Sex, senescence, senolytics, and cognition

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Male-female differences in peripheral cell senescence and the level of systemic inflammation contribute to sexual dimorphism in the prevalence, symptoms, and pathogenesis of age-related diseases, including neurodegenerative diseases. Cellular senescence occurs as a response to damaging or stress-inducing stimuli over the course of aging. The response includes the release of pro-inflammatory cytokines and a state of irreversible growth arrest of cells that normally divide. During middle age, pro-inflammatory cytokines from peripheral senescent cells raise the level of systemic inflammation, contributing to neuroinflammation. brain oxidative stress, and senescent neurophysiology. These physiological changes are protective against excitotoxicity at the expense of a loss of normal neuronal function, contributing to age-related cognitive decline. Senolytics are compounds designed to eliminate senescent cells, reducing systemic inflammation and preserving cognition in aging male, but not female F344 rats. A likely mechanism for the sex difference involves estrogen signaling. Senolytic drugs act on signaling mechanisms that influence growth, proliferation, and cell survival programs in a manner opposite that of estrogen. In addition, senolytics may hasten the loss of follicles, the primary source of estrogen and estrogen has anti-aging effects that are independent of cell senescence, including rapidly modifying senescent neurophysiology. The results indicate that senolytic drugs interact with two fundamental biological processes, sex and aging.

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