The kallikrein-kinin system along the different stages of gestation: Experimental and clinical findings

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We analyse the data accumulated on the description of the uterine kallikrein-kinin system in estrous cycle, pregnancy, pseudopregnancy and hormonal supplementation, and discuss the possible role of these findings in relationship to the vasoactive changes of gestation. We conclude that the evidence supports a participation of kallikrein in implantation and maintenance of uteroplacental blood flow. A decreased urinary kallikrein in women in conditions of an impaired uterine blood flow might be related to a deficient response of this vasodilator system.

Key terms: *egg implantation, gestation, kallikrein, kinins, uterine blood flow, preeclampsia, pregnancy*

INTRODUCTION

It is very significant for us to contribute to this volume with our work on the kallikrein-kinin system in female reproduction, and to honor Prof Héctor Croxatto for his lifetime dedication and contributions to research in vasoactive peptides. Our research line was started with his active collaboration in the late seventies (42), and has later counted with his permanent encouragement.

The kallikrein-kinin system (KKS) has been mainly studied as a counter-regulatory mechanism of the increased vasopressor activity of normal pregnancy (11, 18, 42, 43), the maintenance of normotension and decreased sensitivity to angiotensin II having been related to the increase in endogenous vasodilator agents during physiological pregnancy. On the contrary, pregnancy-induced hypertension in preeclampsia and idiopathic growth retardation are accompanied by decreased circulating and urinary vasodilator agents, including urinary kallikrein (11, 18, 20, 28, 38), reflecting its decreased synthesis in fetal and maternal tissues.

Contradicting this counter-regulatory role, the simultaneous measurements of kallikrein and plasma renin activity reveal that the rise in kallikrein does not parallel that of the pressor systems. Kallikrein increases in women during the first trimester of gestation (11, 43), and in rats on day 4th of gestation, preceding the rise of plasma renin activity by 8 days (37).

We hypothesize that the role of the KKS during pregnancy may be primordial, contributing to: a) early endometrial adaptations of the receptive phase; b) embryo implantation; c) trophoblast invasion; d) maintenance of uterine and feto-placental blood flow, once the placental circulation has been established; and e) parturition.

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In order to support the above hypothesis, we will discuss our own work related to the experimental demonstration of uterine kallikrein, its temporo-spatial localization and its regulation. In addition, data obtained by other groups and information about the KKS in human reproduction will be discussed.

DEMONSTRATION OF RAT UTERINE KALLIKREIN

We demonstrated the presence of kallikrein mRNA in rat uterii obtained in proestrus and day 7th of gestation. In addition, using a highly specific RIA for rK1 or true tissue kallikrein, two fractions of immunoreactive kallikrein-like proteins of approximately 41 and 123 kDa were purified from pregnancy day 7 uterine homogenates. These fractions preincubated with trypsin generated kinins from rat plasma kininogen (44). In uteri from rats in different stages of the reproductive cycle, a positive correlation between the determinations of immunoreactive kallikrein content and kininogenase activity was observed (9).

Working on rat uterii, other authors have demonstrated mRNA for four members of the kallikrein family (rK1, rK3, rK7 and rK9; Clements, personal communication), a kinin-generating enzyme, kininogen, bradykinin receptors and kininases (14, 23, 30), thus demonstrating the presence of all the KKS components.

KALLIKREIN-KININ SYSTEM CHANGES DURING RAT ESTROUS CYCLE AND GESTATION

Estrous cycle

The immunoreactive kallikrein content shows a recurrent pattern, with higher values in proestrus and lower ones in metestrus (8).

Since the KKS acts in a paracrine/autocrine manner, cellular localization by immunocytochemistry contributes to the understanding of its biological role. During the estrous cycle, kallikrein immunostaining is represented by a thin, interrupted rim at the apical border of the luminal and glandular epithelial cells. Occasionally, faint supranuclear staining is also observed. The intensity of the staining increased in proestrus (45).

Staining of bradykinin receptors has also been localized in the luminal and glandular epithelium, and in smooth muscle cells, using antibodies directed to the different domains of the B2 kinin receptor (14).

Early gestation

A rise in kallikrein content, which attains a peak by day 7th of pregnancy, has been observed in the rat (8). Ninety one percent of kallikrein immunoreactivity is localized in the implantation node and 9% in the interimplantation segment (44).

Immunohistochemistry shows at day 5th of gestation, stage in which the embryos contact the uterine wall, that the lineal epithelial reactivity increases in width and length, and in some areas becomes granular. At day 6th, when the trophoblast cells are in close association with the apical surfaces of the uterine epithelial cells, an increased kallikrein staining is observed, with granular accumulations being more numerous and occasionally protruding into the lumen. In some cells, granules occupy the whole cytoplasm and are intensely stained. At day 7th, when the trophoblast is penetrating the epithelial layer and decidual cells are well differentiated, the epithelial cells of the implantation chamber show immunoreactivity at their apical poles (Fig 1A). The immunostaining of glandular epithelial cells in the implantation segment shows a marked increase, while the interimplantation zone has scarce, faintly stained glands. The staining is entirely abolished by co-incubation of the antiserum with rK1 or rK7 (45).

Bradykinin receptor staining in epithelial cells increases in intensity, persists in blood vessels, and appears in decidua (Figueroa & Müller-Esterl, unpublished observations).

Mid and late gestation

Since it is difficult to obtain bloodless uteri, uncontaminated by circulating

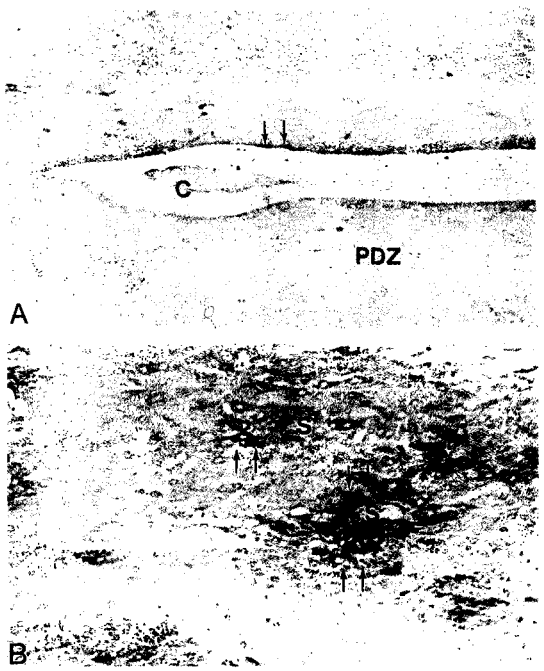

Fig 1. Immunostaining for glandular kallikrein in rat uterus. **A.** Implantation site in day 7th of pregnancy shows conceptus (C), and staining of apical portion of luminal epithelial cells; primary decidual zone (PDZ) is devoid of staining. X 200. **B.** Decidua basalis in day 21st of pregnancy shows staining surrounding sinusoids (S). X 100.

glandular kallikrein, we followed the kallikrein variations during gestation by immunocytochemistry (45).

At days 9th and 10th of pregnancy, an initial stage of placentation, kallikrein staining is neither observed in the cells of the ectoplacental cone, nor in the few and atrophied glands at the periphery of the mesometrial and antimesometrial decidua. At day 12th, immunoreactivity reappears as granules in the whole cytoplasm of fusiform decidual cells beneath the trophoblast invading the blood vessels of the central subplacental region. At day 14th, the extension and intensity of the staining increase. At days 16th and 21st the immunostaining is located in the subendothelial area of the maternal blood vessels at the base of the whole placenta (Fig 1B). At day 16, the staining is completely abolished by rK7, almost completely abolished by rK1, and partially reduced by incubation with rK2.

On day 14th, during established gestation, other authors have reported a kinin-generating enzyme in fetal membranes, placenta and uterine wall (27).

Plasma kininogen levels increase in response to estrogen (24), from day 17th of pregnancy and pseudopregnancy (25, 41). When a depletion of kininogen is produced, pregnancy and parturition are prolonged (26). Bradykinin contracts the myometrium by a direct uterotonic action and a prostaglandin-releasing effect (46). On the other hand, the use of aprotinin, an inhibitor of kallikrein activity, prolongs parturition (47). These effects, added to the presence of bradykinin receptors in the myometrium, support a role for the KKS in parturition.

REGULATION OF UTERINE KALLIKREIN

Kallikrein content was evaluated in pseudopregnancy, a condition that mimics the hormonal *milieu* of early pregnancy. Pseudopregnancy was attained by mating female rats with vasectomized males. Kallikrein rises 1.8-fold from pseudopregnancy day 1, reaching a plateau in days 6th and 7th (9). When intraluminal oil-stimulation was performed at the 5th day in pseudopregnant rats sacrificed 48 hours later, a 3- to 4-fold increase in immunoreactive kallikrein content was observed in the decidualized cornua, compared to the contralateral ones. In unilateral pregnancy, obtained in rats submitted to ligature and section of the left oviduct previous to mating, the fertile horn on day 7th of pregnancy –with the embryo as stimulus– has an immunoreactive kallikrein content 2 to 2.5 times higher than the sterile one. The kininogenase activity of this horn is significantly higher than that of the contralateral one (9).

Immunocytochemical studies reveal an increased kallikrein staining in luminal and glandular epithelial cells of the decidualized horn, as compared to its contralateral control. These findings suggest that the intraluminal stimuli, superimposed over a determined hormonal *milieu*, is a potent trigger for kallikrein biosynthesis (9).

Oophorectomized rats were supplemented with estradiol (0.5 μg/day, sc) or

progesterone (5 mg/day, sc) for 10 days. Estradiol elicited a 1.5-fold rise in uterine kallikrein concentration, while progesterone decreased it by 2-fold (9).

CONCLUSIONS DERIVED FROM THE EXPERIMENTAL MODELS (Table I)

It is interesting to consider that both the kallikrein content and the staining obtained by immunocytochemistry in the uterus increase in proestrus, and with the uterine epithelium preparatory changes coinciding with the day of higher estrogen levels and that which follows the estrogen peak, respectively. This agrees with the rise of kallikrein content observed after estradiol stimulation. The estrogen-dependence of kallikrein content has only been previously described for the rat anterior pituitary (32), where lactotrophs show weak immunostaining for kallikrein in ovariectomized animals, which markedly increases under estradiol (34).

Over the steroid stimulation, the embryo's contact in bilateral and unilateral pregnancy, or deciduomata induction by intraluminal oil instillation, is able to induce a further rise in epithelial staining. This demonstrates that the paracrine stimulation of the luminal epithelium constitutes a more potent trigger than the endocrine one.

With regard to the physiological role of the kallikrein-like enzymes in uterus, the present knowledge only allows the discussion of effects that can be attributed to true tissue kallikrein or rK1. This may generate kinins acting on its natural substrate, low molecular weight kininogen.

The apical orientation of kallikrein in epithelial cells suggests an initial luminal secretion (cycle and gestational day 5th), and a latter secretion to the stromal interstitium (days 6th and 7th), making it likely that the enzyme participates in the subsequent phases of apposition, adhesion and penetration of the initial materno-trophoblast interaction. It is assumed that the blastocysts or oil droplets act on the luminal epithelium and lead to the release of mediators that induce stromal cells proliferation, differentiation, and increased blood vessels permeability. The proposed mediators of decidualization have been histamine, prostaglandins, PAF and leukotrienes (1). The observations described above support the inclusion of the KKS in the cascade of interrelated vasodilator agents acting on endometrial vascular permeability and decidual transformation, as in the inflammatory process (33), which is akin to implantation. Exogenous bradykinin is a potent vasodilator of uterine vasculature (6, 35), and induces gaps in capillary endothelium which increase vascular permeability (15). In addition, bradykinin stimulates histamine release (4, 10, 17), and the vasodilator prostaglandins (PGE_2 and prostacyclin) (29).

Table I

The kallikrein-kinin system role in reproduction

Experimental findings:	Suggested roles:
Presence of kallikrein in luminal fluid and in secretory vesicles.	Blastocyst hatching.
Selective increase of kallikrein at implantation site. Response to luminal stimulation.	Blastocyst adhesion and penetration.
Kallikrein around decidual sinusoids.	Maintenance of blood flow.
Bradykinin contracts myometrium. Bradykinin receptors in myometrium. Parturition is prolonged by kininogen depletion and aprotinin.	Parturition.

Kinins are also mitogenic (36), and bradykinin stimulates the DNA synthesis in the endometrial stromal cells (12). It is worth remarking that, in early pregnancy, stromal cell mitotic activity is confined to the subepithelial and periglandular area (19).

The KKS has been involved in angiogenesis (16). Thus, bradykinin receptors in the ectoplacental cone (an active zone of angiogenesis), and immunoreactive rK1 surrounding the trophoblastic cells (invading the maternal vessels on days 12th and 14th), may promote development of maternal blood vessels in the mesometrial triangle.

On the 16th day, stage of "established" pregnancy, the presence of rK1 surrounding the sinusoids of the mesometrial subplacental triangle supports the intervention of the KKS on uteroplacental blood flow, as previously suggested by the effects of converting enzyme inhibitors in the pregnant rabbit (3, 40). The finding of bradykinin receptors in placenta suggests that decidual kallikrein could act on circulating substrate, and bradykinin could seep into the placental vessels. Here, as well as in the decidual blood vessels, its effect could be direct, or mediated by prostaglandins or nitric oxide (NO). The latter vasodilator agent of endothelial origin has been recently implicated in the maintenance of uterine arterial blood flow (31), and in bradykinin-induced relaxation of uterine arteries (21). Bradykinin constitutes a potent stimulus of NO synthesis, and could be related to the increase of uterine NO in proestrus, during gestation and under estradiol stimulation (49).

Though the KKS acts generally on apposed structures, the intervention of the system in a wider area is feasible through gap junctions, since two gap junction proteins –connexin26 and connexin43– have been found in a spatial pattern (48) that could enable epithelium-generated bradykinin to reach the primary decidual zone, which is provided with bradykinin receptors (Figueroa & Müller-Esterl, unpublished observations).

STUDIES OF THE KALLIKREIN-KININ SYSTEM IN WOMEN DURING GESTATION

In the human uterus, mRNAs for three kallikreins (hKLK1, hKLK2 and hKLK3) have been reported (7), and kallikrein-like activity has been found in the myometrium, placenta and amniotic fluid (22). Kininogen has been immunolocalized in human endometrial glands and myometrial arterioles (13). Bradykinin receptors have been found in epithelial and myometrial cells (14). *In vitro*, bradykinin stimulates the synthesis of vasodilator prostaglandins in the human amnion, decidua and chorion cells (2, 5, 12, 39), and DNA synthesis in endometrial stromal cells (12).

In normal gestation, urinary kallikrein is increased in the first trimester, to fall thereafter, and attain values close to nonpregnancy in the third trimester (11, 42, 43). In women close to parturition, a rise in urinary kallikrein has been observed (42). In late pregnancy, urinary kallikrein excretion is lower in women with pregnancy-induced hypertension, preeclampsia and intrauterine growth retardation (11, 18, 20, 28, 38). Urinary kallikrein excretion could reflect not only renal, but also uterine capacity of synthesis of kallikrein in response to a common stimulus in gestation, and thus could be a marker of the ability of maternal tissues to synthesize this vasoactive enzyme. On the contrary, the low levels of urinary kallikrein observed in late pregnancy in preeclampsia and fetal growth retardation could represent an incapacity to attain high levels in early pregnancy, contributing to the defective placentation and uteroplacental blood flow reported in both conditions.

We consider that the data here presented support the hypothesis that the KKS plays a role along experimental gestation, starting in the preparatory and first stages of the embryo-maternal crosstalk and ending with parturition. In this regard, it is important to consider that a vasodilated, edematous stroma, rich in mitogenic and angiogenic factors, is an ideal environment for an adequate trophoblast invasion, which on achieving a profound penetration of the

maternal uterine wall produces its own vasodilator agents. On the other hand, one might speculate that a vasoconstricted stroma could lie at the base of the shallow placentation observed in preeclampsia, intrauterine growth retardation and possibly preterm labor.

The role of the KKS in reproduction places this system in the most important process of species conservation, emphasizing Prof Croxatto's firm and long lasting belief in the importance of this ubiquitous system. The understanding of this role poses an exciting challenge for collaborative research between investigators in the fields of obstetrics and vasoactive systems physiology.

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