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MicroRNA-132 may play a role in coexistence of depression and cardiovascular disease: A hypothesis

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Different individuals have different degrees of neuroplasticity due to their different experiences. Neuroplasticity may play a role in individual differences among neuropsychiatric disease treatment efficacy. Since the nervous system monitors and coordinates internal organ function, neuroplasticity may be associated with other diseases. Cardiovascular disease (CVD) is associated with depression, which is a disorder of disrupted neuroplasticity. MicroRNA-132 (miR-132) has a roles in neuroplasticity and cardiovascular function. Thus, we hypothesize that miR-132 may play a role in coexistence of depression and CVD.

Key words: microRNA-132 • neuroplasticity • depression • cardiovascular disease

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Background

Neuroplasticity is the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function, and connections [1]. Individuals show different degrees of neuroplasticity due to their different courses of growth [2]. It has been documented that even monozygotic twins may develop differing neural structure and function despite having an identical genetic background [2]. For instance, some monozygotic twins are discordant for many diseases, such as bulimia nervosa, schizophrenia, and bipolar disorders, and even in sexual orientation [3–6]. Experiences prior to a cerebral injury may influence not only spontaneous recovery but also the efficacy of post-injury treatment [7]. Thus, we propose that neuroplasticity may play a role in individual differences in the treatment response of neuropsychiatric diseases [2]. Since the nervous system monitors and coordinates internal organ function, neuroplasticity may be associated with other diseases. Cardiovascular disease (CVD) is associated with depression, and depression is closely related to neuroplasticity. MicroRNA (miR) is receiving intense research interest at present and microRNA-132 (miR-132) has roles in neuroplasticity and cardiovascular function. Here, we focus on miR-132 as a common component to discuss the mechanism of coexistence of depression and CVD.

CVD is Associated with Depression

Depression significantly increases the risk of incident CVD. Many prospective and retrospective studies have investigated the association of depression and incident CVD. These studies showed that depression is independently associated with CVD and mortality due to causes such as coronary heart disease, heart failure, myocardial infarction, ischemic heart disease, and stroke [8–13]. Lifetime association between major depression (MD) and coronary artery disease (CAD) was modest (odds ratio, approximately 1.3). The effect of MD on CAD is largely acute, and the longer-term effects are apparently mediated via recurrence of depression [14]. Some studies have demonstrated a significant positive correlation with a moderate effect size of 1.5–2.7 between depression and CVD [15]. Similarly, several studies have investigated the role of depression status as a prognostic factor in patients with CVD. Meta-analysis of these studies suggests that depressed patients have a 1.6–2.7-fold increased risk for further cardiovascular events within 24 months [16,17].

Depression is a Disorder of Disrupted Neuroplasticity

It is broadly accepted that stress triggers the activation of the HPA axis and causes the brain to be exposed to corticosteroids, affecting neurobehavioral functions with a strong down-regulation of hippocampal neurogenesis, and is a major risk factor for depression [18–20]. Chronic or severe stress and high-dose treatment with glucocorticoids decrease hippocampal synaptic plasticity and morphological neuroplasticity. Prolonged stress can negatively affect hippocampal function and its capacity for neuroplasticity. Additionally, chronic restraint stress leads to significant regression of the apical dendrites of pyramidal cells in the medial prefrontal cortex (mPFC) and negatively affects mPFC function. Glial loss and neuronal abnormalities have been observed in the prefrontal cortex in MD. Noradrenergic axons have been found with decreased axonal arborization and density after exposure to stress. Increasing evidence demonstrates that depression is a disorder of disrupted neuroplasticity [21]. Accumulating evidence shows that antidepressant treatment may reverse the atrophy of hippocampal neurons, increase cell survival, and increase monoamine axonal sprouting [22].

Brain-derived neurotrophic factor (BDNF) signaling, through its tyrosine kinase B (TrkB) receptor, plays an important role in neuroplasticity. BDNF has also been shown to be expressed at high levels in the hippocampus and to play an important role in synaptic transmission and in the plasticity of the hippocampus [23,24]. BDNF also mediates some of the injurious effects of glucocorticoids on the hippocampus [25,26]. BDNF expression is regulated by stress-responsive corticosteroids, and increased glucocorticoid exposure induces a reduction in BDNF level [27]. Chronic stress has been shown to result in alterations in BDNF/TrkB signaling and changes in neuronal functions [28]. Serotonergic axon sprouting appears to be dependent on BDNF, which appears to be decreased after stress exposure. Thus, stress and depression may increase neuronal atrophy degeneration. Furthermore, hippocampal neurons continue to proliferate well into adulthood. This continued neurogenesis depends on the presence of BDNF and serotonin, both of which are altered in depression, and are inhibited by glucocorticoids [29,30]. Most circulating BDNF is produced in the brain and passes through the blood–brain barrier [31], so serum BDNF level can be a biomarker for depression [32].

MiR-132 is an Activity-Regulated MiR Controlling Neuroplasticity

MiRs are short, non-coding, single-stranded RNA molecules approximately 19–23 nucleotides in length that regulate gene expression by binding to complementary elements in the untranslated regions of target mRNAs and inhibiting protein synthesis [33–35]. Based on sequence homology, each miR has the potential to regulate the translation of hundreds of different genes [36], and greater than 30% of all mammalian genes may be regulated by miRs [37].

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MiR-132, a highly conserved miR transcribed from an intergenic region on human chromosome 17 by the transcription factor cAMP response element-binding protein (CREB), is a key coordinator of the intracellular pathways that mediate experience-dependent changes in the brain [38–40]. Using an unbiased genome-wide screen for CREB-bound transcripts *in vitro*, Impey et al. [41] identified 16 non-coding miR that are induced by CREB-mediated transcription. Further characterization of 1 of these, miR-132, has recently revealed that it is induced by BDNF and neuronal activity, being demonstrated to affect neuronal characteristics such as neurite outgrowth and cell excitability [40,42,43]. miR-132 is able to modulate dendritic morphology via suppression of a specific target, p250 GTPase-activating protein, and regulate cellular excitability via regulation of ion channels [40,42,43].

Interestingly, the CREB-dependent miR-132 has been shown to control the development of dendrites and spines, and synaptic integration in cultured hippocampal neurons and newborn hippocampal neurons [40,42,44–48]. For example, it was reported that knockout of the miR-212/132 locus using conditional transgenic mice or knockdown of miR-132 using viral vectors induced reduced dendritic complexity and spine density, respectively, in newborn neurons of the adult hippocampal neurogenic zone [47,48]. The dendritic effect was shown to be preferentially due to miR-132 loss. A recent study has demonstrated that miR-132 is rapidly transcribed in the hippocampus *in vivo* following enhanced neuronal activity and contextual fear conditioning [39]. Based on the documented ability of miR-132 to regulate cellular characteristics in an activity-dependent manner, Lambert et al. [49] has provided evidence that overexpression of miR-132 in cultured hippocampal neurons leads to selective changes in short-term synaptic plasticity.

BDNF is essential for a variety of neuronal aspects, including cell differentiation, survival, and synaptic plasticity in the central nervous system (CNS). Intriguingly, a recent study suggests that BDNF exerts its beneficial effects on CNS neurons via upregulation of miR-132 [50]. BDNF increases CREB activation; the CREB pathways are among the most critical and are the pathways on which BDNF exerts its effects [51]. Therefore, it is concluded that BDNF affects CNS by CREB-miR-132 pathway. Additionally, increased blood levels of glucocorticoids cause suppression in BDNF-dependent neuronal function via reducing miR-132 expression [52].

The dysfunction of adult hippocampal neurogenesis is proposed to be an essential mechanism explaining the etiology of depression. BDNF, CREB, and glucocorticoids are the key components for hippocampal neurogenesis, all of which are directly related to miR-132. Thus, it is suggested that miR-132 plays an important role in the etiology of depression.

MiR-132 has Functions in the Cardiovascular System

There is scant literature on the function of miR-132 in the cardiovascular system. However, the existing literature suggests that miR-132 has functions in the cardiovascular system.

The cardiovascular system is controlled by the nervous system, mainly by the autonomic nervous system; therefore, BDNF can influence the cardiovascular system via the autonomic nervous system. BDNF is important for autonomic nervous system function. BDNF is known to play an important role in regulating the survival of neurons in the autonomic nervous system and the formation of their synaptic connectivity with their peripheral targets in the cardiovascular, digestive, and other organ systems. Emerging evidence suggests that BDNF may also affect the function of the autonomic nervous system during adult life and may, in part, mediate the effects of environmental factors, such as exercise and dietary energy intake, on autonomic nervous system neurons and target cells [53]. BDNF has also been shown to be a modulator of visceral sensory transmission, suggesting that BDNF is involved in maturation and/or plasticity in the arterial baroreceptor pathway [54]. As noted above, BDNF influences CNS via the CREB-miR-132 pathway, and most of circulating BDNF is produced in the brain and passes through the blood-brain barrier. Thus, it is suggested that miR-132 may play an important role in cardiovascular function via the autonomic nervous system. Additionally, BDNF may also influence energy homeostasis through its role in neurogenesis and in the neuroplasticity of the HPA axis [55–57], and is involved in the maintenance of cardiometabolic homeostasis [58]. Therefore, it is suggested that miR-132 may also influence cardiovascular function via the HPA axis.

Endothelial dysfunction is a critical step in development of CVD pathology, such as hypertension, atherosclerosis, and thrombosis [59–61]. The action of vascular endothelial growth factor (VEGF) is essential to maintain proper endothelial and vascular function [62]. The major function of VEGF is angiogenesis [63]. VEGF stimulates virtually all aspects of endothelial function: proliferation, migration, permeability, and nitric oxide production and release. In addition, the action of VEGF makes the endothelium anti-apoptotic. In turn, the inhibition of VEGF action is associated with endothelial dysfunction [62].

The effect of VEGF on the endothelium is related to miR. Research on effects of miR on the endothelium has been conducted, showing that miR-132 is an angiogenic growth factor inducible miR in the endothelium [64,65]. VEGF triggers phosphorylation of CREB and subsequent transcription of miR-132. MiR-132 downregulates p120 Ras GTPase-activating protein, thereby removing the endogenous brake on Ras activity and activating quiescent endothelium [65].

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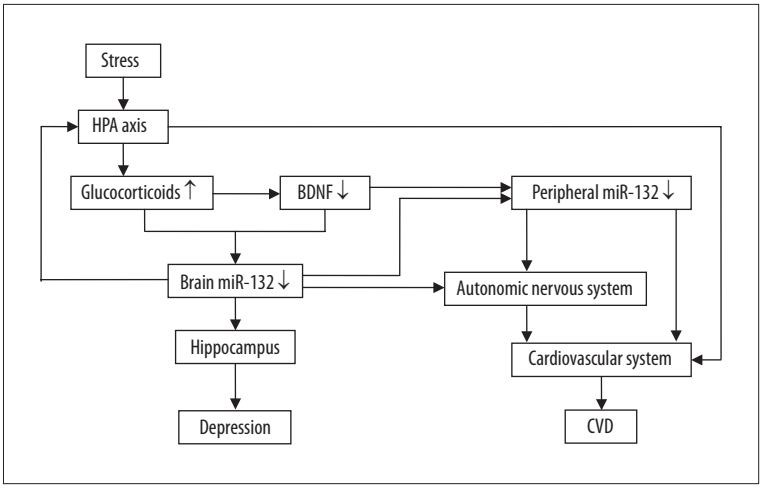

Figure 1. An integrative model that shows the possible role of miR-132 in coexistence of depression and CVD. miR-132 may play a role in pathogenesis of coexistence between depression and CVD. Abbreviations: HPA, hypothalamus-pituitary-adrenal; BDNF, brain-derived neurotrophic factor; miR-132, microRNA-132; CVD, cardiovascular disease.

MiR-132 mediates the deleterious effect of angiotensin II in vascular smooth muscle cells [66]. However, endothelial dysfunction is the first step to CVD and plays a central role in its pathogenesis [67]. Additionally, miR-132 may have an important role in cardiovascular function via the autonomic nervous system and the HPA axis. BDNF also maintains vessel stability in the heart through direct angiogenic actions on endothelial cells [68]. Although at present there is no literature on the role of miR-132 in BDNF-induced angiogenesis, it is likely that CREB and miR-132, which are the common components in BDNF-induced neuroplasticity and VEGF-induced angiogenesis, are involved in the mechanism. Thus, the positive effect of miR-132 on the cardiovascular system may be greater than the negative one. For example, Katare et al. [69] investigated the therapeutic activity and mechanistic targets of saphenous vein-derived pericyte progenitor cells (SVPs) in a mouse myocardial infarction model and concluded that SVP transplantation produces long-term improvement of cardiac function by a novel paracrine mechanism involving the secretion of miR-132 and inhibition of its target genes. Furthermore, a study of long-term β-adrenergic administration on the expression levels of the cardiac L-type Ca channel β2 subunit, which regulates channel trafficking and function, showed that cardiac L-type Ca channel β2 subunit protein expression may be down-regulated by miRs, including miR-132, in response to long-term activation of β-adrenergic signaling, possibly as an adaptive response in cardiac hypertrophy and sustained β-adrenergic states [70].

Hypothesis

MiR-132 has functions in both the nervous and cardiovascular system. Stress decreases BDNF level. Low BDNF level reduces CREB activation, resulting in down-regulation of miR-132, and then disrupts neuroplasticity and leads to depression. Stress also increases the level of glucocorticoid, and increased glucocorticoid level also down-regulates miR-132. MiR-132 may affect cardiovascular function by the autonomic nervous system and the HPA axis. Circulating BDNF, most of which is produced in the brain and passes through the blood–brain barrier [31], may also influence cardiovascular function involving miR-132. In addition, miRs are also found in microvesicles, which are plasma membrane fragments shed from virtually all cells [71]. Microvesicles circulate in peripheral blood, where they transport mRNA and proteins between cells and play a pivotal role in cell-to-cell communication. They are also implicated in the process of angiogenesis [72]. Recent studies also raise the possibility that CNS-derived vesicles may enter the bloodstream and interact with endothelial cells in the peripheral circulation [73], suggesting that the synthesis of miR-132 in the brain may be related to miR-132 level in the cardiovascular system. Thus, we hypothesize that miR-132 may play a role in coexistence of depression and CVD. Figure 1 presents an integrative model that shows the possible role of miR-132 in coexistence of depression and CVD. This model is not intended to be complete or all-encompassing, but rather to highlight and connect certain interesting evidence pointing to this miR-132 role.

Based on this hypothesis, miR-132 may be a potential target for treating depression and CVD. Both depression and CVD may benefit from up-regulated miR-132, and more research should be conducted in this field.

Conflicts of interest statement

None declared.

Statement

The work was done in Guangdong Province Pharmaceutical Association.

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