CHRONIC HYPERTENSION is a major health problem worldwide affecting ~25% of the population. Because it is a key risk factor for cerebrovascular disease and stroke and a leading cause of cognitive decline, chronic hypertension has an enormous negative impact on the brain. Episodes of acute hypertension (hypertension emergencies) present an additional array of cerebrovascular and neurological problems. Risk factors for acute hypertension include preexisting chronic hypertension (14). In individuals who are not chronically hypertensive, other causes of acute hypertension include traumatic brain injury, seizures, and severe preeclampsia and eclampsia (5, 14). For example, the cerebrovascular abnormalities seen in a common model of traumatic brain injury are due to acute increases in arterial blood pressure (15).

Episodes of acute hypertension in which blood pressure exceeds the autoregulatory capacity of the cerebrovasculature (“breakthrough” of autoregulation) result in marked increases in cerebral blood flow (CBF), increases in microvascular pressure, and disruption of the blood-brain barrier (BBB) (6, 8, 10, 11). Clinically, this sequela underlies hypertensive encephalopathy, a condition characterized by headache, seizures, and other neurological symptoms including cerebral edema.

The effectiveness of autoregulation and the loss of BBB integrity during large acute increases in arterial pressure exhibit regional and segmental differences and can change in disease (8, 10, 11). This heterogeneity results from a variety of factors including differences in vascular structure, intrinsic functional properties of blood vessels (mainly at the level of vascular muscle), as well as modulation of autoregulatory responses by endothelial cells, potassium channels in vascular muscle, and extrinsic perivascular innervation by sympathetic, parasympathetic, and sensory neurons (6). As a result, there are regional differences in local hemodynamics including increases in microvascular pressure in capillaries and veins (8, 10). Regional differences in disruption of the BBB during acute hypertension are not due to inherent differences in properties of the BBB but rather arise because of differences in the magnitude of increases in microvascular pressure (8, 10, 11). Molecular changes that underlie increases in BBB permeability at the level of the endothelial cell include alterations in cell surface charge, density of caveolae, phosphorylation of tight junction proteins, and the actin-myosin cytoskeleton (12).

Vascular remodeling represents a three-dimensional rearrangement of the vessel wall around its lumen (2). When accompanied by changes in the cross-sectional area of the lumen, inward or outward vascular remodeling has major effects of vascular resistance and the transmission of blood pressure down the vasculature (Fig. 1). Inward remodeling of cerebral arteries and arterioles occurs in some forms of chronic hypertension (2, 3). This type of remodeling protects the distal microcirculation from full transmission of elevated blood pressure and thus attenuates vascular dysfunction, increases in microvascular pressure, and increases in permeability when local pressure rises (Fig. 1). Such a mechanism protects the BBB during acute hypertension in chronically hypertensive animals (11).

Although large elevations in blood pressure are a key feature of severe preeclampsia and eclampsia, relatively little is known regarding the effects of acute hypertension on the cerebral circulation during pregnancy (5). In this issue of the Journal of Applied Physiology, Cipolla et al. (7) describe a series of studies addressing the hypothesis that changes in the cerebral vasculature during normal pregnancy result in the brain being predisposed to vascular injury during acute hypertension. In those studies, a variety of
complementary measurements were performed using a model that mimicked changes in hemodynamics during severe preeclampsia or eclampsia. The authors made several novel observations. First, they found that disruption of the BBB in both isolated blood vessels and in vivo in response to acute hypertension was increased during pregnancy. The mechanism that accounted for this change is not clear but did not appear to involve differences in expression of key tight junction proteins. Other mechanisms that may have contributed to the loss of BBB integrity include increased oxidative stress, activation of select kinases (rho kinase or protein kinase C), or phosphorylation of tight junction proteins—each of which increases permeability of the BBB in other models.

Second, although there was no effect of pregnancy on resting CBF, reductions in cerebral vascular resistance and increases in CBF during acute hypertension were greater in pregnant animals compared with nonpregnant controls. Several mechanisms could potentially contribute to this key finding. The authors examined responses of isolated cerebral arterioles to acute increases in pressure and found that the intrinsic effectiveness of the myogenic response was not significantly altered during pregnancy. Changes in cerebral vascular resistance and CBF during acute hypertension are dependent in part on vascular structure. In their effort to define a mechanistic basis for the observed hemodynamic differences, the authors also examined structure of pial arteries on the surface of the brain and small arterioles isolated from the brain parenchyma. Although no significant change in structure was noted in pial arteries, outward remodeling of these small arterioles occurred during pregnancy (Fig. 1). Of note, such outward remodeling is the opposite of what is seen in small cerebral arterioles in models of chronic hypertension (2, 3). While inward remodeling attenuates transmission of pressure to the distal microvasculature and thus protects the BBB, outward remodeling would be predicted to have the opposite effect and promote disruption of the BBB during acute hypertension (Fig. 1).

Activity of the transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) in the vessel wall is a key determinant of vascular structure in brain (4, 9). Inward remodeling in cerebral arterioles occurs in mice expressing human dominant negative mutations in PPAR-γ (4, 9) demonstrating that PPAR-γ normally inhibits or protects against this form of vascular growth. Thus increased activation of PPAR-γ, with the subsequent effects on PPAR-γ target genes, is a potential mediator of altered vascular structure during pregnancy. Armed with this knowledge and other evidence that PPAR-γ may play a causative role in severe preeclampsia (1), the authors tested whether activation of PPAR-γ accounted for outward remodeling of cerebral arterioles during pregnancy. They found that chronic treatment with an exogenous ligand for PPAR-γ caused outward vascular remodeling in nonpregnant rats, thus mimicking the effect of pregnancy. In addition, chronic treatment with an inhibitor of PPAR-γ in pregnant animals prevented outward vascular remodeling. These findings provided another example of the dynamic effects of pregnancy on the cerebrovasculature (5) and the first evidence that activation of PPAR-γ is a key element in producing these changes (Fig. 1). While multiple determinants of vascular remodeling are known (13), additional studies will be required to define how targets of PPAR-γ are reprogrammed within the vessel wall during pregnancy to produce outward remodeling and potentially other effects on the vasculature.

Under some conditions, outward vascular remodeling can be beneficial. For example, by reducing minimal vascular resistance and thus promoting higher levels of local perfusion pressure and blood flow in collateral-dependent regions, outward remodeling may reduce susceptibility to focal ischemia. In contrast, hypertension is a common complication of pregnancy (5). Outward remodeling of small cerebral arterioles during pregnancy likely contributes to greater transmission of pressure to the distal microcirculation and thus greater disruption of the BBB and formation of cerebral edema during acute hypertension or other conditions that cause marked increase in blood pressure including head injury.

GRANTS

The author’s work is supported by National Institutes of Health Grants HL-38901, NS-24621, and HL-62984 as well as a Bigher Foundation Award in Stroke from the American Heart Association (0575092N).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES