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Changes in glia-neuron interactions in rat hippocampus induced by aging and inflammation

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Aging is accompanied by a decline in cognitive functions, along with a variety of neurobiological changes. Recently, the term "inflammaging" has been coined to characterize a widely accepted paradigm that aging is accompanied by a low-grade chronic up-regulation of certain proinflammatory responses. The association between inflammation, aging, and Alzheimer Disease, is based on complex molecular and cellular changes that we are only just beginning to understand. The hippocampus plays a critical role in memory formation and is one of the structures more closely related to electrophysiological, structural and morphological changes during aging. In the present study, we examined the effect of normal aging and LPS-induced inflammation on glia/neuron interaction in the CA1 region by confocal immunofluorescence. The density of GFAP positive astrocytes was significantly lower in CA1 region of aged rats, with a mean hippocampal density of 522±8/mm^{2}in the young (n=12) and of 420±16/mm^2 in the aged rat (n=15; -20% vs young rats, $P < 0.0001$) but it did not change in LPS-treated rats (548.5±38/mm^2, n=6, n.s.). Confocal microscopy indicated that in the hippocampus of aged and LPS-treated rats astrocytes were smaller, with thicker and shorter branchings than in young rats and with morphological signs of clasmatodendrosis. In aged and LPS-treated rats apoptotic neurons (as evidenced by AIF or CytC immunohistochemistry) were surrounded by astrocyte branchings, apparently in the process of clearing up the cellular debris. Apoptotic cell debris, scattered throughout the CA1 region, were significantly higher in aged (496±29/mm^2, n=10) and LPS-treated rats (106±25/mm^2, n=6) than in young rats (22.7±5/mm^2, n=12, $P < 0.001$ vs both other groups) and were all juxtaposed to astrocytes cell bodies and branchings. Scarse activated microglia (OX-6 immunopositive) were present in CA1 of young rats (2.5±1, n=10) while substantial infiltration of activated microglia were present in CA1 of aged and LPS treated rats. These cells were hypertrophic, ranging from densely arborized cells to cells with a bushy appearance with swollen cell bodies and intensely stained short processes, often in close association with apoptotic cells. These data show that senescence-induced modifications of astrocytes and microglia in the hippocampus of aged and LPS treated rats may help clearing the cellular debris derived from apoptotic mechanisms. This might be a protective mechanism that possibly controls inflammatory processes and spread of further cellular damage to neighboring tissues.

Key words
Hyppocampus, astrocytes, microglia, apoptosis, inflammaging