J. Physiol. (1952) 118, 282–288

THE ACTION OF ADRENALINE AND NORADRENALINE ON THE PLACENTAL AND FOETAL CIRCULATIONS IN THE RABBIT AND GUINEA-PIG

By A. C. DORNHORST and I. MAUREEN YOUNG

From the Departments of Medicine and Physiology, St Thomas's Hospital Medical School, London

(*Received* 12 *May* 1952)

The original object of the investigation was to find whether the placental barrier was permeable to adrenaline and to noradrenaline. It soon became apparent that whereas the placental vessels were very sensitive to these hormones, the foetus itself was relatively insensitive. These findings will now be described.

METHODS

The observations were made on rabbits, 28–31 days pregnant, and guinea-pigs, 40–63 days pregnant. Light anaesthesia was maintained with urethane 1·5 g/kg body weight, injected intravenously. The guinea-pigs were lightly anaesthetized with ether while a vein was exposed for the injection. A maternal jugular vein was cannulated with fine polythene tubing for the infusion or injection of drugs. The maternal arterial blood pressure was recorded with a capacitance manometer from a carotid artery which was also cannulated with fine polythene tubing. The abdominal wall was opened by a mid-line incision under saline at 38° C. The uterus was cut longitudinally from rump to crown of a single foetus and that foetus was then delivered into the saline and supported throughout the experiment on a gauze sling. The foetal arterial blood pressure was recorded with a capacitance manometer from one carotid artery which was cannulated with a no. 19 record needle. Intrafoetal injections were made into the jugular vein or, in the guinea-pig, into the vitelline vein, towards the foetus.

RESULTS

L-*Adrenaline*, L-*noradrenaline and oxytocin in the maternal circulation*

A continuous infusion of adrenaline, at the rate of 0·6 μg/kg/min, increased the maternal blood pressure by 10–25 mm Hg (with or without accelerating the heart rate) and caused vigorous contractions of the uterine muscle. The placenta became blue, the foetal heart rate fell from an average value of 300 per min to 150–170 per min, and the foetal blood pressure decreased from

an average figure of 30 mm Hg down to 15–20 mm Hg (Figs. 1 and 2*a*). These foetal changes commenced 20–60 sec after the beginning of an infusion and coincided with the change in placental colour; they quickly passed off when

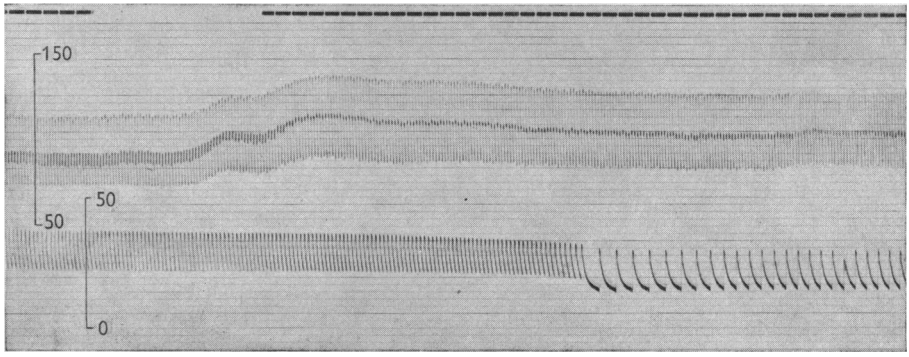

Fig. 1. Rabbit 30 days pregnant. Upper record, maternal B.P. Lower record, foetal B.P. Single maternal injection of 5 μg adrenaline. Foetal bradycardia and fall in arterial pressure started 20 sec after beginning of injection.

Arterial pressures in mm Hg, and time signals in seconds in Figs. 1 and 3–6. Time signa suspended during injection.

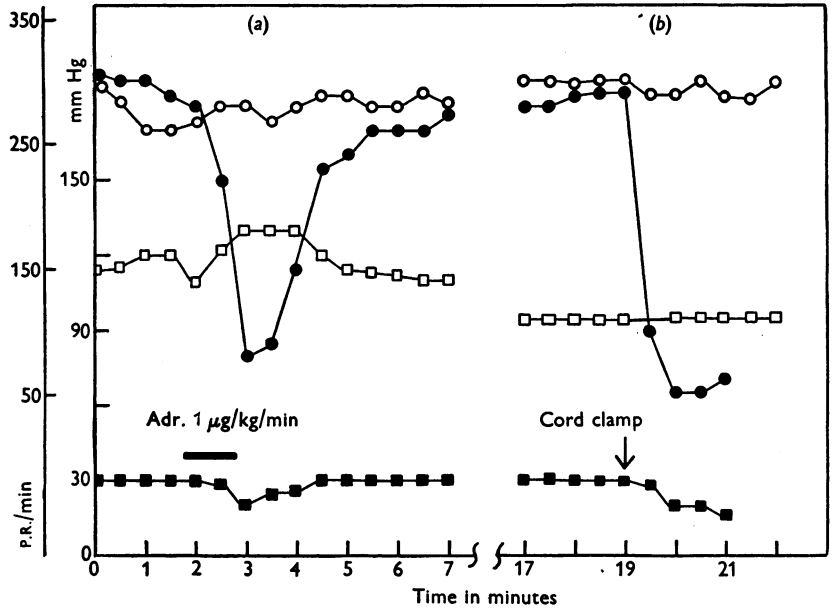

Fig. 2. Rabbit 29 days pregnant. Foetal bradycardia and fall in arterial pressure: (*a*) 45 sec after beginning of maternal infusion of adrenaline; (*b*) 30 sec after clamping the umbilical cord. Blood pressure: maternal, □—□, foetal, ■—■; pulse rate: maternal, ○—○, foetal, ●—●.

the infusion was stopped. Smaller doses gave no response; with larger doses the response was more rapid in onset. A total of seven foetuses in five rabbits were studied. Similar results were obtained, less consistently, in four guinea-pig foetuses. Noradrenaline produced, both in the rabbit and guinea-pig, effects similar to those of adrenaline. None of the foetal circulatory changes was prevented by giving atropine (0·1–1·0 mg/40–100 g foetus).

Oxytocin (0·05–0·10 unit), injected as a single dose in rabbits, produced very strong uterine contractions with blanching of the uterine muscle. There was, however, little alteration in the placental colour, and only a moderate slowing of the heart rate was observed in one foetus out of three.

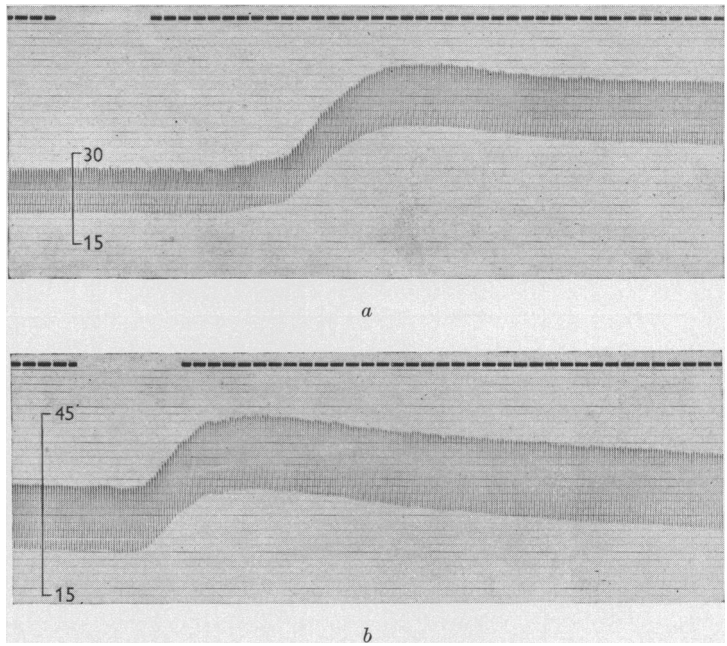

Fig. 3. 58-day guinea-pig foetus. Rise in arterial pressure after intrafoetal injection of: (*a*) 1 μg adrenaline; (*b*) 1 μg noradrenaline.

Adrenaline and noradrenaline in the foetal circulation

Neither the rabbit nor guinea-pig foetus consistently responded to a single injection of 0·25 μg adrenaline, but 0·5–1·0 μg (corresponding to 10–25 μg/kg body weight) was always effective, causing an increase in the mean arterial pressure and an increase in the pulse pressure although there was very little change in the heart rate (Fig. 3*a*). The placenta became a brighter red, but there were no uterine contractions and no alteration in maternal blood pressure and heart rate. Noradrenaline in like doses gave very similar results but the pulse pressure increased less (Fig. 3*b*).

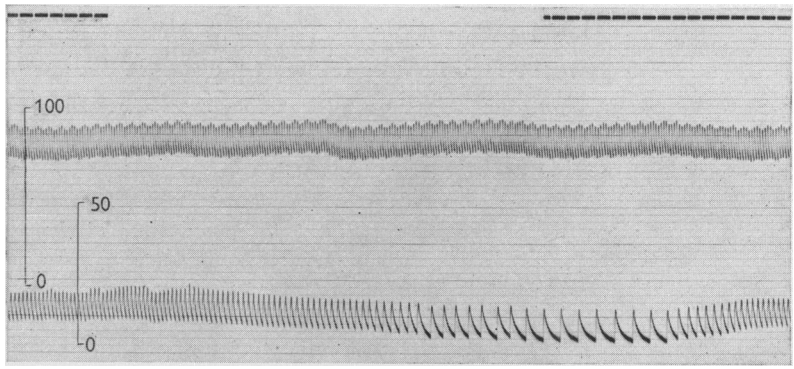

Fig. 4. Rabbit at end of term. Upper record, maternal B.P. Lower record, foetal B.P. Foeta bradycardia and fall in arterial pressure beginning 10 sec after beginning of occlusion of umbilical cord; the occlusion lasted for the duration of the signal.

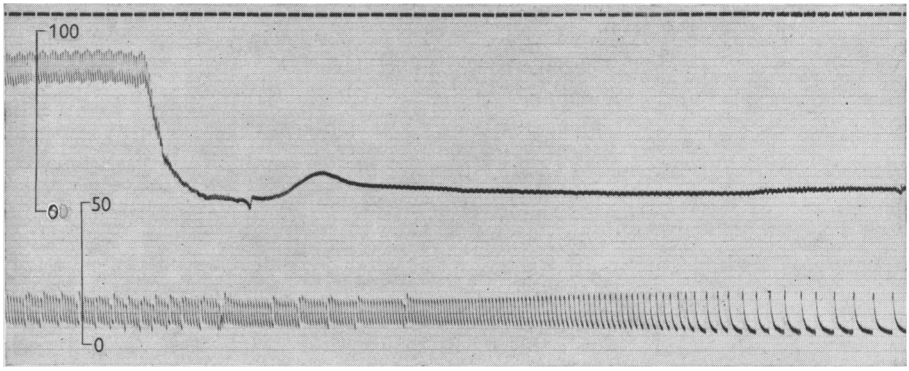

Fig. 5. Rabbit at end of term. Upper record, maternal B.P. Lower record, foetal B.P. Foetal bradycardia and fall in arterial pressure beginning 20 sec after maternal death by intravenous injection of air.

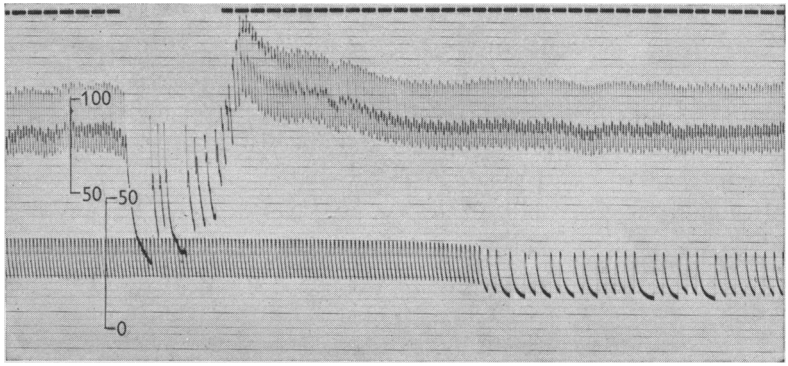

Fig. 6. Rabbit at end of term. Upper record, maternal B.P. Lower record, foetal B.P. Foeta bradycardia and fall in arterial pressure beginning 20 sec after beginning of stimulation of the intact maternal vagus.

Asphyxial slowing of the foetal heart

Figs. 2*b* and 4–6 show the foetal cardiac slowing and fall in blood pressure which occurred, due to asphyxia, 10–30 sec after occlusion of the cord, maternal death or the circulatory disturbance during maternal vagal stimulation. Such slowing was not prevented by atropinizing the foetus.

DISCUSSION

The resemblance between the effect of L-adrenaline, and L-noradrenaline, in the maternal circulation, and that of foetal asphyxia upon the foetal cardiovascular system suggests that these drugs cause foetal asphyxia by reducing the maternal placental blood flow. Cyanosis of the placenta always occurred with effective doses of both adrenaline and noradrenaline and coincided with, or slightly preceded, the foetal cardiovascular changes. This reduction in placental blood flow is probably due to the direct action of adrenaline and noradrenaline on the placental blood vessels and not to the uterine contractions, for with oxytocin, which causes much more vigorous uterine activity, there is less placental cyanosis and consequent foetal cardiovascular changes. Robson & Schild (1938) showed that the blood flow through the uterus was little effected by oxytocin but greatly reduced by adrenaline. Clark (1932) observed, in the cat, that maternal injection of adrenaline caused a fall in the foetal blood pressure, but he concluded that this was due to the vasodilator action of a trace of adrenaline which had crossed the placental barrier. The fall in foetal blood pressure in our experiments was always accompanied by a bradycardia which did not suggest a direct action of adrenaline: moreover, we never observed depressor responses to sub-pressor doses of adrenaline injected directly into the foetal circulation. Clark also found that in his cats pitressin depressed the foetal blood pressure but noted that it had less effect on the foetal circulation than had equipressor doses of adrenaline. Nakagawa (1936) found that adrenaline delayed the placental transfer of micro-organisms and bacteria from the mother to the foetus, and Huggett (1952) has suggested that this was due to constriction of the placental vessels.

The smallest effective doses of adrenaline and noradrenaline in the foetus is weight for weight 20–25 times the minimal effective adult dose; this relative insensitivity of the foetal response to adrenaline was noted previously by Clark (1932) in the cat, and by Burlingame, Long & Ogden (1942) in the rat. The large doses of adrenaline and noradrenaline, when injected intravenously in both rabbit and guinea-pig foetuses, produce changes in the blood pressure resembling those produced by moderate doses in the adult: the rise in the arterial pressure is accompanied by a greater rise in pulse pressure with adrenaline than noradrenaline. However, these large doses of both adrenaline and noradrenaline scarcely alter the foetal heart rate. It was also observed

that, after intrafoetal injection of adrenaline and noradrenaline, the placenta and umbilical vein became a brighter red and the umbilical artery darker in colour. These observations suggest a reduced rate of oxygen uptake from the maternal blood possibly due to constriction of the foetal vessels, and a decreased blood flow on the foetal side of the placenta. Von Euler (1938) found that adrenaline constricted the foetal vessels in isolated perfused human placentae.

The relative insensitivity of the foetus to adrenaline and noradrenaline under the experimental conditions make it unlikely that the transfer of small amounts from the maternal circulation could be detected. No definite conclusion can therefore be reached with respect to the maternal foetal transfer of these two substances.

The comparatively large doses given to the foetus are without effect on the uterine muscle and the maternal cardiovascular system. This suggests that there is no transfer from the foetal to the maternal circulation and agrees with the conclusions of Snyder & Hoskins (1927). The presence of high concentrations of mono-amine oxidase in rabbit and guinea-pig placentas (Thompson & Tickner, 1949) may be responsible for the inactivation of adrenaline and noradrenaline as they are transferred from either maternal to foetal or foetal to maternal circulations. The relative insensitivity of the foetus to adrenaline and noradrenaline may also be due to rapid inactivation but there have been, as yet, no determinations of amine oxidase activity in these foetal tissues.

SUMMARY

1. In the pregnant rabbit and guinea-pig small pressor doses of both adrenaline and noradrenaline cause vigorous contractions of the uterine muscle and impairment of the placental circulation with subsequent slowing of the foetal heart rate and fall in foetal blood pressure.

2. The foetal circulation is relatively insensitive to both adrenaline and noradrenaline. Pressor responses can only be obtained by 20 times the maternal dose; an increase in pulse pressure is always obtained but seldom any alteration in heart rate. No depressor responses were observed.

3. This foetal response to adrenaline in the maternal circulation is due to a reduction in the blood supply to the maternal side of the placenta and the consequent asphyxia of the foetal heart. Similar responses are obtained by clamping the cord, lowering the maternal blood pressure and killing the mother.

4. Oxytocin in the maternal circulation, while causing strong uterine contraction gives very little impairment of the placental and foetal circulations. It is suggested that it is the direct action of adrenaline and noradrenaline on the placental blood vessels and not the uterine contractions which is responsible for the reduction in maternal placental circulation.

5. There is no evidence of the placental transfer of adrenaline and noradrenaline either from mother to foetus or foetus to mother.

Our thanks are due to Mr M. G. Ventom for technical assistance, Prof. E. P. Sharpey-Schafer for apparatus and facilities, and to Prof. Henry Barcroft for suggestions and criticism.

REFERENCES

BURLINGAME, P., LONG, J. A. & OGDEN, E. (1942). The blood pressure of the foetal rat and its response to renin and angiotonin. *Amer. J. Physiol.* **137**, 473–484.

CLARK, G. A. (1932). Some foetal blood-pressure reactions. *J. Physiol.* **74**, 391–400.

VON EULER, U. S. (1938). Action of adrenaline, acetylcholine and other substances on nerve-free vessels (human placenta). *J. Physiol.* **93**, 129–143.

HUGGETT, A. ST G. (1952). *Marshall's Physiology of Reproduction*, 3rd ed., vol. 2, p. 370. London: Longmans, Green and Co.

NAKAGAWA, T. (1936). Über die Durchgängigkeit der Plazenta für verschiedene Mikroorganismen und Bakteriophagen. *Zbl. Bakt.* (1. *Abt. Orig.*), **136**, 147–151.

ROBSON, J. M. & SCHILD, H. O. (1938). Effect of drugs on the blood flow and activity of the uterus. *J. Physiol.* **92**, 9–19.

SNYDER, F. F. & HOSKINS, F. M. (1927). The placental transmission of adrenaline, insulin and pituitrin. *Anat. Rec.* **35**, 23.

THOMPSON, R. H. S. & TICKNER, A. (1949). Observations on the mono-amine oxidase activity of placenta and uterus. *Biochem. J.* **45**, 125–130.