Such studies may provide information concerning the mechanism by which these agents produce their effects. It has been indicated that the rupturing of a carbon-to-deuterium bond is considerably more difficult than a carbon-to-hydrogen bond. Accordingly, if oxidation of carbon-to-deuterium bonds is involved in the metabolism of the drugs synthesized in this study, a pronounced effect on the pharmacological activity should be observed. Such studies are currently being undertaken.

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Effect of Certain Drugs on Perfused Human Placenta V

Use of α and β Adrenergic Blocking Agents to Determine the Specific Effector Site of Vasoactive Substances

By RALPH T. MANCINI and RONALD F. GAUTIERI

In this investigation pretreatment of placental vessels with both an α (phentolamine) and a β (dichloroisoproterenol, DCI) adrenergic blocking agent was performed to determine the specific nature of the effector site upon which epinephrine and isoproterenol act. The results of this combination of blocking agents in producing an almost complete inhibition of the diphasic action of epinephrine provided further support to the hypothesis that both α and β adrenergic receptors exist in placental vessels. In addition, DCI alone had relatively little effect on the action of large doses of isoproterenol in these vessels, but did reverse the vasodilation produced by small doses of this agent. The effects of DCI on the activity of vasodilators and phentolamine on vasoconstrictors were also investigated. DCI appeared to have only a slight, if any, blocking action on the vascular responses to nitroglycerin, papaverine, isosorbide dinitrate, sodium nitrite, sodium cobaltinitrite, and cyclandelate. Likewise, phentolamine had relatively little blocking action on the vasoconstricting effect of vasopressin and oxytocin.

THE HUMAN placenta is a flat discoid organ which at parturition weighs approximately one-sixth the weight of the fetus. From the onset of its development in pregnancy, this highly vascular organ is constantly increasing in size and structure, in order to meet the metabolic demands of its growing fetus, and it acts as the major organ of transfer between the maternal and fetal circulation.

Because it has been shown in many investigations that the placenta and all of the umbilical cord except that portion immediately adjacent to the fetus are devoid of nervous tissue (1–4), the placental vessels respond to enviromental influences without the endogenous release of the normal mediators. However, even without innervation, the placental vessels have been shown to be extremely sensitive to the action of certain drugs (such as 5-hydroxytryptamine) by a direct musculotropic action and/or stimulation of specific receptor sites (5). Poulson *et al.* have demonstrated that 5-hydroxytryptamine possesses teratogenic properties and suggested that its teratogenicity might be due to an action on placental function and blood supply (6). This research in the field of teratology has pointed to the obvious need for enlarging present knowledge concerning the action of all drugs on placental vasculature with particular emphasis on discerning the precise manner in which drugs are capable of eliciting responses in this vascular system.

Recently, in our laboratory human placental preparations were perfused to try to evaluate

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TABLE I.—EFFECTS OF PHENTOLAMINE AND DCI ON THE ACTION OF EPINEPHRINE IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg—Increase	Av. Change	No. Expt.
Before Phentolamine, 3 mg. and DCI, 5 mg.				
Epinephrine, 20 mcg.	S	+4.0 to +6.0	+5.0	3
	L	+4.4 to +62.0	+33.2	2
After Phentolamine, 3 mg. and DCI, 5 mg.				
Epinephrine, 20 mcg.	S	0.0 to +0.8	+0.3	3
	L	0.0	0.0	2

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

more accurately the mechanism of action of catecholamines on the placental vasculature (5). It was observed that these agents produced both vasoconstriction and vasodilatation. The fact that phentolamine (an α-receptor blocking agent) blocked the vasoconstriction produced by the catecholamines and unmasked their vasodilatory action led to the hypothesis that vasoconstriction in these vessels was due to a stimulation of α-receptors and the reversal (vasodilatation) was due to the stimulation of β-receptors. These observations made it imperative to discern whether the vasodilatory response (possibly β-receptor stimulation) of these catecholamines and other known vasodilators on the placental vasculature could be blocked by a β-receptor blocking agent such as dichloroisoproterenol (DCI). If the vasodilatory response of these drugs could be blocked on the placental vessels, this would supply additional support to our previous hypothesis (5). Therefore, the purpose of this investigation was to determine the effects of dichloroisoproterenol (DCI), a β-adrenergic-receptor blocking agent, and phentolamine,[1] an α-adrenergic-receptor blocking agent, on the action of certain drugs which are known to cause vasodilatation and/or vasoconstriction, in order to try to identify the specific mechanism of action and/or receptor sites whereby these agents act.

MATERIALS AND METHODS

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

The procedure concerned with the manipulation, preparation of the placentas for perfusion, and a schematic diagram of the apparatus utilized were described in a previous paper (5). The following drugs were injected into the arterial side of the perfusion in a volume of distilled water not exceeding 10.0 ml.: epinephrine HCl, 0.1%; phentolamine methanesulfonate,[1] 0.3%; dichloroisoproterenol HCl, DCI, 0.5%; isoproterenol HCl,[2] 0.2%; nitroglycerin spirit, 1.0%; nitroglycerin aqueous, 0.1%; papaverine HCl, 0.5%; isosorbide nonnitrated,[3] 0.1%; isosorbide dinitrate,[4] 0.5%; sodium nitrite, 0.2%; sodium cobaltinitrite, 0.2%; cyclandelate,[5] 0.5% in 50% propylene glycol solution or alcohol-20%–propylene glycol-15% solution; vasopressin,[6] 20 units/ml.; and oxytocin,[7] 10 units/ml.

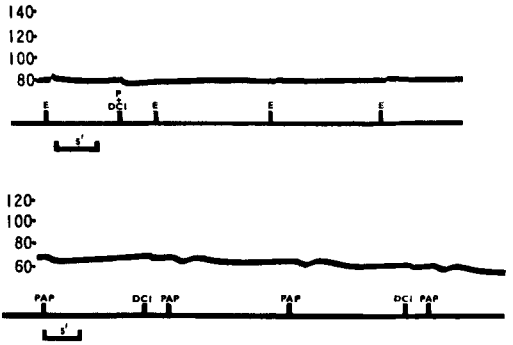

Fig. 1.—(*Top*) Effects of phentolamine and DCI on the action of epinephrine in placental vasculature. Key: P, phentolamine methanesulfonate, 3 mg.; DCI, dichloroisoproterenol hydrochloride, 5 mg.; E, epinephrine hydrochloride, 20 mcg. (*Bottom*) Effect of DCI on the action of papaverine hydrochloride in placental vasculature. Key: PAP, papaverine hydrochloride, 5 mg.; DCI, dichloroisoproterenol hydrochloride, 5 mg. first dose and 10 mg. second dose.

RESULTS

Effect of Phentolamine and DCI on the Action of Epinephrine.—When 20 mcg. of epinephrine was administered alone to placental vessels, its predominant action was stimulation of α-adrenergic-receptors, thus causing moderate vasoconstriction. From Table I it can be seen that when 20 mcg. of epinephrine was administered subsequently to 3 mg. of phentolamine (an α-adrenergic-receptor blocking agent) and 5 mg. DCI (a β-adrenergic-

[1] Regitine. Supplied through the courtesy of Ciba Pharmaceutical Co., Summit, N. J.

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

[3] Supplied through the courtesy of Ives-Cameron Laboratories, New York, N. Y.

[4] Isordil. Supplied through the courtesy of Ives-Cameron Laboratories, New York, N. Y.

[5] Cyclospasmol. Supplied through the courtesy of Ives-Cameron Laboratories, New York, N. Y.

[6] Marketed as Pitressin by Parke, Davis and Co., Detroit, Mich.

[7] Marketed as Pitocin by Parke, Davis and Co., Detroit, Mich.

TABLE II.—EFFECTS OF DCI ON THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg: Increase	Av. Change	No. Expt.	Decrease	Av. Change	No. Expt.
DCI, 1 mg.	0.0 to +6.8	+3.4	2	...	...	...
DCI, 2 mg.	0.0 to +8.0	+4.0	2	−1.0	−1.0	1
DCI, 5 mg.	...	...	...	0.0 to −2.6	−1.6	5
DCI, 10 mg.	...	...	...	−1.4 to −7.6	−3.5	4

[a] Short cord length.

TABLE III.—EFFECTS OF DCI ON THE ACTION OF SMALL DOSES OF ISOPROTERENOL IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg: Increase	Av. Change	No. Expt.	Decrease	Av. Change	No. Expt.
Before DCI, 10 mg.						
Isoproterenol, 10 mcg.	...	...	...	−2.0 to −5.0	−3.1	5
After DCI, 10 mg.						
Isoproterenol 10 mcg.	0.0 to +3.0	+0.8	5	...	...	...

[a] Short cord length.

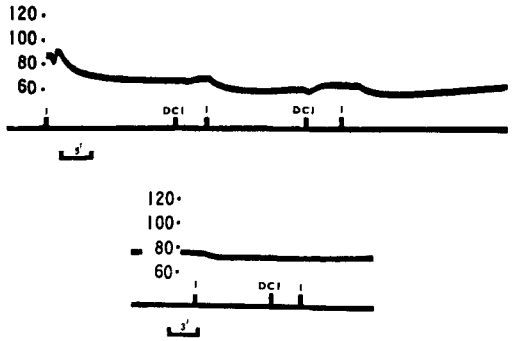

Fig. 2.—(*Top*) Effect of DCI on the action of large doses of isoproterenol in the placental vasculature. Key: I, isoproterenol hydrochloride, 2 mg.; DCI, dichloroisoproterenol hydrochloride, 5 mg. first dose and 10 mg. second dose. (*Bottom*) Effect of DCI on the action of small doses of isoproterenol in the placental vasculature. Key: I, isoproterenol hydrochloride, 10 mcg.; DCI, dichloroisoproterenol hydrochloride, 10 mg.

receptor blocking agent), its diphasic action (vasoconstriction and vasodilatation) was completely blocked in all but one placenta. [Fig. 1 (*Top*).]

Effect of DCI.—When DCI was administered in the dosage range of 1 to 10 mg., it produced variable effects depending upon the amount administered. From Table II it can be seen that with small doses (1 and 2 mg.), its predominant action on placental vessels was vasoconstriction. However, in one placenta slight vasodilatation was observed with a 2-mg. dose. In contrast to the lower doses administered, higher doses (5 and 10 mg.) produced only vasodilatation.

Effect of DCI on the Action of Small Doses of Isoproterenol.—It can be observed from Table III, that when 10 mcg. of isoproterenol was administered prior to 10 mg. of DCI, it stimulated the β-receptor sites within the placental vessels and thus caused vasodilatation. However, when 10 mcg. of isoproterenol was administered subsequently to 10 mg. of DCI, a blocking or reversal of its predominant vasodilatory response occurred. [Fig. 2 (*Bottom*).]

Effect of DCI on the Action of Large Doses of Isoproterenol.—From Table IV it can be seen that when large doses (1 and 2 mg.) of isoproterenol were administered to the placental preparations, marked vasodilation resulted. The degree of vasodilation produced by large doses of isoproterenol was greater than that exhibited by 10 mcg. (Table III). It was also noted that pretreatment of the placental vessels with DCI in doses of 5 and 10 mg. caused only slight but insignificant blocking of the

TABLE IV.—EFFECTS OF DCI ON THE ACTION OF LARGE DOSES OF ISOPROTERENOL IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg: Decrease	Av. Change	No. Expt.
Before DCI, 5 mg.			
Isoproterenol, 1 mg.	−6.8	−6.8	1
After DCI, 5 mg.			
Isoproterenol, 1 mg.	−1.0 to −6.8	−5.3	4
Before DCI, 10 mg.			
Isoproterenol, 1 mg.	−4.0 to −9.0	−7.3	4
After DCI, 10 mg.			
Isoproterenol, 1 mg.	−1.0 to −8.2	−5.5	7
Before DCI, 5 mg.			
Isoproterenol, 2 mg.	−5.6 to −22.0	−11.8	4
After DCI, 5 mg.			
Isoproterenol, 2 mg.	−4.6 to −15.0	−8.4	4
Before DCI, 10 mg.			
Isoproterenol, 2 mg.	−7.6 to −15.0	−10.4	4
After DCI, 10 mg.			
Isoproterenol, 2 mg.	−3.0 to −10.0	−7.8	6

[a] Short cord length.

TABLE V.—EFFECTS OF PHENTOLAMINE AND DCI ON THE ACTION OF ISOPROTERENOL IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg — Decrease	Av. Change	No. Expt.
Before Phentolamine, 3 mg. and DCI, 5 mg.				
Isoproterenol, 2 mg.	S	−8.6 to −14.8	−11.3	3
After Phentolamine, 3 mg. and DCI, 5 mg.				
Isoproterenol, 2 mg.	S	−7.8 to −9.0	−8.5	3
Before Phentolamine, 6 mg. and DCI, 10 mg.				
Isoproterenol, 2 mg.	S	−7.8	−7.8	1
	L	−4.0 to −7.4	−5.7	2
After Phentolamine, 6 mg. and DCI, 10 mg.				
Isoproterenol, 2 mg.	S	−6.0	−6.0	1
	L	−2.0 to −3.8	−2.9	2

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

vasodilation resulting from large doses (1 and 2 mg.) of isoproterenol. [Table IV; Fig. 2 (*Top*).]

Effects of Phentolamine and DCI on the Action of Isoproterenol.—From Table V it can be seen that when isoproterenol was administered in this phase of the investigation, it elicited marked vasodilation similar to that shown in Table IV. The combination of blocking agents (phentolamine and DCI) administered prior to isoproterenol in the doses illustrated in Table V, only slightly inhibited the subsequent vasodilatory action of 2 mg. of isoproterenol.

TABLE VI.—EFFECTS OF DCI ON THE ACTION OF NITROGLYCERIN SPIRIT IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg[b] Decrease	Av. Change
Before DCI, 5 mg.		
Nitroglycerin spirit, 2 mg.	−6.0 to −16.6	−9.9
After DCI, 5 mg.		
Nitroglycerin spirit, 2 mg.	−5.0 to −14.0	−7.9
Before DCI, 10 mg.		
Nitroglycerin spirit, 2 mg.	−2.0 to −6.0	−4.3
After DCI, 10 mg.		
Nitroglycerin spirit, 2 mg.	−2.2 to −6.0	−4.4

[a] Short cord length. [b] Four experiments in each case.

Effect of DCI on the Action of Nitroglycerin Spirit.—The administration of 0.2 ml. (2 mg.) of nitroglycerin spirit produced marked vasodilation which was comparable to that exhibited by 2 mg. of isoproterenol. From Table VI it can be observed that when 0.2 ml. of nitroglycerin spirit was administered subsequent to 5 and 10 mg. of DCI [Fig. 3 (*Bottom left* and *Bottom right*)] its vasodilating activity in the placental vessels was not significantly altered.

Effect of DCI on the Action of Aqueous Nitroglycerin.—The administration of 2 mg. of nitroglycerin dissolved in distilled water produced a moderate degree of vasodilation in the placental vessels. However, this vasodilatory response was neither as pronounced as that exhibited by a comparable amount of nitroglycerin spirit nor inhibited significantly when it was administered subsequent to 5 and 10 mg of DCI. [Table VII; Fig. 3 (*Top left* and *Top right*).]

Effect of DCI on the Action of Papaverine HCl.—From Table VIII it can be seen that 5 mg. of papaverine hydrochloride produced moderate vasodilation when given prior to DCI. In doses of 5 and 10 mg. DCI did not alter the vasodilator re-

TABLE VII.—EFFECTS OF DCI ON THE ACTION OF AQUEOUS NITROGLYCERIN IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg — Decrease	Av. Change	No. Expt.
Before DCI, 5 mg.				
Nitroglycerin aqueous, 2 mg.	S	−6.4 to −7.4	−6.9	3
	L	−4.6	−4.6	1
After DCI, 5 mg.				
Nitroglycerin aqueous, 2 mg.	S	−5.0 to −6.4	−5.1	3
	L	−2.0	−2.0	1
Before DCI, 10 mg.				
Nitroglycerin aqueous, 2 mg.	S	−2.0 to −2.4	−2.2	2
	L	−3.4	−3.4	1
After DCI, 10 mg.				
Nitroglycerin aqueous, 2 mg.	S	−1.4 to −2.0	−1.7	2
	L	−1.8	−1.8	1

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

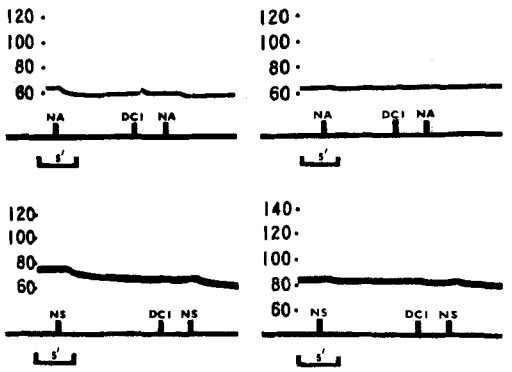

Fig. 3.—(*Top left*) Effect of DCI on the action of aqueous nitroglycerin in the placental vasculature. Key: NA, aqueous nitroglycerin, 2 mg.; DCI, dichloroisoproterenol hydrochloride, 5 mg. (*Bottom left*) Effect of DCI on the action of nitroglycerin spirit in the placental vasculature. Key: NS, nitroglycerin spirit, 2 mg.; DCI, dichloroisoproterenol hydrochloride, 5 mg. (*Top right*) Effect of DCI on the action of aqueous nitroglycerin in the placental vasculature. Key: NA, aqueous nitroglycerin, 2 mg.; DCI, dichloroisoproterenol hydrochloride, 10 mg. (*Bottom right*) Effect of DCI on the action of nitroglycerin spirit in the placental vasculature. Key: NS, nitroglycerin spirit, 2 mg.; DCI, dichloroisoproterenol hydrochloride, 10 mg.

sponses of papaverine in the placental vasculature· [Fig. 1 (*Bottom*).]

Effect of Nonnitrated Isosorbide.—Table IX shows that nonnitrated isosorbide administered in the range of 1 to 10 mg. caused slight vasoconstriction in the placental vessels. This vasoconstrictor activity of nonnitrated isosorbide appeared to be greater with the administration of 10 mg. than with lower amounts.

Effect of DCI on the Action of Isosorbide Dinitrate.—When isosorbide dinitrate was administered in doses of 1 and 2 mg., it elicited moderate to marked vasodilation in contrast to the slight vasoconstriction produced by the nonnitrated parent compound (Table X). Pretreatment of the placental vessels with 5 and 10-mg. doses of DCI only slightly inhibited isosorbide dinitrate's vasodilation in the majority of experiments.

Effect of DCI on the Action of Sodium Nitrite.—Sodium nitrite given prior to the administration of DCI produced marked vasodilation that was almost comparable to that elicited by isoproterenol (1 and 2 mg.). Also, this response to 2 mg. of sodium nitrite was similar in placentas with short or long cords. When sodium nitrite was administered approximately 3 min. after 5 or 10 mg. of DCI, its vasodilatory action was only slightly inhibited (Table XI).

Effect of DCI on the Action of Sodium Cobaltinitrite.—One can observe from Table XII that when sodium cobaltinitrite was administered initially to the placental vasculature, it exhibited marked vasodilation which was comparable to that produced by sodium nitrite. The prior administration of DCI in doses of 5 and 10 mg. appeared to decrease

TABLE VIII.—EFFECTS OF DCI ON THE ACTION OF PAPAVERINE HYDROCHLORIDE IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg[b] Decrease	Av. Change
Before DCI, 5 mg.		
Papaverine HCl, 5 mg.	−2.2 to −4.4	−3.5
After DCI, 5 mg.		
Papaverine HCl, 5 mg.	−2.2 to −4.0	−3.3
Before DCI, 10 mg.		
Papaverine HCl, 5 mg.	−2.2 to −4.0	−3.1
After DCI, 10 mg.		
Papaverine HCl, 5 mg.	−3.0 to −4.0	−3.7

[a] Short cord length. [b] Three experiments in each case.

TABLE IX.—EFFECTS OF NONNITRATED ISOSORBIDE ON THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg[c] Increase	Av. Change
Isosorbide,[b] 1 mg.	0.0 to +5.0	+2.3
Isosorbide,[b] 2 mg.	0.0 to +5.0	+2.3
Isosorbide,[b] 5 mg.	0.0 to +3.0	+1.7
Isosorbide,[b] 10 mg.	+2.0 to +3.6	+2.8

[a] Short cord length. [b] Nonnitrated. [c] Three experiments in each case.

TABLE X.—EFFECTS OF DCI ON THE ACTION OF ISOSORBIDE DINITRATE IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg Decrease	Av. Change	No. Expt.
Before DCI, 5 mg.				
Isosorbide,[b] 1 mg.	S	−3.0 to −6.0	−4.5	2
	L	−4.0	−4.0	1
After DCI, 5 mg.				
Isosorbide,[b] 1 mg.	S	−3.0 to −6.0	−4.5	2
	L	−3.0	−3.0	1
Before DCI, 10 mg.				
Isosorbide,[b] 1 mg.	S	−2.4 to −6.0	−3.7	3
After DCI, 10 mg.				
Isosorbide,[b] 1 mg.	S	−2.4 to −6.8	−4.6	3
Before DCI, 5 mg.				
Isosorbide,[b] 2 mg.	S	−8.0 to −26.0	−14.7	3
After DCI, 5 mg.				
Isosorbide,[b] 2 mg.	S	−6.6 to −10.2	−8.3	3
Before DCI, 10 mg.				
Isosorbide,[b] 2 mg.	S	−2.4 to −6.0	−4.2	2
	L	−3.4	−3.4	1
After DCI, 10 mg.				
Isosorbide,[b] 2 mg.	S	−5.0 to −5.4	−5.2	2
	L	−3.0	−3.0	1

[a] S, short cord; L, long cord. [b] Isosorbide dinitrate.

TABLE XI.—EFFECTS OF DCI ON THE ACTION OF SODIUM NITRITE IN THE PLACENTAL VASCULATURE

Drug and Dose	Cord Length[a]	Range of Pressure Changes, mm. Hg: Decrease	Av. Change	No. Expt.
Before DCI, 5 mg.				
Sodium nitrite, 2 mg.	S	−10.0 to −11.0	−10.5	2
	L	−8.0	−8.0	1
After DCI, 5 mg.				
Sodium nitrite, 2 mg.	S	−4.4 to −6.0	−5.2	2
	L	−7.0	−7.0	1
Before DCI, 10 mg.				
Sodium nitrite, 2 mg.	S	−3.8 to −4.0	−3.9	2
	L	−6.0	−6.0	1
After DCI, 10 mg.				
Sodium nitrite, 2 mg.	S	−2.8 to −5.0	−3.9	2
	L	−4.6	−4.6	1

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

TABLE XII.—EFFECTS OF DCI ON THE ACTION OF SODIUM COBALTINITRITE IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg: Decrease	Av. Change	No. Expt.
Before DCI, 5 mg.			
Sodium cobaltinitrite, 2 mg.	−6.0 to −8.0	−7.2	4
After DCI, 5 mg.			
Sodium cobaltinitrite, 2 mg.	−4.0 to −7.0	−5.8	3
Before DCI, 10 mg.			
Sodium cobaltinitrite, 2 mg.	−4.0 to −6.0	−5.2	3
After DCI, 10 mg.			
Sodium cobaltinitrite, 2 mg.	0.0 to −6.6	−2.9	3

[a] Short cord length.

TABLE XIII.—EFFECTS OF DCI ON THE ACTION OF CYCLANDELATE IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg[b]: Increase	Av. Change
Before DCI, 5 mg.		
Cyclandelate, 2 mg.	+3.0 to +7.0	+5.3
After DCI, 5 mg.		
Cyclandelate, 2 mg.	+4.6 to +6.0	+5.2
Before DCI, 10 mg.		
Cyclandelate, 2 mg.	+3.0 to +6.0	+4.2
After DCI, 10 mg.		
Cyclandelate, 2 mg.	+3.8 to +6.0	+4.9

[a] Short cord length. [b] Three experiments in each case.

TABLE XIV.—EFFECTS OF PHENTOLAMINE ON THE ACTION OF VASOPRESSIN IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg[b]: Increase	Av. Change
Before Phentolamine, 3 mg.		
Vasopressin, 4 units	+2.0 to +7.0	+4.1
After Phentolamine, 3 mg.		
Vasopressin, 4 units	+2.0 to +12.0	+5.6

[a] Short cord length. [b] Five experiments in each case.

slightly the vasodilator produced by the subsequently administered sodium cobaltinitrite.

Effect of DCI on the Action of Cyclandelate.—Cyclandelate (2 mg.) when given prior to the administration of DCI (5 and 10 mg.) elicited a moderate vasoconstrictor response. This response produced by cyclandelate was not altered to any significant degree when it was administered subsequent to DCI (Table XIII).

TABLE XV.—EFFECTS OF PHENTOLAMINE ON THE ACTION OF OXYTOCIN IN THE PLACENTAL[a] VASCULATURE

Drug and Dose	Range of Pressure Changes, mm. Hg: Increase	Av. Change	No. Expt.
Before phentolamine, 3 mg.			
Oxytocin, 4 units	+2.0 to +9.0	+4.0	6
After phentolamine, 3 mg.			
Oxytocin, 4 units	+3.6 to +6.0	+5.0	3

[a] Short cord length.

Effect of Phentolamine on the Action of Vasopressin and Oxytocin.—When vasopressin[6] (4 units, Table XIV) or oxytocin[7] (4 units, Table XV) were administered to the placental vasculature prior to 3 mg. of phentolamine, moderate degrees of vasoconstriction resulted. Phentolamine (3 mg.) was unable in each case to diminish or block another dose of either agent.

DISCUSSION

In the majority of the experiments, the agonist was administered before the antagonist in order to establish a standard response. This standard response served as a means of comparison for the antagonist's action when it was given 3 min. subsequent to the administration of the adrenergic blocking agents employed (Figs. 1–3).

Since it has been shown in a previous paper (5) that an α-adrenergic blocking agent phentolamine[1] caused the reversal of epinephrine's vasoconstrictor action in placental vessels, it was postulated that both α- and β-adrenergic-receptor sites appeared to be present in these vessels. To confirm this postulation, a combination of α- and β-receptor blocking agents was utilized to attempt to block the diphasic action of epinephrine. It was observed that when epinephrine was administered subsequent to the administration of this combination of antagonists (phentolamine and DCI), its diphasic action was completely blocked in all but one placental prepara-

tion where it produced a slight vasoconstriction. This evidence supports the previous hypothesis that both α- and β-receptor sites are present in the placental vasculature (5).

To determine whether vasodilators act *via* the stimulation of specific effector sites or by a direct musculotropic action in the placental vasculature, this laboratory utilized the β-adrenergic blocking agent dichloroisoproterenol (DCI). However, before this was undertaken the effects of DCI alone were determined on these vessels. It was observed that in low doses (1 and 2 mg.) DCI produced a slight to moderate vasoconstriction, though in one placenta a slight vasodilation occurred. In contrast to the results with DCI in low doses, it was demonstrated that high doses (5 and 10 mg.) produced a slight to moderate vasodilation in placental vasculature. When small doses of isoproterenol hydrochloride (10 mcg.) were administered to the placental vessels, a slight to moderate vasodilatory response occurred. However, when it was administered subsequent to 10 mg. of DCI, blocking or even a reversal of its vasodilation was demonstrated. [Fig. 2 (*Bottom*).] This appears to indicate that isoproterenol, like epinephrine, has a diphasic action on this vasculature. Isoproterenol employed in large doses was so profoundly vasodilatory that DCI (5 and 10 mg.) alone or in conjunction with phentolamine was incapable of blocking its vasodilating action.

DCI, in doses of 5 and 10 mg., was incapable of altering to any significant degree the vasodilation produced in the placental vessels by nitroglycerin in aqueous and alcoholic vehicles, papaverine hydrochloride, isosorbide dinitrate, sodium nitrite, and sodium cobaltinitrite. This appears to indicate that these drugs act on these vessels *via* a direct musculotropic action, which is in agreement with those results reported by Ciuchta and Gautieri (7) that nitroglycerin, papaverine hydrochloride, and isosorbide dinitrate act on the placental vasculature by means of a direct negative musculotropic action.

Cyclandelate dissolved in a 50% propylene glycol solution or alcohol-20%–propylene glycol-15% vehicle elicited a vasoconstrictor response in this investigation. However, when the vehicles alone were administered to the placental vessels, they also produced a vasoconstrictor response comparable to that occurring with cyclandelate dissolved in the vehicles. Therefore, this indicates that the effect of cyclandelate on the placental vessels was negligible, and that when it does cause vasodilation in other systems, it acts *via* a method other than a direct negative musculotropic response.

Vasopressin and oxytocin were also investigated for their effects in these vessels, since posterior pituitary extract (2) and vasopressin (8) have been demonstrated to produce vasoconstriction in this preparation. Phentolamine (an α-adrenergic-receptor blocking agent) in the doses employed in this study did not significantly block or inhibit the vasoconstricting action of either of these drugs. Therefore, it may be concluded that posterior pituitary preparations exert their vasoconstricting effects on placental vessels by a simple direct musculotropic action. Hence, with these results in mind, the value of this preparation, pointed out in previous papers (5, 7) as the organ of choice for screening vasoactive compounds that act *via* stimulation of specific receptors (5) or by a direct positive or negative musculotropic action (7), can readily be appreciated.

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