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Role of Sirtuins in Linking Metabolic Syndrome with Depression

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Depression is now widely regarded as a common disabling disorder that affects negatively the social functioning all over the world. Depression is associated with diverse phenomenon in brain such as neuroinflammation, synaptic dysfunction, and cognitive deficit. Recent studies reported that depression occurs by various metabolic changes, leading to metabolic syndrome. Sirtuins (SIRTs) are NAD^+-dependent class III histone deacetylases, known to regulate diverse biological mechanism such as longevity, genomic stability, and inflammation. The modulation of sirtuin activity has been highlighted as a promising approach to reduce neurodegenerative processes. In this review, we summarize the recent discoveries regarding the potential relationship between SIRTs and depression caused by metabolic disorders (Mets). Ultimately, we suggest the possibility that SIRTs will be novel targets to alleviate neuropathogenesis induced by depression.

Keywords: sirtuins (SIRTs), depression, inflammation, neurotransmitter, synaptic dysfunction, metabolic syndrome

INTRODUCTION

The prevalence of depression continues to rise all over the world and yearly prevalence rate is close to 10% (Kessler et al., 2003, 2005, 2011; de Souza and Hidalgo, 2012). According to the world health organization (WHO) ranks regarding depression, depression will be the second leading cause of mortality worldwide in 2030 (Lopez and Mathers, 2006). Moreover, the patients with depression showed decreased expression of synapse related genes, the loss of synapse in hippocampus (Duric et al., 2013) and dendritic atrophy associated with depression-like behaviors (Morales-Medina et al., 2013). Finally, 94% of patients suffering from depression experience cognitive impairment (Conradi et al., 2011) including impairment of executive functions, attention, memory and learning (Jaeger et al., 2006; Murrough et al., 2011; Etkin et al., 2013; Trivedi and Greer, 2014). For these reasons, the increase of patients with depression is an important issue in the view of economical and sociological aspects. The causes of depression are mainly genetic factors (Lohoff, 2010), aberrant inflammatory response (Miller et al., 2009; Dowlati et al., 2010; Harry and Kraft, 2012) and the insufficient level of neurotransmitters including cortisol (Miller et al., 1999), serotonin (Maes et al., 2011), acetylcholine (Picciotto et al., 2015) and dopamine (Nutt, 2008). Furthermore, current studies highlight that depression patients reportedly exhibit the positive correlation with metabolic syndrome including diabetes and obesity (Pan et al., 2012; Silva et al., 2012). People with metabolic disorders (Mets) have higher prevalence of depression compared to those without metabolic syndromes (Pan et al., 2012; Sekita et al., 2013). Sirtuins (SIRTs), which are known as the important metabolism regulator, were categorized seven isoforms (SIRT1–7) characterizing by different substrate and subcellular localization (Michan and Sinclair, 2007; Nakagawa and Guarente, 2011). All SIRTs have different length

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of N-and C- terminal extensions and play variable role in mammal (Schwer et al., 2002; Tennen et al., 2010). SIRTs existed in the nucleus (SIRT1, 6, 7), cytosol (SIRT2), and mitochondria (SIRT3, 4, 5; Morris et al., 2011; Donmez and Outeiro, 2013). Sirtuin's expression increases in cells exposed to conditions of oxidative stress and DNA damage (Cohen et al., 2004; Rodgers et al., 2005). Especially, SIRTs modulate diverse biological mechanisms including oxidative damage, protein aggregation, and inflammatory responses associated with central nervous system (CNS) diseases (Han, 2009) and play protective roles in neuropathological condition (Paraiso et al., 2013). Interestingly, a current study suggested that the expression of SIRT1, 2 and 6 mRNA in blood cells was altered in patients with mood disorders such as depression (Abe et al., 2011). Also, hippocampal SIRT2 enhances the depressant like behaviors by regulating neurogenesis (Liu et al., 2015). Here, we summarized recent evidences that SIRTs is involved in depressive disorder and SIRTs contributes to improve the depressive symptoms associated pathological phenomenon in metabolic stress condition. Thus, our review suggests that SIRTs may be good candidate genes to ameliorate the depressive symptoms.

SIRTUINS AND INFLAMMATION IN DEPRESSION

In a third of patients with depression, the serum and cerebrospinal fluid (CSF) concentrations of inflammatory markers in serum showed the elevation of pro-inflammatory factors such as interleukine (IL)-6, tumor necrosis factor (TNF)-α, and C-reactive protein compared to non-depressed patients (Raison et al., 2006; Dantzer et al., 2008; Dowlati et al., 2010; Liu et al., 2012). One study demonstrated that anti-depressants alleviate depressive state by suppressing the production of pro-inflammatory mediators such as IL-6 and nitric oxide (Hashioka et al., 2007). In addition, major depressive disorder were observed the reduction of natural killer cell cytotoxicity and T lymphocyte activity (Maes et al., 1991; Wong et al., 2008; Blume et al., 2011; Karg et al., 2011). In a clinical research, antidepressant treatment results in the enhancement of inflammatory response such as the reduction of IL-1 in depression patients and alleviates depressive symptoms (Hannestad et al., 2011). Based on various evidences, major depressive disorder leads to the inflammatory response including the activity of natural killer cell and lymphocyte, and the secretion of cytokines in brain. Hence, the decreased of inflammation may be a one of the solution for depression. SIRTs have known that they are involved in the inflammatory mechanisms through anti-apoptotic pathways. SIRT1 modulates the nuclear translocation of Forkhead box-containing protein O (FoxO) which is associated with the anti-apoptotic factor Bcl2 (Daitoku et al., 2004; Hsu et al., 2010). SIRT1 enhances cell survival in various stress conditions through the regulation of several substrates (Vaziri et al., 2001; Bordone et al., 2007). Several studies have mentioned the roles of SIRT1 as anti-apoptotic regulator that SIRT1 deacetylates the DNA repair factor (Jeong et al., 2007; Anekonda and Adamus, 2008; Mallick and D'Mello, 2014), and also inhibits p53 and NF-κB signaling (Cheng et al., 2003; Hernandez-Jimenez et al., 2013). Moreover, SIRT1 promotes growth of neurons and inhibits the death of neurons in CNS through mTOR signaling (Guo et al., 2011). SIRT1 also inhibits the release of pro-inflammatory cytokines in microglia (Ye et al., 2013). SIRT2 inhibits the inflammatory responses in CNS disorders by controlling the activation of microglia (Chen et al., 2015). SIRT2 prevents the excessive activation of microglia through NF-κB deacetylation (Pais et al., 2013) and regulate the cell cycle and the survival of microglia (Nie et al., 2014). SIRT3 protects cells against apoptotic cell death in oxidative stress by regulating anti-apoptotic signaling (Pellegrini et al., 2012; Chen et al., 2013) and by inhibiting the production of ROS (Kim et al., 2010). SIRT3 protects cortical neurons against H_2O_2 stimulated oxidative stress by regulating mitochondrial Ca^{2+} homeostasis and mitochondria dysfunction (Dai et al., 2014; Hu et al., 2014). Taken together, SIRTs have the pro-apoptotic effect via various pathways and is the regulator of cytokine secretion in CNS. Thus, we suggest that SIRTs may be strongly involved in the inflammatory response, leading to depression (**Figure 1**).

SIRTS AND NEUROTRANSMITTER'S INSUFFICIENT LEVEL IN DEPRESSION

Depression has been reported that it is related with the alterations of neurotransmitters such as serotonin (5-HT), norepinephrine and dopamine (Nutt, 2008). In patients with depression, the level and activity of neurotransmitter were founded insufficiently compared to the normal subjects (Ruhe et al., 2007; Nutt, 2008). Considering the clinical research, monoaminergic modulators could improve the depressive symptoms in over 30–40% of all population (Roiser et al., 2012). In the state of depression, the level of serotonin, norepinephrine, and tyrosine known as the precursor of dopamine were insufficiency in the brain (Coppen, 1967) and in the blood of patients (Benkert et al., 1971; Antkiewicz-Michaluk et al., 2014). Also, the activity and level of dopamine associated with attention (Nutt, 2008) is dysregulated in major depressive disorders (Delgado, 2000; Dailly et al., 2004). In patients with major depressive disorders, the decreased level of GABA has been reported in plasma, CSF, and cortex neurons in comparison with the normal subjects (Rajkowska et al., 2007; Maciag et al., 2010). According to knockout mice model studies, the changes in 5-HT1B receptor expression and signaling were observed in the depression model (Lanfumey and Hamon, 2004; Lanfumey et al., 2008; Fakhoury, 2015). The lack of neurotransmitters subsequently alters the second messenger response in cells (Shimon et al., 1997; Coupland et al., 2005). Furthermore, several studies founded that the density of postsynaptic 5-HT receptors is markedly attenuated in patients with depression (Bhagwagar et al., 2004; Drevets et al., 2007). Recent studies demonstrated that SIRT1 affects the levels of neurotransmitter by modulating the mono-amine oxidases MAO-A promoter (Libert et al., 2011) and finally plays a beneficial role in the anxiety and depression (Nordquist and Oreland, 2010). The activation of SIRT1 also contributes to the regulation

of GABA secretion (Prud'Homme et al., 2014). In addition, SIRT2 is involved in motor dysfunction in patients with neurodegenerative disease by decreasing dopamine content in the brain striatum (Wang et al., 2015). SIRT4 has been reported that it could modulate glutamate uptake in CNS (Shih et al., 2014).

In addition, depression is influenced by reduced levels and activity of acetylcholine (Caspi et al., 2003; Meerson et al., 2010). Current study demonstrated that mood and anxiety were regulated by acetylcholine pathway (Picciotto et al., 2015). Several studies suggested that SIRT1 could involve in acetylcholine receptor expression in brain (Huang et al., 2011) and modulates choline's expression (Gareri et al., 2015). Taken together, SIRTs is involved in the level of neurotransmitters in CNS based on recent evidences. Hence, we suggest that SIRTs should be more highlighted the role of it regarding neurotransmitters in depression brain (**Figure 1**).

SIRTUINS AND SYNAPTIC DYSFUNCTION IN DEPRESSION

A loss of synaptic plasticity is commonly observed in patients with depression (Raison et al., 2006; Martinowich et al., 2007). Current clinic study demonstrated that the synaptic dysfunction is strongly influenced by depressive emotional states (McGaugh, 2000; Banasr and Duman, 2007; Kauer and Malenka, 2007; Pittenger and Duman, 2008; Russo and Nestler, 2013). Stress, leading to depression triggers the alteration of presynaptic glutamate secretion and postsynaptic glutamate receptor expression (Yuen et al., 2009). Depression also affects the dendrite spines and finally memory acquisition and long term plasticity (Alvarez and Sabatini, 2007). Recent study reported that SIRT1 affects dendritic development in hippocampal neurons (Braidy et al., 2012). In SIRT1 knockout mice, dendrite branching and branch length of neuron decreased compared to the normal brain (Michan et al., 2010) and impaired synapse plasticity was founded in the hippocampus (Gao et al., 2010). The activity of SIRT1 in dendritic development is related with the Rho GTPases and the ROCK signaling in hippocampal neuron (Negishi and Katoh, 2002; Codocedo et al., 2012). Several studies indicate that the activity of SIRT1 protects the several synaptic proteins in various neurodegenerative diseases (Duan and Mattson, 1999; Patel et al., 2005; Kim et al., 2007). Collectively, SIRTs are associated with the synaptic dysfunction and may contribute to the improvement of synapse plasticity in depression (**Figure 1**).

SIRTUINS AND METABOLIC SYNDROME WITH DEPRESSION

Recently, the elevated level of metabolic factors including blood pressure, cholesterol, C-reactive protein leading to T2DM or obesity (Ali et al., 2006; Barnard et al., 2006) has been considered as the higher risk for depressive symptoms (Hamer et al., 2012; Rotella and Mannucci, 2013). High glucose and insulin resistance in T2DM affect negatively the brain (van Duinkerken et al., 2012a; Antenor-Dorsey et al., 2013; Reijmer et al., 2013) because it aggravates the functional

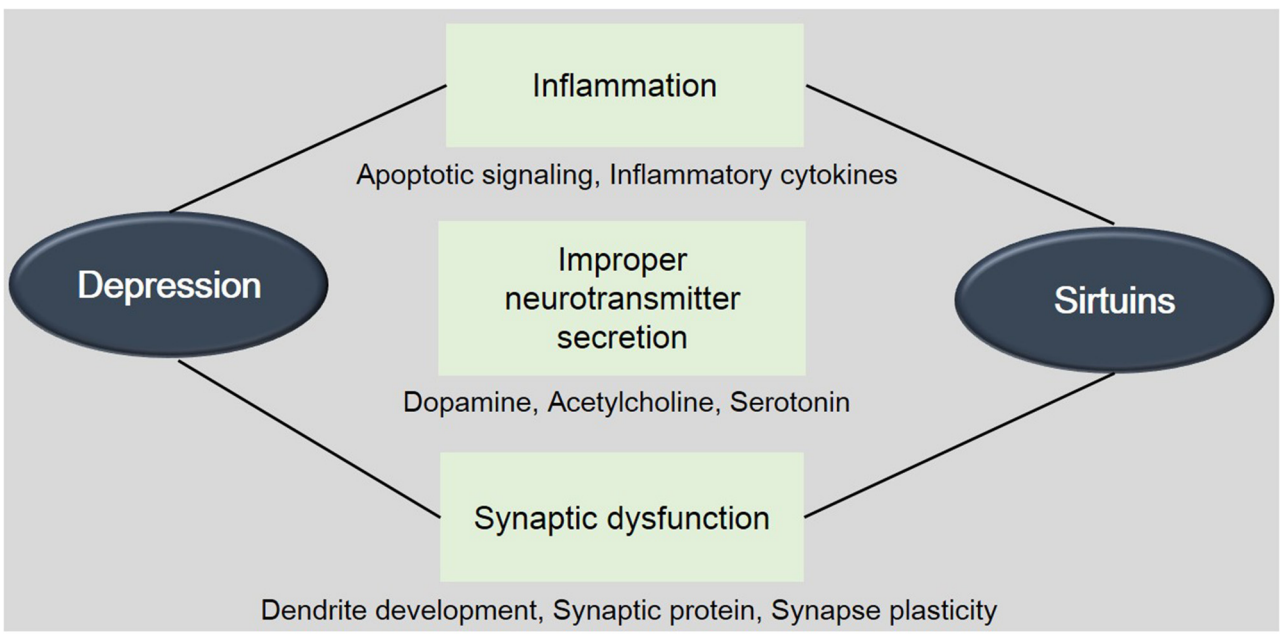

FIGURE 1 | The involvement between Sirtuins (SIRTs) and depression. This schematic image shows the relevance between SIRTs and depression. The onset and progress of depression is related with the inflammation, improper neurotransmitter's secretion, and synaptic dysfunction. This image indicates the involvement of SIRTs in these mechanisms. Mets: Metabolic disorders.

dysconnectivity of brain (Geissler et al., 2003; Sahin et al., 2008; Musen et al., 2012; van Duinkerken et al., 2012b). Hyperglycemia induces the dysregulation of hypothalamic pituitary-adrenal axis and dysregulation of monoaminergic system (Zanoveli et al., 2015). Several studies reported that the patients with obesity and depression have more frequency in comparison with the general population (McIntyre et al., 2007; Blaine, 2008; Luppino et al., 2010; Levitan et al., 2012; Toups et al., 2013). According on previous published evidences, SIRT1 is strongly related with neuropathgenesis caused by T2DM and obesity. SIRT1 has been reported that it plays a cardinal role in glucose metabolism and insulin signaling activation (Guarente, 2006; Barzilai et al., 2012; Wang et al., 2012; Mortuza et al., 2013; Silvestre et al., 2014). The regulation of glucose metabolism is an important issue for anti-aging according several evidences (Colman et al., 2009; Smith et al., 2010). The regulation of glucose metabolism has been demonstrated to suppress against onset age related diseases (Colman et al., 2009; Smith et al., 2010) such as the T2DM and cardiovascular disease (Hammer et al., 2008; Marchal et al., 2012) and especially is associated with the activity of AMPK and SIRT1 related with the NAD^+ biosynthetic activity (Yang et al., 2007) and SIRT6 associated with the regulation of insulin mediated signaling (Xiao et al., 2010). SIRTs improved insulin secretion and glucose homeostasis (Revollo et al., 2007; Caron et al., 2014) via increasing NAD^+ levels (Schenk et al., 2011). Based on the study using SIRT6 (−/−) animals, the deficiency of SIRT6 showed the changes of blood glucose level (Xiao et al., 2010). In addition, in neurons, SIRT1 signaling modulates peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1α) activity and subsequently mitochondrial dysfunction (Chowdhury et al., 2011). SIRT2 also has been reported that it is target for diabetes (Nerurkar and Nerurkar, 2008). Taken together, SIRTs family is associated with the metabolic diseases including the T2DM and obesity and affect neuropathogenesis caused by these disorders (Hamer et al., 2012; Rotella and Mannucci, 2013). Taken together, SIRTs is involved in the progress of depressive symptoms caused by metabolic disease (**Figure 2**). Considering sirtuin's neuroprotective effects including anti-inflammatory

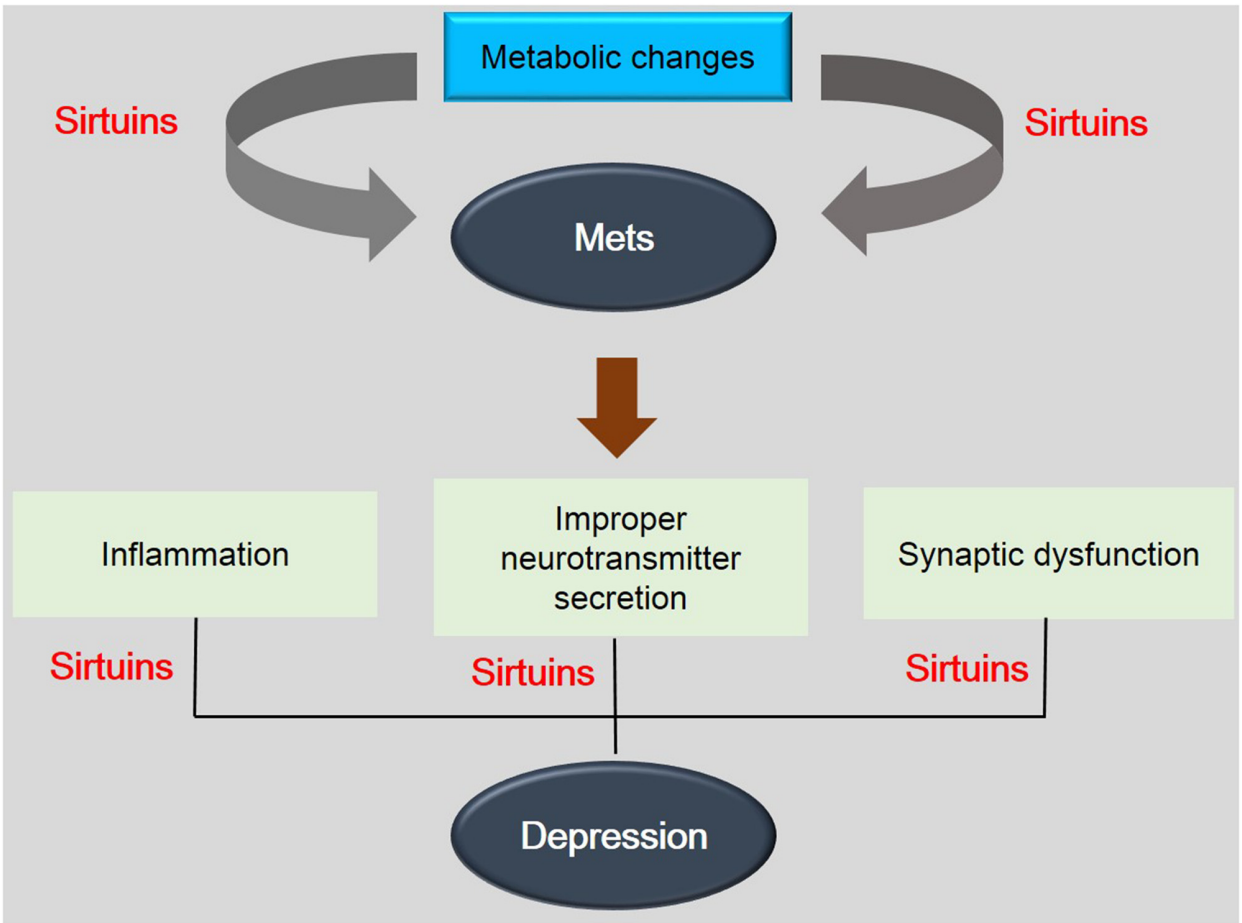

FIGURE 2 | The association between depression and metabolic diseases. This schematic image shows the association between depression and metabolic diseases. SIRTs are involved in the pathogenesis of metabolic disease by metabolic changes and also are related with depression related phenomenon. This image indicates the importance of SIRTs in mechanisms between depression and metabolic diseases. Mets: Metabolic disorders.

effect, regulation of neurotransmitter production, and reduction of synaptic dysfunction, SIRTs could be a crucial target to ameliorate depressive pathology by metabolic alterations.

CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, we suggest that SIRTs are promising therapeutic targets to alleviate depression pathology in four possibilities: (1) SIRTs may control the inflammatory response in depression; (2) SIRTs might regulate the insufficient level of neurotransmitters in depression; (3) SIRTs may improve the synaptic dysfunction caused by depression; and (4) sirtuis may alleviate the cognitive decline caused by depression. As society ages, people suffer from metabolic syndrome such as diabetes, obesity, and cardiovascular disease and subsequently they suffer from depression by metabolic changes. We should investigate to search the therapeutic solution. SIRTs is the metabolism related genes and also ameliorates depression related pathogenesis (Abe et al., 2011; Ferland et al., 2013; Krogh et al., 2014). SIRTs may be a good target to modulate various pathogenesis in depression related with metabolic diseases. Although sirtuin's mechanisms in depression is fully not understood until now, researchers continuously have investigated the novel role of SIRTs such as the regulation of microRNAs by SIRTs (Rao et al., 2013; Deng et al., 2014; Rodriguez-Ortiz et al., 2014). Thus, we propose the necessity of further studies regarding sirtuin's role, suggesting that manipulation of siutuins may be a therapeutic solution for depression.

AUTHOR CONTRIBUTIONS

JS wrote the preliminary draft and revised details of the manuscript. JK revised all manuscript in detail.

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