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Review

Stress habituation, body shape and cardiovascular mortality

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This article is dedicated to the memory of Per Björntorp (1931–2003).

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ABSTRACT

High cardiovascular mortality is well documented in lean phenotypes exhibiting visceral fat accumulation. In contrast, corpulent phenotypes with predominantly subcutaneous fat accumulation display a surprisingly low mortality. The term 'obesity paradox' reflects the difficulty in understanding the biological mechanisms underlying these clinical observations. The allostatic load model of chronic stress focuses on glucocorticoid dysregulation as part of a 'network of allostasis' involving autonomic, endocrine, metabolic, and immune mediators. Here, we expand upon the energetic demands of the brain and show that 'habituators' and 'non-habituators' develop divergent patterns of fat distribution. Central to this process is the recurrent rise in the cerebral energy need (arousal) that non-habituators experience during chronic stress. These neuroenergetic alterations promote visceral fat accumulation, subcutaneous fat loss, and atherogenesis with subsequent cardiovascular events. Habituators are more or less protected against such cardiovascular complications, but there is a metabolic trade-off that we shall discuss in the present paper.

Contents

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1. Introduction

Ten years ago, the American nephrologist Kamyar Kalantar-Zadeh called attention to a series of surprising observations (Kalantar-Zadeh and Kopple, 2006). In patients with chronic kidney disease undergoing maintenance hemodialysis a high body mass was incrementally associated with better survival (Kalantar-Zadeh et al., 2005; Kopple et al., 1999). These counterintuitive findings prompted a long-lasting debate labeled the 'obesity paradox'. In line with these reports, better survival rates have also been documented in obese patients who had suffered from stroke, intracerebral hemorrhage, myocardial infarction, heart failure, sepsis or type-2-diabetes when they were compared with those of lean patients with the same disease (Garrouste-Orgeas et al., 2004; Buettner et al., 2007; Hallin et al., 2007; Fitzgibbons et al., 2009; Kim et al., 2011; Vemmos et al., 2011; Carnethon et al., 2012). Noteworthy, the earlier studies did make use of one anthropometric measure only: the body mass index (BMI).

In the 1980s, the Swedish endocrinologist Per Björntorp emphasized the role of visceral fat (Björntorp, 2001). First, he found that visceral fat mass was associated with hypercortisolemic states (Rebuffe-Scrive et al., 1988). Björntorp liked to recount his problems in publishing data that clearly demonstrated that women displaying visceral fat accumulation were more likely to carry psychosocial burdens. They were more often unemployed, had gone through a divorce, had spent time in prison, or had financial problems. For Björntorp this was a clinical and socioeconomic way to describe stress eventually leading to the accumulation of visceral fat. Initially nobody was willing to publish these data, because they seemed too unlikely. However, Per Björntorp systematically built up a plausible sequence proposing that chronic stress, affecting the hypothalamus–pituitary–adrenal (HPA) axis, would eventually lead to visceral fat accumulation. Second, Björntorp was among the first investigators who reported that visceral fat accumulation was associated with a high cardiovascular mortality risk (Larsson et al., 1984).

Per Björntorp's findings add an important aspect to the 'obesity paradox' debate. The earlier studies – lacking data on visceral fat – showed the often-mentioned U-shaped BMI-mortality curves (Whitlock et al., 2009). In contrast, recent epidemiological studies made combined use of two anthropometric measures: waist circumference (as an estimate of visceral fat) and the BMI (as an estimate of subcutaneous fat). By using mutual statistical adjustment for both of these measures, several large population-based cohort studies from the United States, the United Kingdom, Denmark, Norway, and Mauritius could show a more differentiated picture (Cameron et al., 2012; Berentzen et al., 2010; Petursson et al., 2011; Krakauer and Krakauer, 2012, 2014): First, they showed no U-shaped mortality curves. Second, each of these studies confirmed what Björntorp had described as the risk effects of waist circumference on mortality, and also what Kalantar-Zadeh had reported as the protective effects of high BMI on mortality. In line with these findings, the Whitehall Study and the Aerobics Center Longitudinal Study (ACLS) provided evidence that lean subjects who displayed high waist circumference (or another metabolic abnormality) had the highest mortality risk, while subjects with a high body mass who lacked high waist circumference (or other metabolic abnormalities) had the lowest mortality risk (Hamer and Stamatakis, 2012; Ortega et al., 2013). In all, there is mounting evidence that waist circumference and BMI indicate divergent mortality risks.

Unfortunately, the obesity-paradox debate refers almost exclusively to correlational studies, and the only existing randomized controlled trail in the field does not even support a direct causal relationship between body mass and mortality (Look AHEAD Research Group, 2013). Nevertheless, the opponents in this debate do more and more agree upon 'body shape' as being essential for assessing the cardiovascular mortality risk in general populations: Visceral fat appears to identify the high risk phenotype, while subcutaneous fat doesn't. Although the clinical picture has become much clearer today (Peters and McEwen, 2012), it remains still poorly understood what biological mechanisms underlie the 'obesity paradox' phenomenon. Here we look at its pathophysiology from a neuroendocrine and neuroenergetic perspective and bring together concepts and lines of investigation that highlight the role of toxic stress and the inability to handle daily stressors as fundamental determinants.

2. Allostatic load

In the 21st century, a number of randomized controlled trials concerning chronic stress provided causal evidence for Björntorp's originals ideas. First, chronic psychosocial stress has been shown to increase visceral fat mass in non-human primates (Kaufman et al., 2007). Second, cognitive-behavioral and resource-activating stress management programs have been shown to reduce cortisol stress responses during a standardized psychosocial challenge (Storch et al., 2007; Hammerfald et al., 2006; Gaab et al., 2003). 'Stress reduction' programs in turn have been shown to improve cardiovascular survival (Orth-Gomer et al., 2009; Gullikkson et al., 2011). In detail, two large-scale trials from Sweden have studied patients who had suffered from their first myocardial infarction. The stress reduction program consisted of five key components with specific goals – education, self-monitoring, skills training, cognitive restructuring and spiritual development – and was focused on stress management, coping with stress, and reducing experience of daily stress, time urgency, and hostility. Both studies showed that those in the intervention group had a lower rate of second or third myocardial infarction and a lower rate of cardiovascular mortality as compared to the control group. Thus, chronic psychosocial stress – as Björntorp has predicted – can cause both visceral fat accumulation and cardiovascular death.

Here we refer to the conceptual frameworks of 'allostasis and allostatic load' (McEwen and Stellar, 1993) and the 'Selfish Brain' theory (Peters et al., 2004) to address the question how genetic endowments and life experience interact to differentially affect visceral fat, subcutaneous fat, and mortality. According to the concept of 'allostasis', allostatic regulation occurs when a subject is exposed to a changing environment and engages in behaviors and physiological responses that promote adaptation and increased chances for survival, at least in the short run. As part of allostatic regulation the brain is supplied with extra energy, which in turn can be used to cover the increased brain energy needs arising from enhanced cerebral functioning (e.g. increased vigilance, updating the probability distributions of expected outcomes). Yet, the metabolic and regulatory events occurring during an acute challenge differ from those occurring under chronic inhospitable conditions. According to the concept of 'allostatic load' the mediators of neuroendocrine,