Effect of Certain Drugs on Perfused Human Placenta IV

Detection of Specific Receptor Sites

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The effects of three adrenergic blocking agents (phentolamine, tolazoline, and hydralazine) on the action of epinephrine, norepinephrine, *l*-epinephrine, histamine, and 5-hydroxytryptamine in placental vessels were investigated. The results indicated that phentolamine not only diminished and/or blocked the vasoconstricting action of epinephrine, norepinephrine, and histamine but also caused a reversal of their effects. However, phentolamine could only diminish the vasopressor action of 5-hydroxytryptamine. From the results obtained in this investigation, it appears that the placental vessels have both *alpha* and *beta* receptors.

THE HUMAN BODY is composed of numerous organs consisting of various types of tissues which manufacture chemicals to perform specific functions. Whenever certain organs exhibit a variance in the amount of chemical substances normally produced, the homeostatic processes of the body controlled by these chemicals will usually be altered. However, when the same condition occurs in the pregnant state, not only normal body functions will be altered but also possibly fetal nourishment and development. Therefore, since it has been shown that 5-hydroxytryptamine (serotonin) (1), sympathomimetics, and histamine (2) constrict placental vessels directly and also that the placental barrier is permeable to substances below a molecular weight of 1000 (3), allowing their passage from maternal to fetal circulation, any condition which actually causes an increased level of these normal body chemicals could, *via* placental transfer, ultimately lead to teratogenic effects (4), decreased fetal oxygenation (1, 2), and even fetal death (5, 6).

Many drugs other than natural body chemicals have been shown to affect the placental vasculature. Such drugs include the narcotic analgesics, which cause constriction (morphine, meperidine, and codeine) (1) and certain vasodilators (isosorbide dinitrate, isoproterenol hydrochloride, nitroglycerin, and papaverine) (7). Because some of these agents cross the placental barrier (8, 9) and have been shown in isolated placental preparations to affect directly the placental vasculature (1, 2, 7), it is possible that when such drugs are administered to pregnant women they may disturb the homeostatic conditions of the placenta and exert serious effects on the fetus. Consequently, it is imperative to determine the action of all drugs on placental vasculature.

During the past 45 years, many perfusion experiments have been performed to test the effects of various neurohormones [epinephrine, norepinephrine, *l*-epinephrine, 5-hydroxytryptamine (serotonin)] and histamine on the placental vasculature (1, 2, 7, 10–13). It has been generally shown from these placental perfusion experiments that 5-hydroxytryptamine and histamine cause pronounced vasoconstriction, whereas the catecholamines (epinephrine, norepinephrine, and *l*-epinephrine) produce relatively slight vasoconstriction on isolated placental vasculature.

Recently, Astrom and Samelius (12) demonstrated that the vasoconstricting action of 5-hydroxytryptamine (serotonin) and adrenaline on the placental vasculature was blocked by the adrenergic blocking agent phentolamine (Regitine). This laboratory performed preliminary experiments to confirm these results. It was established that phentolamine not only blocked the action of epinephrine but also caused a reversal of its action on the placental vasculature. However, phentolamine only caused a slight diminution of the effects of 5-hydroxytryptamine.

The dual effect of epinephrine (vasoconstriction and vasodilatation) on the nerve-free placental vessels has raised the question of just how the catecholamines act. Is it possible to credit their action to the activation of specific receptor sites, to direct musculotropic action, or to endogenous release of the normal mediators? Therefore, the purpose of this investigation was to discern the effects of certain adrenergic blocking agents on the action of various catecholamines and attempt

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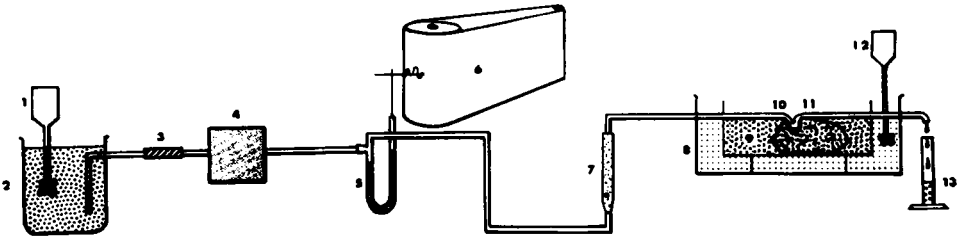

Fig. 1.—Schematic diagram of the apparatus for perfusion of placental vasculature. Key: 1, Bronwill thermoregulator; 2, reservoir, perfusion fluid (Tyrode's with P.V.P.); 3, rubber tubing (injection site); 4, Sigmamotor pump (model TS-8); 5, mercury manometer; 6, Livingston variable-speed kymograph; 7, RGI flowmeter; 8, outer Plexiglas chamber (water jacket); 9, inner Plexiglas chamber (perfusion chamber); 10, arterial cannula; 11, venous cannula; 12, Bronwill thermoregulator; 13, 100-ml. graduated cylinder.

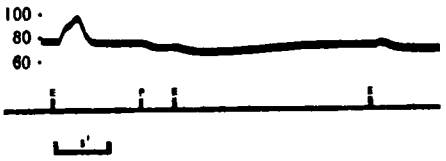

Fig. 2.—Effect of phentolamine on the action of epinephrine hydrochloride in placental vasculature. Key: E, 20 mcg. epinephrine hydrochloride; P, 3 mg. phentolamine methanesulfonate.

to identify the specific mechanism of action whereby these agents affect the placental vasculature.

MATERIALS AND METHODS

The full-term human placentas utilized in this experiment were obtained from the delivery room of the hospital 5–15 minutes after normal delivery. A glass container of Tyrode's solution heated to 38° was employed to transport the placental preparations.

The procedures concerned with the manipulation and preparation of the placentas for perfusion were described in a previous paper (2). A schematic diagram of the apparatus is shown in Fig. 1. Umbilical cords of placentas measuring more than 5.5 cm. in length were designated as long cords; those under 5.5 cm. were designated as short cords.

The placental outflow was measured directly at the onset of the perfusion by means of a 100-ml. graduated cylinder and never reperfused. If the volume of inflow greatly exceeded the volume of outflow or if the perfusion pressure could not be maintained at a constant level, the placenta was discarded. During this study, 51 placental preparations were utilized on which 132 successful experiments were performed.

The following drugs were injected into the arterial side of the perfusion in a volume of distilled water not exceeding 1.5 ml.: epinephrine hydrochloride, 0.1%; *l*-epinephrine bitartrate,[1] 0.1%; *l*-norepinephrine bitartrate (Levophed), 0.2% (0.1% as base); histamine acid phosphate, 0.055% (0.02% as base); 5-hydroxytryptamine creatinine sulfate (serotonin), 0.01%; phentolamine methanesulfonate (Regitine),[2] 0.2%; tolazoline hydrochloride (Priscoline), 2.5%; and hydralazine hydrochloride (Apresoline),[2] 0.4%.

[1] Supplied through the courtesy of Sterling-Winthrop Research Institute, Rensselaer, N. Y.

[2] Supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J.

RESULTS

The following results were obtained on full-term human placental vasculature perfused at the pressure range of 50–90 mm. Hg. This range of perfusion pressure (50–90 mm. Hg) corresponds to 30–70 ml. of perfusion fluid inflow per minute.

Effects of Phentolamine on the Action of Certain Amines in the Placental Vasculature

Epinephrine.—Table I shows that prior to the administration of 3 mg. of the adrenergic blocking agent, phentolamine, 20 mcg. of epinephrine exhibited a moderate vasoconstriction in placentas with both short and long cords. However, the vasoconstrictor action of epinephrine in the placentas with long cords seemed to be more pronounced than in those with short cords.

When 20 mcg. of epinephrine was given subsequent to the administration of phentolamine, not only was the vasoconstrictor response blocked but vasodilatation (reversal) effect of epinephrine also became apparent (Fig. 2). This reversal effect of epinephrine appeared to be similar in placentas with short and/or long cords. A subsequent injection of epinephrine 15–20 minutes later produced a normal response. In one experiment, the placental vasculature did not exhibit a response to the action of epinephrine.

Norepinephrine.—Prior to the administration of phentolamine, 40 mcg. of norepinephrine exhibited a moderate vasoconstriction in the placental vasculature, irrespective of cord length (Table I). Also, when norepinephrine was administered approximately 3 minutes subsequent to the administration of phentolamine, a reversal of its normal vasoconstrictor response occurred (Fig. 3). When 40 mcg. of norepinephrine was administered 15–20 minutes subsequent to the administration of phentolamine, its normal vasoconstrictor response appeared again.

l-Epinephrine.—Table I shows that when 20 mcg. of *l*-epinephrine was perfused through the placental vascular system before the administration of 3 mg. of phentolamine, moderate vasoconstriction occurred in the placentas with short umbilical cords. However, in one experiment in which a long-cord placenta was utilized, the vasoconstricting effect of *l*-epinephrine appeared to be more pronounced than its vasoconstricting action on short-cord placentas.

When *l*-epinephrine was perfused through the placental vasculature following the administration of phentolamine, both vasoconstriction and vasodilatation occurred. However, the vasoconstrictor effect

TABLE I.—EFFECTS OF PHENTOLAMINE ON THE ACTION OF CERTAIN AMINES IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg: Increase	Av. Change	No. Expt.	Decrease	Av. Change	No. Expt.
Before Phentolamine							
Epinephrine, 20	S	+1.9 to +5.4	+3.3	3	...	...	..
mcg.	L	+1.2 to +19.6	+7.8	5	...	...	..
After Phentolamine							
Epinephrine, 20	S	+1.8	+1.8	1	−2.2 to −7.6	−4.5	4
mcg.	L	...	...	..	0.0 to −5.0	−2.3	6
Before Phentolamine							
Norepinephrine,	S	+11.2	+11.2	1	...	...	..
40 mcg.	L	+2.0 to +7.4	+4.3	4	...	...	..
After Phentolamine							
Norepinephrine,	S	...	...	..	−2.6 to −4.0	−3.3	3
40 mcg.	L	...	...	..	−2.8 to −6.4	−3.9	7
Before Phentolamine							
l-Epinephrine,	S	+3.4 to +22.0	+10.4	4	...	...	..
20 mcg.	L	+60.0	+60.0	1	...	...	..
After Phentolamine							
l-Epinephrine,	S	+0.8 to +1.0	+0.9	2	−2.0 to −6.0	−4.0	2
20 mcg.	L	...	...	..	−3.6	−3.6	1
Before Phentolamine							
Histamine, 20 mcg.	S	+2.0 to +64.0	+12.5	11	...	...	..
	L	+1.8 to +136.0	+41.9	16	...	...	..
After Phentolamine							
Histamine, 20 mcg.	S	+3.2 to +5.2	+4.7	9	−2.4 to −2.8	−2.6	2
	L	+1.0 to +110.0	+34.4	11	−1.6 to −4.0	−2.6	5
Before Phentolamine							
Serotonin, 50 mcg.	S	+4.0 to +108.0	+35.0	16	...	...	..
	L	+43.0 to +145.2	+83.2	15	...	...	..
After Phentolamine							
Serotonin, 50 mcg.	S	+1.4 to +93.4	+25.5	16	...	...	..
	L	+10.0 to +164.6	+62.2	15	...	...	..

[a] S, small cord; L, long cord.

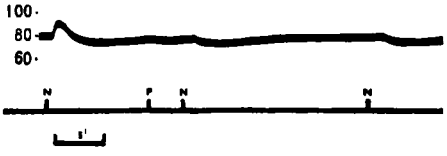

Fig. 3.—Effect of phentolamine on the action of norepinephrine bitartrate in placental vasculature. Key: N, 40 mcg. norepinephrine bitartrate; P, 3 mg. phentolamine methanesulfonate.

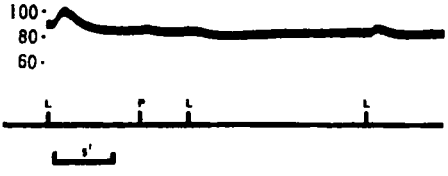

Fig. 4.—Effect of phentolamine on the action of *l*-epinephrine bitartrate in placental vasculature. Key: L, 20 mcg. *l*-epinephrine bitartrate; P, 3 mg. phentolamine methanesulfonate.

Fig. 5.—Effect of phentolamine on the action of histamine acid phosphate in placental vasculature. Key: H, 20 mcg. histamine acid phosphate; P, 3 mg. phentolamine methanesulfonate.

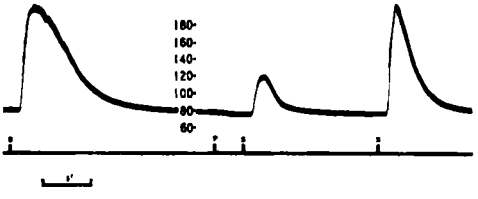

Fig. 6.—Effect of phentolamine on the action of serotonin in placental vasculature. Key: S, 50 mcg. serotonin; P, 3 mg. phentolamine methanesulfonate.

occurring after phentolamine was markedly reduced compared to the vasoconstriction produced originally. The vasodilatation or reversal effect occurring after phentolamine administration was approximately the same in placentas with short or long cords (Fig. 4).

Histamine.—When histamine (20 mcg.) was perfused through the placental vasculature, it exhibited a vasoconstrictor action greater than epinephrine, norepinephrine, or *l*-epinephrine, irrespective of cord length. Table I shows that when histamine was given prior to the administration of phentolamine, its vasconstrictor action generally appeared to be more pronounced in the placentas with long cords than in those with short cords.

When 20 mcg. of histamine was perfused through

TABLE II.—EFFECTS OF TOLAZOLINE ON THE ACTION OF CERTAIN AMINES IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg: Increase	Av. Change	No. Expt.	Decrease	Av. Change	No. Expt.
Before Tolazoline							
Epinephrine, 20 mcg.	S	+3.0 to +36.0	+15.7	3	...	...	..
After Tolazoline							
Epinephrine, 20 mcg.	S	+1.0 to +4.4	+2.8	3	...	...	..
Before Tolazoline							
Norepinephrine, 40 mcg.	S	+1.6 to +4.0	+2.5	3	...	...	..
After Tolazoline							
Norepinephrine, 40 mcg.	S	0.0 to +1.0	+0.5	2	...	...	..
	L	...	...		−7.0	−7.0	1
Before Tolazoline							
l-Epinephrine, 20 mcg.	S	+2.8 to +5.0	+3.9	3	...	...	..
After Tolazoline							
l-Epinephrine, 20 mcg.	S	+2.0 to +2.4	+2.1	3	...	...	..
Before Tolazoline							
Histamine, 20 mcg.	S	+4.6 to +52.0	+13.1	9	...	...	..
After Tolazoline							
Histamine, 20 mcg.	S	+2.8 to +15.0	+10.2	8	−3.0	−3.0	1
Before Tolazoline							
Serotonin, 50 mcg.	S	+26.0 to +88.0	+53.3	9	...	...	..
After Tolazoline							
Serotonin, 50 mcg.	S	+24.0 to +100.2	+57.6	9	...	...	..

[a] S, Small cord; L, long cord.

TABLE III.—EFFECTS OF HYDRALAZINE ON THE ACTION OF CERTAIN AMINES IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg[b]: Increase	Av. Change	No. Expt.	Decrease	Av. Change	No. Expt.
Before Hydralazine							
Epinephrine, 20 mcg.	S	+2.8 to +3.4	+3.1	2	...	...	..
	L	+20.0	+20.0	1	...	...	..
After Hydralazine							
Epinephrine, 20 mcg.	S	+3.0 to +3.6	+3.2	2	...	...	..
	L	+31.6	+31.6	1	...	...	..
Before Hydralazine							
Norepinephrine, 40 mcg.	S	+4.0 to +12.0	+6.3	3	...	...	..
After Hydralazine							
Norepinephrine, 40 mcg.	S	+3.4 to +11.4	+4.4	3	...	...	..
Before Hydralazine							
l-Epinephrine, 20 mcg.	S	+2.8	+2.8	1	...	...	..
	L	+2.0 to +4.0	+3.0	2	...	...	..
After Hydralazine							
l-Epinephrine, 20 mcg.	S	+2.8	+2.8	1	...	...	..
	L	+2.6 to +5.0	+3.5	2	...	...	..
Before Hydralazine							
Histamine, 20 mcg.	S	+3.4 to +101.0	+52.2	2	...	...	..
	L	+40.0	+40.0	2	...	...	..
After Hydralazine							
Histamine, 20 mcg.	S	+3.4 to +110.0	+56.7	2	...	...	..
	L	+20.0 to +30.0	+25.0	2	...	...	..
Before Hydralazine							
Serotonin, 50 mcg.	S	+24.0 to +118.0	+48.0	6	...	...	..
	L	+15.6 to +56.0	+40.4	3	...	...	..
After Hydralazine							
Serotonin, 50 mcg.	S	+12.0 to +109.0	+38.8	6	...	...	..
	L	+20.0 to +60.4	+40.2	2	...	...	..

[a] S, Small cord; L, long cord. [b] No decrease or average change in any of the experiments.

the placental vasculature subsequent to 3 mg. of phentolamine, its vasoconstrictor action was not only markedly diminished (Fig. 5), but also a reversal of its normal pressor action occurred in some experiments (Table I).

5-Hydroxytryptamine (Serotonin).—Of all of the agents used in this experiment, 5-hydroxytryptamine (serotonin) had the greatest vasoconstricting effect on the placental vasculature. Table I shows that the effect of 50 mcg. of 5-hydroxytryptamine on perfused placental vasculature before the administration of phentolamine on the average was greater than the vasoconstricting action exerted when it was administered after phentolamine. However, the vasoconstrictor action of 5-hydroxytryptamine was never completely blocked or reversed (Fig. 6).

TABLE IV.—COMPOSITE RESULTS OF COMPARATIVE ANTAGONISTIC ACTION OF PHENTOLAMINE, TOLAZOLINE, AND HYDRALAZINE ON THE ACTION OF CERTAIN AMINES IN THE PLACENTAL VASCULATURE

Drug	Dose, mcg.	Expt., No.	Degree of Antagonism			
			None	Partial	Complete	Reversal
Phentolamine						
Epinephrine	20	11	..	1	1	9
Norepinephrine	40	10	..	..	..	10
l-Epinephrine	20	5	..	2	..	3
Histamine	20	27	7	12	1	7
Serotonin	50	31	4	27	..	..
Tolazoline						
Epinephrine	20	3	..	3	..	..
Norepinephrine	40	3	..	1	1	1
l-Epinephrine	20	3	..	3	..	..
Histamine	20	9	5	3	..	1
Serotonin	50	9	6	3	..	..
Hydralazine						
Epinephrine	20	3	2	1	..	..
Norepinephrine	40	3	2	1	..	..
l-Epinephrine	20	3	3	..	..	..
Histamine	20	4	1	3	..	..
Serotonin	50	8	3	5	..	..

Effects of Tolazoline on the Action of Certain Amines in the Placental Vasculature

Epinephrine.—As shown in Table II, the vasoconstrictor effect of 20 mcg. of epinephrine in the perfused placental vasculature exhibited the same moderate vasoconstriction obtained under *Effects of Phentolamine*. However, following the perfusion of 5 mg. of tolazoline, 20 mcg. of epinephrine produced a vasoconstrictor response which was greatly diminished compared to the response obtained prior to the administration of tolazoline. It was also observed that tolazoline did not cause reversal of epinephrine effects on the placental vasculature (Table IV).

Norepinephrine.—Norepinephrine (40 mcg.) administered to the perfused placental vasculature prior to the administration of tolazoline exhibited a slight vasoconstrictor response. This vasoconstrictor effect of norepinephrine, in this part of the investigation was not so pronounced as its vasoconstricting effect produced under *Effects of Phentolamine*. When norepinephrine was administered subsequent to the administration of 5 mg. of tolazoline, its vasoconstrictor action was diminished; in one case, a reversal of its action occurred (Table IV).

l-Epinephrine.—*l*-Epinephrine (20 mcg.), perfused through the placental vasculature prior to the administration of tolazoline, exhibited a vasoconstrictor response comparable to that elicited by norepinephrine. When 20 mcg. of *l*-epinephrine was administered subsequent to the administration of 5 mg. of tolazoline, its vasoconstricting response was slightly reduced (Table II).

Histamine.—Histamine (20 mcg.), administered prior to tolazoline, exhibited a marked vasoconstrictor effect on the placental vasculature (Table II). However, this marked vasoconstrictor effect of histamine was slightly diminished when it was given subsequent to the 5 mg. of tolazoline. In only one experiment did a reversal of histamine's action occur—when it was administered subsequent to 5 mg. of tolazoline (Table IV).

5-Hydroxytryptamine (Serotonin).—Table II shows that 5-hydroxytryptamine again exhibited the greatest vasoconstrictor effect on the placental vasculature. When 5-hydroxytryptamine was perfused through the placental vasculature subsequent to 5 mg. of tolazoline, the vasoconstricting response of 5-hydroxytryptamine was, on the average, just slightly increased. At no time was there a reversal of 5-hydroxytryptamine's pressor action (Table IV).

Effects of Hydralazine on the Action of Certain Amines in the Placental Vasculature

Epinephrine.—The perfusion of 20 mcg. of epinephrine through the placental vasculature (Table III) prior to the administration of 4 mg. of hydralazine elicited a vasoconstrictor response comparable to that observed previously for epinephrine under *Effects of Phentolamine* and *Effects of Tolazoline*. Hydralazine did not appear to affect the vasoconstrictor action of epinephrine in short-cord placentas. However, in one experiment utilizing a placenta with a long cord, hydralazine actually caused an increase in the constrictor action of epinephrine (Table III).

Norepinephrine.—When 40 mcg. of norepinephrine was administered prior to the administration of 4 mg. of hydralazine, it produced moderate vasoconstriction on the placental vasculature (Table III). However, when 40 mcg. of norepinephrine was given subsequent to the administration of 4 mg. of hydralazine, there was a slight diminution in its vasoconstrictor action. No reversal of norepinephrine effects was observed with hydralazine (Table IV).

l-Epinephrine.—*l*-Epinephrine (20 mcg.) produced slight vasoconstriction in the placental vasculature when it was given prior to the administration of 4 mg. of hydralazine. This vasoconstrictor action of *l*-epinephrine was not altered to a significant degree by 4 mg. of hydralazine. It was also observed that no reversal response occurred with *l*-epinephrine when it was administered after hydralazine (Table IV).

Histamine.—Table III also shows that 20 mcg. of histamine had a marked vasoconstrictor effect on the placental vasculature when it was administered prior to the administration of 4 mg. of hydralazine. When 20 mcg. of histamine was administered subsequent to the administration of 4 mg. of hydralazine,

a diminution of its vasoconstricting effects occurred only in placentas with long cords. No reversal of histamine vasoconstrictor action was observed when it was administered after hydralazine (Table IV).

5-Hydroxytryptamine (Serotonin).—It can be seen from Table III that 5-hydroxytryptamine (serotonin) appeared to exhibit the greatest vasoconstrictor response of all of the agents used in this study. The vasoconstrictor action of 5-hydroxytryptamine was moderately diminished in those placentas with short cords when it was administered subsequent to the administration of 4 mg. of hydralazine. No reversal of 5-hydroxytryptamine's vasoconstricting action was observed using 4 mg. of hydralazine (Table IV).

DISCUSSION

In the majority of the experiments, the agonist was administered before the antagonist to establish a standard response. This standard response served as a comparison for the agonist's action when it was administered 3 minutes subsequent to any of the adrenergic blocking agents employed. When the agonists were administered 15–20 minutes subsequent to the administration of an adrenergic blocking agent, their responses began to approach those initially produced. This method was utilized to rule out the possibility of tachyphylaxis occurring due to the action of the agonist (Figs. 2–6).

The antagonists (phentolamine, tolazoline, and hydralazine) employed in this investigation exhibited their greatest blocking effect on the action of the catecholamines (epinephrine, norepinephrine, and *l*-epinephrine) and least blocking effect on 5-hydroxytryptamine and histamine. In most experiments, epinephrine, norepinephrine, and *l*-epinephrine usually exhibited a reversal action when given subsequently to phentolamine. However, the occurrence of the reversal action decreased markedly when tolazoline was employed; no reversal occurred when hydralazine was utilized. Thus, as seen from Table IV, the ability of adrenergic blocking agents to antagonize the vasoconstricting action of the agonists employed in this investigation is in decreasing order of potency phentolamine, tolazoline, and hydralazine.

The possibility of endogenous release of normal mediators being the specific mechanism of action of the amines employed can be eliminated, since full-term human placentas have been shown to be devoid completely of nervous tissue (14–17). Also, since the vasoconstricting action of epinephrine, norepinephrine, and *l*-epinephrine can be blocked by the *alpha* receptor adrenergic blocking agent phentolamine, as shown in this study, this would tend to eliminate the factor of general direct musculotropic action. Hence, the only remaining mechanism of action is the activation of specific receptor sites.

In recent years different receptor site theories have been postulated for the action of sympathomimetic amines. Of the theories advanced, the one which seems to be the most popular is that postulated by Ahlquist (18, 19). He suggested two receptor sites, classified as *alpha* and *beta*. The *alpha* adrenergic receptor site, when stimulated, exhibits an excitatory or vasoconstrictor action (with the possible exception of intestinal relaxation), and stimulation of the *beta* adrenergic receptor site exhibits an inhibitory or vasodilator action.

The vasoconstricting action which is produced by the agonists (epinephrine, norepinephrine, *l*-epinephrine, histamine, and 5-hydroxytryptamine) possibly corresponds to the stimulation of the *alpha* adrenergic receptors in Ahlquist's classification. This is substantiated because the vasoconstricting action of these drugs can either be diminished, blocked, or reversed with the use of an *alpha* receptor blocking agent, such as phentolamine. Consequently, because of the blocking of the *alpha* adrenergic receptor site with phentolamine, the secondary effect (vasodilatation or reversal) of epinephrine, norepinephrine, *l*-epinephrine, and histamine also appears. This possibly corresponds to *beta* receptor stimulation, since according to the Ahlquist's theory, vasodilatation is the result of stimulation of *beta* adrenergic receptor sites. Therefore, it appears at this time that *alpha* and *beta* adrenergic receptor sites are present in the placental vasculature. Thus, the hypothesis previously presented by Dornhorst and Young (10), in which they stated that adrenaline and noradrenaline may act on placental vasculature by a simple direct action, must now be modified to a specific action on adrenergic receptors.

Astrom and Samelius (12), in a previous investigation, indicated that the vasoconstrictor action of 5-hydroxytryptamine and adrenaline on placental vessels could be blocked by 3 mg. of phentolamine. This laboratory found that adrenaline could not only be blocked, but also its action could be reversed when it was administered subsequent to 3 mg. of phentolamine. However, it was observed that vasoconstrictor action of 5-hydroxytryptamine could only be diminished with 3 mg. of phentolamine and never blocked completely. Thus, the results obtained previously by Astrom and Samelius could not be confirmed. However, the results of this experiment support other investigations (2, 13), in which it was observed that the catecholamines, epinephrine and *l*-epinephrine, produced slight to moderate vasoconstriction, histamine marked vasoconstriction, and 5-hydroxytryptamine the most pronounced vasoconstriction on the placental vessels.

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