Brief Communication

Arterial Hypertension Injures Brain Capillaries

Definition of the Lesions. Possible Pathogenesis

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SUMMARY Systemic hypertension (secondary to aortic coarctation) produces in monkeys, multifocal brain lesions where capillaries show increased diameter, endothelial degeneration and deposition of collagen and other substances in the basement membrane. In one animal, capillary changes were detected as early as 8 weeks after induction of hypertension. Similar capillary alterations were demonstrated in brain samples of hypertensive humans obtained at autopsy. We suggest that the above abnormalities may be the result of successive episodes of regional ischemia and/or hyperperfusion. Validation of these observations requires careful evaluation of additional human and animal brains.

WE CONDUCTED detailed structural and morphometric analyses on the brains of a) 5 hypertensive cynomolgous monkeys (Macaca fascicularis), b) 2 normotensive controls, and c) 3 hypertensive humans. The abnormalities in the capillaries of both human and animal brains are similar to one another and have not been described before as a sequel of systemic hypertension. We saw pronounced brain capillary injury as early as 8 weeks after induction of hypertension. The purpose of this preliminary communication is to illustrate a plausible hypothesis which may explain the mechanisms that injure the brain in systemic hypertension.

Material and Methods

Subhuman primates were subjected to coarctation of the descending aorta. This procedure induces permanent proximal hypertension with a mean arterial blood pressure (MABP) of 145 mm Hg, and abrupt hyper-reninemia that subsides spontaneously within 4 to 6 weeks. Additional details of the ensuing cardiovascular abnormalities in this well-established model of systemic hypertension have been published elsewhere.1,2 Five monkeys were killed at intervals of 2 months, 6 months, 9 months, one year, and 2 years after the induction of hypertension. Control tissues were obtained from 2 normotensive monkeys of the same species and comparable body weight. Randomly selected samples of human brain from 3 patients with long-standing history of systemic hypertension and aged 31, 68 and 77 years were also included in the study. In vivo fixation of monkey brains was done under general anesthesia, at a pressure equivalent to the MABP of the respective animal. The fixative, a combination of formaldehyde and glutaraldehyde, was perfused through the carotid arteries, following a quick (1–2 min) pre-wash with a heparinized physiologic saline solution. Two hypertensive monkeys surviving 9 months and 2 years, and all human tissues were fixed by immersion in 10% formalin. The average lapse of time between death and fixation of human tissues was 6.8 h.

Brains of hypertensive monkeys were cut serially in a vibratome and slices (75 to 600 μm) were examined with a dissecting microscope. Sites showing "sponginess" (vacuolated neuropil) were removed and embedded in either methacrylate or araldite epon for preparation of histology slides. Samples embedded in methacrylate were used to define by light microscopy, areas of involvement and nature of the lesions. One-micron-thick sections were used to measure at a magnification of 1,000×: a) capillary diameter, and b) percent of areas of "edema," defined as areas of clearing of tissues.8 Ultra-thin sections obtained from areas selected from the one-micron-thick preparations were used to define the capillary changes by electron-microscopy. Percent edema values were obtained from histologic samples by the point-count method.9 Basement-membrane thickness was measured in electron micrographs.

Results

Brains of all 5 hypertensive monkeys contained areas of sponginess measuring 0.5 mm in diameter; these were randomly distributed throughout the entire brain and were more abundant in the monkey that survived 24 months of hypertension. Comparable changes were not detected in the control animals. The histogram in figure 1 illustrates a typical frequency

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distribution of capillary diameters obtained from brain areas of normotensive monkeys and non-vacuolated brain areas of hypertensive monkeys. Figure 2 shows a marked shift to the right in the distribution of capillary diameters in vacuolated brain areas from hypertensive monkeys. Shifts in frequency distributions correspond to changes in mean capillary diameters from a normal of 6.3 μm ± 1.9 to 9.4 μm ± 1.5 (mean ± sp) in vacuolated white matter after one year of hypertension. In addition to the increased diameter, capillaries in areas of sponginess showed pronounced deviations from the normal (fig. 3) that included: flattening/swelling of endothelium, interruptions of endothelial lining, and increased thickening/deformity of the basement membrane (figs. 4-6). The increased basement membrane thickness was attributed, in part, to the presence of fragments of cytoplasm, deposition of collagen fibers and numerous osmiophilic particles of uncertain origin (fig. 6). In some human samples, fibrin deposits could also be clearly identified. Numerous additional abnormalities in circulating cells and surrounding neuropil will be illustrated in a subsequent, longer communication.

Discussion
An extensive review of the medical literature on abnormalities of blood vessels associated with systemic hypertension was published recently. None of the publications reviewed to date describes capillary alterations of the type illustrated in this communication. Superficial similarities seemingly exist between these capillary changes and alterations detected by others in aged human brain. One of our patients was aged 31 years and had a history of hypertension of several years duration which suggests that the capillary changes are not exclusively associated with advancing age. The capillary alterations observed in this study were remarkably similar to those encountered at sites of brain ischemia and reperfusion.

The physical support for the capillary may be largely dependent on the surrounding parenchyma; thus, when the density of the brain tissues decreases, as a consequence of increased water content, the diameter of capillaries might be expected to increase. Some support for this postulate can be inferred from measurements showing increased capillary diameter after brain swelling induced by ouabain and by temporary ischemia (Garcia et al., unpublished obs.).

The average width of basement membranes in capillaries of normotensive monkeys and normal areas of hypertensive animals was 0.02 μm. Such width would contribute only approximately 5% of the support required to maintain capillary rigidity. Basal-}

Capillary Diameter (Microns)

Figure 1. Typical frequency distribution of capillary diameters in both normotensive monkeys and non-vacuolated areas of hypertensive monkey brains. Percent "edema" or vacuolation in these areas was less than 1.0%.

Capillary Diameter (Microns)

Figure 2. Frequency distribution of capillary diameter in an area of vacuolation in the white matter of a monkey made hypertensive for 1 year. Percent edema in this sample was 43%.
**Figure 3.** Normotensive monkey (basal ganglia). Cross section of a capillary whose lumen (L) is lined by an endothelial cell resting in a uniformly thin basement membrane (arrow) and surrounded by compact neuropil. (Orig. Mag. X 7700)

**Figure 4.** Cerebral cortex of hypertensive monkey (2 months) from an area where neuropil is loose due to enlargement of the extracellular space. Endothelial cell is flattened and electron dense. Basement membrane (arrow) is thickened and irregular. Swollen astrocytic foot processes show increased electron lucency. (Orig. Mag. X 6,000)

**Figure 5.** Cerebral cortex of hypertensive monkey (two months) showing a detail of split basement membrane abnormalities. Marked increases in width are accompanied by deposits of both fibrillary and amorphous materials. (Orig. Mag. X 10,000)

**Figure 6.** Basal ganglia of hypertensive monkey (twelve months). Detail of a gap in endothelial lining. Basement membrane, now exposed to the circulation, is markedly thickened and the surrounding brain tissue is markedly vacuolated. (Orig. Mag. X 12,500)
bits made hypertensive by angiotensin injections. Systemic hypertension induces arteriolar (or pre-capillary) spasm that can lead to focal decreases in blood flow. Focal (incomplete) brain ischemia is promptly followed by localized increase in water content and vacuolation of neuropil, which in turn may allow capillary dilatation (due to loss of tissue support). The abnormally expanded capillaries may be more permeable than the normal ones and perpetuate local edema. "Break-through" or hyperperfusion in these distended capillaries, as demonstrated in an animal model of angiotensin-induced hypertension, would also contribute to local endothelial injury and edema. Finally, the increased thickness of basement membranes may well be a necessary response to the loss of tissue support for the capillary bed.

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References

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