



**Karolinska
Institutet**

Institutionen för Neurovetenskap

BEHAVIORAL CHANGES AND MECHANISMS - AN EXPERIMENTAL STUDY ON AGING IN RODENTS

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Karolinska Institutet offentligen försvaras i Hillarpsalen, Retziuslaboratoriet, Retzius väg 8.

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av

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Abstract

In paper I, we studied alterations in behavior with advancing age in female C57BL/6 mice (of Jackson origin). In parallel, growth and survival data were collected. In a protected environment the median survival age was 32 months. Our behavioral data show that aging modulates certain aspects of basic behavior in a continuous manner. However, behavioral aging differentially affects genetically closely related individuals housed under strictly standardized conditions. Thus, subtle environmental factors and epigenetic modifications may be important modulators of aging.

In paper II, we analyzed behavioral changes during aging in male C57BL/6J mice. A group of aged males maintained on dietary restriction (DR) was included. The most conspicuous alteration was the decline in exploration activity with advancing age. Comparison with results from paper I revealed that alterations in aged males and females are similar. Moreover, behavioral indices in 22-month-old males could predict remaining life span; exploratory activity and motor skills accounted for up to 65% of the variance in survival. Consistent with a high level of exploratory activity and preserved motor capacity indicated a long post-test survival, aged mice maintained on DR were more successful in such tests than ad libitum fed age-matched males.

In paper III, we studied changes in DNA methylation during aging in the central nervous system in a Sprague-Dawley rat model. Using the LUMinometric Methylation Assay (LUMA), which assays methylation status in CCGG sequences across the entire genome, and 5-methyl cytosine labelling in neurons, we report a decline in global DNA methylation in several but not all regions examined. In females there was a gradual drop in DNA methylation in the spinal cord, while both cerebellum and striatum were unaffected. The unexpected observation of a decrease in DNA methylation confined to the middle-ages when reproduction ceases suggested that gonadal steroids influence DNA methylation. To test this, ovariectomy was performed in fertile females, resulting in lowered DNA methylation in frontal cortex to levels observed in middle-aged and aged females. In males, DNA methylation was unchanged in the frontal cortex and the decline in DNA methylation in hippocampus occurred at more advanced age than in females. Another conspicuous difference between sexes was the demethylation of DNA in the aged male striatum.

In paper IV, we compared age-related loss of muscle mass (sarcopenia) in C57BL/6J mice (wild type; WT) and a transgenic model with accelerated aging: the mtDNA mutator mice; in an effort to assess if an increased load of mtDNA mutations is sufficient to phenocopy sarcopenia as it occurs in normal aging. We found that both WTs and mutator mice lose muscle mass during aging but that this process is more advanced in normal aging. A distinct difference between WTs and mutator mice, was the dramatic re-expression of γ -subunit of the nicotinic acetylcholine receptor (nAChR- γ) caused by failure of muscle innervations in normal aging. In mtDNA mutator mice increased levels of nAChR- γ were infrequent and importantly seen in both young adults and aged; with only a small increase across adult life-span.