EFFECT OF ADRENERGIC STIMULATION AND BLOCKADE ON THE UTEROPLACENTAL CIRCULATION AND UTERINE ACTIVITY IN THE RABBIT

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Summary. Responses of the myometrial and maternal placental circulations to adrenergic stimulation and blockade have been studied in the rabbit by serial angiography after selective catheterization of the urogenital artery. Changes in myometrial activity and arterial blood pressure have been registered and taken into account. Myometrial and placental blood flow was reduced by a few nanograms of noradrenaline or adrenaline, but increased after blockade of α-adrenoceptors with phenoxybenzamine or thymoxamine. The main effect of phentolamine was to evoke a long series of myometrial contractions, which counteracted the tendency of this drug to improve placental perfusion. The β-blocking agent, propranolol, had no effect at all on the parameters studied. Isoprenaline did not clearly affect myometrial and placental blood flow. Isoxsuprine, however, caused a slight increase by dilating the uterine arteries, possibly due to its papaverine-like properties. Both isoprenaline and isoxsuprine tended to depress myometrial activity. None of the drugs tested markedly affected distribution of uterine blood flow between the uterine wall and the placentae.

INTRODUCTION

A wide range of techniques has been applied to study the responses to various drugs of total uterine blood flow and myometrial blood flow. Little is known about the response of the maternal placental circulation, however, although it is this component that is of decisive importance for the well-being of the fetus. We have already demonstrated that the pharmacodynamics of both the myometrial and the maternal placental circulations can be studied by angiography in the rabbit (Carter, Göthlin & Bengtsson, 1968; Carter & Göthlin, 1970). In the present investigation, the angiographic technique has been used to study the rôle of adrenoceptors in the control of myometrial and placental blood flow in the rabbit. Blood flow through the uterine wall can be influenced by contraction of the myometrium as well as by the vascular smooth muscle itself. Attention has, therefore, been paid to the effects of adrenergic stimulation and blockade on
the myometrial activity, as reflected in alterations of the intrauterine pressure pattern.

**MATERIALS AND METHODS**

Twenty-three rabbits, mainly of the Swedish Land race, were studied at known stages of pregnancy from 18 to 27 days post coitum (full term occurs at 31 to 32 days). The animals weighed between 2.8 and 4.4 kg.

![Text-fig. 1. Schematic drawing of experimental arrangement. The right urogenital artery is catheterized through the right femoral artery (FA). Arterial blood pressure is recorded electromanometrically from a common carotid artery (CA). Intrauterine pressure is recorded electromanometrically through a sponge-tipped catheter in the right horn of the uterus (U). A fourth catheter drains the bladder (B). Intrauterine pressure (UP) and film exposures (EX) are registered on a potentiometer writer (PMR, paper speed 1 cm/min). Intrauterine pressure, film exposures, contrast medium injections (CMI) and arterial blood pressure (BP) are registered on a direct-writing polygraph (PG, paper speed 0.25 cm/sec). Other equipment indicated is X-ray tube (RT), automatic film changer (FC), high pressure syringe (S) and electromanometers (EM).]

The techniques employed have been described in detail elsewhere and will be recapitulated only briefly here. The experimental set-up is shown in Text-fig. 1. General anaesthesia was obtained with intravenous pentobarbitone sodium (Mebumalnatrium 6%, ACO, Sweden) and maintained at a constant level throughout the experiment. A radio-opaque catheter of polyethylene (OPP 60, Portex, England, o.d./i.d.: 1.22 mm/0.76 mm), with a bent tip portion, was used for angiography. It was introduced into a femoral artery and the tip was positioned in the mouth of the urogenital artery during fluoroscopy. Serial
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angiography was made with twofold geometrical enlargement, using an automatic film changer with high definition screens (Carter, Göthlin & Olin, 1971). Usually, a series consisted of eight films at intervals of 1 sec, followed by a further seven films at intervals of 5 sec. Control series of angiograms were compared with series exposed immediately and at various intervals after drug injection.

The water-soluble contrast medium (meglumine metrizoate, Isopaque® Cerebral, Nyco, Norway) was injected with a high-pressure syringe. The course of the injections was recorded on a direct-writing polygraph so that the rate of each injection could be exactly determined. The polygraph also recorded the arterial blood pressure, measured electromanometrically from a catheter in one of the common carotid arteries, and the film exposures. The timing of the films could thereby be related to the contrast medium injection and the blood pressure changes.

Intrauterine pressure was recorded through a sponge-tipped, open-ended vinyl catheter (VX 010, Beckton Dickinson, U.S.A., o.d./i.d.: 0·9 mm/0·5 mm), filled with isotonic saline (Bengtsson, 1968; Carter, Naaktgeboren & Van Zon-Van Wagendonk, 1971). The catheter was placed between the endometrium and fetal membranes in the uterine horn on the same side as the angiography catheter, with its tip opposite one of the placentae. The pressure was measured electromanometrically and registered on a potentiometer writer, together with the film exposures. Supplementary drug injections, without angiography, were made to define myometrial responses.

The actions of the following drugs were studied: adrenaline (ACO, Sweden; 0·005 µg to 10 µg), isoprenaline (Apoteket Kronan, Gothenburg, Sweden; 0·01 µg to 100 µg), isoxsuprine (Duvadilan®, Ferrosan, Sweden; 10 µg to 1000 µg), noradrenaline (Nor-Exadrin®, Astra, Sweden; 0·001 µg to 1 µg), phenoxybenzamine (Dibenylline®, Smith, Kline & French, England; 250 µg to 4000 µg), phentolamine (Regitin®, CIBA, Switzerland; 10 µg to 1000 µg), propranolol (Inderal®, ICI, England; 20 µg to 1000 µg), and thymoxamine (Opilon®, Warner, England; 50 µg to 500 µg). The drugs, diluted in isotonic saline solution, were injected by hand through the angiography catheter.

RESULTS

The rabbit uterus is supplied with blood through long, spiral arteries. Some of these perfuse the myometrium, whilst others enter the placentae, opening into large arterial sinuses which supply the placental labyrinth through wide efferent vessels (Text-fig. 2). In assessing the angiograms, the calibres of the uterine artery and of the larger placental vessels were measured. The blood flow in the urogenital artery was estimated from the known rate of injection of contrast medium and the extent to which the medium was diluted in, or spilled over from, this vessel (Carter, Göthlin & Olin, 1971). The distribution of total uterine blood flow between the uterine wall and the placentae could be assessed by evaluating the opacity of the myometrial and placental blood vessels, as this is dependent upon the amount of contrast medium borne to them. The times taken for first filling of placental sinuses, complete emptying of the spiral
arteries and first filling of the uterine veins were also noted. Wherever possible, the veins which drain the placentae were distinguished from those which drain the uterine wall, as the circulation time through the myometrium is less than that through the placentae.

During the period of pregnancy studied, the spontaneous uterine activity is rather low. A constant pattern of regular changes of small amplitude and variable frequency in intrauterine pressure was recorded. Injection of contrast

**Text-fig. 2.** Schematic drawing of a thick transverse section through the rabbit placenta, demonstrating the maternal blood supply to one of the lobes. A spiral artery, running first in the broad ligament and uterine wall, feeds a large, arterial sinus in the decidual part of the placenta. Efferent arteries proceed from the sinuses towards the fetal surface of the placenta and open into the trophoblastic channels of the placental labyrinth. A rich network of vessels in the uterine wall and beneath the placenta (shaded area) is also supplied by spiral arteries. There appear to be cross-connections between the arteries, which enable changes to occur in the relative distribution of uterine blood flow between the uterine wall and the placental sinuses.

medium alone depressed uterine activity for about 2 min (Text-fig. 4), a factor which had to be taken into account when assessing the myometrial responses to drugs.

**Noradrenaline**

When noradrenaline was injected, the uterine artery and its branches constricted, and both myometrial and maternal placental blood flow decreased (Pl. 1, Figs. 1 and 2). This response was obtained even with doses as small as 1 ng, but it could be blocked by prior administration of phenoxybenzamine (Pl. 1, Fig. 4). Large doses of noradrenaline (0-5 µg to 1 µg) caused almost complete arrest of myometrial and maternal placental circulation but, never-
Fig. 1. Pregnant rabbit, 25 days post coitum. Selective angiogram of the urogenital artery 7 sec after the start of contrast medium injection and before drug administration. The placental arterial sinuses are clearly visible (closed arrows) and a network of myometrial vessels reveals the contour of the uterine wall (open arrows).

Fig. 2. Same as Fig. 1, 31 sec after 0.01 mg noradrenaline, showing constriction of the uterine artery (arrow) and of its branches and a lesser amount of contrast medium in the myometrial and placental blood vessels.

Fig. 3. Same as Fig. 1, 38 sec after 0.1 mg phenoxybenzamine. Note the increased calibre of the uterine artery (arrow) and of its branches and the greater amount of contrast medium in the myometrial and placental blood vessels.

Fig. 4. Same as Fig. 1, 35 sec after 0.01 mg noradrenaline following the previous administration of phenoxybenzamine. There is no constriction of the arteries, which are still of increased calibre as compared with Fig. 1.

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Fig. 5. Pregnant rabbit, 25 days post coitum. Selective angiogram of the urogenital artery 10 sec after the start of contrast medium injection and before drug administration. The arrow indicates one of the efferent arteries from a placental sinus.

Fig. 6. Same as Fig. 5, 24 min after 60 μg phenolamine. Note the change in form of the uterine horn occasioned by uterine contraction, the smaller calibre of the efferent arteries from the placental sinuses (open arrow), and the earlier appearance of contrast medium in the uterine veins (closed arrow).

Fig. 7. Pregnant rabbit, 18 days post coitum. Selective angiogram of the urogenital artery, 6 1/2 sec after the start of contrast medium injection and before drug administration. The closed arrow indicates the uterine artery and the open arrow the arterial sinuses of one placenta.

Fig. 8. Same as in Fig. 7, 28 1/2 sec after 0.005 μg adrenaline. There is constriction of the uterine artery and its branches and less contrast medium in the myometrial blood vessels and placental sinuses.
theless, a small amount of contrast medium appeared in the uterine veins at the usual time.

The typical myometrial response to noradrenaline, a small contraction, 1 to 2 mm Hg in amplitude, followed by a depression of uterine activity, sometimes appeared when 0.2 µg were given. (Text-fig. 3), but was not registered at lower dosages.

**Adrenaline**

Injection of adrenaline led to constriction of the uterine artery and its branches and evoked a pronounced reduction of both myometrial and maternal placental blood flow. Even a dose as small as 5 ng had this effect (Pl. 2, Figs. 7 and 8). The response could be blocked by phenoxybenzamine and was enhanced by propranolol.

Adrenaline, in doses of 0.5 µg and above, elicited a single uterine contraction of 4 to 5 mm Hg in amplitude. This response was also blocked by phenoxybenzamine and enhanced by propranolol. Smaller doses of adrenaline had no discernible effect on the intrauterine pressure pattern.

**Phenoxybenzamine**

When phenoxybenzamine was injected, the uterine artery and its branches dilated, and both myometrial and placental blood flow increased (Pl. 1, Fig. 3). There was sometimes a simultaneous drop in carotid arterial blood pressure. The intrauterine pressure pattern was not noticeably affected by phenoxybenzamine administration.

**Thymoxamine**

Thymoxamine also increased blood flow through the myometrium and placentae. It had no discernible effect on the intrauterine pressure pattern in the doses tested.

**Phentolamine**

A slight increase in uterine blood flow was seen after injection of 30 µg phentolamine but no further effect was seen after doses of up to 250 µg. The initial effect was reversed by a dose of 500 µg, which reduced systemic arterial blood pressure. No change occurred in the calibre of the uterine artery and its branches. In the placentae, however, the calibre of the efferent arteries from the sinuses diminished, and the placental circulation time decreased (Pl. 2, Figs. 5 and 6).

The myometrial response to phentolamine, in doses of 100 µg and above, was very characteristic. It consisted of a series of contractions of 5 to 10 mm Hg in amplitude and lasted for about 15 min (Text-fig. 3). A smaller dose of phentolamine, 30 µg, evoked a slight increase in uterine tonus.

**Isoprenaline**

Isoprenaline did not clearly affect uterine blood flow except in one rabbit, where it improved an unusually small initial flow. Isoprenaline, in doses of 0.1 µg and above, depressed uterine activity for a short period, during which the pressure peaks were absent or of reduced amplitude (Text-fig. 4).
Text-fig. 3. Intraluminal pressure recorded from the left uterine horn of a pregnant rabbit 23 days post coitum. Arrows indicate injections of 0.2 µg noradrenaline (A), 0.4 µg noradrenaline (B) and 500 µg phentolamine (C), given selectively in the left urogenital artery. Angiography was carried out soon after the first noradrenaline injection, as shown by deflections of the lower trace, which records film exposures. The uterus responds to noradrenaline by a single contraction, followed by a period of relative inactivity. Phentolamine elicits a new pattern of activity, with a marked increase in the amplitude of the pressure peaks and a decrease in their frequency.
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Isoxsuprine
When isoxsuprine was injected, in doses of 10 µg and above, the uterine artery dilated, but the myometrial and placental blood flow was only slightly increased. Isoxsuprine had no consistent effect on the intrauterine pressure pattern, although a brief depression of uterine activity was occasionally noted.

Propranolol
Propranolol alone had no clear effect on the myometrial and placental circulations, nor did it influence the intrauterine pressure pattern.

DISCUSSION
The results clearly indicate that the maternal placental circulation is subject to sympathetic control. Blockade of α-adrenoceptors with phenoxybenzamine or
thymoxamine led to an increase in myometrial and placental blood flow. Conversely, stimulation with small amounts of noradrenaline or adrenaline drastically reduced blood flow throughout the myometrium and placentae, except when phenoxybenzamine had already been given.

These effects cannot be interpreted as responses of the vascular smooth muscle unless parallel changes in myometrial activity are taken into account. It is well established that both myometrial and placental blood flow can be reduced by strong uterine contractions, which compress the blood vessels (Prill, 1959; Borell, Fernström, Ohlson & Wiqvist, 1965). There was, however, no myometrial response to small doses of adrenaline or noradrenaline, nor did phenoxybenzamine and thymoxamine affect the intrauterine pressure pattern. Large doses of noradrenaline elicited a single contraction, followed by a depression of uterine activity, a sequence which has been demonstrated before in the rabbit (Cross, 1958; Fregnan & Glässer, 1964). A very pronounced reduction in blood flow was observed even during the period of myometrial inactivity and must have depended primarily on vasoconstriction.

Adrenaline and noradrenaline cause fetal growth retardation when given in large doses to pregnant rabbits (Cliff & Reynolds, 1959; Wier, 1965) and deviant behaviour has been demonstrated in neonatal rats whose mothers received adrenaline or noradrenaline during pregnancy (Thompson, Goldenberg, Watson & Watson, 1963; Young, 1963, 1964; Crist & Hulka, 1970). It has been suggested that these effects result from fetal respiratory distress due to diminished placental blood flow, but direct evidence has not been forthcoming. Robson & Sullivan (1966) found no decrease in the blood supply to the mouse placenta after adrenaline administration. The present study has, however, clearly established that the maternal placental vasculature is extremely sensitive to adrenaline and noradrenaline in the rabbit. The results can presumably be extrapolated to primates, as catecholamine administration to pregnant rhesus monkeys produces a severe fetal asphyxia that is not obtained when the drugs are given to the fetus directly (Adamsons, Mueller-Heubach & Myers, 1971). A substantial reduction in total uterine blood flow by adrenaline and noradrenaline has also been demonstrated in animals that lack the discoid, haemochorial type of placenta, such as pregnant dogs and sheep (Ahlquist, 1950; Adams, Assali, Cushman & Westersten, 1961; Greiss, 1963; Greiss & Pick, 1964).

The effects of phentolamine, which is usually described as a short-acting α-blocking agent, were more complex. Concomitant with the slight increase in uterine blood flow, there was an increase in myometrial tonus. When the phentolamine dose was increased, uterine activity was heightened, and no further improvement of uterine blood flow occurred. This may have been because dilatation of the vessels was balanced by their compression during myometrial contraction. The efferent vessels from the placental sinuses were, indeed, diminished in calibre, causing a decrease in placental circulation time. When the dose of phentolamine was so large as to cause a drop in systemic arterial blood pressure, uterine blood flow decreased again.

The action of phentolamine on the pregnant uterus was quite different from that of the other α-blocking agents studied. This was also unexpected as ac-
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According to Lish, Dungan & Peters (1960), phentolamine exerts no observable influence on the spontaneous activity of the non-pregnant rabbit uterus. In pregnant women, the administration of phentolamine reduces the uterine activity evoked by noradrenaline (Althabe, Schwarz, Sala & Fisch, 1968). Nobel & Hille (1965) found that phentolamine dampened the decreases of uterine blood flow which normally occur during labour contractions in women, and Prill (1959) observed increased myometrial blood flow in two of three women after phentolamine administration.

The β-blocking agent, propranolol, did not affect myometrial or placental circulation. Beta-adrenergic stimulation with isoprenaline gave an increased blood flow through the myometrium and placentae in only one rabbit. It seems, therefore, that if the vascular smooth muscle in the uterus possesses β-adrenoceptors, then these are of subordinate importance for the regulation of uterine blood flow. Greiss (1963) failed to find a consistent effect of isoprenaline infusion on myometrial activity in pregnant sheep but recorded a decrease in blood flow. Later analysis showed no effect of the drug on uterine blood flow, however, and it was concluded that only α-excitatory receptors were present in the ovine vascular bed (Greiss & Pick, 1964). On the other hand, Ahlquist (1950) reported that isoprenaline caused active vasodilatation of the uterine vascular bed in the pregnant dog.

Isoxsuprine has a papaverine-like effect as well as occupying β-adrenoceptor sites (Lish et al., 1960). This might explain why it caused a dilatation of the uterine artery in contrast to isoprenaline. There was only a slight increase in myometrial and placental blood flow after isoxsuprine. Brotanek & Hodr (1967) reported that myometrial blood flow increased in pregnant women during intravenous drip infusion of isoxsuprine.

Although there exist vascular connections which permit a redistribution of uterine blood flow between the myometrium and placentae (Carter et al., 1971), the drugs tested in the present investigation seemed equally to affect the myometrial and the maternal placental blood flows.

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REFERENCES


