Focus on the Locus

This letter is in response to the editorial by Rye and DeLong and the accompanying article by Zarow et al. Our research has focused on the locus ceruleus for many years. We have detailed the mechanism of death of locus ceruleus neurons in Alzheimer disease as follows. We demonstrated that the monoamine oxidase type A metabolite of norepinephrine (NE), 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL), is highly toxic and triggers apoptotic neuron death in vitro and in vivo models of adrenergic neurons. Neither NE nor its other metabolites were toxic in these models. We showed that DOPEGAL but not NE generates free radicals, induces mitochondria permeability transition, and activates caspases. These mechanisms underlie apoptotic neuron death. We also showed that NE, DOPEGAL, and their synthesizing enzymes accumulate in the locus ceruleus neurons in Alzheimer disease. We postulated that the accumulation of DOPEGAL in these neurons is due to defective axonal transport caused by phosphorylation of tau protein, which interferes with assembly of the microtubule transport system. Phosphorylation of tau is triggered by β-amyloid, a protein genetically linked to Alzheimer disease. Alternately, toxic aggregates of β-amyloid, like α-synuclein aggregates, could permeabilize NE storage vesicles. This would allow NE to leak into the cytosol, where it is converted to DOPEGAL. This is perhaps the most complete explanation of the mechanisms underlying neuron death in Alzheimer disease to date.

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Callosal Neglect Reexamined

Heilman and Adams correctly advise caution in performing callosotomy on patients with multiple brain lesions. However, their comments concerning postcallosotomy findings in their patient ignore a plethora of evidence against their theoretical advocacy, as follows. The weakness and apraxia after callosotomy are always indexed to the subject’s laterality of movement control, of which neural handedness is a code. Even voluntary saccades are planned and executed from the major hemisphere; their latency to the left is longer than to the right by an amount commensurate with the interhemispheric transfer time. The improvement of motor neglect is pegged to the patient’s handedness, reflecting the specific excitatory effect of the major hemisphere on the minor hemisphere via the corpus callosum. The authors have completely discounted von Monakow’s transcallosal dischisis in the sensory realm. Evidence indicates that dischisis causes contralateral neglect, which is commonly associated with ipsilesional findings. This is reflected not only in the time-resolved improvement in sensory neglect (as the authors pointed out) but also in the fact that the reaction time of the dominant hand substantially increases when the facilitatory influence of the minor hemisphere on the major hemisphere is abated in the presence of parietal lesions that cause neglect. Evidence shows that this increase in reaction time is topographically related to the lesion site, mainly affecting the foveal vision. Thus, the directionality of callosal traffic underpins both the laterality of movement control and conscious awareness. Neglect is an indicator of the directionality of callosal traffic in the sensory realm.

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Callosal Neglect and Cognitive Impersistence

Heilman and Adams detailed the behavioral neurologic sequelae of a young woman with extensive, chronic, mainly right hemispheric injury who had minimal cognitive deficits until undergoing a complete callosotomy for intractable seizures. She subsequently showed left neglect on various tests. The find-