Regulation of Endothelial Permeability in the Corpus Luteum: A Review of the Literature

Regulation endothelialer Permeabilität im Corpus luteum: eine Literaturübersicht

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Abstract

The development of the human corpus luteum (yellow body) is dictated by a strictly controlled system of mutually communicating cells, the luteal steroid hormone-producing cells and endothelial cells. This cell-to-cell communication facilitates control of neoangiogenesis which is a prerequisite for the development of the corpus luteum and its function, the rapid release of large amounts of progesterone into the blood-vascular system. Preconditions for this process are the hormonal regulation of endothelial cell proliferation as well as of vascular permeability through LH and hCG. The morphological correlates of endothelial permeability are cell-to-cell adhesion molecules such as adherens junctions (AJ) and tight junctions (TJ) that open and close the gaps between mutually interacting, neighbouring endothelial cells like a "zip fastener". Various types of cell adhesion molecules have been detected in the corpus luteum such as occludin, claudin 1 and claudin 5 as well as VE-cadherin. It may be assumed that the regulation of AJ and TJ proteins is of particular importance for the permeability and thus for the function of the corpus luteum in early pregnancy since hCG treatment leads to a down-regulation of cell adhesion molecules in the luteal vessels. This effect is apparently mediated by VEGF. From a functional point of view, the hCG-dependent and VEGF-mediated down-regulation of cell adhesion molecules leads to a reduced transmissibility of cell-to-cell contacts and thus to an increased endothelial permeability. In this process the various cell adhesion molecules are not only directly regulated by VEGF but they also mutually interact and thus influence one another.

Zusammenfassung

Die Entwicklung des humanen Corpus luteum ist durch ein streng reguliertes System von miteinander kommunizierenden Zellen, den lutealen Steroidhormon-produzierenden Zellen und den Endothelzellen, geprägt. Diese Zell-Zell-Kommunikation ermöglicht die Kontrolle von Neoangiogenese, die für die Entstehung des Corpus luteum Voraussetzung ist, und deren Aufgabe die rasche Freigabe von großen Mengen Progesteron ins Blutgefäßsystem ist. Voraussetzung für diesen Vorgang ist die hormonelle Regulation der Endothelzellproliferation sowie der Gefäßpermeabilität durch LH und hCG. Das morphologische Korrelat der endothelialen Permeabilität sind Zell-Zell-Adhäsionsmoleküle wie Adherens Junctions (AJ) und Tight Junctions (TJ), die „reißverschlussartig" den Spalt benachbarter interagierender Endothelzellen öffnen und schließen. Im Corpus luteum konnten verschiedene Zell-Adhäsionsmoleküle nachgewiesen werden, darunter Occludin, Claudin 1 und Claudin 5 sowie VE-Cadherin. Es ist davon auszugehen, dass die Regulation von AJ- und TJ-Proteinen von besonderer Bedeutung für die Permeabilität und damit die Funktionalität des Corpus luteum in der Frühschwangerschaft ist, da hCG-Behandlung zu einer Herunterregulation der Zell-Adhäsionsmoleküle in den Lutealgefäßen führt. Offensichtlich ist dieser Effekt VEGF-vermittelt. Funktionell betrachtet führt die hCG-abhängige und VEGF-vermittelte Herunterregulation von Zelladhäsionsmolekülen zu einer verminderten Durchlässigkeit der Zell-Zell-Kontakte und damit zu gesteigerter endothelialer Permeabilität. Dabei werden die verschiedenen Zell-Adhäsionsmoleküle nicht nur direkt durch VEGF reguliert, sondern sie interagieren auch untereinander und beeinflussen sich auf diese Weise gegenseitig.

Introduction

The corpus luteum (yellow body) is an intermediary, endocrine-active gland that alternately undergoes generation and degeneration in the course of the cycle. Hereby the corpus luteum plays a central role in maintaining pregnancy. The pre-ovulatory LH peak at first triggers ovulation and then induces the very rapid transformation of the ruptured follicle into a corpus luteum. This process proceeds mainly under the control of progesterone that is synthesised by the corpus luteum and is essential for implantation and the maintenance of pregnancy [1]. If a pregnancy does not occur, the corpus luteum degenerates 14 days after ovulation into a corpus albicans with transformed connective tissue. However, if the egg cell is fertilised the persistence of the corpus luteum is ensured both directly and indirectly by the joint effects of LH and hCG [2–7]. This observation is supported by the fact that the corpus luteum can be maintained in the absence of a pregnancy by exogenous administration of hCG [8].

The corpus luteum consists of various types of cells including endothelial cells, luteinised granulosa cells and luteinised theca cells. The endothelial cells are responsible for controlling vascular permeability which represents an indispensable prerequisite for the development of the corpus luteum. The permeability itself is controlled by the strictly regulated opening and closing of the cell-to-cell contacts between the endothelial cells [9–11]. For these reasons, any impairment of the expression of AJ and TJ can lead to a perturbed endothelial cell function with consecutive functional consequences such as, e.g., oedemas or ascites within the framework of an ovarian hyper-stimulation syndrome (OHSS) [12–14]. In such cases, the iatrogenous administration of hCG to support the luteal phase is effective; this increases luteal function but also increases the risk for the occurrence of OHSS [15]. Such a syndrome is characterised by an increased permeability of the capillaries which leads to a fluid shift from intravasal to extravasal spaces and thus to ascites [16]. In the following paragraphs the exact molecular mechanisms that participate in the regulation of endothelial function and thus the fluid barriers of the vessels are described. A better understanding of these mechanisms will hopefully aid the development of novel therapeutic options in the future and thus the ability to limit tissue damage by influencing vascular permeability.

Molecular Regulation of Endothelial Permeability

The paracellular endothelial permeability is controlled by at least two different types of cell-to-cell contacts, the AJ and the TJ. These are formed from various transmembrane proteins that promote homophilic cell-to-cell contacts and transmit intracellular signals [17]. It has been shown several times that these cell-to-cell contacts are dynamically transformed not only during embryonic development but also in resting cells [18]. Adhesion molecules such as AJ and TJ thereby form complexes that regulate the permeability in a zipper-like manner, i.e., the transmissibility of the gaps between neighbouring, mutually interacting cells [19–22].

Endothelial cells express tissue-specific transmembrane proteins: the AJ protein VE (vascular endothelial) cadherin and the TJ protein claudin 5 [9,23]. Claudin 5-deficient knockout mice show a normal embryonic development but die shortly after birth due to a defect of the blood-brain barrier [23]. In comparison, VE-cadherin-deficient mice suffer from numerous severe lethal defects in the course of embryonic angiogenesis [24]. This indicates that adhesion molecules not only have a structural but also a major functional relevance.

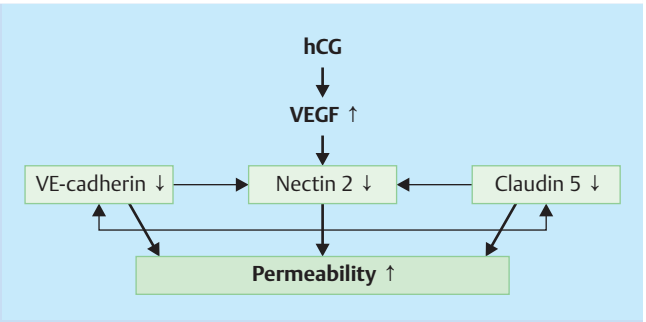

Fig. 1 Model for regulation of the vessel system in the corpus luteum.

Distribution of Cell Adhesion Proteins in the Human Corpus Luteum

Widely differing cell adhesion molecules can be localised in the corpus luteum. These include the TJ proteins occludin, claudin 1 and claudin 5 as well as the AJ protein VE-cadherin. The distribution of these cell-to-cell contacts naturally differs in the various compartments of the corpus luteum. In the human corpus luteum occludin can be detected ubiquitously in the membranes of endothelial cells in the vicinity of granulosa and theca capillaries as well as in the membranes of luteinising granulosa cells themselves. In contrast, however, occludin is not expressed in the domain of luteinising theca cells [25]. The detection of occludin in epithelial and endothelial cells has also been described for other types of tissue such as, e.g., rat lung, human liver, mouse brain, etc. [26–30].

Claudin 1 is exclusively expressed in the domain of the membrane of luteinising granulosa cells. In contrast to occluding, claudin 1 can only be discontinuously detected and not band-like. This distribution pattern is comparable with that which can be observed on the surface of human ovarian epithelium [31]. In contrast to the endothelial cells of the brain and salivary glands, claudin 1 is not expressed in the domain of luteal vessels [32,33]. Claudin 5, on the other hand, is exclusively and specifically localised in the endothelium of the human corpus luteum. Thereby it can be detected above all in the capillaries of the granulosa compartment and in the larger vessels of the theca [25]. VE-cadherin, on the other hand, can be detected not only in capillary endothelium of the granulosa but also in that of the theca. There is no unambiguous explanation for the so widely differing tissue-specific occurrence of these proteins, but it is apparent that in certain cell compartments a combination of various AJ and TJ is responsible for the mediation of cell-to-cell communication and adhesion [25].

Functional Relevance of hCG with Respect to Cell Adhesion Proteins in the Human Corpus Luteum

The cyclic growth and development of the corpus luteum is regulated by gonadotropins. During the normal cycle its life span is limited to 14 days under the influence of LH. In the case of a preg-

nancy the corpus luteum survives for several months due to the effect of hCG, this is known as "luteal rescue". It has been shown for the human corpus luteum that "luteal rescue" is accompanied by an expansion of the luteal vessels [34], which presumably involves a re-arrangement of cell adhesion proteins. Thus, it is of particular interest to examine the effects of hCG on AJ and TJ in the human corpus luteum.

In the "rescued" human corpus luteum of an in vivo pregnancy simulated by hCG, claudin 1 and occludin are significantly down-regulated in the luteinising granulosa cell compartment [25]. In addition, there is a decrease of occludin, claudin 5 and VE-cadherin in the endothelial cell compartment. It may be assumed that this hCG-dependent regulation of AJ and TJ proteins supported by the function of the corpus luteum is of exceptional importance for the maintenance of early pregnancy. The decrease in the expression of cell adhesion molecules in the luteinising granulosa cell compartment appears thereby to be a structural prerequisite for the liberation of steroidogenic molecules such as progesterone or vascular endothelial growth factor (VEGF) [35]. The development of the corpus luteum following "luteal rescue" is characterised by a structural new orientation. The down-regulation of cell adhesion molecules thereby leads to an increase of the intercellular gaps which, on the one hand, favours the expansion and invasion of new vessels and, on the other hand, increases the transmissibility of the endothelium. Both facilitate the distribution or, respectively, release of hormones into the bloodstream, which are necessary for the maintenance of the early pregnancy. This is additionally supported by the fact that hCG increases the permeability of vessels [36,37]. In rats this increase is associated with a lowered level of claudin 5 [37].

Influence of VEGF on Cell Adhesion Molecules in the Corpus Luteum of Primates

As described above in detail, it has been shown that hCG reduces the expression of cell adhesion molecules and thus affects luteal angiogenesis and vascular permeability. In addition it has been demonstrated that the inhibition of VEGF has an inhibitory effect on ovarian angiogenesis, development and function [38–40]. Furthermore, it was shown that VEGF controls cell adhesion molecules in the marmoset monkey.

The amount of occludin localised in the domain of the membranes of luteinising granulosa cells decreases continuously in the course of the ovulation phase until it can no longer be detected [41]. This loss of occludin seems to be involved in the formation of the antrum [42,43]. In contrast, in vivo inhibition of VEGF in marmosets by a VEGF antagonist (VEGF trap) leads to a significant increase in the amount of occludin [41], above all in the cytoplasmic domains where occludin itself has no function [44].

In the marmoset the TJ protein claudin 5 is exclusively detected in theca vessels and its amount increases in the course of follicle maturation. In the corpus luteum, claudin 5 is also expressed in the domain of the vessels. In this case, inhibition of VEGF leads to an increase of claudin 5. Apparently, claudin 5 plays an important part in the contact inhibition of endothelial cells. In this way the rate of proliferation of the cells is reduced and the vessels stabilise themselves [41]. As soon as individual endothelial cells come into contact with neighbouring cells, the adhesion molecules combine to form complexes and the endothelium is less impaired by the pro-angiogenic effect of VEGF. This cell adhesion is essential with regard to the regulation of angiogenesis [45].

For VE-cadherin it has been proven that this inhibition triggers a decline in the rate of angiogenesis and thus of vessel development [45]. Here VEGF acts as the key molecule for regulation of angiogenesis in the ovary [34,35,38,39,46]. Furthermore, a close relationship between VEGF and the signal transduction of cellular adhesion molecules has been demonstrated from functional considerations.

Cell Adhesion Proteins and Permeability

Some time ago it was demonstrated in an in vitro endothelial cell model that hCG apparently has a direct effect on the expression of VE-cadherin and on endothelial permeability [47]. However, the significance and the signal transduction of an assumed LH/hCG receptor are still not clear. It is proposed that the receptor exerts a hormonal transcytosis function and in this way transports gonadotropins directly to the target cell [48]. In order to study the molecular regulation of endothelial cells in the corpus luteum an in vitro co-culture model was developed. This consists of a two-chamber model of endothelial and luteinising granulosa cells in which their interactions can be studied as reactions on stimulating substances [49]. It was shown in vivo in the corpus luteum that the endothelial cell adhesion protein claudin 5 decreases after hCG treatment in the sense of a simulated pregnancy [25]; this was confirmed in the cell culture model described above. In addition, by means of hCG treatment in co-cultured luteinising granulosa cells an effect also on endothelial permeability was demonstrated for the first time [49]. Although a possible direct effect of hCG on endothelial cells cannot be excluded [47], it is apparent that the effects of hCG on claudin 5 and on permeability are of an indirect nature because they are only observed in the presence of luteinising granulosa cells. For this reason an hCG-dependent factor that is synthesised by the luteinising granulosa cells was assumed – and this factor is VEGF. The hCG treatment of luteinising granulosa cells does indeed lead to an increase of VEGF [49–51] and the action of VEGF on endothelial permeability has often been demonstrated in vitro [36, 47]. Thus, VEGF is considered to be an important paracrine factor that controls the regulation of endothelial cell permeability via an influence on adhesion proteins [52,53]. This has found support in observations in which the inhibition of VEGF in vivo suppresses not only angiogenesis but also permeability [45]. Conversely, VEGF in endothelial cells triggers the liberation of VE-cadherin and this, in turn, results in an increased endothelial permeability [49]. This fact does indeed point to a direct relationship between hCG, VEGF, cell adhesion proteins and increased permeability.

Interaction of Cell Adhesion Proteins in Endothelial Cells

Functional interactions of cell adhesion proteins that act as regulators of vascular permeability have been demonstrated for widely differing systems. In spite of the facts that the corpus belongs by far to the most highly vascularised type of tissue and that the control of permeability is of major significance for its function, these relationships have mostly remained unknown.

Cell adhesion proteins as dynamic complexes change their conformation not only during the embryonic development but also

in resting cells of the adult vascular system [54]. They interact thereby also with one another in the sense of a response to extracellular signals [55,56]. Accordingly, the co-existence of widely varying cell adhesion proteins for completely different tissue types in various species has been demonstrated. For the vascular system of the human corpus luteum it has been shown that the AJ protein VE-cadherin as well as the TJ proteins nectin 2 and claudin 5 are co-localised in the middle part of the luteal phase [57]. Treatment of luteinising granulosa cells with hCG in vitro thereby leads via VEGF-mediation to a reduced expression of these proteins. Beyond this, there is a functional relationship since VE-cadherin, nectin 2 and claudin 5 mutually regulate each other. Elimination of VE-cadherin or claudin 5 triggers a down-regulation of the respective other proteins whereas nectin 2 does not have a regulatory influence on VE-cadherin and claudin 5. These interactions are not only of a structural nature but also have a functional impact on the permeability of the endothelium. The hCG-induced down-regulation of the above-mentioned proteins leads to an increased permeability. Moreover, the separate elimination of VE cadherin, claudin 5 and nectin 2 in vitro also respectively leads to an increase in the permeability.

Taken together, this suggests that VE-cadherin and claudin 5 apparently play a significant part with regard to the regulation of permeability via nectin 2. In addition, nectin 2 itself has a direct influence on the permeability.

Since the three proteins discussed above are co-localised in the vascular system of the corpus luteum and can be down-regulated via VEGF by treatment with hCG, it can be assumed that hCG triggers a chain reaction via VE-cadherin and/or claudin 5, in order to control nectin 2 and concomitantly the luteal permeability (**Fig. 1**) [57]. These findings may be of therapeutic relevance in situations with pathologically increased endothelial permeability such as in, e.g. OHSS.

Conclusion for Clinical Practice

The occurrence of an hCG-induced increase of endothelial permeability is apparently mediated by VEGF. In cases of OHSS this mechanism may be responsible for the development of ascites and represent a possible therapeutic option in the sense of VEGF antagonism.

Conflict of Interest

None.

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