Cellular and Molecular Biology

Hajebrahimi *et al. Cell. Mol. Biol.*2016, 62 (13): 71-77
ISSN: 1165-158X
doi: 10.14715/cmb/2016.62.13.13

Review

Type 2 diabetes and mental disorders; a plausible link with inflammation

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Abstract: Mental disorders including depression and anxiety are the prevalent human diseases which are associated with several metabolic and non-metabolic diseases. Recent investigations demonstrated that the mental disorders can be considered as the potential inducers/stimulators of chronic inflammation. Based on the fact that chronic inflammation is a main cause of human diseases, hence, a hypothesis has been raised to explore the interaction between mental disorders and inflammation related metabolic diseases. Type 2 diabetes (T2D), as a complicated metabolic disorder, is associated with inflammation and also mental disorders. Accordingly, it has been hypothesized that depression and anxiety, as mental disorders may be the inducers/stimulators of inflammation in the patients suffering from T2D. This review article collected recent information regarding the roles of mental disorders on the chronic inflammation in the T2D patients.

Key words: Type 2 diabetes, Depression, Anxiety, Inflammation.

Introduction

Type 2 diabetes (T2D) is a metabolic disorder which is associated with several complications including physical and mental disorders (1). The accurate ranges of mental disorders in T2D are variable and different among various ethnics (2). The main mechanisms which lead to induction of mental disorders in the patients have yet to be clarified. There are several hypothesis which are controversy regarding the etiology of mental disorders in the patients suffering from T2D. For example, it has been hypothesized that high blood glucose levels in the patients can alter behavioral functions of the patients (2). Recent data proposed that inflammation can be considered as a main cause of mental disorders in the patients (3). It appears that T2D related inflammation can modulate several behavioral functions which have been reported in several diseases. Based on the fact that the prevalence of the mental disorders is different among human population suffering from T2D (2), hence, it may be hypothesized that the pro-inflammatory molecules expression may be differ in the population. Thus, the main aim of this review article is to explore the prevalence of mental disorders among T2D patients which are reported from researchers from all over the world. Another aim of this article is to evaluate the roles played by inflammation in the induction/stimulation of mental disorders in the patients with T2D. Accordingly, the next sections describe T2D, mental disorders which are explored in this review article and some inflammatory molecules which are associated with mental disorders in T2D. Finally, the link between T2D, mental disorders and inflammatory molecules will be discussed.

Type 2 diabetes

T2D is a chronic metabolic disease which is associated with increased blood glucose (fasting plasma glucose $\geq$ 126 $\pm$ 7 mg/dl), insulin resistance, and in some cases relative lack of insulin (4). It has been estimated that more than 7 % of the world's adult population will affected with diabetes (5). This is a prevalent metabolic disorder in either developed or developing countries. T2D is a high prevalent disease in Iran with more than 24 percent involvement in adult (> 40 years) (6). Increased blood sugar in the patients is an important cause of several complications including cardiovascular diseases, neuropathy, retinopathy, kidney failure, amputations and so on (4, 7). Obesity, unsuitable diet, not enough exercise, genetics, hormones and environmental factors are the main reasons for insulin resistance but some environmental factors such as stress and mental diseases deteriorate the disease (5, 8). Inflammation is a common phenomenon in T2D which is associated with the mentioned complications (1, 9).

Mental disorders

Mental disorders are a set of diseases which are associated with alteration of behavioral functions in the patients (10). The disorders affect human life quality and lead to several complications in some cases (11). Among the mental disorders, depression and anxiety are the most prevalent forms (12), hence, this review article focuses on the mental disorders. Depression is a kind of mental disorders which the affected patients have not

Received July 18, 2016; **Accepted** November 20, 2016; **Published** November 30, 2016

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enough motivation to perform his/her routine functions. The patients suffer from a chronic inappetence, alteration in sleep and weight, qualm and also self-destruction (13). Severe depression is associated with severe impairment in personal and social life and may result in overshadow of the patients health (13).

Anxiety, as another mental unpleasant emotional disorder, is associated with fear, worries, continual tiredness, headache, exhaustion, fear of socializing, nausea, an upset stomach and so on. Although, the symptoms are defined for anxiety but they can also be exhibited with other mental disorders. Obviously, chronic anxiety makes the patients lives difficult (12).

Scientists believe that several mechanisms may induce/stimulate depression and anxiety in T2D including high blood sugar, chronic inflammation and so on. Interestingly, the mental disorders may be the main reason of induction of inflammation in the patients. Next sections discuss the prevalence of depression and anxiety in the patients suffering from T2D and the relation of the mental disorders with inflammation.

Inflammatory molecules

There are several molecules which induce/stimulate inflammation in human and known as inflammatory molecules. Here we describe the important inflammatory molecules which are evaluated in T2D with and without mental disorders briefly.

Innate and adaptive immune cells are the main source of pro-inflammatory molecules including cytokines, co-stimulatory molecules, pro-inflammatory surface molecules and so on (14). They produce the molecules following interaction of PAMPs (Pathogen associated molecular patterns) and DAMPs (Damage associated molecular patterns) with their pathogen recognition receptors (PRRs) (14). Toll like receptors (TLRs), inflammasomes and intracellular sensors are the main PRRs which uses several intracellular signaling molecules such as myeloid differentiation primary response (MYD88) and TIR-domain-containing adapter-inducing interferon- β (TRIF) to activate transcription factors for transcription from pro-inflammatory molecules (14). The main target of the PRRs pathways are nuclear factor kappa-light-chain-enhancer of activated (NF-κB), interferon regulatory factors (IRFs) and activator protein-1 (AP-1) (15). The transcription factors transcript from pro-inflammatory cytokines (including interleukin (IL)-1, IL-6, IL-8, IL-12, IL-18, interferon-gamma (IFN-γ), tumor necrosis factor (TNF-α) and so on), co-stimulatory molecules and pro-inflammatory surface molecules (such as CD40, CD40L and so on) (14). The pro-inflammatory factors induce inflammation in responses to PAMPs and DAMPs in infectious diseases and inflammatory based diseases, respectively (14).

Mental disorders as main inducers of inflammation

It has been hypothesized that depression and anxiety may be considered as modulators of immune system functions. Recent information also confirmed the hypothesis which showed alteration in immune cells functions in the patients suffering from depression and anxiety (16). The published data regarding the relation between depression/anxiety with expression and functions of immune system related molecules showed that the mental diseases induce inflammation in various manners. Some of the literatures indicated that the mental disorders up-regulate pro-inflammatory molecules, and others revealed that depression/anxiety have reduced expression of the regulatory molecules. For example, our previous investigations revealed that depression can increase expression of two important adaptor proteins in the intracellular pathways of TLRs (MYD88 and TRIF), the main innate immunity cell receptors (16). As mentioned in the previous section, MYD88 and TRIF play key roles in transition of intracellular signaling from TLRs to down-stream molecules (17). Previous section showed that TLRs active corresponded cells via interaction with PAMPs and DAMPs (17). It has been reported that several DAMPs including C-reactive protein (CRP), heat shock proteins (HSPs), high mobility group box-1 (HMGB1) and serum amyloid proteins (SAPs) are increased in depression (18-21). A study by Priya et al., revealed that anxiety has a positive relation with inflammation (22). Bakhsh-Aliabad et al., also showed that anxiety is an inducer of CD36 expression on the monocytes of the patients with chronic hepatitis B (23). CD36 is a scavenger receptor and participates in several inflammatory functions of monocytes (24). Additional studies showed that serum levels of anti-inflammatory cytokines were decreased in the depressed patients (25-28). Decreased expression of anti-inflammatory cytokine is associated with increased inflammatory functions of immune system and inflammation induction (29). Increased expressions of pro-inflammatory cytokines in the patients with depression and anxiety have also been reported by several investigators (30-33). A study by Grinberg et al., demonstrated that the microglia cells of depressed patients have produced more levels of pro-inflammatory cytokines in comparison to healthy controls (34). Snyder and colleagues reported anti-depressant drugs reduced serum levels of pro-inflammatory cytokines (35). Interestingly, increased expression of pathogen recognition receptors including TLRs and inflammasomes by mental disorders have been reported in previous investigations (21, 36). Our previous study demonstrated that mRNA levels of NF-κB, as a transcription factor, decreased in the depressed patients (37). Based on the fact that following interaction between TLRs and their ligands and subsequently activation of intracellular signaling pathways, NF-κB is separated from Iκκ, the inhibitor of NF-κB, and translocated to the nucleus for transcription from pro-inflammatory molecules (15), hence, it seems that activation of the pathways do not need up-regulation of NF-κB.

In contrast with the results, no alteration in the intracellular signaling molecules of TLRs in hepatitis B infected patients with mental disorders have been reported when compared with hepatitis B infected patients without mental disorders (38). No relation between anxiety and serum levels of IL-1 β, IL-6 and IL-8, as pro-inflammatory cytokines and IL-10, as anti-inflammatory cytokine, have been reported by Ataseven and colleagues (39).

Although, the studies showed a negative relation between some pro-inflammatory molecules and men-

tal disorders but more than 90 percent of investigations approved the hypothesis. Thus, it seems that depression and anxiety, as mental disorders can be associated with inflammation.

Epidemiology of depression and anxiety in the patients with T2D

It has been documented that depression increases risk of reduced diabetes-related life quality in T2D (40). Furthermore, investigations demonstrated that mental disorders like depression can deteriorate T2D related complications such as neuropathy (41). Interestingly, it seems that depression history can affect T2D onset (42). There are several studies which have evaluated the prevalence of depression and anxiety in the patients suffering from T2D. Accordingly, Arshad et al., revealed that 51 percent of Pakistani T2D patients suffered from depression (43). Another study on an USA population (2182 cases) demonstrated that 10.6 percent of participants were depressed (44). Cols-Sagarra and colleagues showed that the prevalence of depression among a Spanish population were 29.2% (45). A study in Malaysia identified that 41.7% of 700 patients with T2D suffered from depression (46). High prevalence depression and anxiety in T2D patients were also reported in Germany (47), Japan (48), Taiwan (49), Saudi Arabia (50), South Korea (51), Brazil (52), Italy (53), China (54), Bangladesh (55), Norway (56), Iran (57) and so on.

Due to the huge reports regarding the high prevalence of depression and anxiety among the patients with T2D, it seems that the mental disorders may be considered as responsible for some of complications in the population. Based on the relation between depression/anxiety and inflammation induction, a hypothesis has been raised which propose that depression and anxiety may participate in deterioration of increased blood glucose and also induction of T2D complications via induction/stimulation of inflammation. Accordingly, a study reported that antidepressant medication leads to improvement of glycaemic control (58). Next section evaluates the recent information regarding the hypothesis.

Relation between mental disorders and inflammation in T2D

According to the information presented in the previous sections, it seems that depression and anxiety are potentially associated with increased inflammation. Thus, they have been considered as potential candidate for induction/stimulation of inflammation in the T2D patients, the individuals who suffer from inflammation. Interestingly, recent data also confirmed the hypothesis and revealed that depression induces expression of CRP, IL-6 and TNF-α, as pro-inflammatory molecules in elderly patients with T2D (59). Increased serum levels of CRP in depressed patients with T2D have been reported by Au and colleagues (60). A positive association between depression and CRP levels in the patients with T2D has been demonstrated (61). Laake et al., showed that depression leads to up-regulation of CRP, IL-1β, IL-1 receptor antagonist (IL-1RA), monocyte chemotactic protein-1 (MCP-1) and white blood cell count (WBC) in T2D (62). Increased serum levels of IL-6 and CRP were also reported by several investigators (63, 64). Increases expression of pro-inflammatory molecules like CD40, CD40 ligand (CD40L), soluble CD40L (sCD40L), selectin P (CD62P), β-thromboglobulin and platelet factor-4 has been reported in the patients with T2D and depression simultaneously (65). Anxiety also has a positive relation with higher serum levels of pro-inflammatory cytokines in women with diabetes (66).

As mentioned in the previous sections, the pro-inflammatory molecules including cytokines and other molecules like CRP, CD40, CD40L and so on, are the down-stream molecules for PRRs (15). Based on the increased expression of the pro-inflammatory molecules in the mental disorders during T2D, it seems that PRRs and their ligands (PAMPs and DAMPs) may be involved in the inflammatory condition linked between T2D and mental disorders. Interestingly, previous studies approved the hypothesis and revealed that expression of TLRs and inflammasomes, as PRRs, are significantly increased in T2D patients and also the patients suffering from depression and anxiety (16, 67-69). Moreover, anti-anxiety and anti-depression therapy in a Chinese population leads to down-regulation of TLR4 and its intracellular signaling pathways (70). Based on the fact that TLR4 is a unique TLR which uses both adaptor proteins (MYD88 and TRIF), and based on the fact that both adaptor proteins are increased in depression (69) and additionally, TLR4 plays key roles in the pathogenesis of T2D (71), hence, it seems that there as a potential link between mental disorders like depression and anxiety with T2D via TLR4 and its intracellular signaling molecules. Additionally, it has been identified that other PRRs may participate in the pathogenesis of T2D and its related mental disorders (1). For example, high-fat diet, which is associated with T2D, induces anxiety via activation of extracellular signal-regulated kinase (ERK) and inflammasomes pathways (72). Diet-induced obesity also can induces depression and anxiety in T2D through increased endogenous LPS and activation of brain IDO (3). Both of the investigations approved the link between depression/anxiety and T2D.

Conclusion

As mentioned in the previous sections, pro-inflammatory cytokines, co-stimulatory molecules and surface pro-inflammatory molecules (like CD40, CD40L and so on) increased in the patients suffering from T2D and mental disorders. The pro-inflammatory molecules are the target of TLRs and inflammasomes signaling pathways. Increased expression of TLRs and their intracellular signaling such as MYD88 and TRIF as well as inflammasomes in depression/anxiety and also T2D has been reported previously (16, 67-69). Previous investigations also revealed that several DAMPs (ligands for PRRs) are released during T2D and the mental disorders. Therefore, it seems that depression and anxiety may deteriorate T2D complications by increasing the endogenous DAMPs and consequently activation of PRRs and production of pro-inflammatory molecules which are the main causes of T2D complications. The hypothesis have been approved by Pomytkin et al., which showed that increases intestinal peripheral serotonin (5-HT) and decreased serotonin tranporter (5-HTT) functions leads

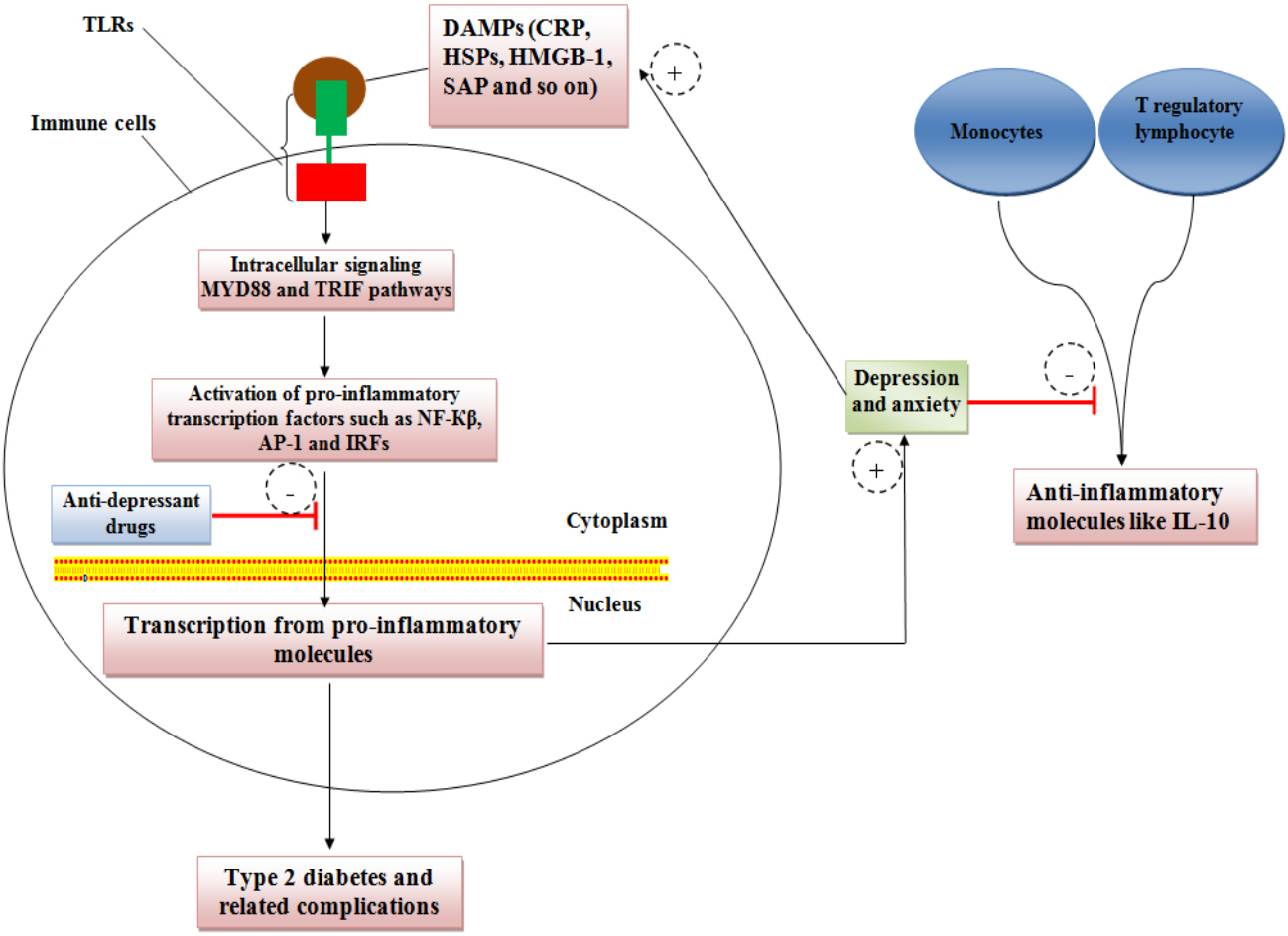

Figure 1. Relation among mental disorders, inflammation and type 2 diabetes. As illustrates in the figure, mental disorders such as depression and anxiety active and inhibit production of pro-inflammatory and anti-inflammatory molecules, respectively. The induced inflammations deteriorate mental disorders and also induce/stimulate type 2 diabetes and its complications. Thus, mental disorders may be considered as a risk factor for deterioration of type 2 diabetes.

to endotoxaemia and consequently leading to TLR4 activation which is a common mechanism for induction of inflammation in the T2D and depression (73). According to the information it seems that both mental disorders and T2D can be considered as risk factor for each other, because all of them are the inducers of inflammation and the inflammation not only can induce the onset of the diseases but also is able to deteriorate them. For approving the hypothesis a 6 years prospective cohort study demonstrated that depression is a risk factor for insulin resistance and consequently increased risk of T2D (74). McIntyre and colleagues also reported that reduced volumes in areas of the depression brain implicated (like hippocampus and amygdale) are associated with T2D (75). It appears that mental disorders and T2D affect each other via up-regulation of pro-inflammatory molecules. Figure 1 illustrates the relation between mental disorders and induction/stimulation of inflammation and its plausible relation with type 2 diabetes. Several mechanisms may participate in the interaction between mental disorders and T2D, for example it appears that inflammatory cytokines can interact with synaptic plasticity, neurotransmitter metabolism and neuroendocrine function which are associated with both mental disorders and T2D. Collectively, it seems that inflammation is the potential link between mental disorders and T2D and it may be hypothesized that therapeutic strategies need to be directed to regulate inflammation in the patients.

Acknowledgments

This study has been supported by Science and Research Branch, Islamic Azad University, Tehran, Iran.

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