BRAIN SCIENCES: NEUROBIOLOGY

Aging-related content to accompany lectures on Motor System

Learning Objectives:

1. Understand the major changes in the motor system associated with aging.
2. Understand the pathophysiology of age-related changes in the motor system.
3. Understand the impact of these age-related changes.

I. Muscle and Innervations

A. Age-related changes in muscle:

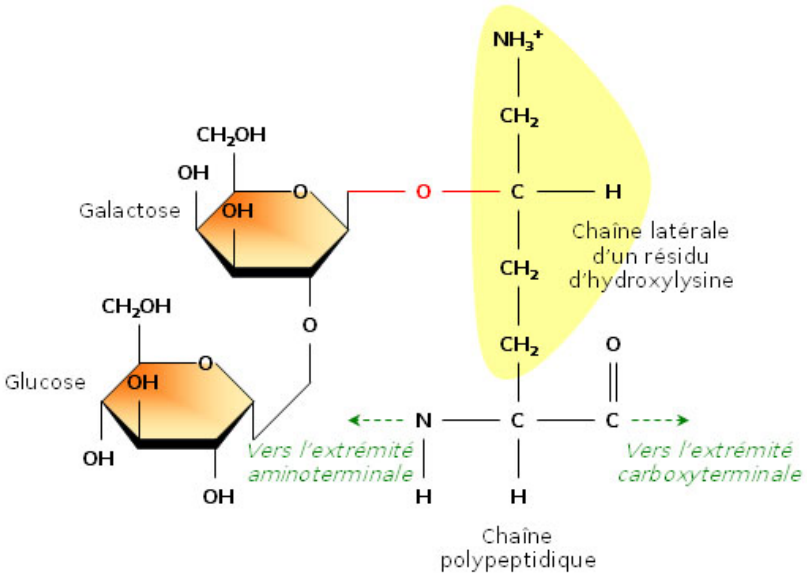
1. Muscle mass is lost at rate of 0.5% to 1.0% per year in adults over 60 years.
2. Muscle strength loss ranges from 20% to 40% from the third to the eighth decades.
3. Reduction in muscle fiber size is disproportionate between the two principal fiber types: Type II ('fast') fibers, which are highly anaerobic, tend to have a marked decrease in size with age; Type I ('slow') fibers, which are aerobic, tend to retain their size during aging.

B. Muscle wasting in frail older persons, a disorder known as sarcopenia, leads to higher incidence of falls and fractures and functional decline, thus impairing quality of life.

II. Spinal Reflex

A. Age-related changes in the spinal reflex:

1. Amplitude of the spinal stretch reflex declines with normal aging.
2. Non-enzymatic glycosylation and cross linking of collagen in tendons increases with aging from divalent to tri- or multi-valent configurations, resulting in increased stiffness. Diagram shows glycosylation of collagen, which increases with age.



B. Changes in muscle-tendon structures with aging leads to decrease in compliance and to decrease in range of motion, which in turn contribute to deterioration of the mechanical stimulus that elicits the stretch reflex.

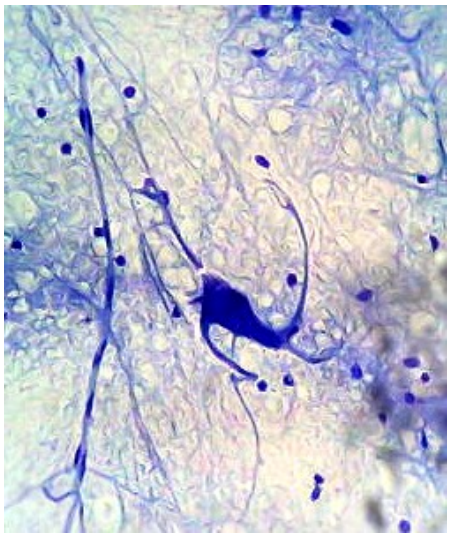
III. Descending Motor Pathways

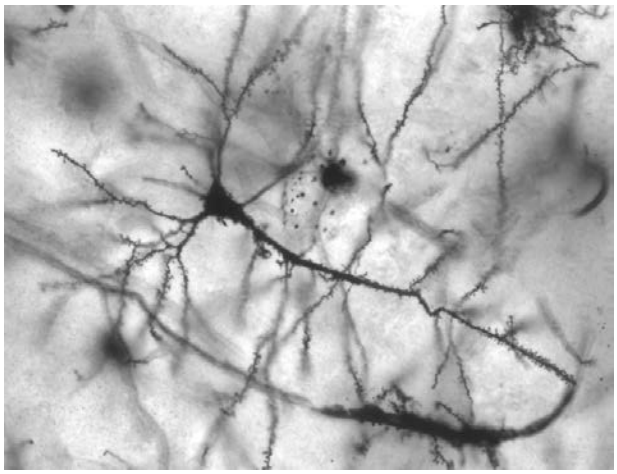
Of the various descending motor pathways, most studies in the literature concerning the effects of aging have focused on the lateral corticospinal tract (LCST). Aging is associated with critical decline in fine motor hand movements, which reflects degeneration of the LCST with aging. In particular, fine motor time increases with age over 60, but not in those under age 60, suggesting perhaps that changes are not due to age alone. Increased motor slowing is associated with increased mortality in older adults.

Fine Motor hand movements declines with age, due to age-related degeneration of the lateral corticospinal tract. (Image from http://commons.wikimedia.org/wiki/File:Tissue_processing_-_Paraffin_ribbon_is_floated_onto_the_surface_of_a_warm_water_bath.jpg)

IV. The Motor Cortex

Age-related changes include decreases in the number of neurons and synapses. One hypothesis is that disuse atrophy occurs, arguing for a "use it or lose it" construct with aging. Atrophic changes in cortical neurons vary widely in different regions of the brain.





Neuron under the microscope (left); Pyramidal hippocampal neuron 40x (right). Neurons and synapses decrease with age.

V. Basal Ganglia

A. Age-related changes in the striatum:

1. Dopamine D1 receptor density in the caudate and putamen declines with age. Age-related loss of dopamine neurotransmission may play a role in the expression of extrapyramidal disorders in older adults.
2. The total volume of the striatum decreases with age.
3. Striatal iron content increases with advancing age. Any regional increase in brain iron concentration may increase the potential for local free-radical formation, since cytotoxic free radicals are generated in the brain by oxidation/reduction reactions that are catalyzed by transition metals such as iron. Free-radical-mediated mechanisms may contribute to neuronal damage in Parkinson's disease (PD), other neurodegenerative conditions also associated with aging, and the aging process itself. A strong direct relationship exists between age and regional iron content in the putamen and caudate, but not in the globus pallidus or thalamus. Consequently, free-radical formation may increase in the striatum, representing a risk factor for the development of neurodegenerative disorders such as PD in which nigrostriatal neurons may be affected by increased oxidant stress.

B. Age-related changes in substantia nigra:

1. The pigmented neurons in the substantia nigra undergo an age-related loss, at about 10% per decade. This is associated with motor dysfunction, including bradykinesia, stooped posture and gait disturbance. These age-associated changes resemble Parkinson’s disease (PD), and may account for the increase in prevalence of PD with age.
2. Aging is associated with pronounced microglial reaction in the substantia nigra, with frequent, intensely stained hypertrophic microglia. The percentage of substantia nigra area occupied by microglial bodies and processes is significantly greater in older adults than in younger subjects. Since microglia are activated by cell death, the marked microglial reaction in normal aging human substantia nigra suggests a pathologic process of age-related cell loss, and may have an additive effect with specific age-related neurodegenerative diseases, including Parkinson's disease.

VI. Cerebellum

A. Age-related changes in the cerebellum:

1. The cerebellum undergoes significant volume loss with aging, especially in the vermis.
2. The anterior lobe of the cerebellum is most affected by the aging process: the total number of granule and Purkinje cells is reduced by about 40%, with significant loss of cortex, mainly of the granule cell layer.

B. Possible Mechanisms of Pathogenesis:

1. The metabolic hypothesis: Cellular energy metabolism progressively declines with advancing age, predisposing selected groups of cells and tissue compartments to age-related pathologies. One study (Bertoni-Freddari 2004) has demonstrated significant decline in both the number and metabolic function of mitochondria in the cerebellum in rats with age, which could explain the progressive decline in

cerebellar function.

2. The nitric oxide hypothesis: Nitric oxide synthase (NOS)-containing neurons are found in many loci throughout the central nervous system, which include the cerebral cortex, the cerebellum, the hippocampus, and the hypothalamus. NO plays a very important role in control of neuronal activity in all of these areas by diffusing into neurons where it activates soluble guanylate cyclase (sGC), leading to generation of cyclic guanosine monophosphate (cGMP) and cyclooxygenase-1, in turn leading to generation of prostaglandins. Both are important mediators of NO actions. In the cerebellum, NO is thought to mediate long-term potentiation in the hippocampus. Various stresses and corticoids have been shown in monkeys and also in rodents to cause neuronal cell death. Cell death may occur by stimulation of glutamic acid release, which causes release of NO, and can then lead to neuronal cell death.
3. The haemodynamic hypothesis: Regional vulnerability of the cerebellum to the effects of aging (e.g., the vermis and the anterior lobe) suggests that multiple risk factors, such as toxins in the high CSF flow, hemodynamic differences, and functional factors such as lack of usage with decreasing mobility, may account for regional age-related influences.

C. Impact:

1. Age-dependent changes must be carefully distinguished from disease related MR changes of cerebellar nuclei in patients with degenerative or acquired cerebellar ataxia.
2. Functional decline of the vermis may lead to impaired gait and balance common with old age.
3. The anterior lobe is functionally related to the spinal cord and is mainly concerned with posture, muscle tone, and gait - motor functions, which are often affected by aging.

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