RECOGNITION OF THE IMPORTANCE of cerebral blood flow (CBF) control can be traced back to the 1890 publication of Roy and Sherrington entitled “On the regulation of the blood supply of the brain” (6). On the basis of limited experimental evidence, these authors postulated that local changes in cerebral functional activity and perfusion are coupled. However, this concept did not achieve wide acceptance for many years until better tools permitted more in-depth investigations into cerebral hemodynamic regulation. The new information gained from the application of these tools to investigations of CBF regulation not only confirmed the linkage between flow and functional activation alluded to by Roy and Sherrington but also permitted researchers to gain an understanding of CBF responses to changes in circulating levels of the vital metabolic fuels, oxygen and glucose, and responses to metabolic “waste products,” like CO₂. Thus dilation of cerebral arteries and increased CBF occurs when blood O₂ or glucose content falls below a certain level or when arterial PCO₂ rises. In the case of O₂ and glucose, the increased perfusion will limit the fall in substrate delivery and possibly prevent neuronal damage.

The expansion of our knowledge of CBF regulation, to an important extent, parallels the evolution of the technologies used in studying cerebral hemodynamics. A milestone in the technologic “evolution,” and the explosion of information that ensued, relates to publications by Kety and Schmidt in 1945 and 1948 (3, 4). These authors used an ingenious approach, based on the direct Fick principle, that involved inhalation of a diffusible inert gas tracer (N₂O) in awake humans. The “Kety-Schmidt” technique, for the first time, permitted accurate quantitation of global CBF levels. Many methodologic advances have occurred since that time, a number of which derive from that original work. These include techniques that permit assessments of temporal and regional aspects of CBF regulation. This was covered in a recent editorial (7).

More recently, attention has been directed toward studies on the mechanisms of cerebral perfusion regulation at the local, cellular, and molecular levels. Evaluations of “local” factors can involve use of both in vivo and in vitro techniques. The latter includes isolated cerebral arteries and arterioles from different brain sites as well as brain slice preparations, which permit measurements of localized neuronal and astrocytic influences on diameter changes of intraparenchymal arterioles in an environment where the anatomic relationships among neurons, astrocytes, and vascular cells are preserved. In vivo assessments of local factors might involve use of methods that measure regional CBF values [e.g., positron emission tomography (PET) or autoradiography techniques]. Another in vivo model often used in the study of “local” influences on cerebrovascular function is the cranial window technique. This is used to monitor pial arteriolar diameter changes during direct applications of specific pharmacologic or molecular-based agents. Studies of cellular mechanisms often employ cultures of vascular cell type that sets the cerebral circulation apart from other vascular beds is the astrocyte. Indeed, not only do astrocytes often outnumber neurons in specific brain regions of mammals, with that ratio increasing as one moves up the phylogenetic ladder, but also they display far greater contacts with intracerebral arterioles than do neurons. As such, they are poised to act as vital transducers and integrators of neurovascular signaling. Astrocytes may also modulate vasodilating responses to the metabolic factors mentioned earlier and may affect the manner in which vascular smooth muscle cells respond to endothelial influences. Another function of astrocytes that may be of relevance to cerebrovascular control relates to their unique communication systems, which allow astrocytes within a discrete brain region not only to behave as a syncytium but also to act as a signaling conduit to different segments of the vascular tree. Thus, for example, by signaling upstream resistance vessels to dilate (e.g., pial arterioles), an even greater level of perfusion control in response to local neuronal activity can be achieved.

The second subcategory of minireviews is entitled “Oxygen and the cerebral circulation.” This trio of papers will consider chronic and acute influences of hypoxia in the adult and fetus, as well as oxygen’s sometimes troublesome “progeny,” the reactive oxygen species (ROS). It is interesting to note that, during increased brain activity, one often sees a disproportionate rise in cerebral glucose consumption (CMRglc) relative to O₂ consumption (CMRO₂). As a result, the CMRO₂/CMRglc ratio declines from the normal value of ~6, with CBF changes, quantitatively, more likely to track changes in CMRglc, rather than CMRO₂. Although the metabolic fate of this “extra” glucose is a subject of debate (1), it has been hypothesized that
astrocytes are the principal glucose-consuming cell, whereas neurons are a major site of O2 consumption (2, 5). On the basis of this apparent compartmentation, one could speculate that the closer quantitative relationship between changes in local CBF and CMRglc during brain activation is a reflection of the higher degree of astrocytic contacts with cerebral arterioles, compared with neurons. Furthermore, the above arrangement implies that energy production in neurons, in comparison to astrocytes, is more dependent on ATP derived from mitochondria rather than the glycolytic pathway. Thus, to support the greater energy demands accompanying increased neuronal activity, the O2 supply to mitochondria needs to be upheld. To establish a blood-to-mitochondrial O2 gradient that prevents mitochondrial Po2 from falling to zero, blood flow must increase in excess of O2 consumption. However, in the case of hypoxia, neuronal activity and energy demand may be unchanged, but CBF increases are still needed to ensure that the mitochondrial Po2 remains above zero so that the energy requirements associated with “resting” conditions can be satisfied. It is interesting to note (as discussed in the paper by Dr. W. J. Pearce) that the fetus seems to possess an extra compensatory mechanism, where hypoxia, in addition to increasing CBF, is accompanied by reductions in cerebral (mitochondrial) O2 consumption.

If O2 delivery is chronically reduced (e.g., high-altitude exposure), another compensatory mechanism comes into play. Thus increased capillary density (angiogenesis) in essence reduces the diffusion distance between the intravascular O2 supply line and the target of O2 delivery—the mitochondrion. This will limit the possibility of mitochondrial Po2 levels falling below what is needed to support basic oxidative function. Some of the mechanisms involved in ensuring adequate O2 supply to mitochondria will be covered in this group of minireviews. The paper by Drs. K. Xu and J. C. LaManna considers cerebral vascular responses to chronic hypoxia (altitude exposure) in adult mammals, with some focus on angiogenesis. The review by Dr. Pearce addresses mechanisms associated with responses in the fetus to acute and chronic hypoxia. The third minireview in this group (by Dr. F. M. Faraci) will discuss cerebrovascular regulation in relation to ROS. The generation of ROS may occur as a consequence of altered O2 handling by mitochondria or as a by-product of enzymatic reactions. Additional consideration will be given to ROS interactions with nitric oxide (NO).

The third subcategory is entitled “Conventional and non-conventional ‘transmitters’ in the regulation of the cerebral circulation: Role of neurotransmitters, gases, and hormones.” This group of minireviews represents a somewhat eclectic compilation. The “conventional” transmitters paper by Dr. E. Hamel integrates very recent with historical information regarding “extrinsic” (i.e., nerves arising outside the central nervous system) but especially “intrinsic” (intracerebral), neuronal factors and some of the specific neurotransmitters involved. That paper also points out that local (intrinsic) neuronal activation does not always lead to the expected vasodilation, but also it may result in transmitter system-specific vasoconstriction. Although this intriguing observation certainly adds to the complexity of neurovascular coupling, it also implies a vascular control system that is exquisitely regulated. The overview concerning “gasotransmitters,” by Dr. C. W. Leffler et al., does not give much coverage to NO as a vasoactive transmitter in the brain, simply because numerous reviews have already been devoted to this subject. Rather, the focus is on two endogenously generated, but less studied, biological gasses, carbon monoxide (CO) and hydrogen sulfide (H2S), and the accumulating evidence regarding their functions as physiological vasodilators in the brain. The third paper of this group, from Dr. D. N. Krause et al., highlights the cerebrovascular influences of sex steroids, estrogen in particular. All three of the major sex steroids (estrogen, progesterone, and testosterone) have reported functions as vasoactive agents and neuromodulators. Furthermore, not only are these steroids delivered to the brain via the circulation but also they are synthesized within the brains of males and females, as products of cholesterol metabolism. Insofar as vascular effects are concerned, estrogen has received the greatest amount of attention. The actions of estrogen can be separated according to acute versus chronic effects and which estrogen receptor (if any) is involved. However, whatever the case, estrogen promotes vasodilation. One of the principal effectors of this vasodilating action of estrogen is the endothelial NO synthase, although other endothelium-dependent vasodilating functions may be influenced as well. Generally speaking, testosterone seems to potentiate vasoconstrictive functions in the cerebral circulation, directly or indirectly counteracting the vasodilating actions of estrogen. If anything, progesterone may support vasodilation, but very little is known regarding progesterone influences on the cerebral vasculature. In short, variations in both the presence of sex steroids within the brain and the signal transduction pathways linked to sex steroid receptors are likely to contribute to gender differences in cerebral hemodynamic regulation.

The nine minireviews in this series devoted to cerebral blood flow regulation represent only a “taste” of the ongoing research into the mechanisms of cerebral vascular control. At the least, these articles are intended to emphasize the complexity of hemodynamic regulation in the brain and that one cannot generalize findings obtained in studies on peripheral vessels to the understanding of cerebral vascular physiology.

REFERENCES


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