Epinephrine and organ blood flow: effects of hyperthyroidism, cocaine, and denervation

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WURTMAN, RICHARD J., IRWIN J. KOPIN, DALE HORST, AND JOSEF E. FISCHER. *Epinephrine and organ blood flow: effects of hyperthyroidism, cocaine, and denervation.* Am. J. Physiol. 207(6): 1247–1250. 1964.—The intravenous administration of 1 μg *l*-epinephrine increases the fraction of the cardiac output, measured by K^{42} uptake, which is delivered to the rat heart. This effect of the catecholamine is potentiated in hyperthyroidism or by a single injection of cocaine. One microgram of epinephrine causes no change in the fractional perfusion of the innervated rat salivary gland, but produces a marked decrease following chronic sympathetic denervation. Processes which interfere locally with the inactivation of circulating epinephrine by binding in sympathetic nerve endings thus potentiate its effects on regional perfusion.

regional blood flow   sympathetic denervation
epinephrine and regional perfusion   cardiac blood flow
supersensitivity to catecholamines   measurement of organ
perfusion   inactivation of epinephrine

THE FRACTION OF THE CARDIAC OUTPUT which perfuses an organ is not proportional to its weight and is not constant. Organs such as heart and kidney receive a considerably greater fraction of the cardiac output per unit weight of tissue than skeletal muscle or testis (7, 13); changes in the physiologic state can alter the relative blood flow to each of these organs. Differences among the percentages of the cardiac output delivered to various organs, and even relatively small changes in the fractional perfusion of a particular organ, may be of great importance in determining how much of at least two types of circulating substances are made available to the organ. These are: *1*) compounds with a very rapid circulatory half-life, such as the catecholamines (17), and *2*) substances which are very effectively cleared from the circulation by the particular organ under study.

Regional blood flow is an inverse function of local vascular resistance; this may be modified by neural, local, and humoral factors (2, 3, 5, 12). Although epinephrine, administered intravenously, may not have a pronounced net effect on the total vascular resistance of the whole body, this hormone markedly alters arteriolar tone in many organs, elevating the resistance in some vascular beds and lowering it in others (10). It has been found that small doses of epinephrine produce marked and rapid alterations in the distribution of the cardiac output. Circulating catecholamines are rapidly inactivated, largely by enzymatic destruction (1) or by being taken up and bound in sympathetic nerve endings in tissue (16). Processes which interfere with the local inactivation of epinephrine have been found to potentiate its effects on regional perfusion.

MATERIALS AND METHODS

Unanesthetized male Sprague-Dawley rats weighing 200–250 g were placed in small restraining cages and given multiple injections into a tail-vein cannula. Animals first received 0.1 ml normal saline containing 1 μg *l*-epinephrine or only the diluent; this was washed in with 0.4 ml saline. Fifteen seconds later the rats were given 0.2 ml normal saline containing 5 mEq $K^{42}Cl$ (Brookhaven National Laboratories) per liter, washed in with 0.4 ml saline. The K^{42} was of sufficient specific activity so that the dose given contained 300,000–600,000 count/min when counted in a gamma well-scintillation counter. Fifteen seconds after receiving the K^{42}, animals were killed by a blow on the head; this was followed immediately by transection with a guillotine across the aortic arch. The organs to be assayed were dissected free of fat and connective tissue, blotted, and weighed, and K^{42} content was determined in a well counter. A correction was made for K^{42} decay by counting 1 % of the injected dose at frequent intervals, and expressing tissue K^{42} as percent of administered dose. It was demonstrated that for both organs studied, heart and submaxillary gland, Sapirstein's criteria (13) for applicability of the K^{42} method for blood flow measurements were satisfied: i.e., for the 1st min after injection, their

K^{42} content remained relatively stable, indicating that their extraction ratios for potassium were about the same as that of the body in general.

Thirty-two rats were made hyperthyroid by the daily intraperitoneal administration of 0.2 ml 0.01 N NaOH solution containing 100 μg Na-l-thyroxine, for 6 days. It has been shown that animals treated in this manner are hyperresponsive to the hypertensive effects of small doses (0.4 μg) of l-epinephrine (17). An equal number of rats, given only the thyroxine vehicle, served as controls. Groups of eight hyperthyroid and eight control rats each received 0, 10, 100, or 1,000 ng l-epinephrine, followed by K^{42}, as described above. L-Epinephrine was dissolved in 0.01 N HCl.

The right superior cervical ganglion was removed from 12 rats; the other ganglion was exposed but not destroyed. All the animals developed the anticipated unilateral ptosis. One week after surgery the K^{42} uptakes of the innervated and denervated submaxillary glands were determined in six animals which had received 1 μg l-epinephrine 15 sec earlier, and in six rats which had received no catecholamine. The innervated left gland served as the control for the denervated organ.

Ten rats were injected with 10 mg/kg cocaine intraperitoneally; an equal number of control animals received the diluent. Ten minutes later, half of each group of rats received 1 μg l-epinephrine intravenously, and 15 sec later, K^{42} was injected and labeled potassium present in the heart was determined as described above.

RESULTS

Potentiation of effect of epinephrine on cardiac fractional blood flow in hyperthyroidism. The percent of the cardiac output (taken as percent of the administered K^{42}) delivered to hyperthyroid and control hearts was increased by the larger doses of l-epinephrine given (Fig. 1). Hearts of control rats which had been given no catecholamine received 1.55 % of the cardiac output; hyper-
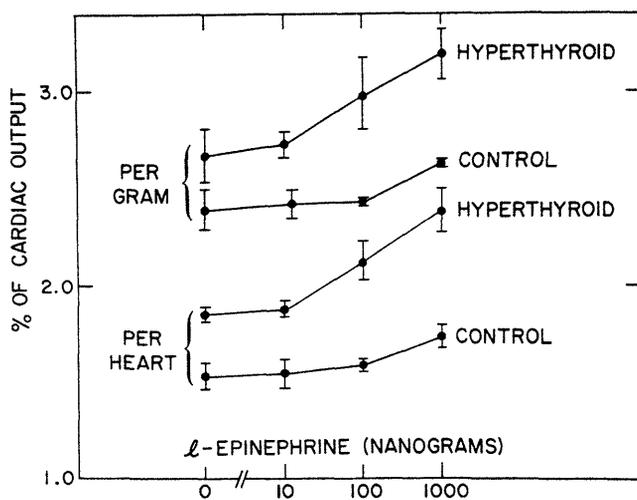

FIG. 1. Effect of varying doses of l-epinephrine on percent of the cardiac output (percent of administered K^{42}) delivered to the normal and hyperthyroid heart. Data are presented as mean ± SE.

thyroid hearts received significantly more (1.88 %, $P <$ 0.01), in confirmation of findings noted earlier (17). These figures are somewhat lower than those reported previously, probably because the animals used here weighed more, and had lower heart weight-to-body weight ratios. When less than 1,000 ng l-epinephrine were administered to control rats, there was no change in the cardiac uptake of K^{42}; hyperthyroid rats, however, showed a greater and significant rise ($P < 0.05$) after one-tenth this dose of catecholamine (Fig. 1).

Hyperthyroidism induces a significant increase in heart weight, and an even greater increase in the ratio of heart-to-body weight in the rat (17). Since blood flow may be related to organ weight, the above dose-response curves were also plotted on the basis of percent of cardiac output delivered to each gram of heart (Fig. 1). Again, hyperthyroid hearts both received more of the cardiac output per gram than control hearts, and showed a steeper dose-response curve to the effects of l-epinephrine.

Potentiation of effect of epinephrine on cardiac fractional blood flow following cocaine administration. The administration of 1 μg l-epinephrine to control rats produced a 45 % increase in cardiac fractional perfusion (Table 1). When rats were pretreated with cocaine (10 mg/kg), the same dose of epinephrine produced a 73 % increment in cardiac K^{42} uptake. Cocaine treatment alone did not produce a significant elevation in cardiac K^{42}. The combined effect of cocaine and epinephrine on cardiac fractional perfusion was significantly greater than the sum of their individual effects, indicating that cocaine pretreatment resulted in a potentiation of this response to injected catecholamine.

Potentiation by sympathetic denervation of effect of epinephrine in decreasing blood flow to submaxillary gland. There was a considerable variation in the weights of the two submaxillary glands from a given animal; this variation was not correlated with the surgical procedure, since the mean weights of right- and left-sided glands were similar. It was thus necessary to express all data on a per-weight basis. Neither sympathetic denervation of the submaxillary gland nor the administration of 1 μg l-epinephrine altered the fraction of the cardiac output delivered to a unit weight of tissue (Table 2). However, denervation followed by epinephrine administration resulted in a significant decrease ($P < 0.05$) in the K^{42} uptake of the salivary gland. Differences in the K^{42} contents of innervated and denervated glands most likely represented actual changes in the rate of blood flow, and not only fractional perfusion, since the cardiac output was, of course, identical for both sides.

DISCUSSION

These data demonstrate that a small dose (1 μg) of l-epinephrine increases the fraction of the cardiac output delivered to the heart of the intact, unanesthetized rat. This effect is magnified when animals are pretreated chronically with thyroxine or acutely with cocaine. The intravenous administration of 1 μg l-epinephrine

TABLE 1. *Effects of cocaine and epinephrine on cardiac fractional perfusion*

Treatment	No Cocaine	Cocaine
None	1.98 ± 0.06	2.15 ± 0.07
Epinephrine	$2.89 \pm 0.10^*$	$3.44 \pm 0.10\dagger$
Increase	0.91 ± 0.07	$1.29 \pm 0.08\ddagger$

Animals received cocaine (10 mg/kg) 10 min before receiving the K^{42}, or *l*-epinephrine (1 μg) 15 sec before the K^{42}. Data are expressed as percent of administered K^{42} taken up per heart $\pm$ SEM. * Differs from no epinephrine, $P < 0.001$. † Differs from no epinephrine, $P < 0.001$; differs from no cocaine $P < 0.01$. ‡ Effect of epinephrine enhanced following cocaine, $P < 0.01$.

TABLE 2. *Effects of epinephrine and sympathetic denervation on submaxillary gland fractional perfusion*

Treatment	Innervated	Denervated
None	1.11 ± 0.23	1.15 ± 0.22
Epinephrine	1.01 ± 0.19	$0.58 \pm 0.08^*$

Animals were given *l*-epinephrine (1 μg) intravenously 15 sec before receiving K^{42}. Data are expressed as percent of administered K^{42} taken up per gram of tissue $\pm$ SEM. *Differs from untreated or denervated, $P < 0.05$.

does not alter the fractional blood flow of the normal rat submaxillary gland, but does markedly decrease the delivery of circulating blood to the sympathetically denervated gland.

The effects of *l*-epinephrine on fractional cardiac blood flow are the result of alterations produced by the catecholamine in the relative vascular resistances of the coronary arteries and the remainder of the systemic circulation.

The proportion of the cardiac output delivered to the heart is increased in the hyperthyroid rat (Fig. 1); this increase is at least as great as the accompanying increase in the weight of the heart (17). It has been amply demonstrated that some hemodynamic (4) and metabolic (14, 15) responses to administered *l*-epinephrine are magnified following thyroxine treatment. When rats were made hyperthyroid by the methods used here, their hypertensive response to *l*-epinephrine was potentiated (17). This "supersensitivity" was attributed to: *1)* an increase in the fraction of an injected dose of epinephrine which is delivered to the heart of the hyperthyroid rat (17, Table 1; this report, Fig. 1); and *2)* a decrease in the efficiency with which the "free" circulating catecholamine was inactivated locally by binding. Hyperthyroid hearts were considerably heavier, both absolutely and per body weight, than those of control animals. This increase in weight represented parenchymal hypertrophy, and would be expected to cause a relative decrease in the number of sympathetic nerve endings—the site of catecholamine binding—within

the heart (8, 16). It is possible that a similar mechanism operates to produce the vascular supersensitivity to epinephrine noted here, i.e., the diminished capacity of the hyperthyroid heart to inactivate the epinephrine delivered to it causes more free catecholamine to be available to act on the coronary arterial bed.

The half-life of circulating epinephrine is very short (1); it is very efficiently cleared from the circulation by many organs, including the heart (6). Hence the fraction of an injected dose of epinephrine which is delivered to and taken up by a particular organ is a function of the percent of the cardiac output delivered to that organ (11). Since epinephrine causes an increase in the fractional perfusion of the heart, it appears that circulating epinephrine alters the distribution of the cardiac output in such a way as to enhance its own delivery to and net uptake by the heart. Hyperthyroidism would be expected to potentiate the effect of epinephrine on any organ whose arterial bed the catecholamine dilates, and decrease the response of organs whose vessels it constricts, provided that the ability of the organ to inactivate epinephrine was diminished.

Previous studies have shown that cocaine treatment markedly decreases the fraction of administered H^3-catecholamine which is taken up and bound by the sympathetic nerves of the heart (9). This interference with catecholamine inactivation could explain the potentiation of the effect of epinephrine on cardiac vascular resistance described here. Cocainization actually results in an increase in the fraction of an injected dose of epinephrine which is delivered to the heart (Table 1). Hence the blockade by cocaine of cardiac uptake of H^3-epinephrine is not the consequence of alterations in regional blood flow.

Unilateral sympathetic denervation of the submaxillary gland results in a marked enhancement in the sensitivity of its vascular resistance to circulating epinephrine. The fraction of the cardiac output delivered to the contralateral salivary gland is not changed (Table 2). Since the cardiac output is the same for both glands (as well as for all the organs in the body), it follows that denervation followed by epinephrine administration results in a relative decrease in blood flow (i.e., the product of K^{42} uptake and cardiac output), and not just fractional perfusion.

All three of the processes described here which enhance the effect of epinephrine on regional perfusion share the ability to interfere with its local inactivation by binding in sympathetic nerve endings: sympathetic denervation destroys the major anatomic binding site for catecholamines in heart and salivary gland; cocaine blocks the uptake of epinephrine into the sympathetic nerve ending, and hyperthyroidism very likely causes a dilution of binding elements within the rat heart as a consequence of cardiac hypertrophy.

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