfused with ketamine, the differences becoming less with cooling.

Left ventricular dP/dt was significantly decreased by ketamine alone, this effect becoming less apparent with cooling. Ketamine combined with norepinephrine, epinephrine, tyramine, isoproterenol, or dopamine significantly increased dP/dt over control, while only ketamine combined with norepinephrine, epinephrine, and tyramine significantly increased dP/dt compared with these vasoactive amines alone. Potentiation of left ventricular dP/dt by ketamine plus epinephrine or tyramine (compared with these amines alone) became less apparent with cooling. When ketamine was combined with norepinephrine, however, similar extents of potentiation were observed at all temperatures compared with norepinephrine alone.

Ketamine plus isoproterenol or dopamine decreased dP/dt compared with the amines alone at 35 C, this effect becoming less apparent with cooling. These results indicate that ketamine, like cocaine, may be a catecholamine Uptake 1 inhibitor.
(Key words: Anesthetics, intravenous, ketamine; Hypothermia; Sympathetic nervous system, catecholamines, epinephrine; norepinephrine; dopamine; isoproterenol; tyramine.)

NEURONAL UPTAKE is an important mechanism for the termination of action of norepinephrine, but is less important in the termination of action of epinephrine and is not needed for the termination of action of isoproterenol.[1] Both ketamine and cocaine inhibit the neuronal uptake of norepinephrine and epinephrine.[2] Inhibition of this mechanism by ketamine or cocaine will presumably potentiate the vasopressors in the order of activities of the uptake mechanism. We could find no previous data describing the influence of inhibition of neuronal uptake on the action of exogenously administered dopamine. Also, the effects of hypothermia on ketamine inhibition of neuronal uptake and its subsequent effects on exogenously administered catecholamines have not been previously reported. Hypothermia to 20 C was selected because of demonstration of maximal potentiation of norepinephrine and epinephrine in a previous study[3] employing a similar temperature.

Methods

The hearts of 45 New Zealand rabbits, 1.8–2.6 kg, were excised after cervical fracture. A time lapse of no longer than 2 min was allowed to isolate the heart and re-establish coronary-artery perfusion via the aorta in a modified Langendorff preparation. This technique has been reported in detail elsewhere.[4] Variables measured were left ventricular dP/dt, left ventricular systolic, mean, and diastolic pressures, and heart rate.

The following protocol was followed. Five groups each consisting of nine isolated heart preparations were studied. In each group the preparations were perfused with one of five vasopressors only (norepinephrine, 0.1 μg/ml; epinephrine, 0.1 μg/ml; tyramine, 2.5 μg/ml; dopamine, 2 μg/ml; isoproterenol, 0.1 μg/ml), ketamine only¶ (500 μg/ml), or ketamine

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¶ Ketaset (Ketamine hydrochloride), Bristol Laboratories, Syracuse, New York.

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TABLE 1. Changes in Heart Rate (Beats/Min) during Perfusion with Ketamine Alone, Ketamine and Vasoactive Amine, and Vasoactive Amine Alone in the Isolated Rabbit Heart (Mean ± SD)

	35 C	30 C	25 C	20 C
Norepinephrine				
Control	129 ± 8	108 ± 8	75 ± 5	52 ± 3
Ketamine only	118 ± 4*	98 ± 4*	70 ± 4	50 ± 4
Ketamine and norepinephrine	149 ± 6*	122 ± 3*	91 ± 4*	72 ± 3*
Norepinephrine only	134 ± 4*†	116 ± 3*†	82 ± 3*†	61 ± 2*†
Epinephrine				
Control	108 ± 4	71 ± 3	45 ± 3	24 ± 3
Ketamine only	98 ± 3*	56 ± 5*	32 ± 2	21 ± 2
Ketamine and epinephrine	166 ± 9*	102 ± 4*	45 ± 2	40 ± 2
Epinephrine only	150 ± 11*†	100 ± 3*	45 ± 2	38 ± 3
Tyramine				
Control	110 ± 5	98 ± 4	72 ± 3	55 ± 6
Ketamine only	101 ± 8*	89 ± 3*	63 ± 5	50 ± 3
Ketamine and tyramine	136 ± 6*	113 ± 6*	76 ± 3*	61 ± 3
Tyramine only	130 ± 5*†	110 ± 5*	76 ± 3*	62 ± 4
Dopamine				
Control	119 ± 6	82 ± 3	60 ± 3	33 ± 5
Ketamine only	98 ± 3*	66 ± 3*	50 ± 2*	30 ± 4
Ketamine and dopamine	146 ± 4*	105 ± 6*	66 ± 3	40 ± 4
Dopamine only	178 ± 5*†	122 ± 3*†	78 ± 4*	51 ± 3*
Isoproterenol				
Control	138 ± 3	126 ± 12	86 ± 9	50 ± 2
Ketamine only	119 ± 4*	114 ± 16	75 ± 10	45 ± 3
Ketamine and isoproterenol	180 ± 14*	143 ± 15*	93 ± 11	58 ± 7
Isoproterenol only	192 ± 19*	159 ± 11*	102 ± 13	68 ± 10

* $P < 0.05$, Student's t test for paired data, compared with control.
† $P < 0.05$, Student's t test for paired data, compared with ketamine/vasoactive amine.

(500 μg/ml) plus the respective vasoactive amine (same concentration as when employed alone), using a constant perfusion pressure of 56 cm H_2O.

After control measurements were made at 35 C, the heart was perfused for 20 min with one of the solutions, randomizing the order of administration. Data collection was accomplished at the end of each 20-min perfusion period. Between successive perfusions, a control solution was administered for 5–10 min to allow return to control values. After the heart had been perfused with all three solutions, a return to the control solution was accomplished, the temperature was lowered to 30 C, and the same sequence was followed. In similar fashion, the heart was cooled to 25 C and then to 20 C, the same protocol being followed at each temperature level.

Statistical significance was calculated using Student's t test for paired or unpaired data. Differences with a probability of 0.05 or less were considered significant.

Results

Ketamine decreased heart rate significantly at 35 and 30 C but not at 25 and 20 C (table 1). Ketamine combined with norepinephrine, epinephrine, tyramine, dopamine, or isoproterenol (table 1) significantly increased heart rate over control values at 35 C. Compared with perfusion with the respective vasoactive amine alone at 35 C, ketamine/norepinephrine, ketamine/epinephrine, and ketamine/tyramine significantly increased heart rate. Compared with perfusion with vasoactive amine alone at 35 C, ketamine/isoproterenol and ketamine/dopamine decreased heart rate. Cooling did not decrease the significance of the ketamine-induced potentiation of norepinephrine. However, cooling to 30 C or lower produced no significant difference in heart rate between ketamine/epinephrine or ketamine/tyramine compared with the respective vasoactive amine alone. Cooling to 25 C decreased the significance of slowing of heart rate by ketamine/dopamine compared with dopamine alone, while further cooling resulted in no significant difference between perfusion with dopamine alone and perfusion with ketamine/dopamine. Cooling to 25 C or lower caused no significant difference in heart rate between those hearts receiving isoproterenol and those receiving ketamine/isoproterenol.

Left ventricular dP/dt was decreased by ketamine

TABLE 2. Changes in Left Ventricular dP/dt (torr/sec) during Perfusion with Ketamine Alone, Ketamine and Vasoactive Amine, and Vasoactive Amine Alone in the Isolated Rabbit Heart (Mean ± SD)

	35 C	30 C	25 C	20 C
Norepinephrine				
Control	938 ± 81	750 ± 90	560 ± 85	435 ± 82
Ketamine only	810 ± 70*	560 ± 105*	500 ± 30	380 ± 73
Ketamine and norepinephrine	1240 ± 125*	985 ± 115*	740 ± 23*	572 ± 66*
Norepinephrine only	1115 ± 76*†	875 ± 70*†	620 ± 26*†	521 ± 41*†
Epinephrine				
Control	1045 ± 88	811 ± 27	660 ± 48	584 ± 26
Ketamine only	930 ± 73*	765 ± 21	628 ± 37	510 ± 92
Ketamine and epinephrine	1342 ± 56*	962 ± 31*	712 ± 26	602 ± 88
Epinephrine only	1233 ± 69*†	846 ± 39†	724 ± 31	591 ± 69
Tyramine				
Control	1370 ± 77	1041 ± 44	634 ± 52	397 ± 46
Ketamine only	1125 ± 42*	771 ± 62*	531 ± 67	329 ± 39
Ketamine and tyramine	1594 ± 82*	1158 ± 66*	675 ± 39	432 ± 41
Tyramine only	1530 ± 91*†	1068 ± 39*†	639 ± 36	440 ± 33
Dopamine				
Control	941 ± 59	806 ± 48	717 ± 61	633 ± 59
Ketamine only	809 ± 71*	769 ± 19*	693 ± 47	619 ± 46
Ketamine and dopamine	1020 ± 39*	886 ± 66*	802 ± 36	683 ± 36*
Dopamine only	1070 ± 42*†	971 ± 44*†	826 ± 39	696 ± 31*
Isoproterenol				
Control	980 ± 84	877 ± 73	736 ± 48	650 ± 73
Ketamine only	854 ± 56*	841 ± 61	672 ± 53	610 ± 41
Ketamine and isoproterenol	1230 ± 88*	1050 ± 52*	854 ± 72	826 ± 93
Isoproterenol only	1266 ± 76*	1092 ± 46*	886 ± 63	844 ± 71

* $P < 0.05$, Student's t test for paired data, compared with control.
† $P < 0.05$, Student's t test for paired data, compared with ketamine/vasoactive amine.

perfusion alone at 35 C (table 2). Cooling to 30 C resulted in inconsistent decreases in left ventricular dP/dt, while cooling to 25 C or lower resulted in no significant difference compared with control. Compared with the respective vasoactive amines alone at 35 C, ketamine/norepinephrine, ketamine/epinephrine, and ketamine/tyramine significantly increased left ventricular dP/dt, while ketamine/dopamine and ketamine/isoproterenol (table 2) decreased left ventricular dP/dt. Cooling resulted in continuing potentiation of norepinephrine when perfused with ketamine, while the significance of potentiation of ketamine combined with epinephrine and tyramine compared with the respective vasoactive amines alone decreased with cooling. Cooling to 30 C did not change the significance of a decrease in left ventricular dP/dt caused by ketamine/dopamine compared with dopamine alone, but further cooling resulted in insignificant differences between these two variables. Cooling to 30 C did not further alter changes in left ventricular dP/dt over values found at 35 C in those hearts perfused with isoproterenol and ketamine/isoproterenol, but further cooling resulted in no significant difference between these values.

Left ventricular mean pressure changes were similar to those found in left ventricular dP/dt when perfused with the respective solutions (fig. 1).

Discussion

The results demonstrate that ketamine-induced myocardial depression is antagonized by hypothermia, confirming earlier work by Goldberg *et al.*[5] Ketamine potentiates norepinephrine > epinephrine > tyramine, but does not potentiate isoproterenol or dopamine. Ketamine-induced potentiation of norepinephrine is not temperature-dependent, while ketamine-induced potentiation of epinephrine or tyramine decreases with cooling.

The reuptake of norepinephrine and epinephrine into the adrenergic neuronal membrane is the major mechanism responsible for terminating their actions.[6] Findings of temperature dependence and inhibition by metabolic inhibitors strongly suggest this is an active transport mechanism.[6] Blocking this membrane catecholamine transport system by cocaine or ketamine[2,7] increases the amount of catecholamine available to receptors, thus potentiating the effects of endogenously released or exogenously administered norepinephrine or epinephrine.

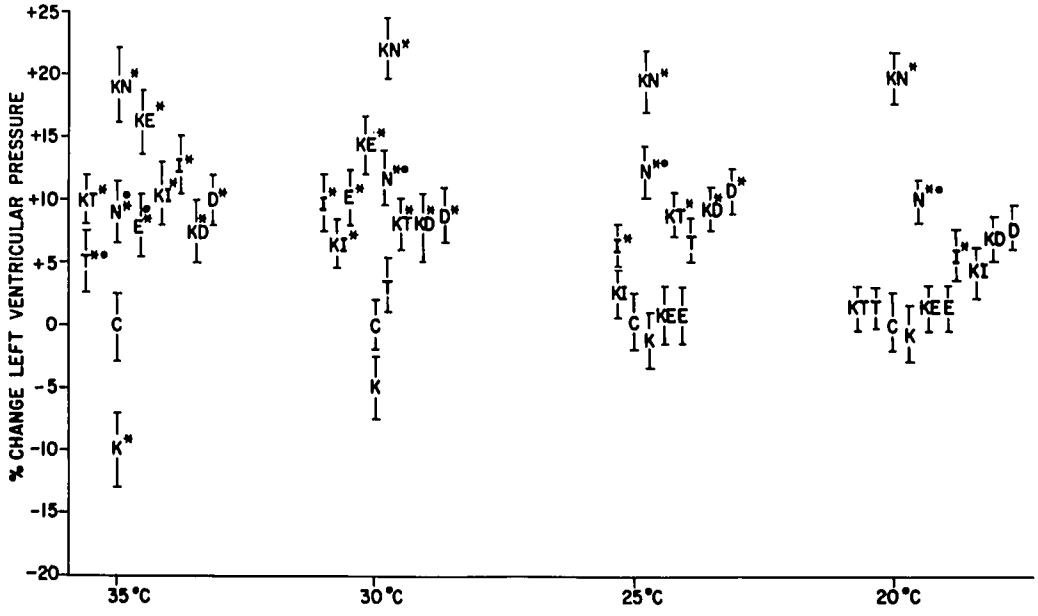

FIG. 1. Percentage changes in mean left ventricular pressure during perfusion with ketamine (K) alone, norepinephrine (N), epinephrine (E), tryamine (T), dopamine (D), or isoproterenol (I) alone, or K plus N, E, T, D, or I, on the isolated rabbit heart. *$P < 0.05$, Student's t test for paired data, compared with control. ●$P < 0.05$, Student's t test for paired data, compared with ketamine/vasoactive amine values.

Iverson[8] has described two different uptake processes for catecholamines. One process (Uptake 1) is intraneuronal, while Uptake 2 is primarily extraneuronal. Uptake 1 has a particularly high affinity for norepinephrine, while isoproterenol, because of low affinity for Uptake 1, is primarily transported by Uptake 2. Metabolism via monoamine oxidase (MAO) and catechol-o-methyltransferase (COMT) play a less important role in the termination of norepinephrine activity.[9]

Hardman *et al.*[1] found greater potentiation of norepinephrine than epinephrine and no potentiation of isoproterenol in the intact dog heart when the uptake process was blocked by cocaine. The same investigators also demonstrated significant myocardial uptake of perfused norepinephrine, less for epinephrine, and very little for isoproterenol. Others[10] have reported no myocardial uptake of perfused isoproterenol in the rabbit heart. The different myocardial uptake rates of these catecholamines seem to be related to their specificities for the uptake mechanism.

Our findings at normothermia are consistent with previously published data. The finding of continuing potentiation of norepinephrine by ketamine with cooling is compatible with the findings of others. Foster[3] reported cooling to below 37.5 C caused a temperature-dependent potentiation of exogenously administered norepinephrine in the relaxation of guinea pig tracheal smooth muscle. Others[11] have reported cooling to decrease neuronal uptake of norepinephrine in the cat heart. Therefore, when ketamine and hypothermia are administered concurrently, greater potentiation of exogenously administered norepinephrine should be expected. Apparently, because of lower affinity for the neuronal uptake mechanism (or Uptake 1), potentiation of epinephrine became less apparent with cooling.

No potentiation of isoproterenol by pharmacologic reuptake inhibition has been reported previously.[1] This may be explained by the specific inhibition of Uptake 1 rather than Uptake 2 by ketamine or cocaine. Possibly because isoproterenol has little affinity for Uptake 1 is primarily transported by Uptake 2,[6] this vasoactive amine is not potentiated. This is supported by Iverson's data,[8] which demonstrated Uptake 2 to be insensitive to cocaine.

The finding of no potentiation of dopamine was unexpected. Dopamine has been shown to have equal affinity for Uptake 1 and Uptake 2[6]; therefore, some potentiation of dopamine would be expected. Perhaps our findings could be partially explained by the concentration of drug employed in our study (0.1 μg/ml). At this concentration, Uptake 1 has been reported to be quickly saturated, leaving the less effective Uptake 2 as the primary transport mechanism for dopamine[6]; therefore, no potentiation was apparent.

Direct myocardial depression in the isolated heart by ketamine has been reported.[5,12] Our data demonstrating a ketamine-induced decrease in left ventricular dP/dt and heart rate support these findings. That hypothermia tends to minimize the depressant effect of ketamine on left ventricular function with cooling is compatible with previously published findings that morphine[4] and methylmethacrylate[13] also have less

depressant effects on the isolated rabbit heart at 22 and 27 C, respectively, than at 37 C.

That ketamine may also potentiate norepinephrine and epinephrine by decreasing their metabolism by MAO or COMT seems unlikely, because COMT inhibitors do not significantly potentiate norepinephrine, but significantly potentiate isoproterenol.[9] Isoproterenol is known to depend primarily on metabolism by COMT for termination of action. Therefore, if ketamine inhibited COMT, potentiation of isoproterenol should have been observed. The response of isolated strips of rabbit aorta to epinephrine and norepinephrine has also been demonstrated to be unaltered by complete inhibition of MAO by iproniazid.[14]

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