A COMPARISON OF THE CARDIOVASCULAR EFFECTS OF BIOGENIC AMINES AND THEIR PRECURSORS IN NEWBORN AND ADULT DOGS1, 2

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ABSTRACT

Privitera, Philip J., Jennifer M. H. Loggie and Thomas E. Gaffney: A comparison of the cardiovascular effects of biogenic amines and their precursors in newborn and adult dogs. J. Pharmacol. Exp. Ther. 166: 293-298, 1969. There is relatively little information regarding the cardiovascular effects of the biogenic amines in newborn animals. In the present study the pressor and chronotropic responses to i.v. injections of norepinephrine, histamine, 5-hydroxytryptamine, their respective precursors and tyramine were compared in vagotomized, 1- to 2-week-old puppies and adult dogs. Norepinephrine and its precursors produced increases in mean arterial pressure and heart rate in the newborns which were proportionately the same as those observed in the adults. Similarly the potency ratios of norepinephrine/dopamine/dopa, as reflected in the above parameters, were the same in both age groups. In addition, the time courses of the cardiovascular responses to dopamine, dopa and tyramine were generally equivalent in the newborn and adult dogs. Histamine produced a depressor response, whereas 5-hydroxytryptamine generally elicited a biphasic effect on mean arterial pressure in both groups of dogs. It is concluded that the circulatory alpha and beta adrenergic receptor systems in the newborn dog are quantitatively similar to the adult. The data also indicate that the cardiovascular system of the newborn dog is as sensitive as that of the adult to the effects of the other biogenic amines and their precursors.

The role of the sympathetic nervous system in the regulation of the adult cardiovascular system has been extensively studied, but there is relatively little information regarding the state of development of the adrenergic nervous system or the cardiovascular effects of adrenergic drugs in newborn animals. For example, the comparative cardiovascular effects of norepinephrine and its precursors dopamine and dopa have not been systematically studied in newborn animals. There is even less information available from studies in young animals about the cardiovascular effects of the other biogenic amines, histamine and 5-hydroxytryptamine.

For these reasons and because of the possible implications of such information in the drug management of circulatory problems in newborn children, we have compared the pressor and chronotropic responses to norepinephrine (NE) and its precursors in newborn and adult dogs. Similarly we have examined the cardiovascular effects of histamine, 5-hydroxytryptamine and their respective precursors in newborns and adults because the endogenous forms of these amines may be involved in the physiologic regulation of the circulation. In addition, we have compared the circulatory effects of tyramine in newborns and adults in order to ascertain whether the newborn is able to release catecholamines in response to drugs.

METHODS. The following drugs were studied: l-norepinephrine bitartrate (NE); 3,4-dihydroxyphenylethylamine hydrochloride (dopamine); L-3,4-dihydroxyphenylalanine (dopa); tyramine hydrochloride; histamine dihydrochloride; l-histi-
dopamine; 5-hydroxytryptamine creatinine sulfate; and l-tryptophan ethyl ester hydrochloride. All doses refer to the weight of the base except for 5-hydroxytryptamine, for which the dosage is expressed as the salt. Two drugs were studied in each experiment. The order of drug administration and the dosage were randomly allocated in each animal, except in those experiments in which tyramine was given. In these experiments randomly allocated doses of tyramine were given before randomly allocated doses of dopa or dopamine. All drugs were studied in animals that were bilaterally vagotomized.

Twenty-eight purebred beagle puppies 6 to 12 days old (305-635 g) and 31 adult mongrel dogs (5.5-16.5 kg) were studied. All animals were anesthetized with sodium pentobarbital; adult dogs received 30 mg/kg i.v., and newborn dogs received 25 mg/kg i.p.

Ventilation was maintained with a positive pressure respirator. Rectal temperature was kept between 36.5° and 38.0°C with electric heating pads. Drugs were given as single i.v. injections through a catheter in the femoral vein. Femoral arterial pressure was measured with a Statham P23DC transducer. Mean arterial pressure was calculated from the pulse-pressure recording as the diastolic pressure plus one-third of the pulse pressure. The half-time of a pressor response was calculated as the length of time required for the increase in mean arterial pressure to return to half the peak value. Heart rate was calculated from an electrocardiogram. The heart-rate response to each intervention was calculated from the maximal increase or decrease in rate observed in any 10-sec interval after the intervention.

Student's t test was used for statistical analyses, and P values equal to or less than .05 were considered significant. Means ± one standard error of the mean are shown in figures.

**RESULTS. General observations.** After pentobarbital administration but before vagotomy, the average mean arterial pressure was 47 ± 2 mm Hg in 28 newborns and 129 ± 4 mm Hg in 31 adults. The average heart rate recorded at the start of the experiment was 192 ± 5 beats/min and 160 ± 5 beats/min in newborns and adults, respectively. Mean arterial pressure and heart rate in the newborns were significantly different (P < .001) from those in adults. Vagotomy had no measurable effect on heart rate or arterial pressure in either adult or newborn dogs.

**Norepinephrine.** In newborn (5 experiments) and adult dogs (7 experiments), the minimal effective pressor dose of NE was 0.1 μg/kg. The absolute increases in mean arterial pressure produced in newborns by the two highest doses of NE tested (1 and 10 μg/kg) were significantly less (P < .05) than in adults (fig. 1A). However, when the pressor effects of NE are expressed as percent change, if anything, there was a greater change in the newborn (fig. 1B). The half-time of the pressor effect of NE was significantly longer (P < .05) in newborn dogs at three of the four doses tested. With 10 μg/kg of NE, the half-time of the pressor response was 131 ± 17 sec in the newborn and 82.7 ± 6 sec in the adult dog.

The increases in heart rate produced by NE in newborn and adult dogs were indistinguishable in terms of either absolute or percent increases (fig. 2, A and B). The smallest dose of NE required to produce a significant increase in heart rate was 1 μg/kg in both age groups; this dose was 10 times greater than the minimal pressor dose.

**Dopamine and dopa.** The percent increases in arterial pressure produced by dopamine, 1 to 1000 μg/kg, in newborns (6 experiments) were
similar to those seen in adult dogs (6 experiments; fig. 1B). The half-time of the response to dopamine was the same in newborn and adult dogs at all but the highest dose, 1000 μg/kg; with this dose the half-time was longer (P < .01) in adults (277 sec) than in newborns (114 sec). Dopamine produced the same increases in heart rate in newborn and adult dogs (fig. 2A). When expressed as percent change, the chronotropic responses to dopamine were the same in both age groups at all doses except 1000 μg/kg, with which a significantly greater increase was seen in the adult (fig. 2B). The minimal pressor dose of dopamine was 10 μg/kg in newborn and adult dogs, whereas the smallest dose required to increase heart rate was 100 μg/kg.

Dopa, 1 to 30 mg/kg, produced similar percent increases in arterial pressure and heart rate in newborn (5 experiments) and adult dogs (7 experiments; figs. 1B and 2B).

Tyramine. Tyramine, 1 to 1000 μg/kg, produced similar percent increases in arterial pressure in newborn (7 experiments) and adult dogs (5 experiments; fig. 3). In newborns tyramine, 3000 μg/kg, produced a biphasic response, whereas 10,000 μg/kg had only a depressor effect. In the adult a biphasic response was seen only at 10,000 μg/kg of tyramine. The half-time of the pressor responses to tyramine, 1 to 1000 μg/kg, were the same in the two groups. Tyramine increased heart rate to about the same extent in the puppy and the adult. Expressed as percent change, the 1000-μg/kg dose increased heart rate more (P < .05) in adult dogs (fig. 3).

Histamine and histidine. Histamine, 0.01 to 100 μg/kg, had greater depressor effects in adult dogs (6 experiments) than in newborns (5 experiments) at the four highest doses tested. This was true whether the depressor response was measured as an absolute or percent change (fig. 4A). It is interesting that the lowest ar-

Fig. 2. Comparison of the chronotropic effects of i.v. norepinephrine (Norepi), dopamine and dopa in newborn and adult vagotomized dogs. A, absolute change in heart rate; B, percent change in heart rate.

Fig. 3. Comparison of the pressor and chronotropic effects of i.v. tyramine in newborn and adult vagotomized dogs. A, percent change in mean arterial pressure; B, percent change in heart rate.
Prenatal pressures achieved after the three highest histamine doses (i.e., the histamine pressure floor) were the same in newborn and adult animals (fig. 4B). Histamine produced no significant changes in heart rate in either age group.

During an observation period of 45 min, histidine, 0.1 to 100 mg/kg, had no significant effect on arterial pressure or heart rate in the newborn (5 experiments) or adult animal (6 experiments).

**5-Hydroxytryptamine and tryptophan.** The effect of 5-hydroxytryptamine, 1 to 1000 µg/kg, on pressure was variable in both newborn (5 experiments) and adult dogs (5 experiments). The most consistent response in the newborn was a rise in mean arterial pressure; in about 30% of the animals, this pressor response was followed by a depressor effect. The majority of adult dogs showed an initial fall in blood pressure followed by a pressor response. The extent of the pressor and depressor effects was similar in both age groups. 5-Hydroxytryptamine (30-1000 µg/kg) produced only tachycardia in the majority of adult dogs. In two adults a biphasic response was seen. The effect of 5-hydroxytryptamine on heart rate in newborns was extremely variable. One animal responded with bradycardia, two had bradycardia at low doses and tachycardia at high doses, and others responded with only tachycardia.

One and 3 mg/kg of tryptophan had no effect on arterial pressure, but 10 and 30 mg/kg produced comparable percent reductions in mean arterial pressure within 5 min after injection in newborns (5 experiments) and adults (5 experiments). Heart rate was unaffected by tryptophan.

**Discussion.** The observation in this study that mean arterial blood pressure was significantly lower in the newborn than in the adult animal is in accordance with the observations of others in the dog (Boatman and Brody, 1967), the cat (Hutchinson et al., 1962), the rabbit (Dawes et al., 1957), the pig (LeBlanc and Mount, 1968) and in man (Young, 1961). Mean arterial pressure increases with increasing age in all of these species. Because of the different basal arterial pressures in newborn and adult dogs, we compared the blood pressure responses as percent change. In their study on the relative sensitivity of fetal, newborn and adult rabbits to catecholamines, Dawes et al. (1957) have also used percent change as their criterion for comparison. They contended that since the basal blood pressure is lower in the newborn than the adult and since the rate of blood flow is of paramount physiologic importance, proportional changes in pressure are more significant than absolute changes.

The i.v. injection of NE and its precursors produced increases in mean arterial pressure in the newborn dog which were proportionately the same as those observed in the adult. This suggests that in the dog the neonatal and adult cardiovascular systems are equally sensitive to the pressor effects of catecholamines and corroborates the observations of Dawes et al.
Young (1952) long in the newborn than in the adult. Boat-similarity in the degree of the pressor response in the mother with responses to single i.v. technique employed. Dornhorst and Young these investigators because of the differences in technique employed. Dornhorst and Young (1952) compared responses to infusions of NE in the mother with responses to single i.v. injections in the fetus, and Boatman et al. (1965) compared newborn and adult hindlimb responses to i.a. injections of NE. Despite the similarity in the degree of the pressor response to NE at the two ages, we observed that the duration of the pressor response to NE was longer in the newborn than in the adult. Boatman et al. (1965) have made similar observations in newborn puppies. There are several possible explanations for the prolonged pressor responses to NE in the newborn. It may be that in the newborn there is a slower reuptake of NE (Glowinski et al., 1964) or that the rate of metabolism of NE is slower than in the adult.

The effects of NE on heart rate in the vagotomized newborn puppy were generally indistinguishable from those in the adult. This suggests that the cardiac beta adrenergic receptor mechanisms in the newborn are similar to those in the adult. Indeed, there is evidence from studies in the chick embryo to indicate that the beta adrenergic receptor sites in the heart are fully functional even before the establishment of an extrinsic nerve supply (Barry, 1950; Fingl et al., 1952; McCarty et al., 1960).

Since differences may exist in drug transport mechanisms and the activity of enzymes between newborn and adult animals, it is of interest that the potency ratios of NE/dopamine/dopa, as reflected by changes in heart rate and arterial pressure, were the same for both newborns and adults. Similarly the time course of the pressor and chronotropic responses to dopamine and dopa were similar in both age groups.

Our finding that the pressor and chronotropic responses to tyramine were comparable in the two age groups indicates that the 1- to 2-week-old puppy is as capable of releasing catecholamines from nerve endings as the adult animal. Furthermore, these observations suggest that the adrenergic sympathetic fibers innervating the heart and blood vessels are functional in the 1- to 2-week-old dog. This is of interest in view of studies by Boatman et al. (1965). These investigators have observed that some adrenergic vasomotor fibers are not functional in the dog for several weeks after birth. These same investigators have also observed that the positive chronotropic response to direct cardiac sympathetic nerve stimulation was present at birth in dogs (Boatman and Brody, 1967).

A critical comparison of the depressor effects of histamine in puppies and adult dogs is difficult because the former have a low basal arterial pressure. A depressor response was elicited in both age groups, which suggests that the cardiovascular systems of both the newborn and the adult react in a similar fashion to this amine.

Conclusion. These data indicate that the alpha adrenergic receptor system in blood vessels and the beta adrenergic receptor system in the heart of the 1-week-old dog are indistinguishable from those of the adult. Identical potency ratios for NE/dopamine/dopa in the newborn and adult provide indirect evidence that the enzyme systems and transport mechanisms for handling NE and its precursors are well developed in the young animal. In addition, the newborn dog is as able as the adult to release catecholamines from nerve terminals in response to the indirectly acting amine, tyramine. Finally, although information gained from animal studies is difficult to translate to the human, these studies suggest that the cardiovascular effects of the biogenic amines in the newborn infant would be the same as in the adult.

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References


