Cognitive Aging, Stress and Pharmacological Intervention

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Aging refers to a process that is associated with chronological age but not identical to it. An important question in the aging study concerns the origin of individual differences that distinguish successful aging (maintenance of functional capacity to the end of a long life) from unsuccessful aging (premature decline or incapacity). With the principle that the phenomenon of individual differences provides a natural experiment for determining the neurobiological basis of functional loss or preservation in the aged, this study of normal aging focused on cognitive capacities and function of hippocampus.

Cognitive decline in ageing, exemplified by spatial learning impairments in rats, has been associated with a decreased efficiency in the physiological regulation of the stress response, characterized by sustained high blood concentrations of circulating glucocorticoids following episodes of stress. Dysregulation of neuroendocrine function involving the HPA axis is also a feature of age-related dementia and appears to be linked to cognitive decline in older adults in the absence of disease. For example, an increase in HPA activity over time has been shown to predict the progression of cognitive decline in an elderly population.

HPA axis function was examined in young and aged male Long-Evans rats that were initially assessed on a version of the Morris water maze sensitive to cognitive impairment during aging (Fig. 1). In behaviourally characterized rats, a 1-h restraint stress paradigm revealed that plasma corticosterone concentrations in aged cognitively impaired rats took significantly longer to return to baseline following the stressor than did those in young or aged cognitively unimpaired rats. No differences in basal or peak plasma corticosterone concentrations, however, were observed between young or aged rats, irrespective of cognitive status (Fig. 2). Using in situ hybridization, we evaluated mineralocorticoid receptor (MR) and GR mRNA abundance in young and aged rats characterized on the spatial task. Abundance of MR mRNA was decreased as a function of age in the hippocampus, and the decrease in MR mRNA was largely unrelated to cognitive status. However, GR mRNA was significantly reduced in several hippocampal subfields of aged cognitively impaired rats compared to either young or aged cognitively unimpaired cohorts, and was significantly correlated with spatial learning ability among the aged rats in each of these brain regions (Fig. 3). These studies describe a

decrease in GR mRNA in a hippocampus that occurs in tandem with impairments of the HPA response to stress and cognitive decline in aging.

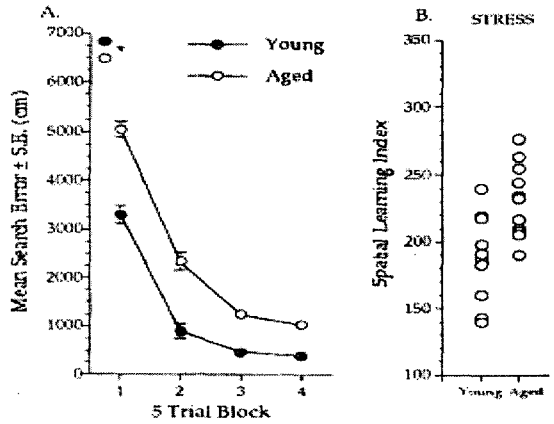

FIG. 1. Performance in hippocampal-dependent spatial learning. (A) Performance of young (filled circles) and aged (open circles) rats during training trials in the spatial version of the water maze as assessed by cumulative search error. Cumulative search error, averaged across blocks of five training trials, measures proximity of the rat to the platform during the course of the training trial. Young and aged rats did not significantly differ on the first training trial (asterisk in upper left) but over the course of training aged rats were reliably impaired relative to young rats in acquiring the task. (B) Distribution of individual learning index scores for young and aged rats

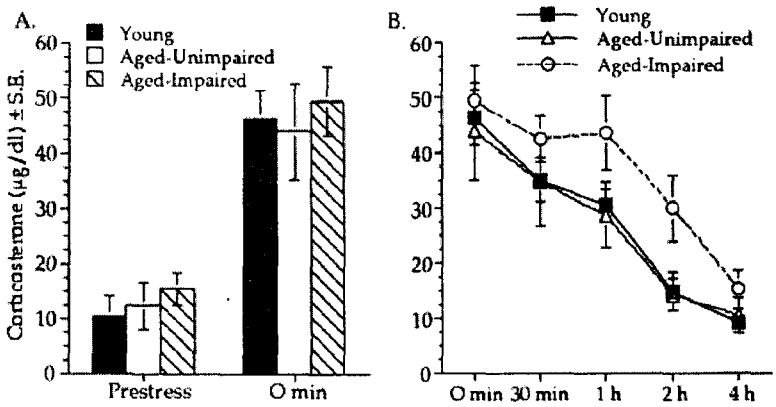

FIG. 2. Plasma corticosterone measured from young and aged rats prior to (prestress) and at five intervals (0 and 30 min, 1, 2 and 4 h) after a 1-h restraint stressor.

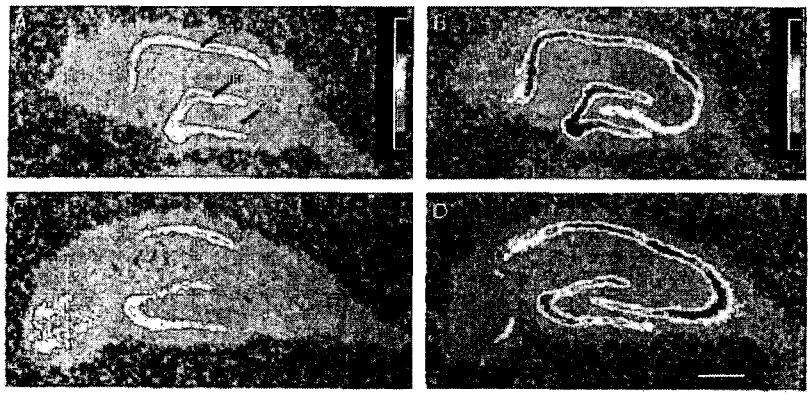

FIG. 3. The GR and MR mRNA labelling throughout the rostrocaudal axis in naive young adult rats. Pseudocolor images of film autoradiograms show (A and C) GR and (B and D) MR mRNA abundance in septal (top panels) and temporal (bottom panels) hippocampus in semiadjacent sections taken from a representative naive rat.

Hippocampal neurodegeneration in Alzheimer's disease and aging occurs in concert with a loss of input from subcortical and cortical afferents, including a major loss of innervation from basal forebrain cholinergic neurons. The effects of selective immunolesions (Fig. 4) of septo-hippocampal cholinergic neurons on hippocampal corticosterone receptor mRNA and on HPA activity were investigated. As evaluated by in situ hybridization, hippocampal GR mRNA, but not MR mRNA, was significantly decreased in lesioned rats compared to controls (Fig. 5). In a companion study, the peak corticosterone response to one hour of restraint stress did not differ between lesion and control groups but the post-stress decline of corticosterone was more protracted in the lesioned rats (Fig. 6). Hippocampal nuclear GR proteins in lesion rat were evidently decreased, relative to control. We conducted to see expression levels of the other protein related the translocation of GR into nucleus and GR function in nucleus, and proteins interacting GR, in hippocampus without cholinergic input (Fig. 7).

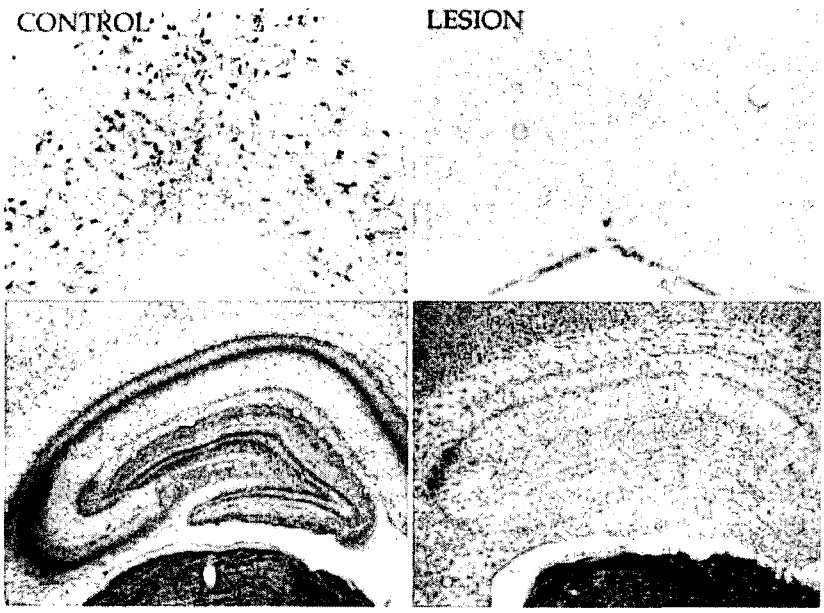

FIG. 4. Top: bright-field photomicrographs showing immunohistochemical localization of ChAT +ve cells in the MS/VDB. Left and right panels show labelling in control and lesioned rats, respectively. Bottom: right panel shows depleted hippocampal AChE staining in a lesioned rat brain compared to control (left panel).

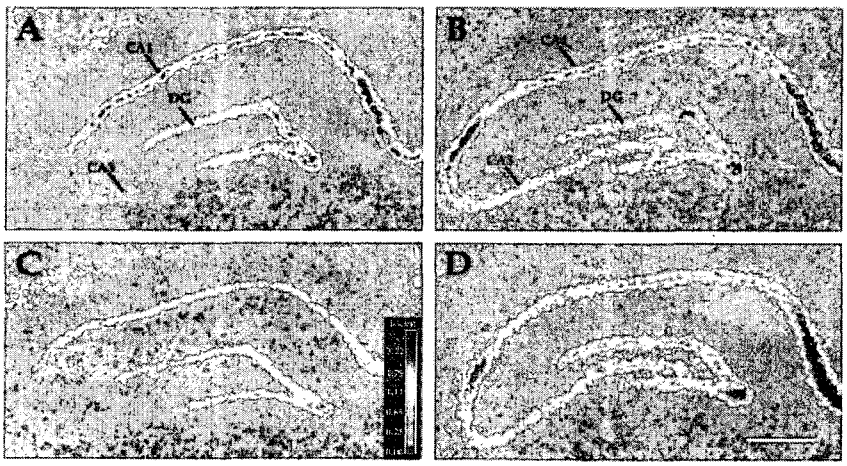

FIG. 5. Pseudocolor images showing hippocampal GR (A and C) and MR (B and D) mRNA expression in representative control (A and B) and lesioned (C and D) rats. Red and blue indicate highest and lowest hybridization densities, respectively (see calibration bar in C). GR mRNA is visibly attenuated in stratum granulosum of the denate gyrus (DG) and CA1 stratum pyramidale of the lesioned rat. In semi-adjacent tissue sections, MR mRNA expression appears similar in both conditions.

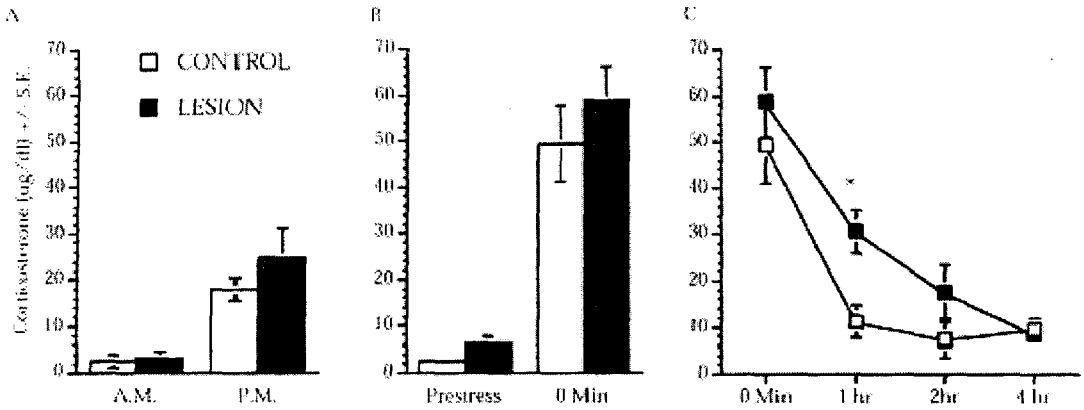

FIG. 6. (A) Bar graph shows no differences in plasma corticosterone concentrations measured in lesioned (black bar) and control (open bar) rats at two time points in the diurnal cycle 48 h before they were killed for in situ hybridization. (B) Bar graph shows no differences in pre-stress and peak corticosterone values in control (open bars) and lesioned (black bars) rats subjected to restraint stress. (C) Line graph shows corticosterone concentrations at four intervals after the stressor (0 min, 1 h, 2 h, 4 h). The groups differed statistically.

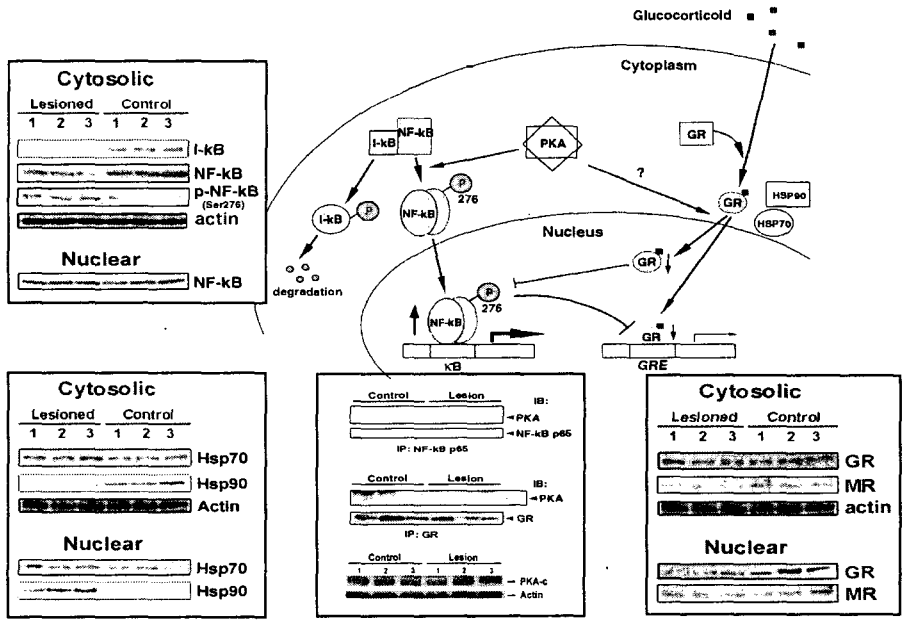

FIG. 7. The schematic signaling pathway in the hippocampus, mediating dysregulation of HPA axis to stress and cognitive decline in aging

A loss of cholinergic innervation reduces the basal expression of hippocampal glucocorticoid receptors and suggests a mechanism whereby age-related loss of basal forebrain cholinergic neurons could contribute to the dysfunction of the HPA axis and the loss of the functional integrity of the hippocampus that occurs during aging. This research strategy promises to advance our understanding of the mechanisms through which aging is regulated and expressed in neural systems and has important implications for the development of therapeutic interventions.