The Ferret as an Animal Model in Cerebrovascular Research

C. Scott Atkinson, MD, Gary A. Press, MD, Patrick Lyden, MD, and Barrett Katz, MD

Clinical and pathologic observations have suggested analogies between the developing nervous system of ferrets (Mustela putorius furo) and those of more traditional animal models employed in stroke research. Experimental work has demonstrated advantages of the ferret as a model of visual development. We performed in vivo cerebral angiography and postmortem neurovascular dissection of latex-injected specimens of adult ferrets. The great vessels include a cervical arterial trunk that gives rise to both carotid arteries. The anatomy of the cranial arteries is similar to that of rabbits. No carotid rete mirabile is present. There are no intracranial anastomoses between the external and internal carotid systems. We present in vivo cerebral angiograms with pathologic correlation that demonstrate that ferrets may provide the same anatomic advantages as a rabbit model for the experimental study of cerebrovascular disease, with the additional advantage of a long extracranial cervical segment of the carotid artery, affording easier access to the intracranial vasculature. (Stroke 1989;20:1085–1088)

Nonprimate animal research in regional central nervous system ischemia and cerebrovascular disease has historically employed rabbits1–4 and rats5–7 as animal models. These two species are appropriate models because most of their cerebral blood flow originates from the internal carotid arteries, without significant contribution from their external carotid system.8,9 In other laboratory animal models, including dogs and cats, the circle of Willis is supplied mainly by branches of the external carotid artery through distal intracranial anastomoses.10,11 This collateral circulation causes unpredictable variations in the size of infarcts following occlusion of a single cerebral vessel.12 Rabbits and rats have been shown to have consistent patterns of infarction following controlled cerebral artery occlusion.2,4,5 We present in vivo cerebral angiograms with pathologic correlation that demonstrate that ferrets (Mustela putorius furo) may provide the same anatomic advantages as the rabbit model for cerebrovascular research.

Materials and Methods

Following the intravenous administration of 35 mg/kg ketamine hydrochloride with 5 mg/kg xylazine, ferrets were restrained in the supine position on an angiographic table (General Electric, Milwaukee, Wisconsin). A common carotid artery was exposed in the neck by direct cutdown. An 18-gauge plastic catheter was inserted into the common carotid artery and sealed with an injection cap. Conray 60 (Mallinckrodt, St. Louis, Missouri) was hand-injected through the catheter, 1.5 ml (undiluted) per standard angiographic or digital filming run. Ventrodorsal and lateral views of the cerebral circulation were acquired in separate runs at a rate of 3 films/sec for 6 seconds. To facilitate twofold linear magnification, we used a 0.15-mm focal spot, a target to film distance of 100 cm, and a target to object distance of 50 cm. Films were acquired using 60 kVp and 2 mAs for both the ventrodorsal and lateral projections. Standard photographic subtraction techniques were used on cut-film angiograms. In one ferret, the external carotid artery was tied off at its origin to allow visualization of the internal carotid artery in a ventrodorsal projection without superimposition of the large lingual artery.

The left heart (atrium or ventricle) was directly punctured through the unopened chest using a 2.5-in. 21-gauge needle attached to a 10-ml syringe containing 6 ml Conray 60 to obtain aortograms. We used a 20–30° RPO (right posterior oblique) projection to obtain 3 films/sec for 6 seconds with 20 kVp and 1.6 mAs.

The thorax was opened after a lethal dose of sodium thiopental was administered, allowing cross-clamping of the aorta and the inferior vena cava. The right atrium was opened for use as a vent. The ferret was perfused with 300–400 ml normal saline until the atrial vent drained clear perfusate. A total
of 24 ml silicone rubber compound was injected into the cervical trunk at high pressure. After injection, the cannulas were ligated and the atrial vent was sewn closed. The ferret was refrigerated for 24 hours. The brain was then removed and placed in 10% formalin. The arterial system was dissected for analysis.

Results

The aorta gives rise proximally to a large arterial trunk (diameter 1.5–2.0 mm), which ascends for 25–30 mm ventral to the trachea (Figure 1). At the thoracic inlet, this arterial trunk divides into the brachiocephalic artery and the left common carotid artery. The brachiocephalic artery further divides into the right common carotid artery and the right subclavian artery. The common carotid arteries are 1.00–1.25 mm in diameter. An occipital artery leaves the common carotid artery before the latter bifurcates into the internal and external carotid arteries. The external carotid artery gives rise to superficial and deep temporal branches as well as to the large lingua artery.

The internal carotid and basilar artery systems combine within the cranium to form the circle of Willis (Figure 2). The basilar artery is larger in diameter than the internal carotid artery. After giving rise to the cerebellar arteries, the basilar artery divides to form the posterior communicating arteries. These in turn supply the posterior cerebral arteries. The small internal carotid artery joins the posterior communicating artery to form the middle cerebral artery. The two anterior cerebral arteries complete the circle of Willis and unite to form an azygos anterior cerebral artery. No branches of the external carotid artery directly communicate with the internal carotid artery, nor is a rete mirabile present. Latex injection dissection confirmed the origin and course of the internal carotid artery and the structure of the circle of Willis demonstrated angiographically.

Discussion

Ferrets are carnivores belonging to the family Mustelidae, which also includes weasels and minks. Young ferrets (kits) are born deaf and blind after a gestation of 42 days. Ferrets reach adult weight by 4 months of age and achieve sexual maturity in the spring following their birth. Two litters (average size eight kits) per year can be obtained if females are bred early in their breeding season. Ferrets typically have genial dispositions and adapt well to the laboratory. Maintenance of colonies is simple, with nutritional requirements met by standard wet-feed mink diet (30% fat, 35% protein, 5% ash) or commercially available cat food. Ferrets are easily available and can be time-bred. They are less expensive to purchase and maintain than cats.

Although their suitability for the study of the cerebrovascular system has not been described, ferrets have been useful as models in the study of the visual system and the cerebral anatomy. Inves-
Atkinson et al  
Ferret as Animal Model  

Figure 2. Standard subtraction films from right common carotid artery injection demonstrate cranial arteries of ferret in ventrodorsal (left) and lateral (right) projections. 0, common carotid; 1, proximal external carotid; 2, internal maxillary; 3, lingual; 4, internal carotid; 5, anterior cerebral; 6, middle cerebral; 7, basilar; 8, first cervical ventral radicular; 9, anterior spinal; 10, vertebral; 11, occipital; 12, common trunk of auricular and superficial temporal; 13, auricular; 14, superficial temporal; 15, deep temporal; 16, external ophthalmic; 17, internal ophthalmic arteries. Arteries 11–17 are best seen in lateral projection.

tigations of the histogenesis of the retina, the influence of retinal afferent connections on the development of the lateral geniculate nucleus, and the development of gyral patterns have successfully employed a ferret model. Relative neurologic immaturity at birth has afforded significant advantages in such investigations. Anatomic studies have shown that the cerebral cortex of ferrets is similar to that of cats, while the retina is similar to that of dogs. In all these investigations, ferrets proved to be easy to handle and breed.

We believe ferrets are an appropriate animal model for the study of the cerebrovascular system. Our results confirm that a long cervical arterial trunk provides an easily accessible site for blood bound for both sides of the brain, as previously described. We find no internal-to-external carotid artery anastomotic channels analogous to the angiographically demonstrable arterius anastomoticus of dogs or the rete mirabile of cats. The existence of some collateral circulation not apparent radiographically or at postmortem examination cannot be completely excluded. It is therefore likely that predictable regional cerebral ischemic lesions can be experimentally produced without extensive intracranial surgical preparation. Angiograms and injected specimens in our study indicate that the basilar artery is the largest-caliber vessel supplying the circle of Willis. It may be that the vertebrobasilar system contributes most of the hemispheric blood supply in ferrets.

We believe that ferrets offer significant advantages in the experimental study of cerebrovascular disease: 1) ferrets are docile laboratory animals that are inexpensive to acquire and maintain, 2) the
central nervous and visual systems of ferrets have been shown to be analogous in structure to those of more intensively studied animals, 3) postnatal neurologic maturation of ferrets provides an opportunity to study development and teratology, 4) in vivo cerebral angiography can be easily and reproducibly performed, 5) no anastomoses between the internal and external carotid artery systems are evident in injected specimens of the cerebral vasculature, and 6) a long extracranial cervical portion of the carotid artery affords easy access to manipulation by experimental means.

References


Key Words • anatomy • animal models • angiography • ferrets