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Regular article

Selective noradrenaline depletion impairs working memory and hippocampal neurogenesis

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Abstract

Noradrenergic neurons in the locus coeruleus play a role in learning and memory, and their loss is an early event in Alzheimer's disease pathogenesis. Moreover, noradrenaline may sustain hippocampal neurogenesis; however, whether are these events related is still unknown. Four to five weeks following the selective immunotoxic ablation of locus coeruleus neurons, young adult rats underwent reference and working memory tests, followed by postmortem quantitative morphological analyses to assess the extent of the lesion, as well as the effects on proliferation and/or survival of neural progenitors in the hippocampus. When tested in the Water Maze task, lesioned animals exhibited no reference memory deficit, whereas working memory abilities were seen significantly impaired, as compared with intact or sham-lesioned controls. Stereological analyses confirmed a dramatic noradrenergic neuron loss associated to reduced proliferation, but not survival or differentiation, of 5-bromo-2′deoxyuridine–positive progenitors in the dentate gyrus. Thus, ascending noradrenergic afferents may be involved in more complex aspects of cognitive performance (i.e., working memory) possibly via newly generated progenitors in the hippocampus.

Keywords

Noradrenaline; Alzheimer's disease; Working memory; Immunotoxin; Adult neural progenitor cells; Rat

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> ...On the other hand, undesired activation of NMDA receptors in the glutamatergic system is observed [4]. Other changes in Alzheimer's disease include global brain atrophy, which also affects serotonergic, dopaminergic and noradrenergic systems [5–7]. So far, there is no effective treatment for Alzheimer's disease [8]....

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> ...Disturbances in these neurotransmitter systems may partially account for age-related changes in memory and attention (Von Linstow et al., 2017). In this context, the increase in NA associated with CR here may have contributed to attenuate memory decline in aged CR rats (Coradazzi et al., 2016; Pyrzanowska et al., 2012), although there were no differences in

hippocampal NA between old Ad libitum and Adult rats, consistent with earlier studies (Lee et al., 1994; Luine, Bowling, & Hearns, 1990; Míguez, Aldegunde, Paz-Valiñas, Recio, & Sánchez-Barceló, 1999; Pyrzanowska et al., 2012) but not with the lower levels reported in old animals elsewhere (Koprowska et al., 2004; Stemmelin et al., 2000). In terms of the dopaminergic system, no changes were evident in hippocampal DA and DOPAC in old Ad Libitum rats, as described previously (Lee et al., 1994; Nakamura & Ohno, 1995; Van Luijtelaar, Tonnaer, & Steinbusch, 1992; Yurek, Hipkens, Hebert, Gash, & Gerhardt, 1998)....

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...Learning and memory are not only modulated by glucocorticoids, but also by another major stress modulator, noradrenaline [35–38]. The hippocampus receives dense noradrenergic input [39,40], and some authors have argued that noradrenergic activity is critical for hippocampal glucocorticoid activity in memory consolidation and retrieval [41,42]. In one animal study, noradrenergic activation by yohimbine (an alpha 2-adrenergic receptor antagonist) increased glucocorticoid-mediated memory enhancement in rats with reduced emotional arousal response due to prior habituation [43]....

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