Editorial Comment

The Hypertensive Rat and Predisposition to Cerebral Infarction

Michael Jacewicz

Since the 1930s, when animal models of focal ischemic stroke were first developed, there has been a great deal of variability in the degree of ischemia and histologic damage produced by occluding a major cerebral artery. This bedeviling interspecies and intraspecies variability has seriously hampered progress in experimental stroke research. It was therefore a welcome development when the spontaneously hypertensive rat (SHR) and its stroke-prone relative (SHRSP) were shown to have much larger and less variable infarcts after middle cerebral artery (MCA) occlusion than most, if not all, other animal models of focal stroke.\(^1\)\(^-\)\(^4\) Not only could pathophysiological investigations and drug testing be conducted with greater statistical power and a reasonable number of inexpensive animals, but now the relation of hypertension to stroke could be directly studied as well. One potential drawback, however, was that the severity of ischemia was so great that otherwise useful therapies might prove ineffective in the SHR. That the hypertensive rat can differ from its normotensive counterpart in its sensitivity to drug therapy is evidenced in a study by Roussel et al\(^5\) reported in this issue. These authors demonstrated that the noncompetitive N-methyl-D-aspartate antagonist MK-801 given 30 minutes before permanent MCA occlusion, results in a 32% infarct reduction 48 hours later in normotensive rats but not in SHR. The lack of efficacy in the SHR may be due to their single dose schedule\(^6\) or, as they suggest, inadequate power to exclude a 25% reduction in infarct volume. However, they rightly point out that it is generally more difficult to achieve pharmacological protection against focal ischemia in SHR than in normotensive rats. Since several laboratories have already shown definitively that MK-801 protects the focally ischemic brain,\(^6\)\(^-\)\(^8\) the effectiveness of MK-801 is not at issue, but the question arises as to why and how the presence of hypertension modifies the drug response by the focally ischemic brain.

It has long been thought that arterial hypertrophy induced by chronic hypertension infringes on the vascular lumen and reduces vascular distensibility, thereby impeding the compensatory vasodilator response to ischemia and aggravating the infarct process. Indeed, focal cerebral ischemia in SHR is anatomically more widespread and the reductions in cerebral blood flow more pronounced than in normotensive rats.\(^9\) However, experimental work in the past decade suggests that cerebrovascular hypertrophy is probably not responsible for the accentuated ischemia in hypertensive rats, and in fact, hypertrophy may actually protect against stroke; when vascular hypertrophy is reduced by chronic sympathetic denervation in SHRSP, the incidence of spontaneous cerebral hemorrhage and infarction increases rather than decreases.\(^5\)\(^,\)\(^10\) What then predisposes the hypertensive rat to infarction?

Early work with the SHR and SHRSP subjected to MCA occlusion revealed some unexpected relations between hypertension and infarct susceptibility.\(^2\)\(^,\)\(^11\) One major surprise was that SHR and SHRSP suffered large infarcts in early youth (5 weeks of age) before either hypertension or pathological changes in the vasculature became established. It was also found that in SHRSP, susceptibility to infarction was inherited through a gene locus best described as autosomal recessive and that susceptibility was due to vascular anastomoses (between the MCA and anterior cerebral artery) whose lumen diameter in SHRSP was only 60% of that in normotensive rats; there was a strong correlation between lumen diameter and amount of cortex spared ischemic damage at the zone of anastomoses. That hypertension was secondary in importance to the vascular collaterals was reinforced by other observations. First, chronic hypertension in rats did not uniformly predispose them to infarction. Approximately 10% of young\(^2\) and adult (unpublished observations from our laboratory) SHR suffered small infarcts or no infarct at all after MCA occlusion, and correlation between preocclusion blood pressure and infarct size was poor.\(^2\)\(^,\)\(^12\) Second, rats made hypertensive by deoxycorticosterone acetate and salt administration failed to develop large infarcts after MCA occlusion.\(^1\) Third, adult SHR, in whom hypertension is treated early and continuously, develop infarcts (after tandem MCA and common carotid occlusion) that are

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only 20% smaller than the very large infarcts in their untreated hypertensive cohorts.  

The overall picture that emerges is that infarct susceptibility in SHR arises from a lack of vascular collateral blood flow that is genetically associated with but not directly linked to hypertension. Since large infarcts after MCA occlusion (presumably due to inadequate collateral blood flow) also occur in a minority of normotensive rats, the gene (or set of genes) governing infarct susceptibility can be disassociated from hypertension and presumably can occur with variable frequency in normotensive populations of rats (and in other species as well). If so, this would partly account for the large variability in ischemic brain damage observed in focal stroke models and perhaps in the human condition as well. One can hypothesize that, although chronic hypertension may cause severe atherosclerosis and occlude a major cerebral artery (e.g., the MCA), one patient may suffer a catastrophic stroke while another can remain asymptomatic because what actually determines outcome is some as yet unidentified autosomal recessive gene (or set of genes) governing collateral blood flow. If this hypothesis is correct and a gene marker for the infarct susceptibility were to be found, it would permit the identification of patients for whom early, aggressive intervention to avoid stroke would be highly desirable. With current techniques in biotechnology, it should be possible to test this hypothesis and to gain new molecular insights into the relation between hypertension and infarct predisposition.

There remains the question of suitability of SHR for drug testing when focal cerebral ischemia is severe. A 15–25% reduction in focal cortical infarct volume has been achieved in SHR with chronic treatment of hypertension, nimodipine pretreatment, or idazoxan treatment. Although a 15–25% protection appears modest, in absolute units (mm³) of salvaged cortex, it is the equivalent of a 30–50% infarct reduction in nonhypertensive models that generate infarct volumes half as large as in SHR. Why then should a 15–25% reduction in infarct volume in SHR be more difficult to achieve than a 30–50% reduction in normotensive rats? There is no obvious answer for this. One may speculate that the proximity of a large ischemic mass somehow complicates the salvage of surrounding cortex in SHR (e.g., by excessive release of diffusible edema, glutamate, lactic acid, and other noxious substances of cell injury), but this remains to be proven. However, to minimize the potential for erroneous or misleading data, it is essential that the investigator adhere to certain principles when using the SHR in drug testing. Therapy should be instituted before the infarct process becomes irreversible (approximately 3 hours after ischemia onset) and match the duration of ischemic conditions (i.e., continue as long as the process of injury is active). Physiological variables, including temperature, blood pressure, arterial pH, oxygen, and carbon dioxide tension, should be monitored throughout the experimental period. Adequate numbers of animals (determined by power analysis) should be used to avoid a type II error, and the experiments should be replicated to avoid a type I error.  

With these caveats observed, the SHR subjected to MCA occlusion offers a stringent test of drug efficacy, and although a negative result may detract from a useful therapy in the setting of less severe ischemia, a positive result suggests a truly robust therapeutic effect and should act as an incentive to proceed with further experimental (and perhaps clinical) testing.

References

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