ANTIOXIDANTS & REDOX SIGNALING
Volume 9, Number 9, 2007

DOI: 10.1089/ars.2007.1713

Forum Review

Physiologic Angiodynamics in the Brain

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ABSTRACT

Hypoxic acclimatization includes increased brain capillary density. Adaptive angiogenesis, which occurs over a 3-week period, is mediated by upregulation of vascular endothelial growth factor induced by hypoxia-inducible factor-1 in concert with the capillary remodeling molecule angiopoietin-2, which is upregulated through cyclooxygenase-2 production of prostaglandin E_2. The process is apparently orchestrated by pericytes, which regulate the microvascular milieu and coordinate the interactions within the neurovascular unit. The return to normoxia is accompanied by microvascular regression and decreasing numbers of capillaries to prehypoxic densities. Regression is the result of endothelial cell apoptosis, suggesting the existence of physiologic mechanisms for adjusting capillary density to balance oxygen availability and oxygen consumption. The capacity for adaptation is diminished in older rats because of the attenuation of the hypoxia-inducible factor-1 response. *Antioxid. Redox Signal.* 9, 1363–1371.

THE MAMMALIAN BRAIN is dependent on oxygen and oxidative phosphorylation for the energy needed for normal function. Any interruption in blood flow to the brain reduces oxygen availability to the brain and is accompanied by immediate unconsciousness. Conversely, the cells of the brain, especially neurons, are vulnerable to too much oxygen because of the deleterious effects of excessive reactive oxygen species. Thus, it is no surprise that the partial pressure of oxygen in the brain parenchyma is well controlled, and normal brain function is exquisitely sensitive to continuous and controlled oxygen delivery.

Exposure to ambient hypoxia, such as that experienced during exposure to high altitude, produces a decrease in the availability of oxygen. As long as arterial blood-oxygen tension stays above ~45 torr, acute compensatory mechanisms are adequate to maintain function. This blood-oxygen level would be reached at about half the sea level pressure, which occurs at an altitude of ~18,000 feet, or a sea level Fio_2 of ~10%.

Continued exposure to mild hypoxia results in systemic and central adaptations that allow acclimatization of the organism (51). One of the more dramatic adaptations to hypoxia in the mammalian brain is the induction of angiogenesis with a near doubling of the capillary density that occurs between 1 and 3 weeks of exposure (12, 23, 58, 65). The cellular mechanisms through which hypoxia stimulates angiogenesis are now beginning to be understood and are the subject of this forum review.

HYPOXIA-INDUCED ANGIOGENESIS

Capillary remodeling

Our model system of hypobaric hypoxia is illustrated in Fig. 1A. After 3 weeks of exposure to 0.5 ATM, 380 torr, simulating an altitude of ~5,500 m, the capillary density in the rat cortex was significantly increased (52). The vascular remodeling occurred over a 3-week time course (Fig. 1B). The first structural changes begin between 4 and 7 days after onset of exposure to hypoxia, appearing initially as hypertrophic elongation and sprouting, followed by hypoplasia and endothelial cell division occurring after 1–2 weeks (40). These microvascular

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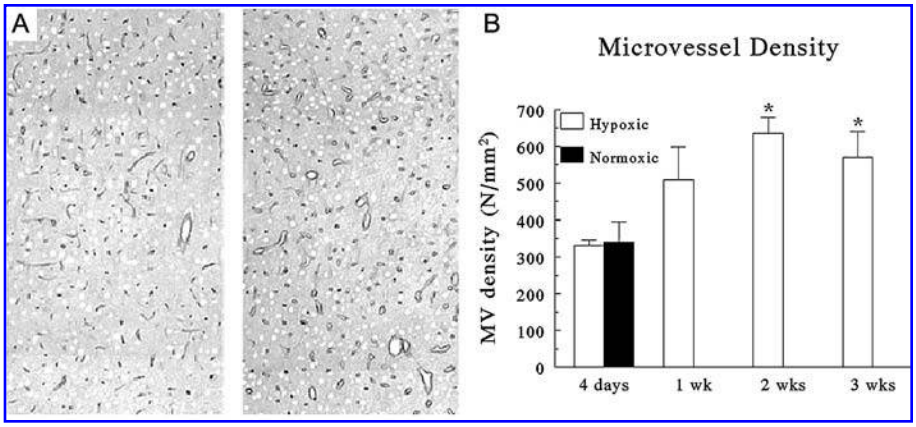

FIG. 1. (A) These are sections from the cerebral cortex of normoxic (left) and 3-weeks-old hypoxic rats immunohistologically stained for the endothelial GLUT-1 glucose transporter at the blood–brain barrier, as a marker of brain capillaries. (**B**) Capillary density counts from GLUT-1–stained rat cerebral cortical sections after 4, 7, 14, and 21 days of exposure to hypobaric hypoxia.

structural changes occur well after the systemic adaptations are established (*e.g.*, red blood cell polycythemia) and after the transiently elevated cerebral blood flow returns to the prehypoxic level (100). For these and other reasons, capillary remodeling appears to be a function of the local tissue oxygen tension (99). The structural changes not only include increased numbers of capillaries, but also increases in capillary-segment length (59), mean capillary diameter (86), and decreased basement membrane thickness (86).

The angiogenic response is similar in many ways to that in wound healing, but importantly, whereas wound healing takes ~3 days to complete, hypoxia-induced cerebral angiogenesis is spread out over a 3-week period. The adaptive response results in the reestablishment of tissue oxygen tension to prehypoxic baseline levels despite continued ambient hypoxia (27).

HIF-1

Low tissue oxygen tension seems to be the stimulus that initiates angiogenesis in this model. Low oxygen is sensed by the hypoxia-inducible factor-1 (HIF-1) (75, 83), a heterodimeric transcription factor with a constitutive component, HIF-1α, that is identical to aryl hydrocarbon receptor nuclear translocator (Arnt); and an inducible component, HIF-1α (94). HIF-1α is continually synthesized in all cells, but in the presence of oxygen, is rapidly hydoxylated and transported by the VHL factor to the proteasome for degradation (80). The levels of HIF-1α increase under hypoxia because of inhibition of the oxygen-requiring prolyl hydroxylase that is responsible for hydroxylating Hif-1α and directing its degradation (31). HIF-1 is a transcription factor complex involved in the activation of >50 genes that contain hypoxic response element(s) (HREs) in their promoter regions (82, 95, 96). Vascular endothelial growth factor (VEGF) is one such gene that is upregulated by HIF-1 and that plays an important role in capillary angiogenesis (30). HIF-1 accumulates rapidly under hypoxic conditions in all cells in the brain, reaching a maximum response within hours. HIF-1 is upregulated in pericytes for at least 72 h. With prolonged hypoxic exposure, overall HIF-1 levels gradually decrease, reaching about half of the maximal levels after 1 week of exposure; these levels persist until capillary restructuring is completed after 2–3 weeks (16).

VEGF

Total tissue levels of VEGF show a complex pattern, increasing rapidly during the first 4 days of hypoxia and then more gradually after 1 week (16, 50, 98). VEGF protein first appears in CNS capillary pericytes within 24 h of exposure to low oxygen (Fig. 2A, B), and in pericapillary astrocytes by 4 days (Fig. 2C). After prolonged periods of hypoxia, immunologically reactive VEGF is expressed throughout the capillary. It is unclear whether this represents synthesis of VEGF by both endothelial cells and pericytes or uptake of VEGF through endothelial VEGFR. It is possible that VEGF must be presented from one cell to another for maximal engagement of VEGFR. This might be expected if pericytes released VEGF very early in the induction phase. Other studies have shown that in the microenvironment, the presence of three-dimensional matrix or scaffolding proteins may be important in VEGF signaling cascades (37). VEGF signaling cascades may require coordinated release of other proangiogenic or synergistic factors (5, 25, 47, 68).

Ang-2

The Tie-2 receptor is important for the maintenance of mechanical stability of the capillary. Under normal conditions, the Tie-2 receptor is activated by its ligand, angiopoietin-1 (Ang-1) (43), which is constitutively expressed in capillary pericytes (87). Angiopoietin-2 (Ang-2), transiently elevated in endothelial cells and pericytes in hypoxic exposure (72), destabilizes the capillaries by occupying the Tie-2 receptor, preventing Ang-1 activation. *In vitro* exposure of pericytes to hypoxia transiently upregulates Ang-2 because of an inhibition of sonic hedgehog expression (53). Ang-1, Ang-2, and Tie-2 have been localized to pericyte interdigitations in endothelial cells at the early phases of rat angiogenesis (93).

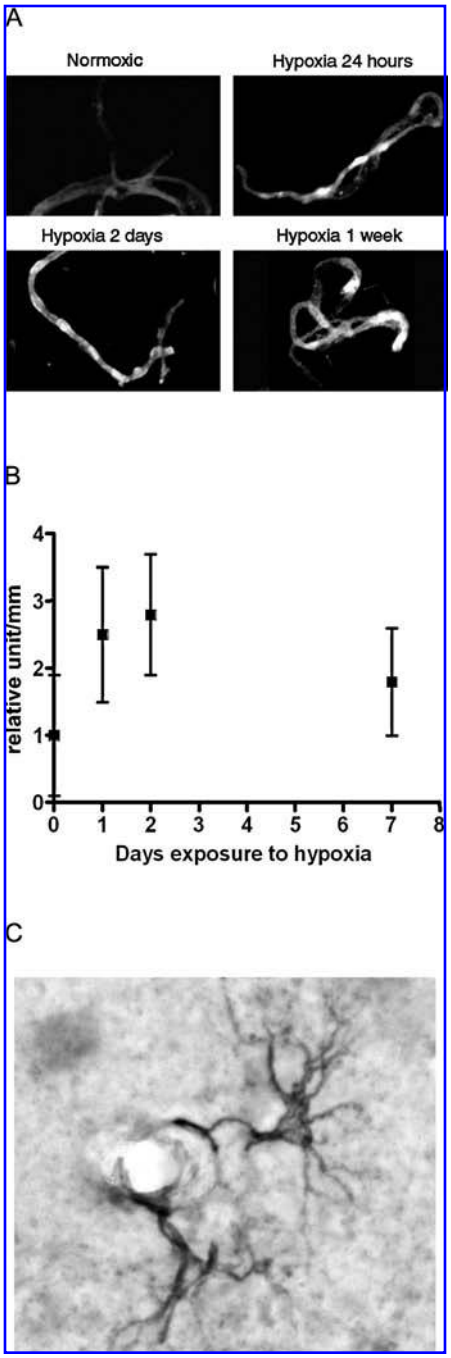

FIG. 2. (A) Cerebral cortical microvessels immunostained for VEGF after isolation from rats exposed to hypobaric hypoxia for 0, 1, 2, or 7 days. (**B**) Quantification of the data shown in **A.** (**C**) VEGF immunostain of a cerebral cortical section from a rat exposed to hypobaric hypoxia for 4 days.

In vitro, in both human umbilical vein endothelial cells (HUVECs) and bEnd3 cells, Ang-2 is induced by prostaglandin E_2 (PGE_2) as a result of hypoxic upregulation of cyclooxygenase-2 (COX-2). This hypoxic Ang-2 induction is independent of HIF-1 (71). The Ang-2 is found primarily in capillary endothelial cells and pericytes. The pericyte expression of Ang-2 is transient and is found to decrease as pericytes migrate from vessels.

PERICYTES AND ANGIOGENESIS

Pericyte-specific signaling in the regulation of angiogenesis has not been well defined. Much of what is known of the pericyte angiogenic response has been inferred from predominantly pathologic studies, and little is known of the role of the pericyte in physiologic angiogenesis (4, 7, 15, 76). Pericytes appear to function at three stages of angiogenesis: (a) initiation (6, 56, 76, 92, 102), (b) sprout extension and connection (34, 67, 85), and (c) termination or maturation of newly formed vessels (7, 29, 81, 87, 93, 104).

At the initiation phase of angiogenesis, pericytes play a central role through their production of TGF-β (20, 92), VEGF (55), and possibly other proangiogenic factors (28, 69, 92). Pericytes undergo changes that effect vascular permeability. They become activated and migrate from the vessel concomitant with an increase in Ang-2, making way for new sprout formation (22, 36, 38, 60). For example, pericytes migrate from microvessels, through a mechanism involving urokinase, into the perivascular space by 24 h after traumatic brain injury (26). Pericyte migration in response to hypoxia in cats has also been reported (35).

Pericyte migration involves a coordinated signaling cascade that involves early release of prostaglandin J_2 (PGJ_2) (25), and cellular and pericellular proteases such as uPA, aminopeptidase, and matrix metalloprotease (91). After exposure to hypobaric hypoxia, the pericyte-to-endothelial cell ratio in isolated capillaries decreases by 1 week and returns to normal by 3 weeks, at which time renewed pericyte coverage occurs.

In later stages of angiogenesis, pericytes guide the migrating endothelial sprouts, regulate proliferation, and form connections between newly formed vessels (63, 64, 66, 93). Pericytes proliferate in response to angiogenic factors such as VEGF (102) and have VEGF receptors. Pericyte replication during angiogenesis may also involve endothelin-1 (101). Pericytes terminate angiogenesis concomitant with recruitment to and renewed coverage of the new capillaries. Pericyte recruitment involves expression of N-cadherin, as pericyte recruitment, but not endothelial cell sprout formation and differentiation, is inhibited in knockout animals (89). Pericyte recruitment to newly formed vessels also requires heparin sulfate proteoglycan tethered PDGF-β (1), and possibly metalloprotease–integrin interactions (15). A reduction in Ang-2 is also essential in pericyte recruitment to newly formed vessels, as this recruitment is inhibited by Ang-2 overexpression (29). Ang-1 is, however, transiently increased in pericytes before renewed pericyte coverage. It is possible that Ang-1/Tie-2 signaling functions during pericyte recruitment (70). Inhibition of Ang-1 decreases hepatocyte growth factor–mediated recruitment of pericytes (49).

TWEAK

TNF-like weak inducer of apoptosis (TWEAK) (TNFSF12) is a novel member of the TNF superfamily (97). TWEAK has an important role in host defense, inflammation, autoimmunity

(2, 14, 103), and differentiation (3, 57, 73). Like most members of the TNF family of proteins, TWEAK exists as a transmembrane protein and a secreted soluble protein. Full-length TWEAK (30–35 kDa) is a type II membrane-bound protein. The processed form of TWEAK (18 kDa) composing the extracellular portion of the intact molecule is the secreted form of TWEAK or sTWEAK. Soluble or released TWEAK has biologic activity, having been shown to induce apoptosis (19, 46, 62), NF-κB activation (13), and proliferation and angiogenesis (45, 54).

Wiley and colleagues (97) identified a novel TWEAK receptor, TWEAKR, by expression cloning by using recombinant soluble Tweak. TWEAKR is identical to the FGF-inducible 14-kDa protein (Fn14). Fn14 was identified as a growth factor–inducible molecule in fibroblasts. TWEAK mediates angiogenesis and proliferation through Fn14 (24, 41). An alternative TWEAK receptor may also exist, as TWEAK-induced differentiation of raw cells into osteoclasts was not mediated by Fn14 (73). TWEAK can be internalized in a variety of cell lines and translocates to the nucleus, colocalizing with glycogen synthetase kinase-3B (GSK-3B) (21). This internalization was independent of Fn-14. It is possible that TWEAK is also capable of using a ubiquitous mechanism of internalization. Thus, TWEAK may exert both receptor-dependent and receptor-independent biologic activity that may regulate vascular remodeling.

WEAK and angiogenesis

TWEAK is expressed, at least at the RNA level, in many normal tissues; however, relatively few cells are functionally sensitive to TWEAK. These cells have the capability of producing TWEAK and TWEAKR protein. Regulation of protein translation, secretion, and autocrine and paracrine regulation is not well understood. TWEAK and TWEAKR are co-expressed in tumor cells, and TWEAK is highly expressed in aortic smooth muscle cells (61, 90) suggesting that it is important in angiogenesis. TWEAK secreted from tumors induced proliferation of HUVECs and tubelike formation and migration (24, 48, 54). Tubelike formation was inhibited with anti-TWEAK neutralizing antibody. The mechanism of TWEAK-mediated angiogenesis is not well understood. TWEAK has been shown both to potentiate VEGF (45) and FGF-2 (24, 54) mitogenic activity, and in another study, to have no effect on VEGF activity (48). It is unclear whether these differences reflect different stages of angiogenesis or differences between angiogenic models. Most studies were performed by using cell lines or HUVEC. Such systems do not reflect the multicellular nature of the vasculature. Both cell lines and HUVEC bear little resemblance to the cells of the blood–brain barrier (BBB).

We found that CNS pericytes express relatively large amounts of TWEAK transcript. The amount of mRNA increases with time in culture and correlates with an increase in pericyte rate of proliferation. Expression of TWEAK transcripts also increased in response to hypoxic stress. Hypoxia-induced TWEAK expression was observed within 18 h after exposure to low oxygen (Dore-Duffy, unpublished observations).

We also investigated the role of TWEAK in hypobaric hypoxia-induced CNS angiogenesis as well as in an *in vitro* model of hypoxia-induced angiogenesis. On exposure to low oxygen, CNS capillary TWEAK and its receptor FN14 are moderately increased (Fig. 3). TWEAK and FN14 do not fundamentally change until maximal capillary density is reached. TWEAK protein is greatly enhanced on restoration of normoxia, suggesting that TWEAK may have a role in vascular regression. Preliminary data indicate that exogenous administration of TWEAK augments the rate of hypoxia-induced pericyte-mediated endothelial cell tube formation *in vitro*. The addition of neutralizing antibody to TWEAK inhibited pericyte-induced tube formation. It is unknown whether TWEAK signaling is restricted to an autocrine function involving the pericyte alone, or whether paracrine signaling of the endothelial cells occurs.

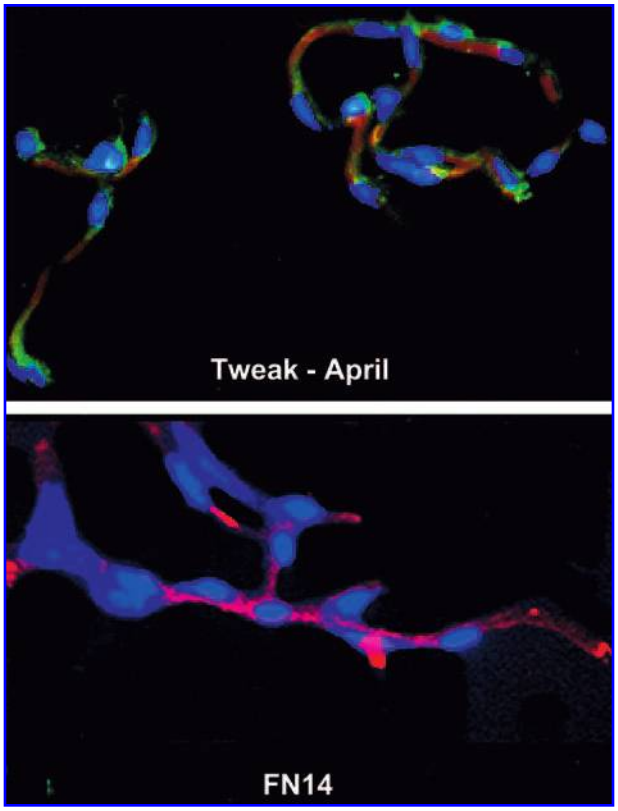

FIG. 3. CNS microvessels express immunologically detectable TWEAK, TWEAKR/FN14, and APRIL. Rat cortical capillaries were isolated, fixed, and permeabilized with Triton X-100 and then stained for expression of TWEAK, its receptor FN14, and TNF family member APRIL. A dual stain for TWEAK (red) and APRIL (green) is shown on the left. TWEAK is expressed in both pericytes and endothelial cells. APRIL appears to localize with round nuclei, consistent with a localization at pericytes. As APRIL is a secreted protein, immune detection within the vessel suggests that APRIL is anchored in by TWEAK and expressed in pericytes as TWEPRIL. The TWEAK receptor FN14 is expressed in both pericytes and endothelial cells (right). Nuclei were stained with DAPI. Representative vessels were chosen.

NORMOXIC PRUNING

When rats that have been previously exposed to hypoxia for 3 weeks are then reintroduced to a normoxic environment, a gradual loss of capillaries is seen over a 3-week period until the original capillary density is restored (39). This capillary regression is associated with increased Ang-2 and is accomplished through an apoptotic process (72). Thus, it is apparent that Ang-2 is necessary for capillary restructuring. In the presence of VEGF, Ang-2 leads to angiogenesis; in the absence of VEGF, Ang-2 leads to apoptosis (42). Under these conditions, an increase in Ang-2, but not HIF-1 was found. This microvascular pruning was mediated through a caspase-3–dependent/ TUNEL-positive mechanism, suggesting a physiologic apoptosis mechanism.

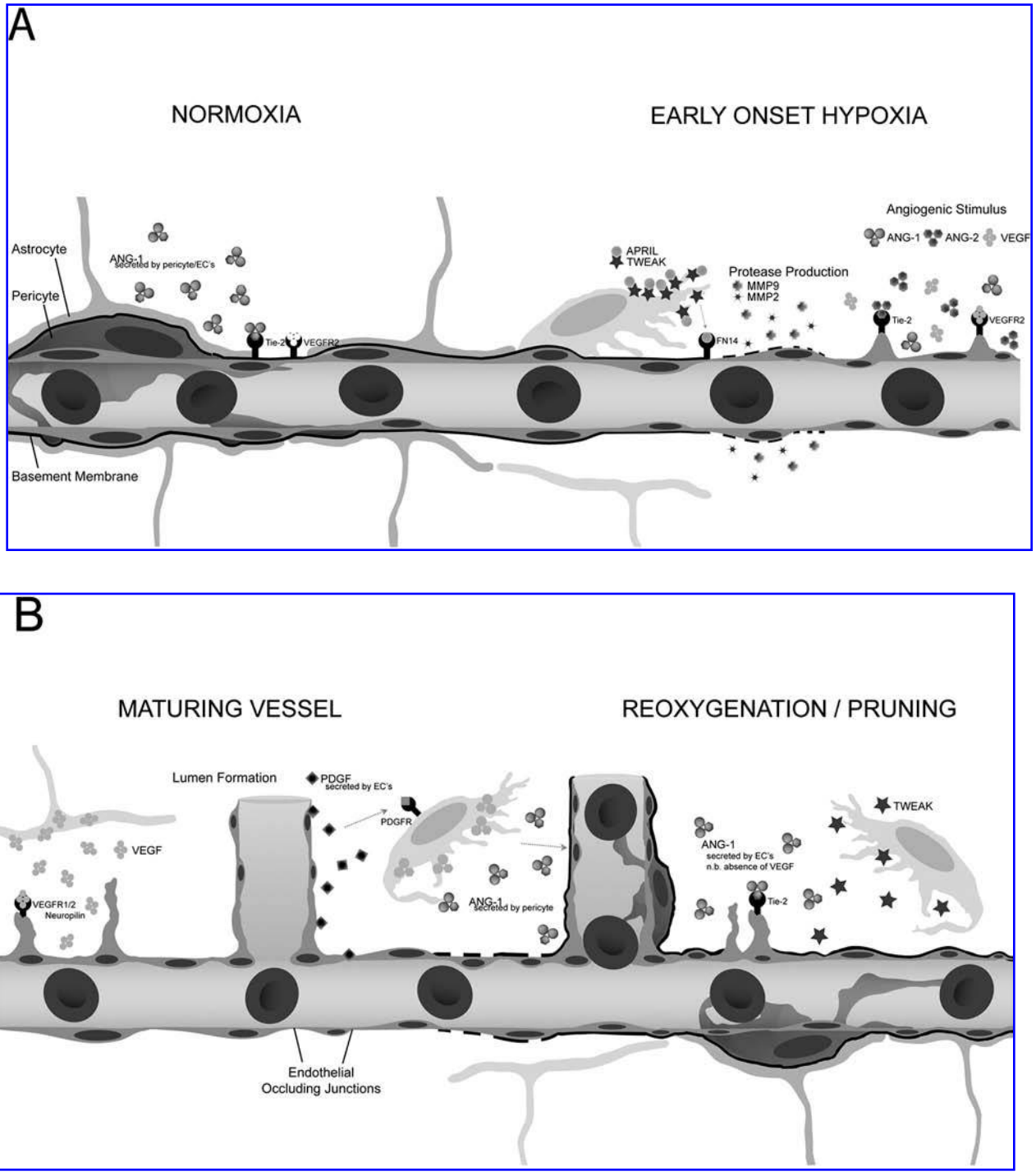

FIG. 4. Scheme depicting the process of angiodynamics.

ANGIODYNAMICS

The scheme shown in Fig. 4 summarizes what is known about capillary homeostasis and remodeling. First is shown the stable capillary. In this state, the capillary endothelium tight junctions and basement membranes are intact. Pericytes are quiescent, and astrocyte endfeet enclose the structure. This state is maintained by activation of endothelial Tie2 receptors by Ang-1 secreted by pericytes and endothelial cells.

On hypoxic exposure, HIF-1 accumulates, leading to upregulation of VEGF. Increased VEGF first occurs in activated pericytes and then after a few days in pericapillary astrocytes. The activated pericytes release, among other things, TWEAK that upregulates MMP9 through activation of the NF-κB signaling pathway. The activated pericytes pull away from the endothelium, and both pericytes and endothelial cells secrete Ang-2, which binds to the endothelial Tie2 receptor, interfering with the Ang-1 signal. Ang-2 is upregulated by PGE_2 that is produced by upregulated COX-2. Thus, the mechanical stability of the capillary begins to be compromised.

Next, VEGF from astrocytes reaches the endothelial cells and stimulates growth and then cell division and the formation of capillary sprouts. Once the new capillaries have become functional and the tissue hypoxic signal is reduced or eliminated, the capillary returns to the stable state. The process of hypoxia-induced angiogenesis requires 2–3 weeks to complete.

If the hypoxic acclimatized rat is then returned to normoxia, COX-2 is again upregulated, by an unknown mechanism, and Ang-2 is produced by pericytes and endothelial cells. TWEAK is also upregulated, and capillary structural stability is again compromised. In the absence of VEGF, the capillary endothelial cells are induced to undergo apoptosis, and the subsequent capillary regression returns capillary density to normoxic levels. This process also takes 2–3 weeks.

Hypoxic stimulation of angiogenesis and the regression that follows renormalization of oxygen are not unique aspects of brain vascular function. Angiogenesis and increased capillary density are found also in training and motor learning (8, 10, 11, 44, 88).

In the adult, a close coordination is found between the rate of oxygen/glucose consumption and capillary density, and if the average energy demand changes over time (as in motor training), then the capillary density apparently adjusts. This process takes a few weeks. These findings suggest that capillary density is dynamic and is influenced by factors such as energy demand and oxygen availability. In addition to oxygen availability, a signal appears to be related to energy substrate availability, possibly related to TCA cycle intermediates such as succinate. Rats kept on a ketogenic diet for >2 weeks exhibit an increase in HIF-1 and an increase in capillary density (74).

This overall process of matching capillary density to the balance of energy/supply can be termed "angiodynamics." The presence of physiologic mechanisms for increasing and decreasing capillary density (*i.e.*, a bidirectional plasticity) gives more support to the idea that a continuous matching of capillary density/structure and tissue oxygen/energy balance occurs. The identification of the mechanism of capillary regression is important because it may be the first example of physiologic apoptosis in the adult mammal. Therefore, activation of apoptotic pathways after pathologic stimuli such as ischemia could occur through augmentation of intrinsic mechanisms, as opposed to initiation of dormant processes. The implications are far reaching. The interference or failure of these mechanisms may play an important role in the pathophysiology of degenerative diseases, epilepsy, ischemia, and any condition that involves metabolic stress or alters the metabolic state of the tissue or the microvasculature.

If indeed mechanisms are responsible for continuous maintenance of capillary density in the brain, then the possibility exists that interference with these mechanisms could lead to pathologic circumstances. In this regard, it is interesting to consider the finding that the responsiveness of HIF-1 to hypoxia, but not to cobalt chloride, wanes with age (18, 32). It is possible that the lack of HIF-1 response results in the lack of VEGF (78) and a failure in the ability to adapt to hypoxia and the diminution in the capacity to match neuronal activity and capillary density (9, 79). Thus, the inability to maintain capillary density results in lack of plasticity, with all the consequences that might be expected for learning, training, and even neuronal survival (32, 77). New insights into the mechanisms responsible for these phenomena might allow therapeutic manipulation (increasing or decreasing, as appropriate) of these pathways, for example through activators of HIF-1 such as IGF-1 (17) or prolyl hydroxylase inhibitors (84), and inhibition of Ang-2 by COX-2 inhibitors (71) or PGE_2-receptor agents (33).

ABBREVIATIONS

Ang-1, Ang-2, Angiopoietin-1 and -2; APRIL, a proliferation-inducing ligand; COX-2, cyclooxygenase-2; Fio_2, fraction of inspired oxygen; HIF-1, hypoxia-inducible factor-1; HRE, hypoxic response element; HUVEC, human umbilical vein endothelial cell; PGE_2, prostaglandin E_2; TWEAK, TNF-like weak inducer of apoptosis; VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau protein.

ACKNOWLEDGMENTS

This research was supported by the National Institutes of Health, R01-NS38632 and P50 GM066309. Constantinos Tsipis, Xiaoyan Sun, Bernadette Erokwu, Michelle Puchowicz, and Kui Xu contributed to the previously unpublished experiments, diagrams, and figures.

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Date of first submission to ARS Central, April 25, 2007; date of acceptance, April 25, 2007.

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