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Childhood trauma and overweight stratify patients with major depressive disorder in 4 separate immuno-metabolic endotypes

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Background: Major Depressive Disorder (MDD) is considered as a very heterogenous disease. Different causal mechanisms have been proposed, including an abnormal state of the inflammatory response system. However, findings have yielded mixed results. Several reports have demonstrated that the present of different factors, such as overweight, may influence the levels of inflammatory parameters in patients. It has been also postulated that the occurrence of atypical features of depression may be more prominent in individuals with MDD with overweight. However, and to the best of our knowledge, the interaction between body mass index (BMI) and other factors, such as childhood trauma with immune/inflammatory changes, and with different symptom profiles, has not been studied, so far. The aim of this study was to investigate the effects of BMI alone, or in combination with childhood trauma (CT) on several immune/inflammatory parameters and on tryptophan breakdown products, and to explore the way these parameters are related to occurrence of specific symptoms of depression.
Methods: We determined, in n=135 patients with MDD and n=200 healthy controls (HC) collected for the EU-MOODINFLAME project: (1) monocyte expression levels of key mitochondrial senescence, pyroptosis, and/or motility/chemotaxis genes by standard q-PCR, (2) serum levels of tryptophan and kynurenine pathway metabolites by LC-MS/MS and/or HPLC, (3) serum levels of pro-inflammatory compounds (e.g., IL-2, hsCRP). We stratified patients with MDD into four groups: (1) no overweight and no CT, (2) non-overweight and CT, (3) overweight and no CT, (4) overweight and CT, and compared the levels of the above-mentioned parameters with the levels found in HC. We then correlated outcomes to the clinical characteristics of patients.
Results: In our study, individuals with MDD (1) with overweight and CT were characterized by a significantly increased expression of pyroptotic genes in their circulating monocytes, by increased levels of pro-inflammatory compounds, and by increased levels of potentially neurotoxic kynurenine pathway metabolites, (2) with overweight and no CT were characterized by increased peripheral levels of pro-inflammatory compounds without monocyte inflammatory gene overexpression. This subgroup showed a significantly decrease in TRP and 5-HIAA serum levels, (3) without overweight and without CT were characterized by an increased expression of mitochondrial senescence genes in their circulating monocytes, but no clear signs of peripheral inflammation (4) without overweight but with a history of CT were characterized by peripheral inflammation, and by an increased expression of mitochondrial senescence genes in their circulating monocytes. The two CT groups were clinically the most severe depressed groups (as assessed by the total IDSC-score), with the highest suicide risk. Overweight patients with CT were characterized by an increased prevalence of body symptoms. Overweight patients without a history of CT were the clinically less severe patients.
Conclusions: Our study shows that MDD is immuno-metabolic heterogeneous. We were able to identify 4 immuno-metabolic subtypes based on a history of CT and overweight. It is likely that these subtypes will react differently to different therapeutic regimens. Stratifying patients with the rostrum of immune and biochemical techniques as described in this report will give opportunities to design personalized therapeutic regimens.
No conflict of interest

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Anti-inflammatory effect of the antidepressant fluvoxamine – a systematic review

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Background: Neuroinflammation corresponds to the immune response of the nervous system to an injury, infection or neurodegenerative disease characterized by the activation of resident glial cells, including microglia and astrocytes, the release of cytokines and chemokines and the activation and migration of leukocytes. Evidence suggests that inflammatory cytokines may be a central factor, affecting multiple neuronal pathways and contributing to the development of depression. Supporting this neuroinflammatory theory, several studies have demonstrated the anti-inflammatory effect of various antidepressant drugs [1]. Fluvoxamine is a selective serotonin uptake inhibitor (SSRIs) used manly in the treatment of depression and anxiety disorders. Recent evidence pointed that a fluvoxamine early treatment on SARS-CoV-2-infected subjets fully prevented COVID-19 symptoms [2]. Thus, it seems relevant to explore the anti-inflammatory mechanism of fluvoxamine.
Objective: The aim of the review was to provide an overview of in vivo studies focused on understanding the anti-inflammatory effect of the SSRI antidepressant fluvoxamine.
Methods: The methodology used to carry out this work focused on a systematic review and summarizes the in vivo anti-inflammatory effects of Fluvoxamine. The Pubmed database was used for the research, with the following search equation: "(Fluvoxamine OR fluvoxamine maleate) AND (inflammatory response OR inflammatory OR inflammation OR anti-inflammatory OR cytokines OR immune response OR interleukine OR interleukines OR IL OR sigma-1 receptor)". Studies were included if the evaluated any anti-inflammatory effect / molecule and addressed fluvoxamine.
Results: Literature evidence suggests that fluvoxamine significantly reduces the production of interleukin (IL)-6, IL-1β, IL-12 and IL-8, induced by lipopolysaccharide (LPS) in human samples. In addition, fluvoxamine was observed to stimulate oligodendrogenase and attenuate inflammation in an animal model of multiple sclerosis. Further evidence for the anti-inflammatory effect of fluvoxamine is based on the fact that depression is mediated by pro-inflammatory cytokines, causing its increase, namely TNF-α, IL-6 and IL-1. Additionally, when compared to other antidepressants, fluvoxamine has beneficial sleep effects in depressed patients, less impact on body weight, good safety profile in patients with cardiovascular diseases and the elderly, and relatively good profile in terms of adverse events. On the other hand, it was also observed a decrease in the expression of cyclooxygenase 2 (COX-2) in macrophage cell lines exposed to fluvoxamine. It has been shown in a small, double-blind, placebo-controlled, randomized study that fluvoxamine can prevent clinical deterioration of patients with mild coronavirus disease 2019 (COVID-19). Fluvoxamine is also an agonist for the sigma-1 receptor, through which it controls inflammation.
Conclusion: In conclusion, the pooled data suggest that fluvoxamine is endowed with anti-inflammatory properties by multiple mechanisms of action. However, physiological, biochemical and pharmacological studies are still scarce. It is important to carry out further studies that explore the anti-inflammatory activity of fluvoxamine mainly inflammatory mediators, such as COX-2, LOX and TNF-α, among others.
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