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Uterine sensitivity for blastocyst implantation

ALEXANDRE PSYCHOYOS
Laboratoire de Physiologie de la Reproduction, CNRS ER. 203, Hôpital Bicêtre, Bâilment, INSERM, 94270-Bicêtre, France

Abstract. Attempting to analyse the role of the ovarian hormones upon the onset, magnitude and loss of uterine receptivity/sensitivity, particular emphasis is given to uterine vascular changes. Information concerning the modulation by hormones of uterine micro-circulation appears essential for the understanding of the receptivity/sensitivity uterine changes. The generation, storage and release of vasoactive mediators and prostaglandins appear involved. As shown in the rat recently, the onset of uterine receptivity/sensitivity is temporarily correlated with the appearance of endometrial PGE binding sites under hormonal control. On the other hand catecholamines may also modulate the uterine vascular functions. Endometrial monoamine oxidase and catechol *O*-methyltransferase two enzymatic activities involved in catecholamine deactivation show hormone dependant changes parallel to the manifestation of uterine receptivity/sensitivity. The precise role of these phenomena is discussed.

Keywords. Uterine; receptivity/sensitivity; blastocyst.

Irrespective of the highly variable way in which egg-implantation occurs in different species, all the events related to this process appear to follow a well-timed schedule. Thus, around the time at which the fertilized egg reaches the blastocyst stage, the uterus enters a phase of optimal conditions for co-participation.

We present here several criteria characterizing this uterine phase of receptivity for blastocyst implantation as defined mainly in rats. Among them we will more particularly describe the endometrial vascular reactivity towards the blastocyst stimulus or towards artificial stimuli leading to a decidual response. This reactivity is expressed by an increase in capillary permeability and appears to be, in all the species studied, a regular index of endometrial receptivity/sensitivity. It may be the result of a cascade-like effect involving various vasoactive tissular mediators, such as histamine and/or certain prostaglandins, just as a common inflammatory reaction.

The existence of an optimal time for the application of the stimulus which will initiate a decidual response is known since the classical studies of Loeb (1908). It has been further shown by De Feo (1967) that under controlled light conditions, the uteri of pseudopregnant rats acquire sensitivity to a knife-scratch trauma between days 5 and 6 of pseudopregnancy. By using the intraluminal injection of chemical inducers instead of a knife-scratch, De Feo demonstrated further that a peak of sensitivity appears around noon of day 5.

Histological examination of rat uteri fixed around noon of day 5 of pregnancy or pseudopregnancy shows an oedematous swelling of the endometrial stroma (Psychoyos, 1967). This transient stromal oedema is one of the phenomena which have to be considered as indicating the manifestation of optimal uterine conditions for

nidation. It occurs at the mid-luteal period, independently of the presence of an implanting ovum, in a variety of species including the human (Noyes *et al*., 1950). The obliteration of the uterine cavity resulting from this oedema must be essential for the implantation process, facilitating the primary contact of the blastocyst with the epithelial surface. Closure of the uterine lumen may also result from some specific functions of the luminal epithelium, namely pinocytosis and endocytosis. These epithelial activities must also be considered as indicators of the sensitive/receptive period. They must contribute to the removal of fluid from the uterine lumen but also to the uptake of material released eventually by the blastocyst.

In the rat, an ultrastructural correlate of the receptive endometrium is the presence, on the luminal surface of the epithelial cells, of sponge-like structures which can be observed under scanning electron microscopy (Psychoyos and Mandon, 1971). They appear to be "pinopodes" involved in the pinocytosis and endocytosis phenomena (Enders and Nelson, 1973; Parr and Parr, 1974; Parr, 1980). Abundant on the day of optimal sensitivity, they disappear thereafter. The presence of similar structures has also been observed in the human endometrium. According to our own observations, they are clearly distinguishable on days 18 and 19 of the cycle, are completely developed on days 20 and 21 and have largely regressed by days 22 and 23 of the cycle (Martel *et al*., 1981). Their presence in the human endometrium appears therefore limited to 24–48 h around the perinidatory period, indicating that the period of optimal conditions for egg-implantation must be short in our species too.

In the rat, either the natural decidualization due to blastocyst stimulus or the experimentally obtained decidual reaction is preceded by a dramatic increase in the permeability of the endometrial capillaries (Psychoyos, 1967). This vascular reactivity appears to be a *sine qua* non condition for the decidual response of the endometrium. Any procedure inhibiting this increase in permeability also inhibits decidualization. In a parallel way, the only period during which the endometrium is able to exhibit a change in vascular permeability in response to a deciduogenic stimulus, is also the only period during which such an endometrial stimulation leads to deciduogenesis. The degree of increase in capillary permeability, observed for instance after a traumatic stimulation, parallels the endometrial sensitivity for a post-trauma decidual reaction (Psychoyos and Casimiri, 1980).

Similar observations, concerning the occurence of an increased capillary permeability at the initiation step of the egg-implantation process, have been made in all the species studied. However, the factors linked to this phenomenon are not as yet defined with certainty. In the pathway leading to endometrial capillary reactivity, we can presume that a primary step may be the production of histamine through an activation of histidine decarboxylase, located near or in the endothelium of uterine small vessels. As known, histamine has been proposed by Shelesnyak several years ago to be involved in deciduogenesis (Shelesnyak, 1957). Recent findings have contributed to renew interest in this vasoactive amine. As shown in the rabbit by Dey and his collaborators, the intraluminal injection of a specific inhibitor of histidine decarboxylase on day 5 of pregnancy, interrupts the implantation process (Dey *et al*., 1978). Furthermore, in this species, the blastocyst itself exhibits a significant histidine decarboxylase activity which appears to reflect its own capacity to produce histamine (Dey *et al*., 1979a). In addition, rabbit endometrial cells were found to contain H^1 receptors (Dey *et al*., 1979b) *via*

which, in other systems, histamine binding can mediate vasodilation and increase vascular permeability.

It is considered that in general, during an inflammatory process, the vascular leakage induced by histamine is potentiated by prostaglandin generation. In the rat, in areas of increased vascular permeability induced by blastocysts or artificial stimuli, the concentration of prostaglandins of the *E* and *F* series and of prostacyclin are found to be increased (Kennedy and Zamecnick, 1978). On the other hand, the inhibitor of prostaglandin synthesis, indomethacin, given to rats on day 5 of pregnancy, inhibits the increase in endometrial vascular permeability in a transitory way (Kennedy, 1977). In pseudopregnant rats treated with this inhibitor, the intra-uterine injection of a saline/gelatin mixture does not increase the endometrial vascular permeability unless it contains prostaglandin E^2 (Kennedy, 1979).

Kennedy *et al.,* (1983 a,b) examined recently the hypothesis that uterine receptivity for blastocyst implantation and sensitivity for decidualization are controlled by the presence of receptors for prostaglandin E^2 in the endometrium. Our studies performed in rats led to the first demonstration of specific binding of prostaglandin E^2 to the endometrium of any species. A substantial increase in the concentration of endometrial binding sites for PGE is observed between days 4 and 5 of pseudopregnancy (Kennedy *et al*., 1983a). In ovariectomized animals the presence of binding sites for this prostaglandin was found to be progesterone dependant and detectable only when progesterone had been administered for 48 h or more. It is also of interest to know that the binding sites for PGE^2 were found to be located only in the stroma (Kennedy *et al*., 1983b). The role of the luminal epithelium may be in this case to produce this prostaglandin or to allow the transit of PGE produced by the blastocyst although both alternatives are also possible.

The decidual metamorphosis of the endometrium requires the involvement of the epithelium. Injury of the endometrial stroma without disruption of the integrity of the luminal epithelium does not induce decidualization (Fainstat, 1963). Similarly, the ability of traumatic stimuli to induce a decidual response is abolished if the luminal surface of the uterus is exposed to – 20°C for a few minutes (Ferrando and Nalbandov, 1968) or if the luminal epithelium is removed mechanicaly *in vivo* (Lejeune *et al.,* 1981). According to our recent observations, ablation of the epithelium interferes also with the occurrence of a post traumatic increase in capillary permeability (unpublished data). Obviously some factor essential for the uterine vascular reactivity is missing under these conditions.

Catecholamines may also modulate the vascular reactivity of the uterus. Monoamine oxidase and catechol *O*-methyl transferase, the enzyme complexes involved in their deactivation, show an increased activity during the luteal phase. We have shown that in the rat, the endometrial activity of both of these enzymes increases sharply by day 3 of pseudopregnancy remaining from then on at a plateau of high level (Rath *et al.,* 1979).

Catechol *O*-methyl transferase is also involved in catechol estrogens metabolism. The catechol structure of these hydroxylated estrogen products appears to confer to them an increased chemical reactivity and their physiologic role is the subject at the present time of intensive studies. Catechol estrogens appear to be involved in prostaglandin production. In homogenates of rat uteri, addition of 2-hydroxyestradiol increases the production of certain prostaglandins 4 fold, as compared with the increase induced by

the addition of estradiol-17β (Kelly and Abel, 1980). Through their agonistic or antagonistic effects towards estrogens, the catechol estrogens may also participate in the hormonal control of vascular reactivity of the uterus, particularly through the bias of their effects on prostaglandin production.

It is still too early for conclusions concerning the chain of events involved in uterine receptivity for nidation. It can however be considered that in terms of vascular reactivity, the presence of binding sites for prostaglandins at the stromal level favours their involvement in this reactivity. It seems also that the luminal epithelium is an indispensable intermediate for the vascular reactivity preceding decidualization. There are in these new informations several points which deserve to be further explored.

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