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Comparison in Conscious Goats of the Effects of Epinephrine, Norepinephrine, and Tyramine on Blood Pressure* (33967)

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There are certain advantages to the use of the goat in experimental studies. The goat offers some advantages in bridging the gap between laboratory animals and higher primates because its neuromuscular coordination is of a superior type, it has a life span of about 10 years, and it is easy to condition to accept experimental procedures. They are also inexpensive and easy to maintain. Fletcher (1) in a report containing a comprehensive list of references, discussed the use of the goat in research. To date, specific detailed information on drug responses of the cardiovascular system of the goat is limited, particularly in conscious animals.

Rangsit (2) reported a marked increase in arterial blood pressure in unanesthetized sheep when given 1–3.5 ml of a 1:10,000 solution of epinephrine intravenously. Halmagyi (3), in normotensive sheep, found that norepinephrine infusion produced a statistically significant rise in systemic arterial pressure from 102 to 123 mm Hg.

The present report describes the results obtained when epinephrine,[1] norepinephrine,[1] and tyramine were administered to conscious goats.

Methods and Materials. Five sexually mature male goats (Spanish type) weighing between 21 and 45 kg were used for this study. They were previously surgically prepared with unilateral exteriorized carotid artery loops [Flournoy *et al.* (4)] and were drug free for at least 3 weeks prior to the initiation of the study. To record blood pressure from an exteriorized carotid artery, an 18-gauge silicon coated needle attached to silicone coated polyvinyl tubing was inserted into the carotid. Heparin (2000 units/100 ml of saline) was used to prevent clotting in the tube leading to the blood pressure transducer. Arterial blood pressure was recorded with a P-1000 Linear Core transducer used in conjunction with a Physiograph Four. A jugular vein was catheterized for the intravenous injections. All injections of pressor compounds were administered in single doses to individual goats and a minimum of 5 min of steady blood pressure recordings were obtained between injections. Each goat served as its own control. A regression analysis was used to establish the nature of the pressor responses and duration of action to the different injections.

Results. The dose–response relationships of the pressor responses to tyramine, epineph-

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TABLE I. Dose–Response Relationships of Pressor Responses to Epinephrine in Unanesthetized Goats.

Dose (μg/kg)	Pressor response (mm Hg)						Duration of action (sec)					
	Animal no.						Animal no.					
	46	002	72	032	009	Mean ± SE[a]	46	002	72	032	009	Mean ± SE[b]
Control	140	140	110	115	120	125 ± 7.6						
0.5	160	158	120		155	148 ± 8.4	56	43	30		70	50 ± 9.4
1.0	166	170	138	140	164	156 ± 7.6	61	46	46	72	80	61 ± 8.4
1.5		190	145			167 ± 12.1		56	64			60 ± 13.4
2.0	180	206	148	172	198	181 ± 7.6	78	68	95	104	114	92 ± 8.4
2.5			160			160 ± 16.9			112			112 ± 18.9
3.0	210	210	170	202	208	200 ± 7.6	91	110	107	159	135	120 ± 8.4
3.5		216	180	200		199 ± 9.8		126	124	178		141 ± 10.9
4.0	188		185		200	191 ± 9.8	120		118		132	123 ± 10.9
4.5			189			189 ± 16.9			126			126 ± 18.9
5.0			190			190 ± 16.9			151			151 ± 18.9
5.5			190			190 ± 16.9			152			152 ± 18.9
6.0			210			210 ± 16.9			171			171 ± 18.9

[a] Standard error is based upon the pooled experimental error plus residual from the fitted equation of the regression analysis. The square root of the mean square error for pressor response was 16.9.

[b] Standard error is based upon the pooled experimental error plus residual from the fitted equation of the regression analysis. The square root of the mean square error for duration of action was 18.9.

rine, and norepinephrine are shown in Tables I–III. Intravenous injections of 0.5–6.0 μg/kg of epinephrine and 0.5–5.0 μg/kg of norepinephrine produced an immediate increase in blood pressure of practically the same amplitude. The pressor responses to both compounds were dose-dependent and an occasionally resulting tachycardia was consistently followed by reflex bradycardia in the presence of intact vagus nerves during the peak of increased blood pressure. Doses of 1.0–2.0 μg/kg of epinephrine showed activation of α and β receptors as evidenced by a pressor response followed by a depressor response then a return to a hypertensive state. Frequently muscle tremors would develop following several injections of norepinephrine. Several animals were not tested using doses higher than 4.0 μg/kg of epinephrine because they became extremely nervous. Also, higher dose–responses would not have been in the limits of rectilinear recording. Goat 72 was very cooperative and responses were recorded from doses of 0.5 to 6.0 μg/kg. Tables I and II show the duration of action and pressor responses for epinephrine and norepinephrine. The duration of action was generally longer for norepinephrine than for epinephrine.

Tyramine produced a pressor response that was dose-dependent. The increase in blood pressure was not as immediate as in the case of epinephrine and norepinephrine. A minimum of 30 sec was required for responses to reach peak pressure. Higher doses such as 4.0 mg/kg required 60 sec to reach increased peak pressure.

In goat 032, peak pressure was observed with a dose of 0.25 mg/kg. Possibly higher doses could have been administered if the control pressure had been in the range of 110–120 mm Hg instead of 130 mm Hg (Table III).

A brief increase in heart rate from 90 to 110 was noticed from recordings of electrocardiograms after tyramine injection. The tachycardia appeared immediately before peak pressure and lasted only for a few seconds at which time it returned to normal. Duration of tyramine action was considerably

TABLE II. Dose–Response Relationships of Pressor Responses to Norepinephrine in Unanesthetized Goats.

Dose (μg/kg)	Pressor response (mm Hg)						Duration of action (sec)					
	Animal no.						Animal no.					
	46	002	72	032	009	Mean ± SE[a]	46	002	72	032	009	Mean ± SE[b]
Control	140	140	120	120	116	127 ± 7.6						
0.5		186	150			168 ± 12.0		68	48			58 ± 18.4
1.0	180	200	160	155	156	170 ± 7.6	62	85	72	45	57	64 ± 11.6
1.5	180	202	170		165	179 ± 8.5	55	125	101		108	97 ± 13.0
2.0	198	218	170	170	178	187 ± 7.6	70	100	105	87	113	95 ± 11.6
2.5		216				216 ± 17.0		155				155 ± 26.0
3.0	205	218	180	175	192	194 ± 7.6	106	161	166	100	122	131 ± 11.6
3.5		212				212 ± 17.0		172				172 ± 26.0
4.0	208		185	185	206	196 ± 8.5	109		189	129	171	150 ± 13.0
5.0	214		190	186	212	20. ± 8.5	118		202	159	205	171 ± 13.0

[a] Standard error is based upon the pooled experimental error plus residual from the fitted equation of the regression analysis. The square root of the mean square error for pressor response was 17.0.

[b] Standard error is based upon the pooled experimental error plus residual from the fitted equation of the regression analysis. The square root of the mean square error for duration of action was 26.0.

longer than that obtained following either epinephrine or norepinephrine. Statistical analysis revealed that there was a significant relationship at the .001 level between dose and pressor response and dose and duration of action for epinephrine, norepinephrine, and tyramine.

Discussion. As would be expected, there was an increase in blood pressure with dose of norepinephrine, epinephrine, and tyramine. Norepinephrine and epinephrine produced very similar pressor responses when equivalent doses were used. The onset of pressor activity was more rapid during epi-

TABLE III. Dose–Response Relationships of Pressor Responses to Tyramine in Unanesthetized Goats.

Dose (mg/kg)	Pressor response (mm Hg)						Duration of action (sec)					
	Animal no.						Animal no.					
	46	002	72	032	009	Mean ± SE[a]	46	002	72	032	009	Mean ± SE[b]
Control	120	110	105	130	110	115 ± 5.0						
0.05		126	135			131 ± 7.9		138	100			119 ± 66.3
0.10	164	140	140	166	152	152 ± 5.0	308	240	240	271	208	253 ± 41.9
0.125			155			155 ±11.1			296			296 ± 93.4
0.20	180	166	172	204	175	179 ± 5.0	335	304	293	637	326	379 ± 41.9
0.30	196	195	190		210	198 ± 5.5	586	377	417		377	439 ± 46.7
0.40	210	196	202			203 ± 6.4	762	493	445			566 ± 54.0

[a] Standard error is based upon the pooled experimental error plus residual from the fitted equation of the regression analysis. The square root of the mean square error for pressor response was 11.1.

[b] Standard error is based upon the pooled experimental error plus residual from the fitted equation of the regression analysis. The square root of the mean square error for duration of action was 93.4.

nephrine injection, which demonstrated the relative potency of this catecholamine in comparison to norepinephrine. When doses below 2.5 μg/kg were used, activation of both α and β receptors was observed. Alquist (6) classified receptor sites as α and β on the basis of their responses to a variety of sympathomimetics. Usually, the effect on α receptors is excitatory (vasoconstriction) and inhibitory (vasodilation) on β receptors, although this is by no means an absolute rule. Doses of epinephrine too small to act on α receptors lower blood pressure by their β-receptor action. Larger doses activate α receptors in addition and the effect is activation of both α and β receptors which causes a rise in peripheral resistance and consequently a rise in blood pressure. As systolic pressure increases, there is a concomitant increase in pulse pressure which is probably due to elevated venous return to the heart according to Goodman and Gilman (5). Norepinephrine acts primarily on α receptors as observed from the blood pressure recordings. The usual ECG change was sinus bradycardia resulting from compensatory vagal reflex activity.

The transient apnea which was observed with epinephrine reflects either brief depression of the respiratory center or of the carotid body reflex. Often the apnea was succeeded by a compensatory increase in rate and depth.

Tyramine did not produce the immediate pressor effect similar to epinephrine or norepinephrine. The increase in systolic pressure produced a subsequent increase in pulse pressure which lasted for several minutes. Perhaps the onset of pressor response was delayed due to its indirect action on the cardiovascular system. According to Bhagat (7, 8) and Burn and Rand (9) tyramine is generally believed to owe its sympathomimetic effects mainly to release of endogenous norepinephrine from postganglionic sympathetic nerves.

Summary. Dose–response relationships of the pressor compounds, epinephrine, norepinephrine, and tyramine were determined on the arterial blood pressure of conscious goats. Statistical analysis revealed that there was a significant relationship between dose and pressor response at the .001 level for all three compounds. Activation of both α and β receptors by epinephrine and α receptors by norepinephrine was observed from the tracings of blood pressure which suggest the presence of α and β receptor sites as confirmed by other investigators using mammals.

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