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✓ The authors, at the invitation of the Editorial Board, have outlined their general interpretation of the role of monoamine neurotransmitters following injury to the central nervous system. Their work on experimental stroke is discussed, and its relevance to spinal cord injuries accompanied by comparable hemorrhage and ischemia involving neurons is implied.

KEY WORDS · monoamine · neurotransmitter · dopamine · norepinephrine · serotonin · stroke · spinal cord injury

WHEN the blood supply to the myocardium is severely compromised, the resulting impairment in membrane function allows a large protein, the enzyme glutamic-oxaloacetic transaminase, to escape into the extracellular space and thence into the general circulation. Once outside its cell of origin, this enzyme apparently lacks significant biological effects; however its presence in the blood does provide a convenient index of myocardial cell death.

When brain or spinal neurons become severely ischemic as a consequence of thrombi, emboli, or the vasospasm that can follow hemorrhage or trauma, they too probably "leak" various intracellular constituents that they normally store in high

concentrations. The resulting inappropriate loss of several of these compounds, the monoamine neurotransmitters norepinephrine, dopamine, and serotonin, may exacerbate the pathophysiological changes caused by the initial ischemia (Fig. 1). If these molecules remain within synaptic clefts, they might be expected to flood the receptors of post-synaptic neurons; this would cause long-lasting hyperpolarization or depolarization, depending upon whether the monoamine neurotransmitter was inhibitory or excitatory, and thereby interfere with whichever brain functions the post-synaptic neurons subserved. At least two of the mechanisms normally used to terminate the physiological activity of monoamines released into synapses, namely, oxidative deamination

Monoamine neurotransmitters in stroke and CNS trauma

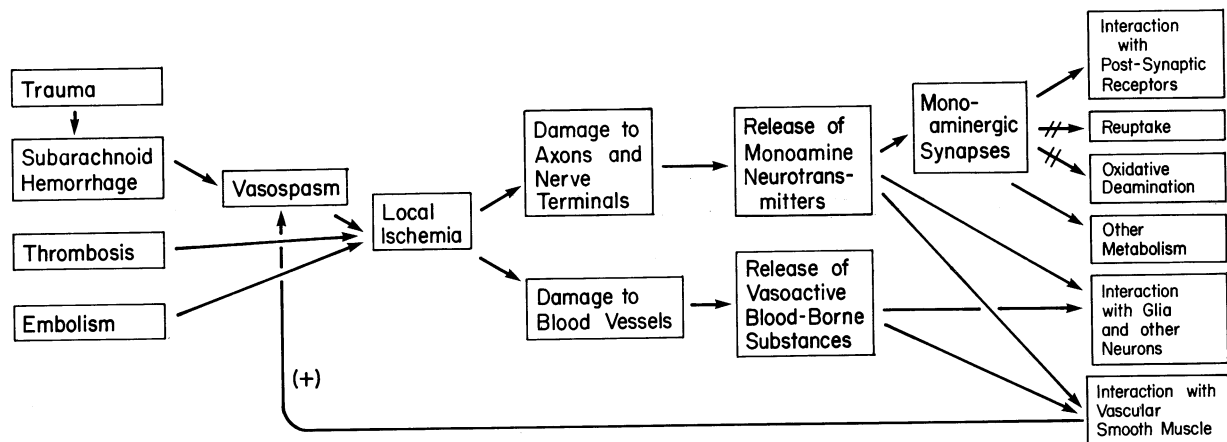


FIG. 1. Hypothetical effects of CNS ischemia on monoamine neurotransmitters. Local ischemia, caused by thrombosis, embolism, or vasospasm secondary to trauma or hemorrhage, could sufficiently damage monoaminergic axons or terminals within the ischemic area to render them incapable of storing the monoamines against the physiological concentration gradient. The monoamines would, as a result, be released into synapses and into the surrounding extracellular region. Within synapses, the monoamines would continue to interact with post-synaptic receptors and to be metabolized by enzymatic pathways not requiring oxygen; however, depending upon the extent of the ischemia, they probably would not be metabolized by oxidative deamination, nor would they re-enter their presynaptic neuron-of-origin by the process of reuptake. In the extracellular space, the monoamines could interact with vascular smooth muscle, possibly causing vasospasm, and exacerbating the ischemia; they could also interact as false neurotransmitters with neurons that normally do not receive monoaminergic synapses. Local ischemia might also allow the serotonin, and perhaps other vasoactive substances released from platelets, to enter the extravascular space, after which it could also cause vasospasm or interact with monoamine-sensitive neurons.

and reuptake into the presynaptic neuron of origin, require the availability of oxygen. Since these mechanisms are probably impaired, if not altogether inoperative, within ischemic areas, the potency of the monoamines may be greatly enhanced.

If, as seems likely, the monoamine molecules that escape from ischemic neurons can also pass into the extracellular space, they might act on local blood vessels, perhaps causing further ischemia (Fig. 1), as Osterholm and Mathews have suggested occurs in the traumatized spinal cord.² These molecules could also act as "false neurotransmitters" on nearby neurons that do not normally receive monoaminergic inputs, or even on monoamine-sensitive glia. The concurrent intravascular release of serotonin and other vasoactive substances from platelets trapped within ischemic brain regions might also be expected to worsen the vasospasm and ischemia (Fig. 1).

Although the evidence in support of this formulation is fragmentary, and even controversial, it does seem reasonable to us that the community of physicians that deals most

often with CNS ischemia, neurosurgeons and neurologists, should now work at characterizing the possible consequences of the "leakage" of monoamines and other biologically active molecules from "sick" neurons. From this effort and from the judicious application of the tools of contemporary neuropharmacology, there might arise both a better understanding of the natural history of neurovascular disease and new therapies to lessen the awful human wastage that can follow vascular or traumatic CNS lesions.

We have recently observed that unilateral lesions of the middle cerebral artery in monkeys, or of the common carotid artery in gerbils,¹ cause major ipsilateral reductions in brain dopamine, but not norepinephrine;³ 24 hours after the gerbil's carotid artery is ligated, the concentration of dopamine in the ipsilateral brain is reduced to less than half that present in the contralateral side.² This decrease probably reflects the leakage of dopamine from ischemic neurons, including axons of the nigro-neostriatal tract that pass through the internal capsule. That at

least some of the dopamine is liberated in an active form, without prior intracellular catabolism, is suggested by the tendency of the gerbils to exhibit turning behavior, which can be a sign of central dopaminergic stimulation. It can be conjectured that this "free" dopamine could act on postsynaptic dopaminergic receptors, on neurons that do not normally receive dopaminergic inputs, and on local blood vessels. The effects of dopamine on blood flow in the brain remain to be characterized; however, this monoamine is known to act with considerable potency on blood vessels in other parts of the body, for instance, the kidney.

Obviously, further studies are necessary to determine the causes and consequences of the depletion of brain dopamine that follows such experimental strokes: Which particular dopaminergic neurons are involved, the nigro-neostriatal tract to the basal ganglia, or the dopaminergic projections to the hypothalamus or the limbic areas? Do similar changes occur in the brains of humans suffering spontaneous strokes? Is the dopamine released in a biologically-active form? If so, does it affect structures beyond dopaminergic synapses, and how are its actions terminated? Might there be any therapeutic advantage in using drugs to block dopaminergic receptors soon after middle cerebral or carotid artery strokes? Conversely, do humans or experimental

animals who have survived such strokes suffer chronically from inadequate dopaminergic stimulation, and might there be therapeutic advantage in treating them with drugs like L-dopa and apomorphine which stimulate central dopaminergic receptors? Fortunately, experimental approaches have already been developed which should make it possible for investigators to answer such questions fairly quickly. Perhaps strokes, like Parkinson's disease, will someday be treated with drugs designed to modify the levels or actions of brain monoamines.

References

1. Kahn K: The natural course of experimental cerebral infarction in the gerbil. **Neurology** 22:510-515, 1972
2. Osterholm JL, Mathews GJ: Altered norepinephrine metabolism following experimental spinal cord injury. Part 2. Protection against traumatic spinal cord hemorrhagic necrosis by norepinephrine synthesis blockade with alpha methyl tyrosine. **J Neurosurg** 36:395-401, 1972
3. Zervas NT, Wurtman RJ, Lavyne M: Reduction in brain dopamine following experimental cerebral ischemia. **Nature** (in press)

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