Biological Aspects of Late-life Depression

Milaneschi, Y.

2012

document version
Publisher's PDF, also known as Version of record

Biological aspects of late-life depression

Depression is a major public health problem worldwide and especially in older persons may result in lethal health consequences, complicating chronic illness and increasing the risk of disability and death. Despite the relevance of depression in terms of public health, its etiology and pathophysiology have not yet been elucidated and treatments available nowadays of depression are far from ideal in terms of efficacy. More recently, advances in basic science and clinical observations highlight the potential role of new molecular mechanisms.

This thesis aimed to explore, from an epidemiological point of view, new biological aspects of late-life depression. We used data from two well-known cohorts of older persons, the InCHIANTI Study from Italy, and the Health ABC Study from the USA. After the theoretical background and research model is presented in **Chapter 1,** Chapters 2 trough 6 report on research outcomes.

In **Chapter 2**, we tested the hypothesis that in older persons higher plasma levels of inflammatory mediators predict the development of clinically relevant depressed mood over time. Among the different inflammatory mediators, we showed that participants with higher serum concentrations of Interleukin-1 receptor antagonist (IL-1ra) had higher depressive symptoms at baseline and had a higher risk of developing depressed mood after 6 years.

The first aim of the study presented in **Chapter 3** was to examine whether depressive symptoms were prospectively associated with increases in levels of inflammatory markers. We indeed found evidence of an association between high depressive symptoms at baseline and an increase of Interleukin-6 (IL-6) levels over six years of follow-up. Moreover, we showed that adherence to a Mediterranean-style diet modified the association between depressive symptoms and IL-6 increase: in participants non-adherent to a Mediterranean-style diet, as compared to those adherent, higher depressive symptoms were associated with a steeper increase of IL-6 levels over time. These findings suggest that a healthy (Mediterranean-style) diet is able to buffer the inflammatory response boosted by depression in older adults.

In **Chapter 4** we evaluated the interplay between depression, inflammation and an important component of the antioxidant system, carotenoids, which are considered a good indicator of fruit and vegetable intake. We found that participants with lower total carotenoid levels had higher depressive symptoms at baseline and were more likely to develop incident depressed mood after six years of follow up. Moreover, plasma carotenoids were inversely associated with inflammatory markers. Among these inflammatory molecules, we found evidence that IL-1ra partially mediated the relationship between carotenoid concentrations and development of depressed mood.

In **Chapter 5**, we reported the first longitudinal study examining the relationship between vitamin D, as measured by serum 25(OH)D, and depressive symptoms over a 6-

year follow-up in a representative group of older adults. Participants with low 25(OH)D serum levels experienced a greater increase in depressive symptoms over the follow-up period. Moreover, among participants free of clinically relevant depressive symptoms at baseline, a higher risk of depressed mood onset was found for those with low serum 25(OH)D. The strength of this prospective association was more distinctive in women than in men.

In **Chapter 6**, we examined whether serum leptin concentrations in older adults were associated with an increased risk of developing clinically relevant depressive symptoms. We found that in older men high serum levels of leptin were associated with an increase in depressive symptoms over a 5-year period. Moreover, the impact of high serum levels on depression onset was especially evident in men with abdominal obesity. Since the presence of hyperleptinemia in obese persons may be considered an indicator of leptin resistance, the latter finding may suggest that leptin resistance may contribute to alterations of affective status.

The thesis ends with a general discussion (**Chapter 7**) of the findings of Chapter 2 through 6. We identified new biological mechanisms related to late-life depression, including inflammation, dietary patterns and dietary antioxidant biomarkers, vitamin D and leptin. Results from this thesis suggest strategies that may be relevant from a public health standpoint. For example, there is a pressing need to investigate strategies to disrupt inflammatory signaling in persons with depression who show indication of a proinflammatory state. Moreover, intervention aimed at improving the quality of diet may be effective in buffering depression through modulation of inflammatory and metabolic pathways. Assessment and normalization of vitamin D levels may become part of the treatment of older depressed patients who are at risk of hypovitaminosis.

Taken together, the results presented in this thesis significantly contribute to the re-appraisal of the biological underpinnings of late-life depression, to identify new risk factors that may become target for interventions aimed at reducing depressive mood in the elderly and to prevent its deleterious consequences on morbidity and mortality.