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Review

Late-life depression and Alzheimer's disease: The glutamatergic system inside of this mirror relationship

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ABSTRACT

Late-life depressive syndromes often arise in the context of predementia, dementia syndromes, and Alzheimer's disease (AD). Conversely, patients with a history of mood disorders are at higher risk of developing cognitive impairment. The high rate of co-occurrence of these two disorders is becoming a major health problem in older subjects for both their epidemiological impact and the negative outcomes in terms of disability and increased mortality. In this perspective, it is possible to speculate on the presence of a mirror relationship between depressive and cognitive disorders in late-life. Indeed, although a causal contribution of genetic, environmental, and social factors is widely recognized in these disorders, the neurobiological links still remain largely unknown. L-glutamic acid and γ-aminobutyric acid are the principal excitatory and inhibitory neurotransmitters in the central nervous system, respectively, and increasing evidence suggests that alterations in this neurotransmitter system may contribute to the neurobiology linking depression and cognitive impairment. In the present review article, we examined the neurobiological bases of the relationship between late-life depressive syndromes and AD, with a particular attention to glutamatergic pathway signalling like a bridge connecting these two conditions. In addition, attempts have been made to explain changes in glutamatergic pathway, depression in older age, and dementia through the analysis of signal transduction mechanisms associated with these disabling disorders.

Abbreviations: 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; Aβ, β-amyloid; AD, Alzheimer's disease; AMPA, a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; AEA, anandamide; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CA1, cornu ammonius 1; CB_1, cannabinoid receptors of type 1; CNS, central nervous system; CRF, corticotropin-releasing factor; CSF, cerebrospinal fluid; DG, dentate gyrus; DHA, docosahexaenoic acid; EC, endocannabinoid; EAAT, excitatory amino acid transporters; EPA, eicosapentaenoic acid; GABA, γ-aminobutyric acid; GC, granule cells; Gln, glutamine; Glu, L-glutamic acid; GSH, glutathione; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; LLD, late-life depression; LTP, long-term potentiation; MDD, major depressive disorder; mGluR, metabotropic glutamate receptor; NFT, neurofibrillary tangle; NMDA, N-methyl-D-aspartate; PAF, platelet activating factor; PFC, prefrontal cortex; PUFA, polyunsaturated fatty acid; SLE, stressful life events; SP, senile plaque; VGLUT, vesicular Glu transporters

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Contents

1. Introduction

With a global increase in population size and life expectancy, Alzheimer's disease (AD) has become a world health problem, with 5.3 million of estimated AD cases in the U.S. (Alzheimer's Association, 2010), over 26 million affected worldwide in 2010, and an expected increase to more than 106 million by 2050 (Brookmeyer et al., 2007). Intraneuronal protein clusters composed of extracellular aggregates of β-amyloid (Aβ) [senile plaques (Sp)] and paired helical filaments of hyperphosphorylated tau protein [neurofibrillary tangles (NFT)] are the principal hallmarks of AD pathology, resulting in neuronal synapse dysfunction and compromised cellular integrity (De Strooper, 2010). In adults older than 65 years, another recognized public health problem is late-life depression (LLD), a common and heterogeneous condition that refers to depressive syndromes according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) and the International Classification of Disease-10 (ICD-10) criteria (World Health Organization, 1992). The term LLD encompasses both late-onset and early-onset cases that recur or continue into later years of life (Panza et al., 2010). Various studies present an age range from 45 to 65 years as the lower limit for defining LLD onset (Potter and Steffens, 2007). Estimates of the prevalence of LLD vary widely (from 1.6% to 26.9%) depending on the population studied, sample size, definition of depression, and method of diagnosis (Gottfries, 2001). Among patients with LLD, a subset often develop a reversible form of significant cognitive impairment, commonly called "pseudodementia" or depression with reversible dementia. These patients have a significantly increased risk of developing true dementia at rates as high as 40% over 3 years (Alexopoulos et al., 1993). In addition, a meta-analysis and meta-regression analysis have shown that depression is not only a frequent "prodrome" of AD (Ownby et al., 2006), but a history of depression likely confers an increased risk for later development of AD (Butters et al., 2008). Clearly, depression appears to be closely linked to neurodegenerative processes, and its relationship with cognitive impairment may be bidirectional.

The etiology of late-life depressive disorders is largely unknown, although a causal contribution of genetic, environmental, and social factors is widely acknowledged (Caspi et al., 2003). L-glutamic acid (glutamate, Glu) and γ-aminobutyric acid (GABA) are the principal excitatory and inhibitory neurotransmitters in the central nervous system (CNS), respectively, and increasing evidence suggested that alterations in this neurotransmitter system may contribute to the pathophysiology of depression (Krystal et al., 2002; Cryan and Slattery, 2010). Nonetheless, it remains to be fully elucidated if these molecular abnormalities are the cause or consequence of an altered governing mood structure. In fact, the recent developments based on neuroimaging technologies have permitted in vivo characterization of the anatomical, physiological, and neurochemical correlates of mood disorders. This has resulted in neurocircuitry-based models in which both functional and structural brain pathology play a role in the development of mood alterations (Irani et al., 2007; Konarski et al., 2007). In particular, medial prefrontal cortex (PFC) and related limbic structures are related to disturbances of emotional processing (Lee et al., 2008), cognitive performance (Goto and Grace, 2005), neurotransmission (Murase et al., 1993), autonomic regulation (Carney et al., 2005), and neuroendocrine responses (Gold et al., 2002). Finally, these alterations are associated to mood disorders in a complex perspective integrating neurological, psychiatric, and immunological aspects (Drevets et al., 2008). In the light of this model, it is likely that a significant sub-population of depressed older adults may have depressive symptoms reflecting brain impairment and represent a serious risk for neurodegenerative diseases or neural injury.

Several susceptibility genetic factors could influence the development of LLD and AD. Genetic polymorphisms of the pro-inflammatory cytokine interleukin (IL) 1-beta promoter (McCulley et al., 2004) or brain-derived neurotrophic factor (BDNF) have been found to play a role in the susceptibility to both LLD and AD (Borroni et al., 2009). These genetic association studies provide support to the view that there is a relationship between LLD and AD. In fact, these conditions may share common risk factors and neuropathological processes like enhanced oxidative stress and neuroinflammation. Despite many psychological and biological theories regarding the pathogenesis of mood disorders, the possible etiologies of LLD and molecular aspects of cognitive impairment in LLD remain largely unknown and are still under investigation.