Local adjustment of blood and lymph circulation in the hormonal regulation of reproduction in female pigs – facts, conclusions and suggestions for future research

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SUMMARY

Arteries, veins, capillaries and lymphatic vessels situated in the mesovarium and mesosalpinx of domestic animal species (pig, cow, sheep) form the periovarian vascular complex. Particular components of the periovarian vascular complex interact functionally and morphologically creating a specific environment for numerous physiological processes. The complex plays an essential role in the system of the retrograde transfer of the ovarian hormones. This phenomenon is especially well documented in pigs. The efficiency of the retrograde transfer of estradiol and progesterone from blood and lymph leaving the gonad to blood of the ovarian artery (expressed as percentage of their concentration in the ovarian venous blood) as well as the rate of the retrograde transfer of these hormones to the ovary (measured in nanograms or picograms per minute) is presented and discussed in this paper. No simple relationship was found between hormone concentration in ovarian venous effluent and the efficiency or the rate of their retrograde transfer during the estrous cycle. It appears that two processes contribute to the highly efficient retrograde transfer of ovarian hormones into the ovary in the periovarian vascular complex: 1/ direct hormone permeation from the ovarian vein into the adjacent branches of

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the ovarian artery through the counter-current mechanism; 2/ indirect permeation of ovarian hormones consisting of two stages. The first stage includes the permeation of hormones from lymph leaving the ovary via the subovarian lymphatic vascular network as well as lymph and venous blood, leaving the mesosalpinx and going to capillaries and tiny venous vessels in the entire mesovarium. These tiny mesovarium vessels connect and then branch out again to form the veno-venous network on the surface of branches of the ovarian artery. The second stage includes the permeation of hormones from the veno-venous blood into the branches of the ovarian artery. The authors present a hypothesis that the retrograde transfer of ovarian hormones may participate in the feedback regulation of ovarian function. The relationship between the retrograde transfer of ovarian hormones in the area of periovary vascular complex and local elevation of steroid hormone concentrations in blood supplying the oviduct and uterus is presented. The paper also includes suggestions for future research. 

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I. RETROGRADE TRANSFER OF OVARIAN HORMONES IN THE PERIOVARY VASCULAR COMPLEX

Arteries, veins, capillaries and lymphatic vessels situated in the mesovarium and mesosalpinx of domestic animal species (pig, cow, sheep) form the periovary vascular complex. The vessels composing the periovary vascular complex are presented in figure 1 and they include:

- numerous, tortuous branches of the ovarian artery, which entwine or cover the branches of ovarian vein [4];
- tiny branches of the ovarian artery directed towards the muscular coat of the mesovarium and the mesosalpinx;
- arterio-arterial anastomoses carrying blood from the ovarian artery to the branches of the uterine artery supplying blood to the oviduct and uterine horn;
- capillaries of the entire mesovarium;
- tiny venous vessels carrying blood out of the mesovarium to the branches of the ovarian vein;
- the network of tiny venous vessels covering the surface of the branches of the ovarian artery [4, 34], identified as the veno-venous network [5, 26, 27, 31];
- subovarian lymphatic plexus and its outgoing pre-collector and collector lymphatic vessels passing through the mesovarium to the nearest lymphatic node [5, 6, 14, 15];
the ramified, dense network of tiny arterial, capillary and venous vessels of the mesosalpinx covering the entire area of the ovary, adjacent to the surface of the ovarian follicles and corpora lutea.

Fig. 1. Schematic diagram of the periovarian vascular complex and the mutual morphological and functional connections of the blood and lymphatic vessels; 1/ ovarian artery and its ramification; 2/ one of the helices of the arterial branch covered with veno-venous network; 3/ ovarian vein; 4/ uterine vein; 5/ arterio-arterial anastomoses connecting branches of the ovarian artery and uterine artery; 6/ uterine artery; 7/ lymphatic vessels carrying lymph from the ovary; 8/ lymphatic vessels carrying lymph from the uterus; 9/ lymph node.
The components of the periovarian vascular complex interact functionally and morphologically creating a specific environment for numerous physiological processes. The complex is known to play an essential role in the retrograde transfer of the ovarian hormones. This phenomenon is especially well documented in pigs [22, 23, 25, 26-31, 42, 43, 49]. To extend our knowledge gained from the previous studies conducted with the use of radio-labeled hormones, in our recent experiment we have used autologous blood and ovary as a source of endogenous hormones. This experiment performed on porcine reproductive organs supplied with autologous blood has shown for the first time that the ovarian artery blood flowing through its 10-15 cm long segment in the mesovarium is locally enriched with a surprisingly large amount of ovarian hormones [49]. The concentration of progesterone (P₄) in blood reaching the ovary was 46% higher in the luteal phase and 83% higher in the follicular phase, when compared to the concentration of the hormone at the beginning of the ovarian artery. The estradiol (E₂) concentration increased even more significantly: by 84% in the follicular phase and by 61% in the luteal phase of the estrous cycle. Thus, there is a retrograde transfer of ovarian hormones from blood and lymph leaving the gonad to vessels returning to the ovary.

In view of these data the following questions arise: 1/ What is the physiological mechanism of the significant retrograde transfer of ovarian hormones? 2) What are the physiological consequences of such local increase in ovarian hormones in arterial blood, which, in addition, vary in different phases of the estrous cycle?

Information concerning the regulation of the retrograde transfer of hormones in the periovarian vascular complex is limited. The counter-current transfer of radioactive steroid hormones from the ovarian vein into the ovarian artery was briefly reported in 1976 in sheep. Then it was extensively described in pigs [22, 26, 27, 31], sheep [10] and cows [23, 29]. In addition, the counter-current transfer of iodine-labeled oxytocin [43], relaxin and thyrozin [42] was documented in sheep and oxytocin in cows [25]. All in vitro or in vivo experiments conducted with radioactive hormones enabled to show only the transfer of hormone molecules from venous and lymphatic effluent to the arterial blood. They also allowed to determine the direction of the transfer. Such experimental model, however, was not helpful in determination of the efficiency and rate of the transfer.

This was due to either the difficulties in measuring blood flow in vessels or the presence of endogenous hormones which were transferred competi-
tively with isotope labeled exogenous hormone molecules. The mechanism
of hormone permeation remained still unexplained. Krzymowski and his
co-workers [27] investigated the veno-venous network covering the branches
of the ovarian artery and its origin. They presented a hypothesis that the
lymphatic vessels taking lymph with high concentration of the ovarian hor-
mones from the ovary [22, 44], might participate in the retrograde transfer
of ovarian hormones into the ovary [27]. A detailed map of these vessels and
their structure were not known at that time. Experiments [5, 14, 15] carried
out in the 1990’s revealed the presence of the subovarian plexus of lymphat-
ic vessels. At this time a structure and a course of the pre-collector and
collector lymphatic vessels in the mesovarium were reported [14, 15]. It was
also demonstrated that lymphatic vessels transport lymph from the sub-
varian plexus to the nearest lymph node situated in the mesovarium. They
encountered there a fascicle of lymphatic vessels carrying lymph from the
uterus and oviduct. These vessels were covered with a dense network of tiny
capillaries and formed a close connection with the rich vascularization of the
mesovarium [5, 15]. Tiny pores and fenestrated spaces able to change their
size and structure depending on the phase of the porcine estrous cycle were
found in the walls of the lymphatic vessels [6, 7]. Moreover, the presence of
endothelin and nitric oxide synthase was reported in lymphatic vessels [8].
This suggests that vasodilative factors as well as ovarian hormones may
participate in the regulation of the permeation of hormones, cytokines and
other regulatory factors through the walls of the lymphatic vessels. Recent
experiments on the role of lymphatic vessels in the retrograde transfer of
ovarian hormones were conducted using porcine isolated mesovarium sup-
plied with autologous blood [49]. These experiments showed that in both
phases of the estrous cycle, P4 infused into mesovarium lymphatic vessels,
close to the area of the removed ovary, reached both the ovarian vein and
the ovarian artery.

Studies on the vascular mesosalpinx provided new information that
appeared to be crucial for understanding the role of the retrograde transfer
in controlling the function of the ovary. The entire surface of a pig ovary is
tightly covered with the richly vascularized mesosalpinx. The dense vascular
network of the mesosalpinx is adjacent to the surface of corpora lutea and
ovarian follicles. Blood flow in the mesosalpinx fluctuates during the cycle:
it is high in the pre-estrous and estrous periods and significantly reduced
in the luteal phase. The experiments with radioactive testosterone demon-
strated that steroids which reach the mesosalpinx with blood, permeate directly into the follicles and corpora lutea, probably in accordance with their concentration gradient [28, 30]. This was also true for PGF$_{2\alpha}$ [24]. Moreover, it was demonstrated that ovarian P$_4$ may permeate in the opposite direction, i.e. from corpora lutea into the blood vessels of the mesovarium [1]. As already known, venous blood and lymph from the mesosalpinx can enrich the mesovarium with steroid hormones. This increase in hormone concentration may also influence the course of the retrograde transfer of hormones into the ovary [49].

Recently we demonstrated that due to the retrograde transfer in the periovarian vascular complex, every minute, a pig ovary obtained 18 pg of E$_2$ more than the normal hormone concentration in the peripheral arterial blood would ensure. Similar phenomenon was observed for P$_4$ but the enhanced amounts of the hormone were different during the phases of the estrous cycle: 35 ng in the luteal phase and 3 ng in the follicular phase. Approximately 17.5% of the P$_4$ and 12.6% of the E$_2$ found in the ovarian venous effluent was retrogradely transferred from the ovarian venous blood to the ovary during the luteal phase (see fig. 2; [49]). It was also demonstrated that the efficiency of the retrograde transfer of P$_4$ and E$_2$ into the ovarian artery supplying the ovary (expressed as percentage of their concentration in the ovarian venous blood) and the rate of the retrograde transfer (measured in nanograms or picograms per minute), depend on the phase of the estrous cycle (fig. 2). Studies conducted during the porcine estrous cycle did not reveal only an existence of a simple relationship between the hormone concentration in the ovarian venous effluent and the efficiency and the rate of their retrograde transfer. While the P$_4$ concentration in the venous effluent was ten times higher during the luteal phase than during the follicular phase, the efficiency of the retrograde transfer was similar in both phases of the cycle (fig. 2). The E$_2$ concentration in the ovarian venous effluent was twice as high in the follicular phase as in the luteal phase, yet the efficiency of the retrograde transfer was doubled in the luteal phase. In contrast, the rate of the E$_2$ transfer was similar in both phases (fig. 2).

The scheme of blood circulation in the mesovarium and its adaptations ensuring the high efficiency and the high rate of the retrograde transfer of hormones in the periovarian vascular complex is shown in figure 3. This figure is based on our results pertaining to permeation of radioactive steroids and vascularization of the mesovarium [26, 27, 28, 30, 31, 49] as well as the results of other researchers studying morphology of the lymphatic system in the mesovarium [5, 8, 14, 15].
Fig. 2. Concentration of progesterone (P₄) and estradiol (E₂) in ovarian vein blood, the efficiency of the retrograde transfer and the rate of the retrograde transfer of P₄ and E₂ in the luteal and follicular phase of the porcine estrous cycle. The data are presented as means ± SEM. The calculations were carried out according to the formulas: E=(a-b)x100/c and R=(a-b)xV; where: E – the efficiency of the retrograde transfer of the hormone to the ovary expressed as a percentage of the hormone concentration in the ovarian venous effluent, R – the rate of the retrograde transfer of hormone to the ovary measured in nanograms or picograms per minute, a – the hormone concentration in blood supplying the ovary in nanograms or picograms per ml, b – the hormone concentration in blood infused into the ovarian artery in nanograms or picograms per ml, c – the hormone concentration in the ovarian venous effluent in nanograms or picograms per ml, V – the volume of blood plasma infused into the ovarian artery in ml per minute.
Fig. 3. Schematic diagram demonstrating blood vessels supplying the mesovarium and the direct or indirect retrograde transfer of hormones; 1/ branch of the ovarian vein; 2/ branch of the ovarian artery covered with the veno-venous network; 3/ small ramification of the ovarian artery to the muscular layer of the mesovarium; 4/ small venules carrying venous blood from muscular layer of the mesovarium; 5/ the outlet of small venules formed from the veno-venous network into the branch of the ovarian vein; 6/ lymphatic vessels.
As shown in figure 3, direct and indirect permeation mechanisms contribute to the highly efficient retrograde transfer of ovarian hormones in the periovular vascular complex [50]:
1/ direct hormone permeation from the ovarian vein into the adjacent branches of the ovarian artery, which is carried through the counter-current mechanism; it is unclear whether this is an effect of an active transfer of hormones or occurs in accordance with the concentration gradient; it is also unknown if this permeation mechanism is influenced by other ovarian hormones or cytokines present in blood leaving the ovary.
2/ indirect permeation of ovarian hormones consists of two stages. The first stage includes the permeation of hormones from:
a/ lymph leaving the ovary via the subovarian lymphatic vascular network [5, 14, 15], transporting high concentration of ovarian hormones [16, 22];
b/ lymph and venous blood leaving the mesosalpinx and going to capillaries and tiny venous vessels in the entire mesovarium. Tiny venous vessels transporting blood from the dorsal and ventral lamina of the muscular coat and connective tissue of the mesovarium connect and then branch out again to form the veno-venous network on the surface of branches of the ovarian artery.

The second stage includes the permeation of hormones from the veno-venous blood into the branches of ovarian artery.

II. LOCAL ELEVATION OF STEROID HORMONE CONCENTRATIONS IN BLOODSUPPLYING THE OVIDUCT AND UTERUS

The local elevation of ovarian steroid hormone concentrations in the arterial blood supplying the oviduct and the uterus was demonstrated in experiments performed either on anaesthetized or conscious gilts. This was true in the follicular [48] and the luteal phase [45] of the estrus cycle as well as in early pregnancy [47].

The ovarian artery branches form near the ovarian hilus three to five arterial anastomoses, which connect the ovarian artery and the neighboring branch of the uterine artery supplying the oviduct and the uterine horn (fig.1). In contrast, in cows [25] and in sheep [4, 34] there is only a one arterial vessel several millimeters in diameter. Therefore, the increase in the ovarian hormones concentration in blood supplying the oviduct and the uterus is a result of the following (fig. 4):
- the rate of the retrograde transfer of ovarian hormones in the periovarian vascular complex
Fig. 4. Schematic diagram representing the efficiency of retrograde transfer of progesterone and estradiol into the ovary, oviduct and uterus during the luteal phase of the porcine estrous cycle.
- the function of the arterio-arterial anastomoses which can supply the uterine artery with varying volumes of blood from the ovarian artery. The latter vessel always contains higher concentrations of ovarian hormones than blood in the uterine artery.

In the experiments performed on cyclic gilts [45], blood was repeatedly collected from the cannulated branch of the uterine artery in four two-hour periods: 1/ under anesthesia during the surgery (day 10 of the cycle); 2/ under anesthesia after closing the abdomen on day 10; 3/ on conscious gilts standing in their stalls in the morning of day 11; 4/ on conscious animals in the afternoon of day 11. We demonstrated that the concentrations of progesterone and androstenedione in blood supplying the oviduct and the uterine horn were significantly higher (p<0.0001), 35% and 46% respectively, than the concentrations of the respective hormones in the peripheral blood. There were no significant differences in the hormone concentration between the blood samples collected from anesthetized and conscious gilts. Similar experiments were conducted on gilts on days 17 and 18 of the estrous cycle. It has been found that the concentrations of estrone and androstenedione were higher in the blood supplying the oviduct and the uterine horn than in the peripheral blood, by 45% and 66%, respectively [48]. Furthermore, we demonstrated [48] that during maternal recognition of pregnancy, formation of corpus luteum, implantation of embryo and elongation of placenta, the oviduct and uterus were also locally supplied with the arterial blood of significantly higher concentration of the ovarian hormones when compared to their concentrations in the peripheral blood (p<0.001). In blood collected from the uterine artery branch situated close to the ovary and connected to the ovarian artery by the anastomoses, the concentrations of progesterone, estradiol, estrone, androstenedione and testosterone were higher, from 18% to 69%, than those found in the peripheral blood. It was also demonstrated that the arterial blood reaching the part of the uterine horn distal to the ovary (adjacent to the uterine body) was also – although to a lesser degree – enriched in the ovarian hormones. The concentrations of ovarian hormones there were from 7% to 31% higher than those in the peripheral blood. Such phenomenon may be explained by the presence of arch-like junctions between the branches of the uterine artery running below the uterine horn. The junctions enable the arterial blood to flow from the branches placed closer to the ovary into the branches supplying the part of the uterine horn that is distant from the ovary.
COMMENTARY

The facts described in the previous paragraphs, show that 10–15 % of estradiol and progesterone, transported from the ovary with the lymph and venous blood are retrogradely transferred and returned to the ovary with the arterial blood. It is due to the functioning of a very complex system of the retrograde transfer of ovarian hormones. The difference between the concentrations of hormones in blood leaving and reaching the ovary is one of the factors affecting the transfer.

In 1982 we suggested [27] that subovarian mechanism of reabsorption and secondary utilization of hormones produced by the ovary forms a short regulatory loop. It is surprising that the physiological mechanism of such key importance in ovarian functions has not yet been elucidated. It has been known since the 1970's that the estradiol and progesterone secreted by the ovary participate in regulating the blood flow via the ovarian artery [11, 12, 37, 41]. It is also generally accepted that in the ovarian artery progesterone increases whilst estradiol decreases the blood flow [41], whereas in the area of the uterine artery these hormones work to the opposite effect [12]. Moreover, it has been reported that the neuro-adrenergic system participates in blood flow regulation through its alpha and beta receptors [12, 46]. We also know that locally formed dihydroxysterogens affect the alpha adrenergic receptors, contract the ovarian artery and limit blood flow into the ovary and oviduct [11, 50]. In addition, some reports were presented on local inflammations modulating the retrograde transfer of ovarian hormones, and thus influencing the hormone concentration in blood reaching the oviduct and uterus [32].

These discoveries formed foundation for a new approach towards the relations among the ovary, the oviduct and the uterus. The existence of the physiological mechanism that guarantees the satisfaction of the needs of the main reproductive organs (the uterus and oviduct) for ovarian hormones has been demonstrated. At the same time this mechanism maintains the steroid hormone concentration in blood reaching the central nervous system at a lower level. It is now known that in the early stages of pregnancy, the oviduct and the uterine horn are supplied with blood containing locally elevated steroid concentration [47]. Their highest concentration reaches the oviduct and the uterine horn adjacent to the ovary where the most important processes associated with implantation and embryo development take place. Moreover, according to Einer-Jensen [9], it can be assumed that the system of retrograde transfer of ovarian hormones ensures the transport
of free molecules – not associated with binding proteins – of steroid hormones to ovarian arterial blood supplying the ovary, oviduct and uterus. Our yet unpublished data (Stefańczyk-Krzybowska et al.) indicate that during pregnancy steroid hormones reach, via arterio-arterial anastomoses oviduct and uterus in increased amount as free particles.

Physiological regulation of the retrograde transfer of ovarian hormones has not been fully understood. The efficiency of the retrograde transfer of the ovarian hormones in the periovian vascular complex is the key factor affecting the transfer. Another essential factor is the volume of the arterial blood flowing through the arterio-arterial anastomoses. It is obvious that the blood flow via anastomoses determines inflow of hormone molecules to the oviduct and uterus. Moreover, it is known that estrogens reduce whilst progesterone increases the blood flow via the ovarian artery [11, 12, 37]. It is of interest that these hormones exert quite the opposite effect in the uterine artery. Thus, an important question arises: how are the arterio-arterial anastomoses connecting these two differently reacting areas of blood vessels regulated by progesterone and estrogens?

The local alterations in blood and lymph circulation – through changes of ovarian hormone concentrations in blood supplying the ovary, the oviduct and the uterus – are important for early pregnancy. In the early stages of pregnancy in pigs, cows and mares, 10 to 40% of embryos die for unknown reasons [33, 51]. It is also known that over 70% of the deaths were not caused by infections [2]. The true reasons, however, still remain undiscovered. In prior research careful attention was paid to \( P_4 \) which is responsible for creating suitable conditions for the development of the embryo and pregnancy [17, 18, 19]. Efforts were made to find the relationship between progesterone concentration in mothers’ peripheral blood and deaths of embryos [13, 38, 40] or infectious diseases of the uterus [3]. Moreover, Kucharski and Fitko [32] documented that infections of the periovian vascular complex influence the concentration of the steroid hormones in blood reaching the oviduct and uterus. There were no attempts, however, to examine whether an incorrect and limited transfer of \( P_4 \) or other physiological regulators from the periovian vascular complex into the oviduct and uterus is the cause of embryo deaths and uterus infections.

We are aware that the venous blood and lymph leaving the uterus and oviduct passes through the mesovarium which is adjusted to retaining and retrograde transferring ovarian hormones. It should be considered if other physiologically active compounds (prostaglandins E and F, growth factors, tumor necrosis factor, interferons and interleukines) leaving the oviducts
SUGGESTIONS FOR FURTHER RESEARCH

It is necessary to further analyze the demonstrated permeation of the steroid hormones directly from the surface of corpora lutea and ovarian follicles into the mesovarium vessels and from the mesovarium into corpora lutea and ovarian follicles. It is also necessary to determine whether, apart from steroids and prostaglandins, other factors like oxytocin, inhibin, activin and cytokines may also permeate from lymph and venous blood into other vessels. An intriguing issue is to investigate physiological consequences of such permeation.

It is very likely that fluctuating concentration of hormones in blood reaching the ovary affects ovarian function through local feedback. This hypothesis supported by the results of in vitro experiments of Leung et al. [35, 36] was previously presented. However, it has never been confirmed in in vivo conditions. Research should be aimed at exploring the effect of the increased – through the retrograde transfer – concentrations of steroid hormones (progesterone, estradiol, estrone, androstenedione and testosterone), oxytocin and cytokines in blood supplying the ovary. The influence of ovarian steroids on steroidogenesis has been reported to demonstrate the negative or positive feedback [35, 36]. It would be interesting to examine whether retrogradely transferred hormones have a direct influence only on their own synthesis or the syntheses of other regulatory factors.

In addition, it is important to analyze the role of activin and inhibin – the two main regulators of proliferative and secretory activity of granulosa and theca interna cells. It is very probable that the secretion of active dimers of activin (βA/βB) and inhibin (αA/βA) occurs through combining monomers that are excessive in the ovary. It was demonstrated that granulosa cells synthetize and release more α subunits than β. Thus, α subunits occur in significant quantities as monomers [20, 21]. The physiological role of inhibin monomers remains unknown. It is not clear if dimers, and especially monomers (10-15 kD) may be retrogradely transported to the ovary from
venous blood and lymph. It would be interesting to test whether secretion of activin and inhibin could be affected by the increased – as a result of the retrograde transfer – concentration of ovarian hormones in blood supplying the ovary. It is possible that various ovarian disorders such as the formation of ovarian cysts or persistent corpora lutea, disturbances in follicular maturation and lack of ovulation are caused by dysfunction in the retrograde transfer of the ovarian hormones in the periovarian vascular complex. This concept is supported by our observations of the reproductive organs of gilts carried out during laparotomy or slaughter. They reveal that serious pathological changes in the ovary, influencing the hormone secretion often take place only in one of the two active ovaries. It could suggest that the cause of serious disturbances in regulation of the female reproductive system may be the violation of not only central, as it is generally believed, but also of local physiological regulations.

To explain the relations among the ovary, the oviduct and the uterus, it is essential to answer the following questions:

1. What compounds, other than steroid hormones secreted by the ovary, are locally transferred from the periovarian vascular complex into the oviduct and the uterus during different reproductive stages? What is the significance of this transfer in regulation of the reproduction in females?

2. Whether, and if so, what physiologically active compounds secreted by the oviduct and uterus in different reproductive periods, may be retrogradely transferred into the oviduct and the uterus? What is the role of the periovarian vascular complex and arterio-arterial anastomoses connecting the ovarian artery with the uterine artery in this process?

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