REVIEW

Department of Pharmacy, Anhui Mental Health Center, Hefei, PR China

Novel insights into the pharmacological effects of resveratrol on the management of depression: a short review

Y.Y. Xu, J. Liang, Q.R. Xia*

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** Corresponding author: Q. R. Xia, Associate Professor of Pharmacy, Department of Pharmacy, Anhui Mental Health Center, 316 Huangshan Road, Hefei 230032, PR China*
ahmcxqr@163.com

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Recently, it was suggested that resveratrol (RES), a natural polyphenol, possesses beneficial therapeutic roles in depression. The aim of this review is to discuss the novel potential pharmacological effects of RES on depression. We first consider the pathophysiology of depression and then review the potential antidepressant effects of RES. Apart from the alternation of the monoaminergic system and the molecular markers related to depression, RES might exert an antidepressant-like effect through modulating the HPA axis, BDNF and synaptic vesicle proteins, inflammatory cytokines and oxidative stress, and thyroid hormones. Consumption of RES may represent an alternative strategy to delay the onset and progression of depression, and depressive-like symptoms through multiple pharmacological activities.

1. Introduction

Depression is among the leading causes of disability, with affecting up to 120 million people worldwide (Kim et al. 2016). It causes different negative effects on social activities, and adversely effects family and career responsibilities. According to World Health Organization Global Burden of Disease, depression has been anticipated to become the leading cause of long-term disability by the year 2030. Based on the monoaminergic hypothesis of depression (Baldessarini 1975), raising monoamine levels in synaptic clefts has been a major strategy for treating depression over the past 60 years. Unfortunately, not all depressed patients respond to the existing antidepressants, and months of treatment are usually required to produce a response (Ford 2012; Ioannidis 2008), suggesting that monoamine depletion might not be the only pathogenic process of depression. In addition to this, there are adverse reactions of antidepressants, including dizziness, tremor, cognitive impairments, urinary retention, and sexual dysfunction (Givens 2016; Uher et al. 2009). Thus, a deeper understanding of the pathogenesis of depression and better antidepressants are needed to improve the efficacy and safety of depression treatment. Although the exact mechanisms underlying the multiple pathophysiology of depression remain unknown, depression was associated with stressful life events (Shapero et al. 2014), metabolism regulation (Wu et al. 2016), immuno-inflammatory reaction (Kohler et al. 2016), and imbalances in thyroid hormones (Berent et al. 2014).

Resveratrol (*trans*-3,5,4′-trihydroxy-trans-stilbene, RES), a polyphenol component found mainly in grape and *Polygonum cuspidatum*, possesses multiple biological and pharmacological activities, including metabolism regulation, anti-oxidant, anti-inflammatory and anti-cancer effects (Park and Pezzuto 2015). Recently, RES was reported to exert antidepressant-like effects through alleviating depressive-like symptoms/behaviors in rodent animal models (Ge et al. 2013a; Hurley et al. 2014; Liu et al. 2016). Moreover, the monoaminergic system (Yu et al. 2013) and the molecular markers related to depression (Liu et al. 2014b) were also altered by RES treatment. However, there is only an insufficient number of studies that have involved intervention with RES on the multiple pathophysiology of depression and depressive-like symptoms. Therefore, the present paper aims to critically review the available literature regarding the novel antidepressant effects of RES on depression.

2. Effect of RES on the HPA axis

Stressful life events and the resulting hypothalamic-pituitary-adrenal (HPA) axis hyperactivity are proposed to be among the causal factors for triggering depressive episodes (Swaab et al. 2005). Clinical studies have demonstrated that abnormalities in the HPA axis function are well documented in depressed patients, with hypersecretion of cortisol (Pirnia et al. 2016). Consistently, in preclinical studies, hyperactivity of the HPA axis along with upregulated corticosterone in serum was observed in animal models for the development and progress of clinical depression, maternal separation (Biggio et al. 2014), chronic restraint stress (Maghsoudi et al. 2014) and chronic unpredictable mild stress (CUMS) (Xu et al. 2015).

As one of the most widely used animal models in research on depression, the CUMS rats displayed an elevation of both serum corticosterone concentration and hypothalamic corticotropin-releasing hormone (CRH) mRNA expression, indicating hyperactivity of the HPA axis (Ge et al. 2014a). Preliminary results have shown that treatment with RES could alleviate the depressive-like behaviors of CUMS rats, as indicated by increased sucrose preference and decreased immobility in forced swimming test and tail suspension test. Moreover, the elevation of serum corticosterone was decreased by RES treatment, suggesting that RES exerts its antidepressant-like effect mainly through its amendatory effect on the HPA axis activity (Ge et al. 2013a). Similarly, RES treatment significantly revised the increased serum corticosterone level in a stress-based animal model by repeated corticosterone treatment, which has been performed widely in adult rodents in the depression models (Ali et al. 2015). Pang et al. (2015) studied the effect of RES isomers on the HPA axis. The study showed that trans-RES may exert antidepressant-like effects against post-stroke depression through modulating the HPA axis. Unfortunately, although RES in doses ranging from 200 mg to 1000 mg daily was used in clinical trials and was well tolerated (Anton et al. 2014; Chow et al. 2014), until now few studies have examined the effect of RES on the disordered activity of the HPA axis in the depressed patients.

3. Effect of RES on BDNF and synaptic vesicle proteins

Brain-derived neurotrophic factor (BDNF), a protein belonging to the neurotrophic family of growth factors, has significant influence on the crucial process of brain development, including neurogen-

esis, neuronal differentiation, synaptogenesis and memory formation (Ge et al. 2015a). The remarkable role of BDNF in the mechanism of depression has been clearly demonstrated by a number of studies (Shen et al. 2016; Zhang et al. 2016b). Decreased serum levels of BDNF were found in depressed patients (Yoshida et al. 2012). Moreover, the BDNF mRNA and protein levels were suppressed in postmortem brains of depressed patients (Banerjee et al. 2013). Consistent with the above human studies, BDNF expression was also found to be reduced in the hippocampus and prefrontal cortex (PFC) in animal chronic stress studies. More recently, Wang et al. (2016) studied the effect of RES on chronic restraint stress (CRS)-induced depressive-like behavior. The results showed that RES reversed CRS-reduced BDNF expression in the astrocytes in the hippocampi, supporting that RES treatment might exert its antidepressant action through improving BDNF production from astrocytes. Similar effect of RES on BDNF levels in the hippocampus and amygdala were found in the CUMS rats (Liu et al. 2014a). In addition, Hurley et al (2014) investigated whether RES would manifest an antidepressant effect in Wistar-Kyoto (WKY) rats, a putative animal model of depression and irresponsive to selective serotonin reuptake inhibitors (SSRIs). Their results indicated an antidepressant-like effect of RES possibly *via* the activation of hippocampal BDNF, suggesting a therapeutic potential of RES in at least a subpopulation of depressed patients who are insensitive to SSRIs.

Synaptic vesicle proteins have been identified as possible factors involved in the pathophysiology of psychiatric disorders including depression (Ge et al. 2015b). Synaptotagmin I and synapsin I are major component proteins of the synaptic vesicle membrane and are required for vesicle fusion and neurotransmitter release (Thome et al. 2001). Region specific changes in the expression of synaptotagmin I and synapsin I have been reported to be induced by both the stress and antidepressant (Dagyte et al. 2011; Muller et al. 2011), suggesting a regulatory role of synaptotagmin I and synapsin I in the pathogenesis of depression. Our previous study demonstrated that the mRNA expression levels of synaptotagmin I and synapsin I were both increased in the hypothalami of chronically stressed rats (Ge et al. 2013b). Consistent with these findings, stress-induced changes in these two proteins in the hippocampus or cortex after chronic stress have also been observed in other studies (Thome et al. 2001; Wu et al. 2007). Moreover, it has also been reported that antidepressant treatment could alleviate depressive symptoms through inhibiting their expressions (Dagyte et al. 2011; Muller et al. 2011). The results of our recent study showed that treatment with RES could alleviate the depressive-like behavior of the subclinical hypothyroidism rats, through modulating the reduced protein levels of synaptotagmin I in the hippocampus (Ge et al. 2015a). Apart from depression, recent studies have also indicated that RES could reverse the synaptic plasticity deficits in several cognitive-associated diseases (Feng et al. 2016; Li et al. 2016; Tian et al. 2016), indicating a neuroprotective role of RES in the treatment of various neurodegenerative disorders. Given the role that synaptic vesicle proteins are crucial for neurogenesis, neuronal differentiation, synaptogenesis and memory formation, the therapeutic potential of RES on the synaptic vesicle proteins might involve in its antidepressant effect, which needs to be confirmed in the future studies.

4. Effect of RES on inflammatory cytokines and oxidative stress

Current evidence supports the view that depression is accompanied by the activation of the inflammatory-response system, and overproduction of pro-inflammatory cytokines may play a role in the pathophysiology of depressive disorders (Lang and Borgwardt 2013; Maes et al. 2014). Meta-analyses have indicated that the most robust evidence-based inflammatory markers associated with depression include interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) (Dowlati et al. 2010). Moreover, an increasing number of studies have demonstrated that elevated levels of plasma IL-6 and CRP levels are associated with an increased risk of depression (Liu et al. 2014c; Wium-Andersen et al. 2014), and can even predict subsequent depressive symptoms (Valkanova et al. 2013). In animals, it has been shown that depressive-like behaviors were induced by cytokines (Sukoff Rizzo et al. 2012) and cytokine inducers, including lipopolysaccharide (LPS) administration (Zhang et al. 2016a) and chronic mild stress (You et al. 2011).

Given the role that inflammation may play in depressive disorders, anti-inflammatory agents may prove useful as an antidepressant therapy or adjuvant to traditional therapies. Studies involving RES treatment in the rodent models of inflammatory diseases have demonstrated downregulation of inflammation-induced biomarkers including pro-inflammatory mediators (IL-1β, IL-6, TNF-α and TNF-β) (Rahal et al. 2012), and upregulation of inflammation-reduced biomarkers including anti-inflammatory protein (IL-10) (Imler and Petro 2009). Thus, as one of the initial pharmacological activities, the anti-inflammatory activity of RES might be involved in its antidepressant-like effect.

Systemic administration of LPS is frequently used to survey the inflammation-associated depression in experimental animals (Ge et al. 2015c). Recent studies showed that the activation of nuclear factor-κB (NF-κB), which can induce cytotoxic products that exacerbate inflammation and oxidative stress, and inflammatory mediators (IL-1β and TNF-α) release were both attenuated by RES treatment following LPS administration, suggesting that the inhibition of pro-inflammatory cytokine release by RES is dependent on the regulation of NF-κB signaling pathway (Ge et al. 2015c). Moreover, LPS-induced microglial activation and subsequent production of multiple pro-inflammatory and cytotoxic factors such as TNF-α, nitric oxide (NO), and IL-1β were significantly inhibited by RES (Zhang et al. 2013). Furthermore, Finnell et al. (2017) confirmed that increased pro-inflammatory proteins (IL-1β, TNF-α, and granulocyte-macrophage colony stimulating factor (GM-CSF)) in the locus coeruleus (LC), a noradrenergic brain region implicated in depression, were blocked by RES in socially defeated rats, driven by stress-induced neuro-inflammation. Taken together, it has been proposed that RES may be of therapeutic potential in inflammation-related depression.

Clinical studies have shown that oxidative stress in major depression was increased in frontal regions of patients compared to those of matched controls (Michel et al. 2007). Moreover, animal studies have been demonstrated that oxidative stress was observed in the chronic stress-induced animal depression model, mainly expressed as increased lipid peroxidation and decreased endogenous antioxidant defense in the cerebral cortex, striatum and hippocampus (Ahmad et al. 2010). RES, recognized as a natural antioxidant, has been reported to be beneficial in depressive disorders by attenuating the oxidative stress. *In vivo* studies, repeated treatment with RES restored the CUMS-induced lipid peroxidation and superoxide dismutase (SOD) levels, suggesting that RES could exert antidepressant properties by modulating antioxidant enzymes and antioxidant responsive elements (Liu et al. 2016). In line with this, chronic administration of RES could significantly decrease the serum malonaldehyde (MDA) concentration in CUMS rats, again indicating the antioxidant effect of RES in the treatment of depression (Ge et al. 2013a). Consistently, *in vitro* studies, our previous results showed that RES could remarkably reduce the elevation of the MDA level in the supernatant of corticosterone-stimulated cells (Ge et al. 2013a).

5. Effect of RES on thyroid function

Imbalances in thyroid hormone homeostasis are associated with both functional and structural brain alterations, resulting in neurobehavioral alterations, including depression (Guimaraes et al. 2009; Taskin et al. 2011). Subclinical hypothyroidism (SCH), defined as an elevated plasma thyroid-stimulating hormone (TSH) level associated with normal total or free thyroxine (fT4) and triiodothyronine (T3) levels, is associated with neuropsychiatric disorders such as cognitive dysfunction (Zhu et al. 2006) and depression (Chueire et al. 2007). Clinical studies have demonstrated that depression was observed more frequently among individuals with

SCH than those with overt hypothyroidism (Chueire et al. 2007), and SCH patients exhibit a twofold higher prevalence of depressive-like symptoms than healthy individuals (Almeida et al. 2007). Animal studies have shown that a SCH rat model, induced by hemi-thyroid electrocauterization, could result in depressive-like behavior (Ge et al. 2014b). Further results revealed that treatment with RES could improve depressive-like behavior, with decreasing both the plasma TSH concentration and the hypothalamic thyrotropin-releasing hormone (TRH) mRNA expression in SCH rats (Ge et al. 2016). Although the specific mechanism remains unknown, this effect might be partly attributable to the capacity of RES to regulate TSH secretion by manipulating the levels of silent mating type information regulation 2 homolog 1 (SIRT1) (Akieda-Asai et al. 2010). Compared with the possible adverse effects of levothyroxine treatment, including cardiovascular events and symptoms associated with excess thyroid hormone, such as nervousness and palpitations (Helfand and Force 2004), the credible efficacy with high safety margins of RES (Timmers et al. 2013) make it a promising candidate for the treatment of SCH-associated depression. In this regard it would be of considerable interest to investigate possible interactions between depression and thyroid function, particularly following long-term RES treatment.

6. Conclusions

Depression is one of the most common neuropsychiatric disorders with considerable prevalence. Although different classes of antidepressant drugs have been offered till now, most of them are not completely effective and associated with many serious adverse effects. Recent studies have demonstrated the pathophysiological role of the HPA axis, BDNF and synaptic vesicle proteins, inflammation and oxidative stress, and thyroid function in the initiation and progression of depression. On the other hand, extensive experimental studies have shown the promising role of RES intervention as adjunctive agent in improving the quality of life, increasing therapeutic outcomes, as well as slowing the onset and progression of the depression through the forementioned pathophysiology. However, additional experimental and clinical studies are needed to elucidate the mode of action of RES as an alternative agent for the management of depressive-like symptoms in animals and humans.

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