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Mechanisms underlying the neuroprotective effect of brain reserve against late life depression

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Abstract Depression is common and medically relevant illness that has been associated to a state of "accelerated aging" and can significantly compromise successful aging. In recent years, the concept of "brain reserve" has emerged to describe some individuals having an increased "baseline adaptive neuroplasticity", providing greater dynamic capacity for adjusting and remodeling cortical circuits to various stressors. We hypothesize that brain reserve may have neuroprotective effects against late life depression. Here, we discuss the modulatory capacity of stress and corticosteroid hormones on hippocampal plasticity and neuronal viability in late life depression as well as the anti-depressive of ketamine and scopolamine mediated by stimulation of the mammalian target of rapamycin, increased inhibitory phosphorylation of GSK-3β, and increased synaptogenesis. This review shall shed light on complex neurobiological mechanisms that underpin late life depression and help to better understand neural correlates of resilience. Investigating how rat models of increased cognitive reserve mitigate a chronic mild stress-elicited depression will afford new insights in the search for new therapeutic targets to treat this neuropsychiatric disorder.

Keywords Aging · Brain reserve · Resilience · Stress · Cognition · Autophagy · mTOR signaling

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Late life depression

Aging is one of the most challenging public health issue that is faced by the developed countries today. With the growth in aged population, there has been an expansion in initiatives and interventions to promote successful aging and to reduce disparities in attaining maximum healthy life expectancy (Depp et al. 2012).

Among elderly individuals, depressive symptoms are common and burdensome (Kessler et al. 2005, 2010; Luppa et al. 2013). In a given year, between 1 and 2 % of individuals over the age of 65 will meet the criteria for major depressive disorder (Kessler et al. 2003). Even though this 12-month prevalence seems quite low compared to the about 6 % observed in adults, several parameters have to be take into account. First, it has recently been demonstrated that the apparently lower prevalence estimates of depression in older adults might be biased by incorrect inclusions of individuals, notably patients with sub-threshold hypomania; and to a lesser extent, to the increase in general medical condition depressive disorders with age. Second, another 15–25 % of elders experience depressive

symptoms that, while not meeting criteria for major depressive disorder, do cause significant distress and interfere with daily functioning (Brevik et al. 2013). Third, with the ongoing demographic changes, an ever-increasing number of older adults with mental illnesses, notably late life depression, is expected (Grav et al. 2012). Overall, among the aging population, individuals experiencing late life depression display greater functional disability (Dombrovski et al. 2007) and cognitive decline than healthy ones (Lenze et al. 2005).

Depression and accelerated aging

Depression is an independent risk factor for early mortality (Gump et al. 2005). Patients with major depression have an increased onset risk of aging-related diseases affecting the cardiovascular, cerebrovascular, neuroendocrine, metabolic, and immune systems (McIntyre et al. 2007; Bauer 2008; Wolkowitz et al. 2010; Warsch et al. 2013). Depression can, thus, significantly compromise successful aging defined subjectively as freedom from chronic disease and disability, along with high physical and cognitive functioning and social engagement (Berkman et al. 1993; Jeste et al. 2013). Successful aging contrasts with "accelerated aging" that has been associated with premature aging.

A recent theory regarding the pathophysiology of depression posits that age-related pathogenic processes, which occur in the brain and in the periphery, can culminate in cellular aging, cell damage and ultimately disease (Wolkowitz et al. 2010). For example, age-related disturbances in insulin-glucose homeostasis, immune status, adipokine metabolism, signaling cascades, and mitochondrial respiration have been implicated in the pathophysiology of depressive disorders (McIntyre et al. 2007). This theory predicts innovative treatments for mood disorders, which primarily target aberrant metabolic networks.

It has been speculated that "accelerated aging" is caused by specific biochemical mediators that are altered in depression at cellular level (Wolkowitz et al. 2010). Various explanations for "accelerated aging" in depression have been proposed such as the "glucocorticoid cascade" hypothesis (Sapolsky 1999; Swaab et al. 2005) or the "allostatic load" (McEwen 2002). "Allostasis" represents the concerted action of the neuroendocrine system, autonomic nervous system and immune system to maintain homeostasis in response to stressors (McEwen 2002; Sterling and Eyer 1988). Further, the cumulative wear and tear that the body experiences as a result of daily life experiences, has been coined "allostatic load" (McEwen 1998).

The hippocampal response to glucocorticoids is essential for an effective stress response. The "feedforward cascade" of the glucocorticoid hypothesis is centered on role of the hippocampus as a negative-feedback mediator of glucocorticoid (GC) secretion. In particular, chronic hypercortisolemia endangered the hippocampus and has been proposed to result in cell death (Sapolsky 1999; McEwen 2002).This "feedforward cascade" was thought to explain the parallel emergence of hippocampal neuron loss and the rising basal levels of GCs in the aged rat (Sapolsky 1999). The validity of the glucocorticoid vulnerability has been subsequently questioned and proposed that rather a chronic stress history, which includes repeated elevation of glucocorticoids, may make the hippocampus vulnerable to potential injury (Conrad 2008).

Mechanistically, a GC excess causes abnormalities in intracellular glucose homeostasis and impairs the glutamate clearing activity of astrocytes at the synapse. The resulting excitotoxicity results in the release of calcium into the cytoplasm that triggers oxygen-free radical formation and cytoskeletal proteolysis, which contributes to diminished cell viability and cell death. Later it was proposed that persistent upregulation of systemic mediators of adaptation to challenges of daily life such as adrenalin from the adrenal medulla, glucocorticoids from the adrenal cortex and cytokines from cells of the immune system may cause tissue damage (McEwen 2002).

At genome level, accelerated biological aging has also been associated with telomere shortening. In a recent study done on 1,900 patients with major depressive disorder it was shown that patients with a history of depression had shorter telomeres than their peers (Epel et al. 2004; Verhoeven et al. 2013).

Aging, stress and resilience

Every individual experiences stressful life events. In some cases, acute or chronic stress leads to depression and other psychiatric disorders (Kendler et al. 1999), but most people are resilient to such effects.

Elderly people face mostly health-related, chronic, and uncontrollable stressors rather the acute stressors involving decision-making younger adults face (e.g., bereavement, caregiving, abuse) (Maggio et al. 2013; Vink et al. 2008). Even though the impact of psychosocial stress on the aging brain has long been examined, a more recent body of work has highlighted the characteristics of resilience to stress. Greater resilience and less depression are expected to be among the strongest variables associated with self-rated successful aging (Fig. 1). If a stressful event leads or not to depression may depend on critical individual differences in resilience to both the behavioral and the neurochemical effects of stress (Feder et al. 2009). Indeed, it is clear that chronic unremitting stress in older adults influences a

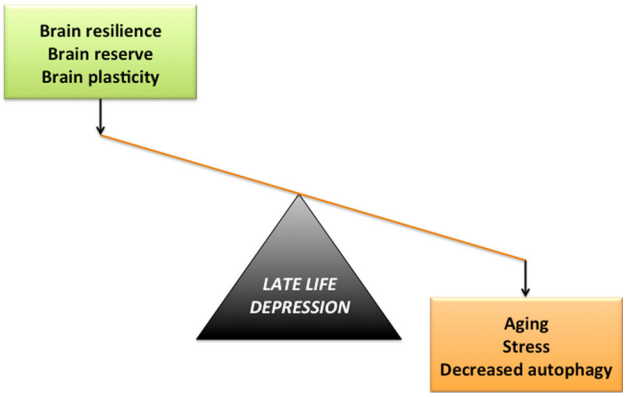

Fig. 1 Late life depression depends on the balance between the endogenous brain defense activity including "brain reserve", brain resilience, neuroplasticity and a few fundamental biological processes and common pathogenic mechanisms including decreased synaptic plasticity, stress and aging

network of physiological processes that often results in neuronal degeneration. Specifically, the stress-associated stimulation of the hypothalamic–pituitary–adrenal axis results in the secretion of glucocorticoids, such as cortisol, which is associated with damage to various brain structures (Pruessner et al. 2007; Maheu et al. 2005; Vachon-Presseau et al. 2013). This factor, associated notably to reduced hippocampal volume, may explain the well-documented links between depression and anxiety with cognitive impairment in later life. However, there are some individuals who do not experience the deleterious effects of stress. Notably, behavioral coping strategies may reduce the impact of stress on the brain. Resilience has been the focus of a small body of the literature (Lamond et al. 2008). However, with regard to cognitive health, resilience represents a trait that may buffer the effects of stress on the brain. Further research is, therefore, mandatory to understand its underlying biological mechanisms.

Successful aging, late life depression and brain plasticity

Functional decline in aging is a direct consequence of brain machinery wearing down over time. However, studies of brain plasticity have shown that a substantial improvement and/or recovery of some functions can be achieved by engaging older adults in demanding sensory, cognitive and motor activities (Mahncke et al. 2006).

One possible conceptual approach is to consider "brain reserve" as an index of brain plasticity, i.e., some individuals have an increased "baseline adaptive neuroplasticity" that is providing greater dynamic capacity for adjusting and remodeling cortical circuits (Mercado 2008). Neuronal plasticity is associated with depression, most likely as a result of a sustained modified expression of proteins required for synaptic resiliency (Marsden 2013). Antidepressants can stimulate the first stages of brain cell regeneration, or brain plasticity. Chronic treatment of adult mice with agomelatine, a MT(1)/MT(2) receptor agonist and 5-HT(2C) receptor antagonist (Calabrese et al. 2011; Ladurelle et al. 2012) or fluoxetine (a serotonin-specific reuptake inhibitor) caused changes to granule cells of the hippocampus which appeared to undergo serotonin-dependent "dematuration" that increased their activity and reversed adult-type plasticity into an immature state (Kobayashi et al. 2011).

Successful aging processes may protect against late life depression

It has been hypothesized that "brain reserve" may account for inter-individual differences in the recruitment of neural networks and cognitive processes, and may thus compensate for age-related brain dysfunction.

Unfortunately, despite of obvious clinical relevance that successful aging may protect against late life depression, the underlying mechanisms are unknown. Therefore, it is urgently needed to develop animal models for such investigations. Among available rodent strains, the LOU/C/Jall rat seems to be of particular interest in this context. Indeed, the LOU/C/Jall rat is described as a model of successful/healthy aging. As compared to the Wistar strain from which it is originated, LOU/C/Jall rats have a higher longevity living 5–8 months longer than other commonly used strains and display delayed-onset cognitive deficits associated with age (Kollen et al. 2010). In addition, electrophysiological investigations reported intact hippocampal functioning in aged LOU/C/Jall rats. Particularly, the capacity to regulate long-lasting changes in neuronal communication such as long-term potentiation (LTP) that underlies memory formation, is maintained throughout lifespan in this model (Kollen et al. 2010).

Long-term potentiation (LTP) regulates the strength of synaptic transmission and the formation of new synapses in many neural networks and has been described to be highly sensitive to stress (Timmermans et al. 2013). More recently, further experimental evidence showed that aged LOU/C/Jall rats display potent neuronal–glial cross-talk within the glutamatergic tripartite synapse that is reported as a key mechanism underlying age-related LTP deficits and cognitive defects (Turpin et al. 2011; Haxaire et al. 2012). It could, therefore, be speculated that such a cross-talk may be used as a mechanism to mitigate late life depression. Indeed, it was recently reported that mice displaying overexpressed D-serine-dependent neuronal–glial cross-talk showed a reduced depression-related behaviors in several specfic tests (Otte et al. 2013).

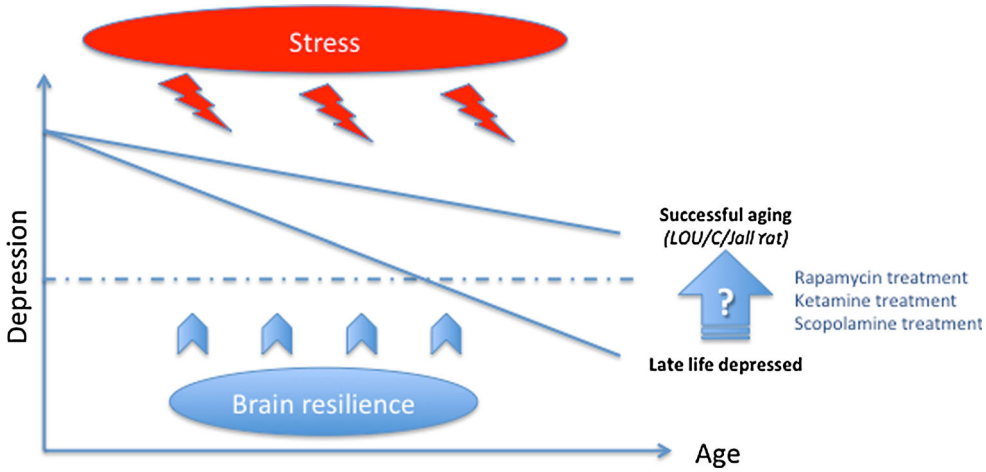

Fig. 2 Brain resilience, along with brain reserve, brain plasticity and rapamycin treatment may reverse the precipitation of late life depression by aging, stress and a decreased brain plasticity

In addition, it has also been demonstrated that LOU/C/Jall rats do not accumulate body fat during aging (Alliot et al. 2002). Moreover, in contrast to other rat strains that develop visceral obesity in response to high-fat diet, LOU/C/Jall rats are resistant to diet-induced obesity (Helies et al. 2005). Therefore, it seems that LOU/C/Jall rat may live in a constant state of caloric restriction. Such a "way of life" has been related to a strong genetic determinism and complex pathways involving numerous candidate genes and processes, notably in accordance with the metabolic theory of feeding behavior control (Paban et al. 2013; Marissal-Arvy et al. 2013). Taken together with the known effect of caloric restriction on life span extension, these results may explain the long and healthy aging of LOU/C/Jall rat (Barzilai and Bartke 2009).

Even more interestingly, LOU/C/Jall rats exhibit lower corticosterone levels across the circadian rhythm and during the recovery following a restraint stress as compared with other rat strains (Marissal-Arvy et al. 2007). The successful aging LOU/C/Jall rats seem, thus, more resilient to stressful events. Overall, these results reinforce the relevance of using this rat strain model to investigate underlying mechanisms of neuroprotective effect against late life depression (Fig. 2).

Depression, synaptic plasticity and mTOR signaling

The primary signaling mechanisms that become defective in aging to cause depression are unclear. Recently, it has been proposed that prolonged abnormalities in intracellular glucose homeostasis, in particular glucose intolerance and insulin resistance may cause telomeres shortening and ultimately accelerated biological aging (Epel 2009).

Accumulated evidence indicates that sporadic AD is associated with disturbed brain insulin metabolism, and AD has been recognized as an "insulin-resistant brain state" (Correia et al. 2011; Chen and Zhong 2013). AD patients had been shown to have decreased insulin receptor (IR) density suggesting that abnormalities in insulin signal transduction are major factors that mechanistically influence the onset of sporadic AD pathology (Takeda et al. 2011). Indeed, it has been shown that insulin administration improves cognitive performance in AD subjects (Watson and Craft 2004).

Thus, the insulin/IGF-1 (insulin-like growth factor 1) signaling pathway is mechanistically linked to both depression and cognitive disorders. This pathway is aberrantly overactivated in AD brain at the level of increased activation of the serine/threonine kinase Akt and the phosphorylation of its downstream targets, including mTOR (mammalian target of rapamycin) (Lipinski et al. 2010). Along this line of evidence, using a model of successful cognitive aging it has been shown that memory-impaired old rats presented higher mTOR activity in the hippocampus CA1 subfield (Ménard and Quirion 2012). In contrast, reduced autophagy ("self-eating") has been associated with accelerated aging (Cuervo et al. 2005; Hars et al. 2007; Simonsen et al. 2008; Tsakiri et al. 2013).

At molecular level, aging induces an increase in protein damage due to various post-translational modifications that include oxidation of amino acid side chains by free radicals, racemisation of aspartyl and asparaginyl residues, deamidation of asparaginyl and glutaminyl residues, and oxidation of sulfhydryl groups. Therefore, proper brain proteome dynamics (proteostasis) is critical to normal brain development and to optimal aging, especially in non-proliferative cells like neurons, and persistent deregulation of proteostasis may lead to a number of the neurodegenerative diseases in the elderly population (Jana 2012; Casoli et al. 2012; Tanaka and Matsuda 2013).

Among pharmacological interventions to normalize the decreased protein turnover and slow aging, the nutrient response pathway defined by the mammalian target of

rapamycin (mTOR), also known as mechanistic target of rapamycin (mTOR), appears to be a leading target. Indeed, rapamycin treatment initiated at 20 months of age led to significant increase in life span in both male and female mice (Miller et al. 2011). Likewise, inhibition of this pathway extends lifespan in model organisms and confers protection against a growing list of age-related pathologies (Johnson et al. 2013).

The mTOR signaling pathway in neurons plays a central role in controlling protein homeostasis and hence, neuronal functions. Rapamycin, a clinically important immunosuppressant, is a specific and potent inhibitor of mTOR signaling which is a negative regulator of macroautophagy and a modulator of synaptic plasticity and synaptic transmission, both being reduced with increased age. Besides, a large body of evidence implicates mTOR dysregulation in the etiology of various neurological and psychiatric diseases. mTOR signaling is hyperactive in neurological syndromes in both humans and mouse models that are characterized by neurodegenerative diseases (Ghavami et al. 2013). Two recent studies pharmacologically restoring mTOR signaling with rapamycin rescued memory deficits and slowed pathological manifestations in these neurodegenerative rodent models (Caccamo et al. 2010; Spilman et al. 2010).

The regulation of synaptogenesis contributes to synaptic plasticity, a fundamental feature of the brain. Basic and clinical studies have shown that depression is associated with decreased densities in neuronal synapses in the prefrontal cortex and hippocampus, two brain regions that regulate mood and cognition (Duman and Aghajanian 2012). Recent molecular and cellular studies in rodent models have shown that ketamine, a non-selective NMDA receptor antagonist, stimulates synaptogenesis in the prefrontal cortex (PFC). Low dose of ketamine also reversed the effects of chronic stress and produced rapid antidepressant actions in behavioral models of depression (Berman et al. 2000; Zarate et al. 2006; Li et al. 2011). Mechanistically, the beneficial effects of ketamine are mediated by stimulation of mTOR, increased inhibitory phosphorylation of GSK-3β, and increased synaptic spine density (Duman and Aghajanian 2012; Liu et al. 2013). A similar antidepressant effect that requires mTORC1 signaling and is associated with increased glutamate transmission, and synaptogenesis has been recently reported for scopolamine, an antagonist at muscarinic acetylcholine receptors (Voleti et al. 2013).

Conclusions

In recent years, the concept of "brain reserve" has emerged to describe some individuals having an increased "baseline adaptive neuroplasticity", providing greater dynamic capacity for adjusting and remodeling cortical circuits to various stressors. We hypothesize that brain reserve along with stimulation of mTOR signaling may have neuroprotective effects against late life depression (Fig. 2). Future strategies may be focused on mTOR-related autophagy regulation to retard or halt depressive symptoms.

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Conflict of interest None to declare.

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