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REVIEW

HPA axis and aging in depression: Systematic review and meta-analysis

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Summary One of the most consistent findings in the biology of depression is an altered activity of the hypothalamic—pituitary—adrenal (HPA) axis. However, data concerning this issue have never been examined with a focus on the older population. Here we present a systematic review and meta-analysis, based on studies investigating levels of cortisol, adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) in depressed participants older than 60 and compared with healthy controls. We found 20 studies, for a total of 43 comparisons on different indices of HPA axis functioning. Depression had a significant effect (Hedges' *g*) on basal cortisol levels measured in the morning (0.89), afternoon (0.83) and night (1.39), but a smaller effect on cortisol measured continuously (0.51). The effect of depression was even higher on post-dexamethasone cortisol levels (3.22), whereas it was non-significant on morning ACTH and CRH levels. Subgroup analyses indicated that various methodological and clinical factors can influence the study results. Overall, older participants suffering from depression show a high degree of dysregulation of HPA axis activity, with differences compared with younger adults. This might depend on several mechanisms, including physical illnesses, alterations in the CNS and

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immune-endocrinological alterations. Further studies are needed to clarify the implications of altered HPA axis activity in older patients suffering from depression. Novel pharmacological approaches might be effective in targeting this pathophysiological feature, thus improving the clinical outcomes.

Contents

1. Introduction

One of the most consistent findings in the biology of depression is an altered activity of the hypothalamic—pituitary—adrenal (HPA) axis. However, data concerning this issue have never been examined with a focus on older adults.

The HPA axis is one of the main biological systems mediating the effects of stress in the body and in the central nervous system (CNS): a large body of evidence indicates that its activity is significantly heightened in patients suffering from depression, compared with healthy controls (Stetler and Miller, 2011; Zunszain et al., 2011). Abnormalities in HPA axis functions seem to have direct implications for the pathogenesis of depression. For example, the experimental manipulation of HPA axis' feedback mechanisms can lead to the occurrence of depressive-like behavior. Also, early life trauma and repeated psychosocial stress — known risk factors for depression — are characterized by hyperactivity of the HPA axis (Pariante and Lightman, 2008). Lastly, the modulation of HPA axis activity seems to play an important role in the biological response to antidepressant drugs (Anacker et al., 2011). Hence, targeting the abnormalities of HPA axis activity is considered a promising strategy for developing novel antidepressants drugs (Bosker et al., 2004).

The HPA axis might undergo substantial modifications along the aging process: the levels of cortisol — the main HPA axis' hormone — were increased and followed a flatter circadian rhythm in studies comparing healthy older adults with younger individuals (Deuschle et al., 1997; Ferrari et al., 2001). Furthermore, the responses to psychological and pharmacological challenges seem to increase with age (Gotthardt et al., 1995; Otte et al., 2005). Still, the HPA axis activity can display considerable variability between individuals, and it needs to be underlined that aging does not necessarily lead to HPA axis hyperactivity (Lupien et al., 1996). However, despite the possibility of age-related modifications, the status of HPA axis has rarely been investigated in late life depression. Studies have yielded discordant findings: compared with age-matched controls, depressed older adults had higher levels of basal (O'Brien et al., 2004; Kohler et al., 2010; Kuo et al., 2011) and post-dexamethasone cortisol (O'Brien et al., 1996) or similar cortisol levels