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ACTION OF ADRENALINE, ACETYLCHOLINE AND OTHER SUBSTANCES ON NERVE-FREE VESSELS (HUMAN PLACENTA)

By U. S. v. EULER[1]

From the National Institute for Medical Research, Hampstead, London

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Recent years have witnessed a rapid progress of knowledge concerning the nature of the chemical transmitters of neuromuscular excitation, and the manner in which the arrival of impulses at the nerve endings causes the release of these substances. Concerning the mode of action of these substances on effector cells, such as muscle cells, on the other hand, knowledge has advanced but little. There is, in the fully developed animal, a striking and specific localization of the action of adrenaline, when artificially applied, to cells which are innervated by adrenergic nerves, and of the action of acetylcholine to cells innervated by cholinergic nerves, though, even in the adult, it is not certain that the action does not extend to some cells which do not receive the corresponding innervation. For example, there are arteries involved in the general vasodilator response to an injection of acetylcholine, for which a corresponding cholinergic innervation has not been demonstrated. On the whole, however, the correspondence is in each case so close as to raise the question whether the response is due to some property or structure conferred on the muscle cell as the result of the particular innervation, or whether it is an inherent property, possessed by the cell before innervation, which the nerve merely uses for the chemical transmission of its effects. Elliott [1905], considering the meaning of the close correspondence between the effects of adrenaline and those of sympathetic nerves, suggested that the union of the sympathetic nerve with the muscle fibre caused the development in the latter, probably in relation to the nerve ending, of a special structure, neither nervous nor contractile, which he referred to as the "myoneural junction", and which he regarded as

[1] Fellow of the Rockefeller Foundation.

possessing the specific sensitiveness to adrenaline. When this structure had once developed as the result of innervation, degeneration left it intact, and the cell still sensitive to adrenaline. Langley [1905], on the other hand, regarded the persistence of the response to adrenaline after denervation as indicating that the specific sensitiveness was not the result of innervation, and, in further support of that conception, put forward observations on the response to adrenaline of the smooth muscle in the amnion of the developing chick, which has no nerve supply. These observations have been more recently confirmed by Baur [1928], using an improved technique. Baur obtained definite responses of the amniotic muscle fibres, not only to adrenaline, but to a number of other substances, some causing contraction, others inhibition of the spontaneous activity.

In addition to these experiments on the avian amnion, observations have been recorded on the effects of adrenaline and other substances on mammalian fœtal structures, such as the vessels of the umbilical cord and placenta, which apparently lack any nerve supply. Thus Schmitt [1922], having satisfied himself by histological examination that the placenta contains no nerves, made an extensive study of the actions of a number of substances on its perfused blood vessels. He observed constriction in response to histamine, post-pituitary extract (pituglandol) and barium chloride and dilatation with amyl nitrite, but detected no response to adrenaline. With isolated portions of vessels he observed, in a few instances, weak contractions in response to adrenaline in strong concentrations, but drew the conclusion that the absence of any strongly marked sensitiveness of the placental vessels to adrenaline is connected with their lack of innervation—a conclusion in general conformity with Elliott's suggestion.

Several later investigators have described a constrictor effect of adrenaline on the blood vessels of the human placenta and umbilical cord [Kosakaé, 1927; Budelmann, 1929; Baur *et al.* 1929; Küstner & Siedentopf, 1930; Ueda, 1931]. Ueda [1932] could not detect this action of adrenaline on the vessels of placentæ obtained before the sixth month, but observed it in those from stages of pregnancy later than this. This change, however, cannot be attributed to the appearance of nerves, since many attempts to demonstrate these histologically have failed to reveal them even in the full-term placenta [cf. Schmitt, 1929; Baur *et al.* 1929; Guarna, 1934].

There is some conflict of evidence as to whether the action of acetylcholine on the heart can be detected before the vagus fibres have made

connexions with the muscle cells. As early as 1880 Krukenberg had observed that muscarine, so closely resembling acetylcholine in effects of this type, had no action on the heart of the embryo chick, and this finding was later confirmed by Pickering [1893]. Armstrong [1935] states that even comparatively large doses of acetylcholine have no inhibitory action on the embryonic heart of the fish *Fundulus*, before it has been functionally innervated by the vagus. Cullis & Lucas [1936], on the other hand, find that acetylcholine causes a slowing of the rhythm of the aneural heart of the early chick embryo, and that this effect is prevented by atropine. Baur [1928] described actions of acetylcholine on the muscle of the chick amnion, but the responses, like those of the placental vessels which I describe later, were not very pronounced.

Methods

Human placentæ at full term were used throughout[1] and in most cases prepared within ½–1 hr. after the delivery. Cannulæ were inserted into the two umbilical arteries 5–10 cm. from the placenta, and connected to a Dale-Schuster perfusion pump.

As perfusion fluid Locke-Ringer solution of the following composition was used: NaCl 0·9 p.c., KCl 0·042 p.c., $CaCl_2$ 0·024 p.c., $NaHCO_3$ 0·1 p.c., glucose 0·1 p.c. In several experiments the Locke solution was mixed with 5 p.c. hæmoglobin solution, prepared by the method of Amberson & Höber [1932], as modified by Brown & Dale [1936], in the proportion 5–10 parts to 100 parts of Locke. The addition of hæmoglobin solution regularly caused a large increase of the peripheral resistance and a corresponding rise in the perfusion pressure. If the proportion of hæmoglobin solution was raised to 20 : 100 the vaso-constriction was sometimes so strong as to render further perfusion impossible. In some instances the hæmoglobin-Locke solution seemed to improve the reaction of the vessels to the substances added, but in others the reactions and the time of survival (as measured by the reactivity) seemed to be just as favourable with plain Locke solution. Œdema was never observed during the perfusion, whatever fluid was used.

The temperature of the perfused solution, as measured by a thermometer near the cannula tip, was kept at about 37° (36–38°) and the placenta was placed in a thermostat with a temperature of about 35°. Greater variations in temperature were avoided, since it was observed, in confirmation of Schmitt [1922] and others, that the placental vessels

[1] I am much indebted to the Superintendent and the Sisters of the Maternity Ward of the New End Hospital, Hampstead, for supplying the placentæ.

are sensitive to temperature changes, constricting at lower and dilating at higher temperatures.

Probably on account of the low temperature, the vessels of the placenta at the beginning of the perfusion were strongly contracted, and a high pressure was necessary to start the perfusion. When the placenta became warm and the flow through it free, the perfusion rate reached a fairly steady level within about a further 15 min. The rate of perfusion in different preparations has been between 10 and 60 c.c. per min., varying with changes in the arterial pressure produced by adjusting the rate and stroke of the pump, the condition and size of placenta and the composition of the perfusion fluid. Such rates were obtained with arterial pressures of 40–100 mm. Hg. According to Haselhorst [1929] the physiological pressure in the umbilical arteries varies between 46 and 110 mm. Hg with an average of 70–75 mm. The preparations have been supplied with fresh solution during the whole experiment. The plain Locke solution was not oxygenated, but in one case in which hæmoglobin-Locke solution was used, this was oxygenated in advance by bubbling oxygen through it. Differences in reaction referable to the state of oxygenation of the solution have not been observed. It is to be remembered that the fluid passing through the umbilical arteries is normally venous; oxygen has been found [Schmitt, 1922] to cause the arteries to contract strongly.

The time elapsing between delivery and the start of the perfusion does not, within limits, seem to exert a noticeable influence on the reactions to adrenaline and other substances. Thus, some quite fresh and still warm preparations, rapidly brought to a constant venous outflow, have reacted feebly to most of the substances added, whereas other preparations, kept for several hours at room temperature or in the ice chest, have reacted well. These wide variations in sensitivity might, on the other hand, provide an explanation for the varying results reported by different investigators. Again, a high sensitivity of the placental vessels to one vaso-motor agent did not necessarily imply an equal sensitivity to others.

The substances which have been tested with regard to their action on the placental vessels have either been injected in volumes of 0·05–1 c.c. into the rubber tubing near the arterial cannulæ, or, in some instances, have been added, by infusion from a Mariotte burette, to the stream of fluid on the intake side of the pump. Information has thus been obtained as to the actual concentrations of the active substances reaching the placenta, by determining the rate of such addition and the perfusion

rate concurrently. The substances have been dissolved in Locke solution or, in some cases, in plain physiological saline, acidified with HCl to *p*H about 4. Control injections have been carried out as a routine and have shown, in the majority of experiments, that volumes of up to 1 c.c. of either of these solutions, injected at room temperature, have not caused any significant vascular reaction, as judged by the perfusion pressure and perfusion volume.

The rate of perfusion has been recorded either by direct determination of the amount of fluid leaving the umbilical vein during a measured time, or by means of the Gaddum outflow recorder [1929]. The perfusion rate and pressure have generally been constant or shown only smooth changes, but in some instances the pressure curve has been irregular, indicating spontaneous variations in the muscular tone.

Results

The following substances have been examined for vascular effects on the placenta: adrenaline, acetylcholine, vasopressin, histamine, adenosine and prostaglandin; in addition, some observations have been made on the actions of ergotoxine, cocaine, atropine, eserine and barium chloride.

(*a*) *Adrenaline* (*ergotoxine, cocaine*). As already mentioned, Schmitt [1922] was unable to observe any action of adrenaline even in strong concentrations, on the human placenta perfused under a constant, non-pulsatile pressure, whereas other investigators have observed an effect.

In most of my experiments adrenaline produced a definite vaso-constrictor effect (see Table I), appearing as a rise in the perfusion pressure and diminution of the rate of the venous outflow. Reactions have been observed on direct injection of amounts as small as 2 μg., and in some instances 5 μg. have produced a considerable effect (Fig. 1 A). The most common type of response is illustrated in Fig. 2. Occasionally, however, only very small reactions or none at all were obtained with doses up to 0·5 mg. This failure to react has been observed even in quite fresh preparations, which showed good vaso-constrictor reactions to other substances. The lowest effective concentrations of adrenaline, given by infusion, have been of the order of 1 : 2·5 millions, though in several experiments the actual concentration necessary to produce a reaction has been considerably higher. In no case has vaso-dilatation been observed.

In those experiments where a definite reaction to adrenaline has been obtained it has always been possible to abolish it with ergotoxine (Fig. 1 D),

which itself caused a long lasting vaso-constriction when added in sufficient concentrations. Abolition of the adrenaline effect has been observed with a dose of 0·05 mg. ergotoxine, which did not cause a noticeable effect by itself, whereas 0·25 mg. or more caused vaso-constriction.

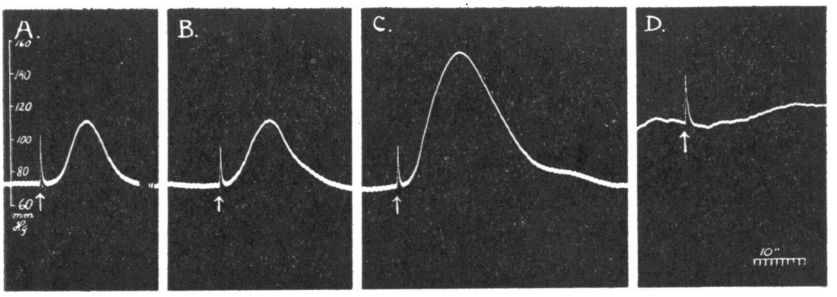

Fig. 1. All figures are from the pump-perfusion of the human placenta. Where not otherwise stated the record is of the perfusion pressure. A, 5 μg. adrenaline; 10 min. before B 1 mg. cocaine hydrochloride. B, 5 μg. adrenaline; 3 min. before C 1 mg. cocaine hydrochloride. C, 5 μg. adrenaline; between C and D 0·25 mg. ergotoxine ethanesulphonate. D, 5 μg. adrenaline.

Since cocaine is known to enhance the actions of adrenaline, the effect of this substance on the response to adrenaline was tested in some experiments. According to Burn & Tainter [1931] cocaine exerts its sensitizing effect on the adrenaline actions by some process occurring peripherally of the nerve endings. It might be expected, therefore, that cocaine would produce its characteristic action even on nerve-free muscle, and in two out of eight experiments such an action has been demonstrable (Fig. 1 C), and a doubtful effect in two others. In my experiments the best effect was obtained with a dose of about 2 mg. of cocaine hydrochloride, injected 2–5 min. before the adrenaline. In doses higher than 5 mg. cocaine regularly caused vaso-dilatation, and after doses of 20 mg. and more complete insensitivity to all substances tested has been observed, apparently due to paralysis of the smooth muscle. With the small doses required for sensitization, no definite direct effect of cocaine has been observed.

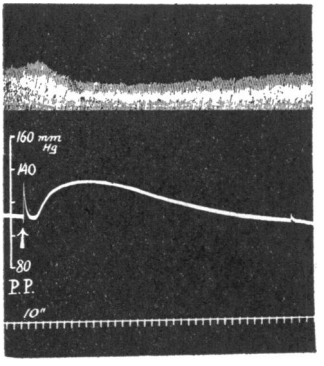

Fig. 2. Upper curve: venous outflow. Lower curve: perfusion pressure. At arrow 10 μg. adrenaline.

These experiments have thus shown that the action of adrenaline on a nerve-free preparation is abolished by ergotoxine and may be enhanced by cocaine, as on ordinary, sympathetically innervated smooth muscle. These substances must, therefore, like adrenaline, have their point of attack in the muscle cell itself.

(*b*) *Acetylcholine* (*atropine, eserine*). Whereas the action of adrenaline could be demonstrated with a fair degree of regularity, it has been

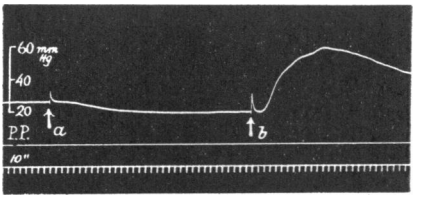

Fig. 3. *a*, 0·2 mg. acetylcholine; *b*, 25 μg. adrenaline.

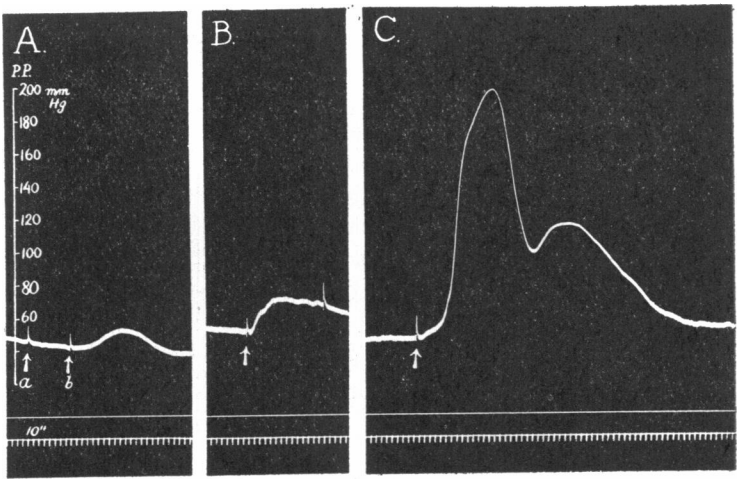

Fig. 4. A: *a*, 0·2 c.c. acid saline; *b*, 10 μg. acetylcholine. B, 0·2 mg. eserine. C, 10 μg. acetylcholine + 0·2 mg. eserine.

possible to obtain definite and regular effects of acetylcholine only on an occasional preparation. In some cases a small decrease in pressure, corresponding to a vaso-dilatation has been observed (Fig. 3 *a*). This effect has always been very weak, however, even if the existing vascular tone has been good. During the period of increased pressure due to an injection of adrenaline, the effect of acetylcholine was sometimes seen as a depression in the curve. In certain preparations, however, a rise in

pressure, due to vaso-constriction, has been produced by acetylcholine. This effect has varied within wide limits, from a just perceptible retardation to an almost complete arrest of the perfusion. Strong reactions of this kind have been obtained even with comparatively small doses of acetylcholine, of the order of 5–25 μg. (Fig. 4). The pressor response was occasionally enhanced in strength and duration by a previous or a simultaneous dose of eserine (0·2 mg.). It is noteworthy that this pressor effect of acetylcholine has not been obtainable repeatedly on the same preparation, unless sufficient time was allowed to elapse between successive doses. When, for instance, a second, identical dose was injected, immediately after the definite effect of a first dose had passed off, it produced only a very weak response, or none at all; only some 15–20 min. later would a second dose produce a similar effect to the first. Eserine by itself, in the amounts used (0·1–0·2 mg.), caused a moderate vaso-constriction.

These effects of acetylcholine were readily abolished by atropine, which thus produces its typical effect independently of the presence of nerves. In Fig. 5 the prevention by atropine of the pressor response to acetylcholine is illustrated. Atropine itself caused no effect in amounts of 0·1–1 mg.

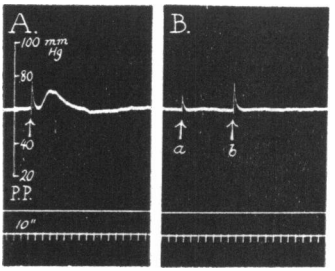

Fig. 5. A, 25 μg. acetylcholine. B: *a*, 1 mg. atropine; *b*, 25 μg. acetylcholine.

In view of these varying effects of acetylcholine on placental vessels, it is of interest to note that Baur *et al.* found variations in the response of human umbilical vessels to pilocarpine, which in some cases caused vaso-dilatation and in others vaso-constriction. Ueda [1931] reports that lower concentrations of acetylcholine produce vaso-dilatation in placenta, and higher concentrations vaso-constriction. These findings are not supported by my results, in which no relationship between dose and action can be observed. Moreover, the response to acetylcholine has been absent, or insignificantly weak, in the majority of experiments.

Incidentally, it was observed that a previous dose of quinine (0·2–1 mg.) caused an increase of the pressor response to acetylcholine (25 μg.). A sensitizing effect of quinine, on the response of various test objects to acetylcholine, has recently been described by Kahlson & Uvnäs [1938].

(*c*) *Histamine.* Schmitt [1922] found histamine very active as a constrictor of the human placental vessels, and the same observation

was made for the umbilical vessels by Baur *et al.* [1929]. The last-mentioned authors found, however, considerable variations in the response to histamine, without any apparent reason. My own experience confirms these observations, though in most of the experiments the action has been weak, even with doses of 10–20 μg. The only effect observed has been vaso-constriction. It was also repeatedly noted that a previous dose of histamine diminished the response to a subsequent dose, if the interval between the injections was short (Fig. 6). This effect may possibly

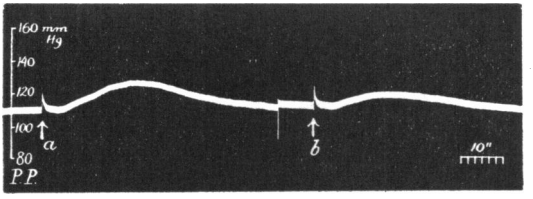

Fig. 6. *a*, 20 μg. histamine. *b*, same dose 6 min. after the previous one.

be of a similar nature to the desensitizing effect of a persistent concentration of histamine, as found by Barsoum & Gaddum [1935] on the guinea-pig's intestine.

(*d*) *Vasopressin.* Previous investigators have observed either vaso-constriction or no action with pituitary preparations, except Kosakaé [1927], who regularly obtained vaso-dilatation after a short vaso-constriction. In the experiments recorded here pitressin (Parke, Davis and Co.) has been used, and in most cases produced vaso-constriction, though in a few instances no effect was obtained even with doses as high as 10 I.U. The vaso-constrictor effect has been small even with doses of 2–5 I.U., and the response has consisted of a slow rise followed by a slow fall in pressure (Fig. 7), different in type from that obtained with adrenaline.

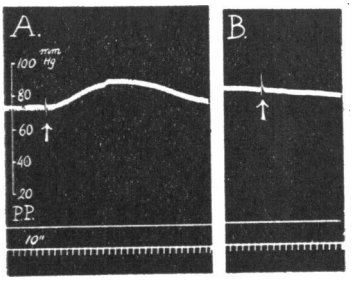

Fig. 7. A, 2 I.U. pitressin. B, 4 I.U. 8 min. later.

The characteristic diminution of the response to a second and following doses, administered within a short time after the first dose, well known from the action of posterior pituitary lobe extract on the general blood pressure, could be demonstrated also on the placental vessels.

It is of interest that in one instance, where 2 I.U. of pitressin caused a definite action, the preparation was insensitive to adrenaline even in a dose of 0·5 mg., whereas in another case pitressin was without action in 10 I.U. and adrenaline well active. In two other experiments both substances produced a reaction, and it could be shown that adrenaline was active even when the vessels were "refractory" to pitressin, after the first dose.

(*e*) *Adenosine.* Adenosine does not seem to have been tested previously on normally nerve-free preparations. On innervated vessels the responses are mostly vaso-dilatation [Bennet & Drury, 1931], but vaso-constriction has been observed on the lung vessels of the rabbit and other animals.

The effect on the placental vessels was not constant in all preparations. In two experiments doses of 0·1–0·3 mg. produced no perceptible reaction, whereas 0·4–0·6 mg. caused a rise in perfusion pressure (Fig. 8 B).

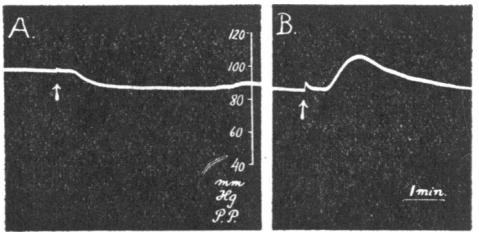

Fig. 8. A, 10 mg. sodium nitrite. B, 0·5 mg. adenosine.

This effect could be readily repeated in the same preparation. In view of the similarity found by Drury between the action of adenosine and nitrites, it was of interest to find that, in preparations in which adenosine caused vaso-constriction, the injection of sodium nitrite in an amount of 5–10 mg. caused a pronounced vaso-dilatation. In one experiment, however, the response to 0·1–0·3 mg. adenosine was a definite decrease in pressure, indicating vaso-dilatation, and no certain effect was obtained with 0·4–0·6 mg.

Comparing the reactions to acetylcholine and adenosine of the lung vessels of the rabbit and of the vessels of the human placenta, it seems noteworthy that both organs respond to these substances with vaso-constriction, which is an exceptional reaction.

(*f*) *Prostaglandin.* This substance has recently been described by the present writer [Euler, 1936], who found it in prostatic secretion and extracts of the prostate of man and certain animals. Normally it produces

a long persistent lowering of the arterial pressure when injected intravenously into rabbits, cats or dogs, also after atropine. It produces an increased activity of the intestine and uterus of a number of animals. The injection into the perfusion fluid of 1–2 units (1 "unit" causing a fall of 30 p.c. in the blood pressure of a rabbit of about 2·5 kg.) regularly produced a vaso-constriction of long duration in the placenta (Fig. 9), a type of effect which has not been previously observed. Since the active substance has not been chemically isolated, the activity of the extract was tested after inactivation of the prostaglandin by treatment with *N* HCl for 10 min. at 100°, in order to exclude the action of a possible contamination with histamine. After neutralization, however, a corresponding dose now produced no significant action, so that the action before hydrolysis was not due to histamine.

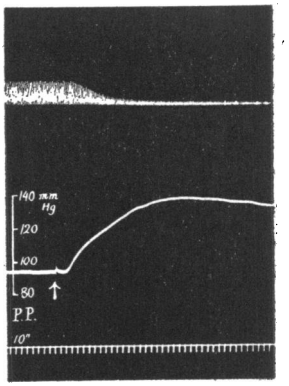

Fig. 9. Upper curve perfusion rate, lower curve perfusion pressure. At arrow 1 unit prostaglandin.

(*g*) *Barium chloride.* In the cases where barium chloride was tested it produced a vaso-constriction, even when the vessels did not respond to adrenaline, as observed already by Schmitt [1922].

The main results have been collected in Table I, which shows the effects of the different substances alone and in relation to others.

TABLE I. Effects

Substance	Definite	Weak or absent	Constriction	Dilatation	Doses
Adrenaline	11	5	13	—	2–500 μg.
Acetylcholine	2 (constr.)	10	5	3	5–500 μg.
Histamine	2	3	3	—	5–20 μg.
Vasopressin	1	4	3	—	2–10 I.U.
Adenosine	3	—	2	1	0·1–0·6 mg.
Prostaglandin	3	—	3	—	0·5–2 units
Ergotoxine	—	—	3	—	0·02–1 mg.
Cocaine	—	—	—	6	1–20 mg.
Atropine	—	2	—	—	0·1–1 mg.
Eserine	—	—	4	—	0·1–0·2 mg.
Quinine	—	1	—	—	0·1–1 mg.
$NaNO_2$	1	—	—	1	5–20 mg.
$BaCl_2$	2	—	2	—	5–50 mg.

Modifying effects of other substances

	Increased	Abolished	Unchanged
Adrenaline by cocaine	2 (+2)	—	4
Adrenaline by ergotoxine	—	4	—
Acetylcholine by eserine	1	—	3
Acetylcholine by atropine	—	1	—
Acetylcholine by quinine	1	—	—

Discussion

My observations are fully in accord with those of earlier observers in showing that the smooth muscle of the placental vessels possesses a natural tone, sensitive to oxygen tension, as earlier shown by Schmitt [1922] and by Baur *et al.* [1929], and especially to temperature. There are no nerves to affect this tone, and there is no ground for assuming any hormonal control of it. My experiments with substances which might function as hormones, such as adrenaline and vasopressin, show that the reactions of the placental vessels to these, as to other substances affecting their tone, though definite, are weak and variable in comparison with those of other blood vessels. It seems probable that, while the placenta is still functional and protected from temperature changes, the only condition likely significantly to affect the tone of its vessels is the oxygen supply.

It will have been seen that both the known transmitters of nervous excitation, adrenaline and acetylcholine, have effects on the tone of the placental vessels, those of adrenaline being the more regular. These effects, like those earlier observed on the amniotic membrane, show, indeed, that these transmitters are not without action on plain muscle cells which have never been innervated. They do not, on the other hand, exclude the possibility that connexion with nerve endings may confer, on muscle cells which acquire it, a sensitiveness of higher degree and greater specificity for one or the other of these substances. Indeed, the relatively weak and somewhat variable reaction exhibited by the placental vessels might well be regarded as representing a primitive power of response to these transmitters. In somatic arteries which acquire a nerve supply, this power of response to adrenaline would accordingly not be evoked as an entirely new property by union with nerve fibres of the sympathetic system, but would, nevertheless, be greatly enhanced thereby and given a definite direction. The rival conceptions of earlier investigators might, on these lines, be harmonized.

In some of the experiments acetylcholine showed a definite constrictor action on the placental vessels—an action which, like its other peripheral effects, is readily abolished by atropine. It is worthy of note that such a vaso-constrictor action of acetylcholine in small doses has elsewhere been regularly observed on the pulmonary vessels of the rabbit [Euler, 1932]; and it is tempting to correlate this similarity of response with the fact that the arteries of both the placenta and the lungs are conveying venous blood, and are structurally adapted to withstand only moderate

pressures. There is a similar resemblance between the response of the placental and the pulmonary vessels to adenosine, which causes constriction of both, in contrast to its general vaso-dilator action. These vaso-constrictor effects of acetylcholine and adenosine on the placental vessels are not seen in all experiments. Both, on occasion, have caused vaso-dilatation, and the question arises whether their actions, in causing an increase of the resistance to perfusion, are necessarily, or entirely, upon the blood vessels. If the placenta contained extravascular contractile tissue, responding to these substances by contraction, its reaction might cause an obstruction to the flow stimulating a vaso-constriction, and even, perhaps, masking a concomitant relaxation of the vascular walls themselves. In a tissue like that of the placenta it is practically impossible to determine, by histological examination, whether a spindle-shaped cell is contractile or not. There is, accordingly, no evidence that such extravascular contractile tissue is present, or any ground for assuming, if it were, that its reactions to these drugs would be in a different sense from that of the arteries; and, if its presence were invoked to explain an increase of resistance to perfusion sometimes caused by the generally vaso-dilator acetylcholine, it would leave unexplained the fact that another general vaso-dilator substance, adenosine, may produce a similar obstruction of flow through placentæ on which acetylcholine has no effect.

Though the effects on the placental vessels of the various substances tested must, in the absence of nerves, or any structures associated with innervation, be attributed to direct actions on the plain muscle cells, it is unlikely that they act directly on the contractile elements of these. If two substances both caused vaso-constrictor action by directly stimulating the contractile elements, we should expect to find that their actions would appear with approximately constant relative intensities in different experiments, and that failure to react to either would mean failure with both. This is by no means the case. It would appear, then, that even these primitive cells, with no nerve supply, possess some structure responsible for fixing the chemical stimulants or procuring their access to the contractile elements, and probably for determining the direction in which the contractile function will be affected by them; and that this structure may show independent variations in its fixative power or its permeability for different active substances. In other words, they must possess something corresponding to what Langley termed "receptive substances". It is upon the fixing power or permeability of such that atropine must be supposed to act, when it renders the placental

vessels insensitive to acetylcholine or pilocarpine [Ueda, 1931], and leaves their reaction to other substances unaffected.

Summary

1. The effects of a series of substances on the blood vessels of the perfused human placenta have been observed, with the following results:

Adrenaline. Constriction seen in most experiments with doses of 2 μg. or more, and reproduced with repeated application. Effect sometimes enhanced by cocaine and always abolished by ergotoxine.

Acetylcholine. Usually no effect, but occasionally weak dilatation, or a pronounced constriction enhanced by eserine and abolished by atropine.

Histamine, vasopressin. Constriction, usually weak, a second dose producing a diminished effect or none.

Adenosine. Dilatation or constriction, the latter in cases showing dilatation with nitrites.

Prostaglandin. Pronounced constriction.

2. It is concluded that all these substances, including the chemical transmitters of nervous effects, have direct actions on the muscle cells, but, from the variations in their relative potencies, that these actions are not on the contractile substance directly.

3. The similarity between the responses of placental and pulmonary vessels to certain substances is noted.

It is a great pleasure for me to express my grateful acknowledgement to Sir Henry Dale for the facilities placed at my disposal during this work. I also wish to thank Dr G. L. Brown for much valuable advice.

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