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Reduction in Brain Dopamine following Experimental Cerebral Ischaemia

ALTHOUGH considerable information is available concerning the effects of discrete electrolytic lesions on the concentrations of the monoamine neurotransmitters in mammalian brain, little is known about the neurochemical effects of experimental vascular lesions. Such information would be useful in understanding the natural history of cerebral infarction and other neurovascular diseases; furthermore, it might suggest new therapies for treating the acute and chronic sequelae of such diseases. The observations reported here show that ligature of the middle cerebral artery in monkeys, or of the common carotid artery in gerbils, causes profound decreases in brain dopamine but not noradrenaline.

Six squirrel monkeys (*Saimuri sciura*) were subjected to transorbital ligature of the left middle cerebral artery, as described by Hodgins *et al.*[1]. Three hours later they were guillotined and the left and right cerebral hemispheres assayed for dopamine by the method of Carlsson and Waldeck[2]. Ipsilateral to the vascular lesion, the brain dopamine concentration was 0.64 ± 0.10 $\mu g\ g^{-1}$; in the contralateral hemisphere, this concentration was 1.13 ± 0.15 $\mu g\ g^{-1}$ ($P<0.02$).

In developing an experimental preparation that might allow us to accumulate data from relatively large numbers of animals, we examined brain catecholamines in the Mongolian gerbil (*Meriones unquiculatus*). The blood supply to the gerbil brain is unique in lacking connecting arteries between the basilar and carotid circulations; hence, unilateral hemispheric infarction can be produced by ligaturing a common carotid artery[3]. A 50% mortality rate, equal to the infarction rate, is observed within 5 d of ligature[4]. Before death, animals may exhibit various clinical signs of infarction, including external rotation of paretic limbs when walking, hypokinesia of the contralateral side of the body, ptosis of the contralateral eyelid, and circulating behaviour, usually towards the ischaemic hemisphere and around a progressively decreasing diameter[4].

Mature mongolian gerbils (60–70 g) were anaesthetised lightly with diethylether, and the left common carotid was exposed through a ventral midline cervical incision. After the vagus nerve and the jugular vein had been dissected free, the artery was doubly ligatured with 4–0 silk sutures, and transected as previously described[3]. Groups of twelve animals were guillotined after various intervals, and their left and right cerebral hemispheres assayed for dopamine[2] and noradrenaline[5]. Brains from other animals prepared similarly were dissected into neostriatum, nucleus accumbens plus olfactory tubercle, hypothalamus, and the rest of the hemisphere, and pooled samples ($n=4$–5) were assayed for dopamine and noradrenaline. Twenty-four hours after unilateral carotid ligature, brain dopamine was reduced by 46% on the infarcted side (2.09 ± 0.39 $\mu g\ g^{-1}$ compared with 0.97 ± 0.24 $\mu g\ g^{-1}$, $P<0.02$). Brain dopamine was not significantly reduced among gerbils killed 2 h after lesioning, but was depressed among animals killed after 3 h. Brain noradrenaline concentrations were not dissimilar ipsilateral and contralateral to the lesion (that is, 1.19 ± 0.076 $\mu g\ g^{-1}$ compared with 1.04 ± 0.093 $\mu g\ g^{-1}$) among animals killed after 24 h.

Large brain dopamine reductions were observed in three parts of the cerebrum known to receive dopaminergic projections[6], but apparently not in the rest of the hemisphere (Table 1). The largest decreases were in the hypothalamus and the nucleus accumbens–olfactory tubercle (Table 1). Among sham-operated animals in which the common carotid artery was exposed, but not ligatured, brain dopamine was unchanged in all regions examined (Table 1).

Subtotal ischaemic necrosis of the telencephalon and diencephalon ipsilateral to the vascular lesion probably accounts for the profound decreases in dopamine concentrations within these brain regions. The area of infarction would be expected to include several dopaminergic tracts, that is, the nigro-neostriatal pathway, the tubero-infundibular pathway, and the cephalic portion of the meso-limbic pathways[3,4]. The major difference in the apparent susceptibility of noradrenergic and dopaminergic neurones to the ischaemia produced by left common carotid ligature could result from any of the following mechanisms: (1) the caudal location in the brain stem of noradrenergic cell bodies, which would continue to be nourished by the basilar artery; (2) the existence in gerbils of a single anterior cerebral artery, which would allow noradrenergic terminals in the anterior pole of the left hemisphere to be nourished by blood from the right carotid artery, and (3) differences in the susceptibility of noradrenergic and dopaminergic neurones to anoxia. The blood supply to the gerbil hypothalamus is provided by a rather large and consistent end artery derived from the anterior circulation; it is not surprising that the decrease in dopamine is most marked in this region.

Dopamine liberated from infarcted or severely ischaemic neurones could diffuse beyond synaptic clefts and interact with intracerebral blood vessels, glia, or as a false neurotransmitter with neurones that do not normally receive dopaminergic inputs. Since the inactivation of dopamine by oxidative deamination and by re-uptake into presynaptic neurones both require oxygen, the physiological effects of any dopamine released within ischaemic areas might be expected to be potentiated. Osterholm and his colleagues have suggested that, following experimental trauma to the spinal cord, noradrenaline liberated within the injured tissue causes intraspinal blood vessels to constrict, and thereby exacerbates tissue damage[7]. While the effects of dopamine on cerebral blood vessels await characterisation, this amine is known to modify vascular tone in peripheral organs[8]; hence, the possibility that brain blood flow is altered by the release of very large amounts of the amine after strokes merits exploration.

Just as the excessive release of dopamine might contribute to the acute pathophysiology of middle cerebral artery strokes, the neurological status of animals and humans who survive such strokes might also be complicated by a chronic decrease in central dopaminergic tone. That changes in brain dopamine similar to those reported here may also occur in human patients is suggested by the observation that the internal capsule of the human brain contains high concentrations of homovanillic acid[9], and thus probably dopaminergic neurones.

Table 1 Effects of Ligaturing Left Common Carotid Artery on Regional Brain Dopamine Concentrations in Gerbils

	Sham-operated $\mu g\ g^{-1}$		Common carotid ligature $\mu g\ g^{-1}$	
	Left	Right	Left	Right
Neostriatum	1.12, 1.15	1.19, 1.18	0.69, 0.83	1.05, 1.06
Hypothalamus	1.86, 1.93	1.75, 1.83	0.80, 0.70	1.75, 1.19
Nucleus accumbens–olfactory tubercle	1.30, 1.59	1.40, 1.29	0.91, 0.71	1.58, 1.32
Rest of hemisphere	0.35, 0.37	0.34, 0.31	0.24, 0.14	0.13, 0.37

Two experiments were performed using groups of five and four animals respectively; tissues were pooled prior to assay. Animals were killed 24 h after placement of lesions.

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