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Calbindin-D28K, Parvalbumin and Calretinin in Young and Aged Human Locus Coeruleus

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We have previously shown that calbindin is present in some noradrenergic locus coeruleus (LC) neurons, while other calcium binding proteins such as parvalbumin and calretinin are absent. The LC is vulnerable to early degeneration in Alzheimer's disease (AD) with tangles present as early as the third decade of life. The cholinergic neurons of the basal forebrain (BFCN) are also vulnerable to early degeneration. BFCN are rich in the calcium binding protein, calbindin-D28K (CB) which displays significant loss over the course of aging. In AD, CB loss is associated with tangle pathology and BFCN loss. The purpose of the present study was to quantitatively determine the density of CB immunoreactive LC neurons in the human brain, and to assess potential age-related changes in the density of these neurons. Blocks of brainstem containing the LC from five young (20-63 years old) and five aged (70-77 years old) cognitively normal human brains were fixed in 4% paraformaldehyde for 30-36 hours at 4^{o} C and taken through sucrose gradients for cryoprotection. Blocks were sectioned at a thickness of 40 µm on a freezing microtome and 1 in 24 series of sections were stored in 0.1 M phosphate buffer until use. One series of sections from each brainstem were immunohistochemically stained using a double chromogen procedure for the monoaminergic synthetic enzyme tyrosine hydroxylase (TH) and CB, using diaminobenzidine (brown reaction product) and benzidine dihydrochloride (blue / black granular reaction product) as chromogens respectively. Quantitative analysis was performed on digitized images to determine the total number of TH- and CB-positive LC neurons in each case. Overall, a relatively small proportion of TH-positive LC neurons contained CB. There was no significant difference ($p>0.05$) in the percentage of CB-positive LC neurons when young individuals (5.28% - 14.01%) were compared with the aged (8.33% -20.75%). Similarly, there was no significant difference ($p>.05$) between the young and aged groups in the average number of TH-positive (young=435, old=305) or the average number of CB-positive LC neurons (young=49, old=37). While CB immunoreactivity is present is a proportion of LC neurons, there does not appear to be any age-related changes in the number or proportion of CB-positive LC neurons. Therefore, unlike the BFCN, CB immunoreactivity in LC neurons is unlikely to contribute significantly to the vulnerability of these neurons to neurodegeneration.

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