Combined obesity and psychosocial stress is a worldwide health problem and a paracrine disorder

Commentary

Society is confronted with two major health problems: obesity and psychosocial stress. Obesity is reaching pandemic proportions worldwide and has destructive effects on global health [1]. Psychosocial stress also has an increased impact on modern society, aggravated by the growing interference of social media and the need to maintain the social-self. Psychosocial stress and obesity co-exist in many individuals [2], but it remains unclear how the combination of both impacts the physiology of different organs. More specifically, it is unclear how psychosocial stress affects cardiac and hippocampal function in obese subjects.

Different animal models have been developed to study the adverse synergy of obesity and psychosocial stress on overall health. However, most studies focus on the central nervous system (CNS) [3] or lipid metabolism [4] and only one study evaluated how the association between chronic stress and a high-fat diet affects the autonomic control of heart rate [5]. The study by Agrimi and co-workers published in this issue of *EBioMedicine* is the first to study the effects of the combination of obesity and psychosocial stress on cardiac function, on the communication between brain and heart, and on the brain-derived neurotrophic factor (BDNF)/tyrosine kinase receptor B (TrkB) pathway [6]. The paracrine factor BDNF and its associated receptor – tyrosine kinase receptor B (TrkB) – are essential for optimal brain health and neuroplasticity, and are required for normal myocardial function. Both obesity and psychosocial stress are known to decrease BDNF and TrkB bioavailability [7]. But it was undetermined whether changes in local BDNF are involved in cardiac pathophysiology and behavioural abnormalities.

In the current study, obesity was induced by feeding adult C57BL/6 and TrkB null mice with a high-fat diet for 18 weeks. Psychosocial stress was triggered by the resident-intruder paradigm; mice under investigation were placed as an intruder in the cage of resident mice that consider the cage as their territory and consistently respond by attacking the intruder. Cardiac performance was evaluated by cardiac ultrasound and invasive haemodynamic measurements, and behaviour tests of anxiety-like behaviour and spatial memory were performed in an elevated plus maze and a Y-maze. The animals were randomly assigned to control, high-fat diet, psychosocial stress, and high-fat diet + psychosocial stress [6]. This approach allowed the researchers to determine whether there is a synergistic effect of psychosocial stress with pre-existing obesity on myocardial and/or vascular performance and to unravel the underlying mechanism, which are the main novelties of this paper. Another elegant feature of the present study is that the authors made a detailed study of both function and morphology of the heart and the brain.

Obese C57Bl/6 J mice exposed to psychosocial stress showed a decline in cardiac performance and increased cardiomyocyte apoptosis, cardiac fibrosis, and vascular remodelling. The cardiac phenotype shows primarily systolic dysfunction with a dilated heart. Moreover, they observed a clear reduction in both BDNF and TrkB expression in the LV, indicating that downregulation of the BDNF/TrkB pathway might be involved in the pathogenesis. Consistent with this hypothesis, deletion of cardiac TrkB in mice mimics the pathophysiology of the combination of obesity and psychosocial stress. Similar observations were seen in the CNS:
combination of obesity and psychosocial stress in C57Bl/6J mice resulted in drastic changes in behaviour; hippocampal morphology was altered, and BDNF and TrkB expression levels were reduced.

Although data from the present study indicate that the BDNF/TrkB pathway plays a previously unknown role in the pathophysiology of obesity- and psychosocial stress-induced cardiac and neural dysfunction, many unanswered questions remain. For instance, the present study lacks data about circulating BDNF levels. Previous research shows that measures of blood and plasma BDNF levels reflect brain-tissue BDNF in rat and pig, but this positive correlation was not confirmed in murine samples [8], an issue requiring further in depth research. It is also unclear which cardiac cell types – endothelial cells, cardiomyocytes, fibroblasts – are involved in the BDNF/TrkB pathway; eg, what cell type is the main source of BDNF? Furthermore, it is unlikely that the BDNF/TrkB pathway is the only or even the most important pathway in tissue dysfunction induced by obesity and psychosocial stress, thus it would be of interest to perform an unbiased transcriptomics or proteomics approach to unravel underlying pathways in this clinically-relevant model.

An open question remains whether pharmacological administration of BDNF can compensate for the negative effects of obesity...
and psychosocial stress. The therapeutic potential of BDNF in obesity, psychosocial stress, or a combination of both should be addressed in future studies. However, this therapeutic potential could be hampered by the fact that the authors also observed a down-regulation of the TrkB receptor. On the other hand, the cardioprotective properties of BDNF have been demonstrated before in multiple studies. Another open question is whether exercise training could overcome the observed phenotype in obesity and psychosocial stress, as it has been shown that exercise increases BDNF levels [9].

In the last couple years, BDNF has emerged as an important paracrine factor, not only in the nervous system, but also in the heart. Paracrine signalling between different cell types – endothelial cells, cardiomyocytes, vascular smooth muscle cells, neurons, and astrocytes – is crucial for normal functioning of the heart and neural system [10]. The study of Agrimi and co-workers contributes to our understanding of paracrine signalling in different tissues by identifying the BDNF/TrkB as a player in the pathogenesis of cardiac and neural dysfunction in obesity combined with psychosocial stress. The BDNF/TrkB pathway could represent a potential therapeutic pathway for treatment of obesity- and psychosocial stress-induced organ dysfunction.

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