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**Why do we not reverse the path? Stress can cause depression, reduction of brain-derived neurotrophic factor and increased inflammation**

Claro AE *et al*. Depression and inflammation

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**Abstract**

The aim of this paper is to describe the direction of the link between stress, depression, increased inflammation and brain-derived neurotrophic factor (BDNF) reduction. We hypothesize that severe stress or prolonged stress can be the driving factor that promote the onset of depression. Both stress and depression, if not resolved over time, activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines. This cascade fosters systemic chronic inflammation and reduced plasma BDNF levels. Since people with depression have a 60% increased risk of developing type 2 diabetes (T2D) and show high levels of inflammation and low levels of BDNF, we hypothesize possible reasons that might explain why T2D, depression and dementia are often associated in the same patient.

**Key Words:** Depression; Inflammation; Brain-derived neurotrophic factor; Type 2 diabetes mellitus; Dementia; Psychological stress

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**Core Tip:** This paper proposes a distinct interpretation of the link that exists between increased inflammation and reduction of brain-derived neurotrophic factor (BDNF). We describe why most of the people with altered inflammatory status and low BDNF do not automatically have depression, and why some people become depressed without diverging from average serum levels of these markers. We also suggest a reason why the use of tumor necrosis factor-α inhibition has no effect as a therapy in patients with resistant depression and high inflammatory levels.

**TO THE EDITOR**

We read with great interest the work of Porter and O’Connor[1] describing how brain-derived neurotrophic factor (BDNF) and inflammation are considered key players in the pathogenesis of depression.

We found the ideas of our colleagues very interesting and sharable. In this letter, we would like to suggest a different way to evaluate the link between BDNF, inflammation and depression. Following the “*social signal transduction theory of depression”*[2] we consider stress as the main cause of development of depressive symptoms; depression, in turn, is able to induce increased inflammation and reduced BDNF production.

It has been demonstrated that when a person lives in an environment characterized by numerous stressful situations (physical and social threat, or internal perceived stressors, like internal thoughts) that are severe or prolonged over time and he is not able to eliminate or psychically rework them, he displays a greater risk of developing depression[2,3].

Stress and depression, if not resolved over time, can activate brain regions connected with pain. These areas will project into lower regions that regulate inflammation *via* the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system (SNS)[3]. The SNS, in the first stage of modulation, will set up the production of epinephrine and norepinephrine. These neurotransmitters will activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines that will foster major inflammation or Systemic Chronic Inflammation (SCI)[2]. If this state is sustained for years, there is a high risk of developing inflammation-related disorders, quickened biological aging, infections, and premature mortality[4].

Moreover, stress and chronic inflammation are capable of inducing reduction of BDNF and indeed plasma BDNF levels are significantly lower in depressed patients compared with matched controls[5].

These considerations might explain why most of the people with altered inflammatory status and low BDNF do not automatically develop depression, and why some people become depressed without presenting the serum levels of either of the two markers far from the average[1]. It is neither the reduced BDNF nor the increased inflammation that induces depression, but rather it is stress itself that is able to promote the onset of depression. Moreover, if stress and depression last over time they can lead to increased inflammation and decreased BDNF[1]. Following this reasoning, it appears clearer why pharmacological intervention with tumor necrosis factor-α antagonist as an anti-depressant treatment in patients with resistant depression and high inflammation does not give positive results, while the same type of intervention is quite effective in treatment resistant patients with high inflammation and without depression[6,7]. That is because in patients with inflammatory diseases inflammation recognizes physical causes as an origin while in patients with depression it recognizes stress as the underlying cause of inflammation. If patients are not able to eliminate the source of stress, this will continue to generate depression, inflammation and reduced BDNF.

The article by Porter and O’Connor[1] allowed us to move even further and to hypothesize a possible link between stress, depression, inflammation, development of type 2 diabetes (T2D), BDNF reduction, and dementia.

Patients suffering from depression have high levels of stress which lead them to overeating, in particular food rich in carbohydrates or snacks, because this high-calorie food acts as a self-medication and is able to increase serotonin levels[8,9]. These patients are accordingly more prone to develop overweight and obesity, the strongest risk factors for the onset of T2D[10-12]. It has been showed that people with depression have a 60% increased risk of developing T2D[13] and 25% of patients with T2D have depression[14]. Nevertheless, depression in T2D patients is frequently unrecognized and therefore not treated[15-17].

Thus depression, untreated for years, contributes to maintain T2D and both depression and T2D can lead to increased SCI and decreased BDNF. In this way, the reduction of neurogenesis and synaptogenesis, a reduction of the vascular bed and vascular support and neuroinflammation are determined, finally leading to an increasing risk of dementia onset. Low BDNF levels are present in dementia patients[18,19] and patients with T2D are approximately two to four times more likely to develop dementia than individuals without T2D. These associations might explain why T2D, depression and dementia are often associated in the same patient[20-23]. We are aware that these are hypotheses, but we can consider them as useful reflections inspired by the article by Porter and O’Connor[1] to be validated in future studies.

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