Comparison of Nerves to Cerebral and Extracerebral Blood Vessels: A Differential Effect of Alpha Methyl Tyrosine on Norepinephrine Content

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SUMMARY Alpha methyl tryosine (AMT), an inhibitor of norepinephrine (NOR) synthesis, was injected intraperitoneally (200 mg/kg) in Sprague Dawley rats, kept in a cold room, or at room temperature for 16 hours. Using formaldehyde induced NOR fluorescence, nerve counts were made on whole mounts of cerebral and femoral arteries 14–300 pm in diameter, utilizing a grid superimposed on the vessels. Cold had no effect on the number of visible (i.e., fluorescing) nerves. AMT had an appreciable effect but only on nerves to femoral arterioles, where a significant reduction in nerve count was observed in both cold stressed and non stressed rats, when compared with animals not given AMT. Since the counting technique is sensitive only to large depletions of NOR, we cannot conclude that AMT failed to affect NOR content in cerebrovascular nerves. However, if such an effect was present, it was much less than the effect of AMT on nerves to femoral vessels.

We suggest that the differential effect of AMT on these 2 vascular beds may indicate a lower basal level of NOR release from cerebrovascular nerves, which would correlate with the difficulty of demonstrating basal sympathetic tone in this vascular bed.

Methods

Male rats, Sprague Dawley strain, were used. Four were injected with 200 mg/kg alpha methyl tyrosine (AMT) and immediately placed one to a cage, as recommended by Gordon et al., 4 in a cold room at 4–6 degrees C. Four others were similarly treated, except that they were injected with only the diluent and kept at room temperature for 16 hours. Using formaldehyde induced NOR fluorescence, nerve counts were made on whole mounts of cerebral and femoral vessels (CBV) and nerves to extracerebral vessels (ECV). This new data may imply some difference between the nerves to cerebral blood vessels (CBV) and nerves to extracerebral vessels (ECV). Such data is of importance because of the, as yet, unsolved enigma concerning the function of nerves to CBV.

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Results

Although rats were exposed to cold for 16 hours we were unable to find a depletion of NOR in the cold treated animals as compared with controls, even after AMT (200 mg/kg intraperitoneal) was used, as recommended by Gordon et al., 4 The AMT blocks NOR synthesis and thereby makes it easier to demonstrate NOR depletion by preventing accelerated synthesis from compensating for the NOR release. Perhaps the small sample size mitigated against showing an affect of cold. However, we were able to demonstrate another, unexpected, phenomenon. Both control and cold-stressed rats showed an affect of AMT, greater on the nerves to femoral branches than on nerves to cerebral vessels. The NOR was significantly depleted only from nerves to the former. This is reflected in the nerve counts shown in the accompanying table.

Discussion

The data suggest either (1) a difference in synthesis or release rates for NOR in nerves to CBV as compared to ECV, or else (2) a difference in concentration of AMT in nerves to the former as compared to the latter. If there were
a low level of NOR release from nerves to the CBV this would account for the low or absent neurogenic tone reported by many workers,2 and would provide an explanation for our data, since release might be so slow that inhibition of synthesis would fail to deplete NOR sufficiently to be reflected as a diminution of nerve counts. Alternatively, AMT levels might remain lower in nerves to CBV than in nerves to ECV, since concentration of AMT in the nerve might be related to NOR turnover. In any case, it appears of special interest that the differential functioning of the nerves to CBV and ECV, since reduced affects of drugs on NOR concentration in cerebrovascular nerves do not appear limited to the affects of reserpine as reported earlier,1,2 but are also seen with AMT, as reported here.

**References**

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**Sudden Death from Stroke**

**Lawrence H. Phillips II, M.D., Jack P. Whisnant, M.D., and Thomas J. Reagan, M.D.**

**SUMMARY** Sudden death is defined as any death that occurs less than 24 hours after the onset of first symptoms. Strokes account for 10 to 20% of all sudden deaths. The records of all residents of Rochester, Minn., who had their first stroke during the period 1955 through 1969 were analyzed. Among 255 deaths caused by the first stroke, 52 were sudden. Twenty-six of the deaths were due to primary intracerebral hemorrhage, and 20 to primary subarachnoid hemorrhage. Only two of the sudden deaths were caused by infarction: one by pontine and cerebellar infarct and the second by a cortical infarct, which resulted in death from status epilepticus. Among the nine patients who died within 2 hours of the onset of symptoms, six had primary subarachnoid hemorrhage. Hypertension was noted in 23 of the 26 patients (88%) who died of primary intracerebral hemorrhage; 8 patients with primary intracerebral hemorrhage were on long-term oral anticoagulant therapy, and all 8 were hypertensive.

**SUDDEN DEATH** is commonly defined as any death that occurs less than 24 hours after the onset of clinical symptoms and is not attributable to trauma or known preexisting illness. The most frequent cause is cardiovascular disease, specifically coronary artery disease. It has been reported to have been responsible for between 50 and 90% of all sudden deaths.1

Neurologic disease, although not a common cause, has been responsible for many sudden deaths. The most common disease of the central nervous system responsible for sudden death is stroke. In a review that pooled the results of 10 studies of sudden death, 14% of all deaths were found to have a neurologic basis, and the major, if not the only, diagnosis was some type of cerebrovascular disease.8 In general, most studies have found that stroke accounts for 10 to 20% of sudden deaths.1,8,9

Patients who have fatal intracranial hemorrhage usually die more quickly than do those who die after ischemic infarction.10 In a study done between 1929 and 1938 at Charity Hospital in New Orleans, Newbill11 found 63 cases of stroke among 296 autopsied cases in which death occurred within 24 hours of onset of symptoms. Only 18 cases of stroke were attributed to thrombosis or embolism. The remaining cases were diagnosed as being due to hemorrhage, types not otherwise specified.

The literature contains some confusing and at times contradictory conclusions concerning the timing of sudden death from stroke. Secher-Hansen12 found that 100 of 130 patients who died suddenly from subarachnoid hemorrhage in a forensic series died instantaneously. In a series of 250 medicolegal cases of subarachnoid hemorrhage from intracranial aneurysm, Freytag13 found that 60% of patients had "no survival" and another 29% died within 24 hours.
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