Pathogenesis of Transient Ischemic Attacks and Stroke in Baboons

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We describe a series of experiments in which a subhuman primate model was used to create temporary and permanent cerebral ischemia by three separate mechanisms. In the first group of five baboons, a hemodynamic model was produced by creating unilateral and bilateral carotid stenotic lesions of varying degrees with and without associated reduction in systemic perfusion pressure. Only global ischemic changes and no focal changes resulted. In the second group of three baboons, a macroembolic model was produced by introducing solid particulate material into the extracranial circulation. No reversible contralateral focal neurologic changes resulted. In the third group of 11 baboons, cerebral ischemia was produced by introducing agents known to cause platelet aggregation (arachidonic acid, adenosine diphosphate, and collagen) into the extracranial arterial circulation. Arachidonic acid caused seizures, adenosine diphosphate caused severe postural hypotension, and only collagen fibrils produced a picture resembling a transient ischemic attack. We propose a theory that intravascular activation of the prostaglandin cascade by chemical initiation may result in the pathophysiologic changes of transient cerebral ischemia. (Stroke 1989;20:386–389)
to the respective roles played by hemodynamic opposed to embolic mechanisms in causing transient and permanent strokes in both animal models and in patients. Indeed, no convincing evidence exists that the pathogenetic mechanisms of stroke and TIA are the same.

The object of our series of experiments was to develop a subhuman primate model in which the same stimulus could be used to produce both temporary and permanent ischemia by varying the magnitude of the stimulus. The ischemic stimulus was produced by three separate mechanisms, each of which is more likely to operate in atheromatous disease than temporary interruption of blood flow in a major vessel by an occluding device.

Materials and Methods

We used male baboons (Papio ursinus) weighing a mean of 25 (range 17–32) kg anesthetized with ketamine and pentobarbitone. Baboons were intubated and ventilated with 100% oxygen and killed at the end of each experiment. Continuous electroencephalographic (EEG) recordings were obtained using a sixteen-channel Galileo E18D machine (OTE, Biomedica, Florence, Italy). Three channels were monitored on each side of the head using eight leads according to the method described by Killam and Gehrmann. Blood pressure was continuously recorded via a 20-cm intra-arterial 16-French femoral artery catheter using a Gould Statham physiological pressure transducer (Cleveland, Ohio) and a Devices Lectromed eight-channel recorder (Lectromed Ltd., Jersey, Channel Islands).

We carried out three groups of experiments. In the hemodynamic model (Group I, n=5), ischemia was produced by unilateral and bilateral carotid stenotic lesions of varying degrees with and without associated reduction in systemic perfusion pressure. This model was a prelude to the embolic models to be produced by introducing solid particulate material into the extracranial circulation.

In Group II, autologous blood clots were formed by 48-hour preservation of clotted whole blood. The clots were fragmented to a size visible to the naked eye and directly introduced into the internal carotid artery circulation via an external carotid artery cannula. Four baboons received 2–10 mg arachidonic acid (Sigma Chemical Co., St. Louis, Missouri), according to the method described by Passero et al16; three received 5–500 μg adenosine diphosphate (ADP) (South African Institute for Medical Research, Johannesburg, South Africa), and four received 0.025–0.35 ml/kg collagen fibrils (Kol-


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lagenreagen Horn, München, FRG). The dosage of platelet aggregating agent was adjusted within each subgroup of baboons to obtain a reproducible effect and to establish a dose–response curve. The baboons were observed clinically and electrophysiologically for up to 8 hours and then killed.

The protocol was approved by the Animal Ethics Committee of the University of the Witwatersrand (no. 83/1).

Results

In Group I, no baboon was clinically affected by alterations in carotid artery blood flow. At postmortem examination, two carotid arteries that had been stenosed were found to be occluded; these occlusions appeared to have occurred as silent events without clinical or pathologic sequelae. Exsanguination of the five baboons of Group I produced only global clinical and EEG changes. Maximal changes occurred at a systolic blood pressure of 38 mm Hg. In no baboon was a focal neurologic deficit produced as a consequence of carotid stenosis or occlusion either unilaterally and bilaterally, even in the presence of marked reduction in the systolic perfusion pressure.

In Group II, nonreversible contralateral focal neurologic changes were observed in each baboon. These changes appeared irreversible both clinically and electrophysiologically over the period of the experiment.

In Group III, in each baboon receiving arachidonic acid, contralateral clinical focal seizures together with ipsilateral EEG features of spike and polyspike focal seizure discharges were produced (Figure 2). Macroscopic and microscopic evidence of ipsilateral focal cerebral edema with early infarct changes were also observed. Administration of ADP produced no focal changes, but severe systemic hypotension limited the study. Collagen fibrils at 0.025 ml/kg produced reproducible clinical and EEG features compatible with transient focal cerebral ischemic episodes. Increasing the dose of collagen fibrils above this level resulted in a more generalized cerebral ischemic pattern, with bilateral flaccidity and coma.

Discussion

Our study confirmed that in the absence of intracranial disease or interruption of both large and small cerebral vessels, baboon models are not successful in causing focal changes with hemodynamic alteration. Our extensive interruption of the extracranial circulation failed to produce any focal neurologic deficit; when the entire cerebral perfusion was reduced, global rather than focal neurologic deficit resulted. This may be due to the excellent collateral cerebral circulation of the subhuman primates. Certainly our results do not exclude the possibility that in diffuse atherosclerosis in elderly humans with impaired autoregulation, hypotension may produce focal symptoms of the TIA type. The introduction of cohesive macroemboli produced changes of irreversible stroke similar to the experiments of Hill et al. In our baboon model only collagen fibrils introduced into the extracranial circulation produced a picture resembling clinical TIA. ADP caused severe hypotension, and arachidonic acid produced pathologic edema. These substances (especially arachidonic acid) have been used to produce TIA in animals with greater success by other authors.

While there is little doubt that macroemboli cause irreversible stroke, either immediately as demonstrated in our study or after a long period, reversibility depends on fragmentation of the embolic material. On the other hand, we have demonstrated that a reproducible TIA-like phenomenon may be produced by liberation into the circulation of an agent that is known to stimulate the intravascular aggregation of platelets. Similar observations have been made by Passero et al.

Our theory to explain the facts we observed is that TIA may result from the liberation of chemical substances from complicated atheromatous plaques, resulting in intravascular platelet aggregation, which is in turn responsible for the TIA. On the other hand, strokes might then be caused by solid material embolizing from the same lesion. This theory would explain the well-established association of TIA and stroke in the presence of extracranial
vascular stenosis. Our theory would further explain the observed reduction in TIA in patients treated with antiplatelet agents. Strokes resulting from the embolization of solid material from the same complicated atheromatous plaque would not be as dramatically affected by such antiplatelet agents since a degree of healing in the plaque may have to ensue to reduce the occurrence of stroke.

In the past, the role of chemical activators in causing TIAs was not considered important because severe histologic edema and inflammatory changes were found in models using these substances. With the demonstration using MRI of similar changes in humans with TIA, the role of intravascular platelet aggregation in the pathogenesis of TIAs gains new significance. Further support is lent to this argument by the fact that symptomatic TIA patients may have had hemorrhages into carotid plaques, which may also release chemical agents into the circulation. The substances found in atheromatous plaques are very potent platelet aggregating agents.

Previously, TIAs have been considered to be due to large emboli that fragment easily. However, the small intra-arterial emboli that have been seen in the fundus of patients with TIAs are made of platelet material that would be too small to cause neurologic symptoms. Similarly, Barnett has published striking photomicrographs showing cholesterol escaping from deep within carotid atheromatous plaques. The cholesterol in these emboli is capable of inciting platelet adhesion and aggregation but is frequently too small to cause neurologic symptoms itself as a result of arterial occlusion.

In conclusion, the concept of TIAs being small strokes due to mechanical vascular occlusion has been questioned in this study. We theorize that in the highly intricate chemical pathway of the human brain, the mechanism of TIAs may be due to the activation of the prostaglandin cascade by chemical initiators liberated from atheromatous plaques. This results in an intravascular abnormality such as platelet aggregation causing a temporary and reversible disturbance of cerebral perfusion.

References

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