Reflex Vasodilatation in the Cat and Dog Anesthetized with Ketamine[1] (37570)

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In a previous investigation it was found that baroreceptor induced reflex vasodilatation was greater in the dog then in the cat hindlimb (1). Reflex vasodilatation was quantitated by determining the ratio of the maximal reflex vasodilator response (MRR) elicited by intravenously injected norepinephrine, and the maximal vasodilator response produced by a vasodilator agonist (MAR) such as acetylcholine injected intraarterially. The ratio MRR/MAR obtained in the dog exceeded significantly that found in the cat. The marked difference found between the reflex vasodilator responses obtained in these species appeared to have been accounted for by a smaller active component of the response in the cat. Active reflex vasodilatation as envisioned by Beck (2) and Beck and Brody (3) is that portion of the reflex effect which is produced by the release of a vasodilator transmitter rather than by passive withdrawal of adrenergic vasoconstrictor tone. Because reflex vasomotor regulation in the cat has been found to be susceptible to the depressant effect of barbiturates (4, 5) and possibly other anesthetics, it is conceivable that active vasodilatation in the cat (6) was depressed by the anesthetics employed in the previous study (1). Ketamine is a dissociative anesthetic of the cyclohexanone series and is believed to act on the higher centers but not on the brain stem (7). Administration of this agent produces a sustained pressor effect (8, 9) which appears to be neurogenically mediated (10, 11). The hypertension results from an increase in both peripheral resistance and cardiac output (9, 12). Since little or no information is available concerning reflex vasodilator mechanisms in ketamine anesthetized animals, we decided to compare the norepinephrine evoked reflex response and degree of sympathetic vascular tone in the ketamine anesthetized dog and cat.

Methods. Experiments were carried out on 7 cats and 6 dogs of either sex weighing 3.3 to 4.5 and 14.5 to 18.9 kg, respectively. The cats were anesthetized with 20 mg/kg of ketamine injected im and when they became light this was supplemented with doses of 5 mg/kg. In all but 2 experiments, the cats were allowed to breath spontaneously; however, when necessary a Harvard respirator was employed in presence of skeletal muscle relaxation with decamethonium bromide, 0.25 mg/kg iv. The dogs were anesthetized initially with 20 to 25 mg/kg of ketamine im or iv, and in addition 0.5 to 1 mg/kg of morphine sulfate was employed to pretreat 3 animals prior to ketamine, since the latter drug alone was short-acting in the dog. The drug combination of morphine and ketamine was a more effective anesthetic. Supplemental doses of 2.5 to 5 mg/kg of ketamine were given during the experiment when needed and a total dose of 35 to 70 mg/kg of ketamine was employed in these experiments on dogs. In all of the experiments involving dogs artificial respiration was employed after administration of decamethonium bromide, 0.25 mg/kg.

Constant flow perfusion of the hindlimb was carried out in the dog and cat, as previously described (1). Heparin sodium, 500 to 1000 units/kg, was administered to pre-

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vent blood clotting. The left hindlimb was perfused with a Sigmamotor pump, and flow was maintained constant throughout any given experiment. Blood flow averaged 84 ml/min in the dog and 10 ml/min in the cat, and produced mean perfusion pressures of 114 and 112 mm Hg, respectively. Perfusion and systemic arterial pressures were recorded on a Gilson polygraph. Collateral flow to the limb was eliminated by ligation of the aorta below the origin of the left renal artery. The tie was made around a catheter placed in the aorta to withdraw blood to supply the pump. The circulation of the paw was occluded with a tight clamp. In order to avoid different degrees of blood loss into the perfusion tubing, the relative volumes of tubing were made equivalent with respect to body weight. The tubing comprised 55 ml and 13 ml in the dog and cat experiments, respectively. This amounted to an average blood loss of 3.3 mg/kg in these experiments. The animal's body temperature was maintained by either heating a coil of tubing interposed in the perfusion line or with a heating pad. The coil of tubing was also employed to extend the time between the moment of the iv injection of norepinephrine and its arrival in the perfused hindlimb. In this manner the reflex vasodilator response elicited by norepinephrine could be quantified precisely and separated in time from the vasoconstrictor action of the agent in the limb. In each experiment the maximal reflex vasodilator response (MRR) was determined by increasing the iv dose of norepinephrine until no further increment in the vasodilator response was attained. Also, the maximal agonist elicited vasodilator response (MAR) in the limb was ascertained by increasing the dose of intra-arterially (ia) administered agonist (acetylcholine, methacholine or histamine) in a similar fashion. We have noted previously that the MAR obtained with these various vasodilators is the same.

Drugs and chemical agents employed were: norepinephrine bitartrate, methacholine chloride, acetycholine bromide, ketamine hydrochloride (kindly supplied by Parke Davis Co., Ann Arbor, MI) and histamine diphosphate.

Results. Maximal reflex vasodilator response in ketamine anesthetized cat and dog. Mean systemic blood pressure in the cat averaged 136 ± 5 (SE) mm Hg prior to the iv administration of the dose of norepinephrine that evoked the MRR. The dose of norepinephrine which elicited a MRR ranged between 0.25 and 2 μg/kg and the mean pressor response was 55 ± 4 mm Hg. The mean MRR was equivalent to a 32% decrease in hindlimb perfusion pressure (Fig. 1). Depending on the experiment either histamine, acetylcholine or methacholine was injected ia in progressively larger doses (from 1 to 4 μg) until a MAR was attained. The mean MAR was equivalent to a 49% decrease in hindlimb perfusion pressure (Fig. 1). A ratio of MRR/MAR was determined in each experiment and the mean was 0.67 ± 0.03. A recording from a typical experiment in a cat is shown in Fig. 2. In this experiment graded reflex vasodilator responses were elicited by norepinephrine in doses of 0.5, 1 and 2 μg/kg. The MRR was obtained with 2 μg/kg of norepinephrine and the MAR was 4 μg of histamine. Subsequently, the lumbar sympathetic trunk was sectioned at L_3 and at L_5, and the sustained decrease in perfusion pressure was determined. This decrease was measured when the perfusion pressure reached a stable level, some 5 to 17

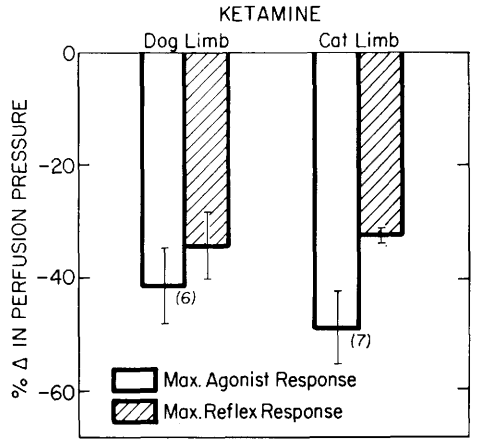

FIG. 1. Maximal agonist responses (MAR) and maximal reflex vasodilator responses (MRR) elicited in dog and cat hindlimb. Values are expressed as mean percentage changes in hindlimb perfusion pressure ± SE.

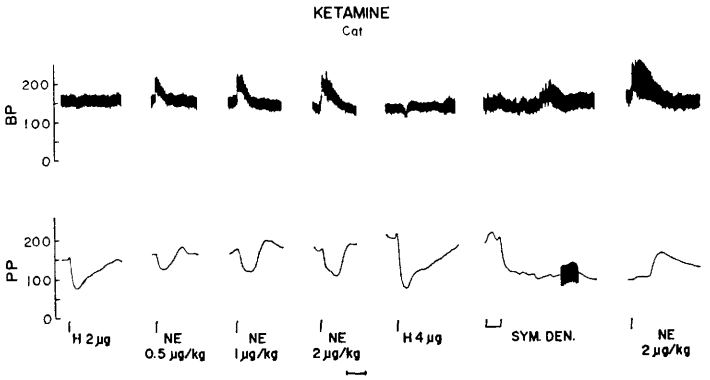

FIG. 2. Systemic blood pressure and hindlimb perfusion pressure tracings from experiment employing ketamine anesthetized cat. Limb blood flow was 10 ml/min and cat weighed 4.4 kg. Graded responses to norepinephrine (NE) injected iv prior to sympathetic denervation and response to 2 µg/kg of NE after denervation are shown. Histamine (H) was given close ia. Time interval of 1 min is at bottom of figure.

min later, and represents the loss of sympathetic tone. The mean decrease calculated as a percentage of the control perfusion pressure in the cat limb was 40 ± 4%. Norepinephrine was also injected iv after the acute denervation to verify abolition of the reflex response (Fig. 2). This is indicated by the absence of any fall in perfusion pressure. The only response in the limb remaining after denervation was the delayed direct vasoconstrictor action of norepinephrine.

The mean systemic blood pressure in the dog immediately prior to the dose of norepinephrine employed to elicit MRR was 147 ± 12 mm Hg. The change in blood pressure produced by this dose of norepinephrine (from 0.5 to 2 µg/kg) was a mean of 52 ± 6 mm Hg. The MRR and MAR obtained in these experiments are also in Fig. 1. It is apparent that the mean MRR of 34% was similar to that obtained in the cat, whereas the mean MAR of 42% was less than in the feline. The mean ratio of MRR/MAR was 0.78 ± 0.08 and tended to be greater than in the cat, but not significantly so. Acute denervation resulted in a smaller sustained decrease in perfusion pressure in the dog (21 ± 7%) than that obtained in the cat. This effect was determined when the perfusion pressure reached a stable level 4 to 9.5 min after denervation. Since this response was approximately one-half of that in the cat, there was much less sympathetic tone in the dog than in the cat. There did not appear to be any difference between the results obtained in the ketamine anesthetized dogs pretreated with morphine and those without morphine.

Active component of reflex vasodilatation in cat and dog. As postulated previously (2, 13) the difference between the fall in hindlimb perfusion pressure attained during the reflex vasodilator response and the sustained decrease in perfusion pressure following acute sympathetic denervation represents the minimal active component of the reflex vasodilator response. Plotted in Figs. 3 and 4 are the changes in perfusion obtained during the MRR and after sympathetic denervation in the cats and dogs, respectively. The top of the bar indicates the pressure existing prior to the MRR or denervation, and the bottom of the bar indicates the pressure established during the MRR or after denervation. In the cat, the control perfusion pressure (top of bar) was higher prior to denervation (mean = 150 ± 17 mm Hg) than prior to eliciting the MRR (mean = 113 ± 12 mm Hg) because the vascular resistance tended to rise during the experiment or during the manipulation required for denervation. There was clearly no significant difference between the levels of perfusion attained during the MRR and after denervation (mean = 3 ± 3 mm Hg) in the 7 experiments as depicted in Fig. 3. In the dog (Fig. 4) the control perfusion pressure (top of bar) prior to eliciting MRR

was a mean of 110 ± 3.7 mm Hg and before denervation was a mean of 114 ± 8.1 mm Hg. The level of perfusion pressure attained during the MRR was lower than that after sympathetic denervation in 5 of 6 experiments and the difference of 25 ± 6 mm Hg was significant ($p < 0.005$).

Discussion. Baroreceptor reflex evoked vasodilatation in the hindlimb can be demonstrated in the dog and cat anesthetized with ketamine as in the barbiturate (2) or chloralose anesthetized dog and cat (1). A similar vasodilator response has been elicited by carotid sinus stimulation in the unanesthetized dog (14). There was a comparable degree of vasodilatation in the hindlimb of the ketamine anesthetized dog and cat based on calculations of the MRR as a percentage of the control perfusion pressure and as a fraction of the MAR. When other anesthetics were employed, there was a significant difference between the MRR in the dog and cat based on these same calculations (1). This difference was accounted for by the relative contribution of an active component of the reflex. Evidence for this was based on the findings that (a) the MRR exceeded the level of perfusion pressure after sympathetic denervation to a greater extent in the canine than in the feline and (b) the reflex vasodilator response was essentially eliminated in the cat, but not in the dog, after adrenergic blockade with beta xylocholine (1). Although there was no apparent difference in the degree of reflex vasodilatation between the ketamine anesthetized dog and cat as mentioned above, the relative contributions of active and passive components of the reflex response differed. In all but two experiments in cats the MRR did not exceed the decrease in perfusion pressure following sympathetic denervation (Fig. 3). This indicates that the complete withdrawal of sympathetic tone could account for the MRR. Thus, as in the previous investigation a passive mechanism could totally account for reflex vasodilatation in the cat. Because the level of vascular tone during the MRR was significantly below that established after acute sympathetic denervation, it appears that in the ketamine anesthetized dog (Fig. 4) an active component participates in the reflex, as in the dog anesthetized with other agents.

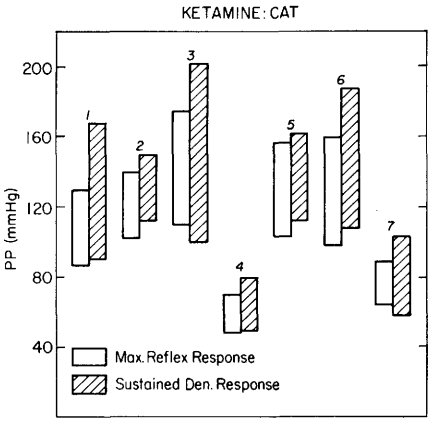

FIG. 3. Comparative changes in perfusion pressure (mm Hg) obtained during the maximal reflex vasodilator response and the sustained response to sympathetic denervation in 7 experiments in cats.

The relatively greater reflex vasodilator response found in the ketamine cat than that obtained previously in the chloralose anesthetized cat is attributable to the greater degree of sympathetic tone present during ketamine anesthesia. This high degree of sympathetic tone was not found in the ketamine anesthetized dog. It is known that species differences exist in the response to ketamine (8), and this could account for the difference in the relative degrees of sympathetic tone in the ketamine anesthetized animals.

Conclusion. Reflex vasodilatation elicited

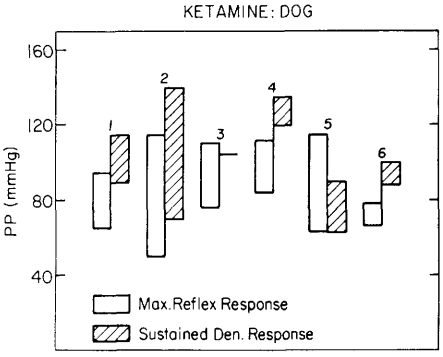

FIG. 4. Comparative changes in perfusion pressure (mm Hg) obtained during the maximal reflex vasodilator response and the sustained response to sympathetic denervation in 6 experiments in dogs.

by iv administration of norepinephrine was of a similar magnitude in the ketamine anesthetized dog and cat. In the dog an active component of the response was clearly manifested, whereas in the cat this was not the case. The cat anesthetized with ketamine, however, had a high degree of sympathetic vascular tone which appears to have accounted for a greater reflex vasodilator response than that obtained in the chloralose anesthetized animal.

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