A major consideration in the evaluation of experimental models of ischemic stroke in animals is the clinical relevance of the models. Difficulties arise in relating studies of models of focal cerebral ischemia to the clinical situations of strokes in humans because of many factors, including species differences, the effects of anesthesia, and the progressive nature of atherosclerosis. However, certain physiological and chemical studies cannot be done in humans. Thus, it is important to know in what ways experimental models of ischemia are similar to or different from strokes in humans.

Neurological Deficits

Neurological deficits, particularly hemiparesis, may be difficult to assess in small mammals such as rats and gerbils. Abnormalities of respiration, seizures, circling movements, ptosis, and impairment of consciousness often accompany cerebral ischemia in these animals, depending on the anesthetic agent used. In gerbils with occlusion of one carotid artery, hemiparesis may develop, but impaired consciousness and the occurrence of seizures are more easily recognized.

In larger mammals, including subhuman primates, neurological deficits caused by cerebral ischemia are variable. A standard system has not been established, but impairment of consciousness, weakness or lack of use of one or more of the extremities, and forced motor activity (particularly tonic deviation of the head and circling movements) can be evaluated and graded. These changes are much the same as in humans with acute ischemic cerebral infarcts, except that in humans forced motor activity such as tonic head deviation occurs only with massive lesions of one hemisphere.

The neurological deficits in experimental models of focal cerebral ischemia may clear rapidly, within a few hours or days of onset, particularly in cats. However, in subhuman primates neurological deficits may persist indefinitely, as in humans.

The extent and severity of the neurological deficits in the experimental models are directly related to the size and location of the infarcts resulting from the focal ischemia, and there is considerable variation in size and location of infarcts depending on the model used. In general, infarcts are relatively larger in experimental animals than in humans with strokes; the models are more analogous to massive hemispheric infarcts than to localized strokes such as those in the internal capsule.

In models of focal cerebral ischemia in cats and subhuman primates, as well as in smaller mammals, forced motor activity and circling movements almost invariably occur shortly after the onset of ischemia if not prevented by anesthesia. The forced motor activity is probably due to ischemia of the caudate nucleus or other basal ganglia; these structures generally are affected by vascular lesions used for models of ischemia, such as occlusion of one middle cerebral artery. Hemiparesis or impairment of the use of one or more extremities appears to be related to involvement of the internal capsule.

Neurological deficits develop immediately after occlusion of a middle cerebral artery in unanesthetized cats. In humans, since the actual moment of the onset of ischemia cannot be determined, the duration of ischemia required to produce a neurological deficit is unknown. However, it can be inferred from the studies in animals that acute vascular obstruction is accompanied by an immediate drop of regional cerebral blood flow (CBF) with an associated lack of availability of oxygen and glucose and that neuronal function is impaired quickly after the onset of ischemia.

Regional Cerebral Blood Flow and Neuronal Function

It is well known that ischemia interferes with cerebral vascular reactivity and the usual circulatory responses to intrinsic and extrinsic stimuli. Abnormal pressure-flow responses ("autoregulation") frequently accompany acute cerebral ischemia, both in animal models and in humans. Similarly, there are derangements of the usual cerebral vascular responses to changes of arterial carbon dioxide tension.

Regional CBF changes with time in experimental models of acute focal cerebral ischemia, as well as in humans with acute ischemia and infarction. For example, CBF and oxygen availability may decrease immediately after occlusion of a middle cerebral artery in cats and subhuman primates, often in unmeasurable levels; there may then be a relatively quick recovery of
CBF to nearly normal or even hyperemic values, persistence of severely impaired perfusion, or any state between these extremes. CBF values then may stabilize, fluctuate, or change gradually in one or another direction.

Ischemia is not always accompanied by the development of neurological deficits or followed by cerebral infarction. There appears to be a critical level of CBF below which ischemia causes impairment of neuronal function and perhaps infarction as well. Surprisingly, this critical level is similar for different species, although among these species normal values for regional CBF are different.

In humans, electroencephalographic changes occur at CBF values of approximately 20 ml/100 g/min. In cats impairment of neuronal function, manifested by disappearance or abnormalities of single unit activity, also occurs at about the same measured value for CBF. In subhuman primates neurological deficits, abnormalities of evoked responses, and histological evidence of infarction are associated with approximately the same CBF. Certain chemical changes, particularly changes of local electrolyte balance, occur only at levels of CBF that are still lower.

Less severe impairment of neuronal function may be associated with values for CBF above 20 ml/100 g/min. It is interesting to speculate that such impairment may be reversible, even if it is of long duration, if perfusion improves or if oxygen availability is increased.

The reasons for this apparently tremendous reserve of CBF are unknown. CBF is closely coupled to cerebral metabolic and neuronal function, even at the “normal” levels that appear to be far in excess of what is needed to maintain the integrity of cerebral neurons.

The hyperemia that can occur after a period of ischemia of cerebral tissue may develop because of a redistribution of the flow of blood through collateral channels or because of a breaking up of aggregates of blood elements that had formed earlier in small blood vessels. Whatever the cause, postischemic hyperemia and peri-infarction hyperemia are common findings in experimental models of acute focal cerebral ischemia. It has not been fully established whether such reactive hyperemia is beneficial, of no importance, or of harm to the organism. Because CBF must be decreased to quite low levels before there is an obvious impairment of neuronal function or change in the structural integrity of the brain, it seems doubtful that hyperemia could be of much benefit, even if more oxygen and glucose are made available to ischemic areas and acidic metabolites are more quickly removed. There is some evidence that hyperemia may have an unfavorable influence on an unstable situation after acute focal cerebral ischemia by causing increases of the extent or severity of ischemic cerebral edema.

Ischemic Cerebral Edema

Ischemic cerebral edema can cause massive increases of intracranial pressure in experimental models of acute focal cerebral ischemia and cerebral infarction, particularly if infarction takes place within a closed skull containing normal amounts of cerebrospinal fluid (CSF). However, even with a closed skull, the animal models of cerebral ischemia are not strictly analogous to the usual clinical situations of strokes in humans. In animal models, infarcts generally are relatively large and involve a great deal of cerebral tissue in proportion to the size of the animal’s brain. CSF volumes are relatively small, and the cranial capacities of animals used for experimental cerebral ischemia are much less than the capacity of the human skull. Thus, in animals there is less capability than in humans of compensating for the increases of tissue volume that are caused by ischemic cerebral edema; yet, because of the relatively larger infarcts, much more swelling of the brain develops than in humans. Again, experimental models of acute focal cerebral ischemia are more analogous to massive hemispheric infarcts in humans than to the more common focal infarcts.

Chemistry of Cerebral Ischemia

In addition to local acidosis, changes of metabolic activity, electrolyte balance, and neurotransmitter activity occur during acute cerebral ischemia. It is reasonable to assume that the changes are similar in the brains of animals and humans. However, studies in humans are difficult.

In experimental models heterogeneity of chemical changes accompanies heterogeneity of morphological changes. Certainly, this heterogeneity can account for the sometimes conflicting results that have been described for chemical measurements.

Recovery From Ischemia

As in humans reperfusion of ischemic cerebral tissue is possible in experimental models of acute focal ischemia. The perfusion may be accompanied by an improvement or a worsening of neurological deficits. The exact time required for ischemia to cause irreversible changes of neuronal function or structural damage to the cerebral parenchyma has not been established; the severity as well as the duration of ischemia must be a factor. In subhuman primates reperfusion can take place as long as 24 hours after occlusion, and with reperfusion there may be no permanent neurological deficit. More commonly, however, ischemia of such duration will cause permanent changes. Whatever the critical time, focal ischemia is clearly different from global ischemia such as occurs with cardiac arrest. More than five minutes of focal ischemia is required for detectable permanent damage to cerebral tissue.

Conclusion

Experimental models of acute focal cerebral ischemia in subhuman primates and in larger mammals are probably similar to massive hemispheric infarcts in humans, particularly if the ischemia occurs
within a closed skull containing cerebrospinal fluid. Relevance to other kinds of ischemic strokes is limited.

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