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Why do we not reverse the path?-Stress can cause depression, reduction of Brain-Derived Neurotrophic Factor and increased inflammation

Depression and Inflammation

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Abstract

The aim of this paper is to describe the direction of the link that do exists between stress, depression, increased inflammation and BDNF reduction. We hypothesize that stress, severe or prolonged over time, is the driving factor that promote the onset of depression. Stress and depression then, if not resolved over time, will activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines that will foster Systemic Chronic Inflammation and reduced plasma BDNF levels. Since people with depression have a 60% increased risk of developing T2D, have high levels of inflammation and low BDNF we hypothesize further why T2D, depression and dementia are often associated in the same patients.

Key Words: Depression; Inflammation; Brain-Derived Neurotrophic Factor; Diabetes Mellitus Type 2; Dementia; Psychological Stress.

Claro AE, Palanza C, Mazza M, Rizzi A, Tartaglione L, Marano G, Muti-Schuenemann G, Rigoni M, Muti P, Pontecorvi A, Janiri L, Sani G, Pitocco D. Why do we not reverse the path? Stress can cause depression, reduction of Brain-Derived Neurotrophic Factor and increased inflammation. *World J Psychiatry* 2022; In press

Core Tip: This paper does propose a distinct interpretation of the link that exists between increased inflammation and reduction of 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 suggest also a reasoning that can explain why the use of TNFα 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 & 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. But in this letter, we would like to suggest a different way to evaluate the link between BDNF inflammation and depression. Therefore, following the "*social signal transduction theory of depression*" [2] we have taken into account stress as the main cause of depression development; depression in turn, is able to induces increased inflammation and reduced BDNF production.

Indeed, when a person lives in an environment that presents numerous stressful situations (physical and social threat, or internal perceived stressor, like internal thoughts) severe or prolonged in time and is not able or cannot eliminate them, he displays a greater risk of developing depression [2,3].

Stress and depression, if not resolved over time, can switch on brain regions connected with pain. These areas will project into lower regions that regulate inflammation *via* the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) [4]. 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, infection, and premature mortality [5].

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 [6].

Such a reasoning might explain why most of the people with altered inflammatory status and low BDNF do not automatically have depression, and why some people become depressed without having either of the two serum levels of the markers far from the average [1]. It is not the reduced BDNF and increased inflammation that induce

depression, rather it is stress that is able to induces depression. Moreover, if stress and depression last over time they can lead to increased inflammation and decreased BDNF [1]. Following this way of reasoning, appear clearer why pharmacological intervention with TNFα 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 [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 & O'Connor [1] allowed us to move even further and to hypothesize a possible link between stress, depression, inflammation, development of T2D, BDNF reduction, and dementia.

Patients suffering from depression have high levels of stress which lead them to overeating of foods, such as foods rich in carbohydrates or snacks, acting as self-medication because able to increase serotonin levels [8-10]. These patients are accordingly more prone to develop overweight and obesity, the strongest risk factors for the onset of T2D [11-13]. Indeed, people with depression have a 60% increased risk of developing T2D [14], and 25% of patients with T2D have depression [15], nevertheless, depression in T2D patients is frequently unrecognized and therefore not treated [16-18].

Thus depression, untreated for year, contribute to maintain T2D and both, depression and T2D, 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. Indeed, low BDNF levels are present in dementia patients [19,20] and patients with T2D are approximately two to four times more likely to develop dementia than individuals without T2D. These associations could might explain why T2D,

depression and dementia are often associated in the same patients [21-23]. We are aware that a letter cannot prove these hypotheses but it seemed to be useful reflections to be validated in future studies that the article by Porter & O'Connor [1] has provoked in us.

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