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Review

So as we worry we weigh: Visible burrow system stress and visceral adiposity

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HIGHLIGHTS

- Stress induces redistribution of adipose tissue stores, yet exact mechanisms remain unknown.
- Subordinate rats in the visible burrow system gain visceral adipose tissue mass while decreasing subcutaneous stores.
- This review summarizes stress-induced responses within the visceral and subcutaneous depot that promote central adiposity.

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ABSTRACT

The visible borrow system (VBS) simulates a natural rodent habitat that supports genuine stress provoking social interactions. This model allows investigation of behavioral, neural and endocrine alterations caused by chronic stress. The Sakai lab further used this model to investigate metabolic outcomes of stress in relation to dominance hierarchies formed within the VBS. Communal social conflict occurs among all VBS rats, but only the SUB rats succumb to the redistribution of lipids in the visceral cavity and consequent metabolic dysregulation, such as hyperinsulinemia. These increases in visceral adipose tissue occur after two cycles of VBS stress and recovery bouts and are associated with decreases in subcutaneous adipose tissue. Traditionally, distribution shift in lipid deposition is predominately thought to occur by characteristics specific to the visceral depot, but evidence supports that decreased subcutaneous adipose tissue deposition may be linked to enhanced visceral adipose expansion. This review will discuss VBS stress and redirection of adipose tissue in SUB rats. There will be specific focus on the enhanced adipogenic capacity of visceral adipose tissue as driven by glucocorticoid receptor density, 11-hydroxysteroid dehydrogenase type 1 (11-HSD1) and lipoprotein lipase (LPL). Additionally, the proposed contribution of decreased subcutaneous adipose expansion via stress-induced inhibition of lipid uptake, storage and cellularity will be discussed. Overall, this review will summarize how stress-induced visceral obesity may result from a combination of maladaptive responses within the visceral and subcutaneous depot.

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1. Introduction

My first interaction with Randall Sakai occurred when I was a graduate student attending a scientific meeting. I observed, from far, his prominent personality and contagious laughter. He knew how to work a crowd and was often the center of many scientific socials. I recall being intimidated by his status, popularity and wit. I knew, however, that I wanted to work with him because he was fun, smart and the most eclectic and quirky senior scientist I had ever encountered. In retrospect, he was an approachable person who was lighthearted with a touch of "bust your chops" antagonism - this I found hilarious. Randall never knew a stranger, he took well to most people he interacted with and was overwhelmingly kind and generous to those he considered close friends. I began to know Randall better when I got the opportunity to join his and Steve Wood's lab in 2007 after completing a two-year post-doc with Mary Dallman. Randall was just as affable in the workplace as he was at social engagements, yet he had an inherent talent for giving engaging scientific talks, assessing experimental design and personal encouragement. He was truly connected to his mentees and ultimately wanted to see all of us succeed. One of the most common phrases I have heard from Randall to me and many others was, "Are you afraid of success?". To me, in the context in which he would use it, I interpreted his messages as, "you will never know unless you try and the sooner you try the better". This statement still resonates with me today.

My move to the University of Cincinnati was influenced by many factors but central was Randall's personality and laboratory interests. Our interests overlapped in the area of stress, food intake and adiposity and the Sakai lab was well positioned to investigate the intersection of these things with the visible burrow system (VBS). Using the VBS I planned to gain new insights and expand my research training in factors that influence detrimental adipose tissue expansion. A specific goal was to learn more about this model of social physiological stress as it pertained to increases in visceral adipose tissue expansion. Below I will review the Sakai's laboratory findings that excited my interest as an adipose tissue researcher and extrapolate mechanisms responsible for adiposity changes following VBS exposure.

2. Stress, food intake and body mass

The number of overweight and obese individuals has reached considerable proportions. The National Center for Health Statistics reported in 2014 that ~70% of adults in the United States were overweight, and half of those individuals where further characterized as obese [1,2]. Excessive adiposity/obesity is considered a precursor for a number of chronic diseases including, but not limited to, type-2-diabetes, cardiovascular disease, insulin resistance and dyslipidemia (for review see: [3–5]). The fundamental drivers of obesity are physical inactivity and increased intake of foods high in sugar and/or fat. Psychosocial stress, however, also contributes to the rising incidence obesity rates. Epidemiological studies suggest psychosocial stressors such as job-related demands, financial challenges and family relations are associated with weight gain in both men and women [2,6]. Studies further demonstrate stress induced weight gain is more prevalent in women than men [7] and can be prompted early in childhood [8].

Many laboratory models have been established to investigate the metabolic outcomes of psychosocial stress. The overall objective is to elucidate how stress-induced increases in body and adipose mass and consequent comorbidity occurrence (i.e. type II diabetes, high blood pressure, heart disease, some cancers, and compromised immune responses) may transpire [9,10]. However, rodent models do not always best translate to human related stress. A predominate number of humans respond to day-to-day stress by increasing their food intake [11,12] whereas most rodents tend to decrease their food intake to most stressors. Most rat and mice models decrease food intake and subsequently body weight in response to swim stress, restraint [13], handling, immobilization [14], foot shock or social stress [15]. In humans comparable decreases in food intake and body weight typically only occur in response to an exceedingly traumatic environmental stressor [16].

There are, however, rodent models of social stress that induce increases in food intake and body mass. When housed in groups, both Syrian and Siberian hamsters gain body and adipose mass [9,17–19]. This body mass increase can be experimentally recapitulated with a social stress interaction model known as the resident-intruder model. In Syrian hamsters weight gain induced in the resident-intruder model predominately occurs in the intruder which is the smaller subordinate [20]. Similar changes are also demonstrated to occur when Swiss mice are exposed to the resident-intruder paradigm [21]. Last, C57BL/6 mice increase food intake and body mass when subjected to chronic psychosocial stress such as social defect, overcrowding [15,22] or isolation [23]. Overall, differential metabolic outcomes of psychosocial stressors can be attributed to animal strain and/or stressor type, intensity or length.

3. Visible burrow system and adiposity redistribution

The visible burrow system (VBS), much like the previously mentioned forms of social stress, was developed to investigate how psychosocial stress contributes to the susceptibility of metabolic pathology. Unlike other forms of stress, this apparatus was designed to simulate, in the laboratory, the underground multi-chambered burrows that rodents (rats) live in. Unlike other forms of social stress, this system requires minimal interruption from laboratory investigators and creates a more ethologically appropriate environment of genuine social interaction [24]. With the inclusion of female rats a social hierarchy naturally forms among the males within a few days of VBS exposure [24]. Traditionally, VBS experiments categorize male rodents into two groups, subordinate (SUB) and dominant (DOM) [24–26]. Rats are confirmed to be SUB by behavioral, physiological, and neuroendocrine measures [24–26]. Observed behavior of SUBs in the VBS include decreased aggression, increased avoidance of threat area, decreased activity, immobility, sheltering, and low back postures. Wounds on SUB animals are typically located on the back and tail areas from bites received while retreating. DOM behavioral response include, but are not limited to, pursuing and instigation of fighting with chases, nips that advance to bites, kicking and pushing. DOMs tend to have conflict wounds located on their face. The psychosocial stress that occurs while in the VBS causes both DOM and SUB rats to lose weight, however this decrease, resulting from a decrease in both lean and fat mass, is far more extensive in SUB animals [24,26–28].

Psychosocial stress-induced weight loss that occurs in rats within the VBS opposes the characteristic human response to day to day stress of increases in body mass. Adiposity increases in rats that recapitulate the human stress response occur following secession of VBS social conflict when animals are returned to seclusion. Here SUB rats enter a period of amplified metabolic activity characterized by increased food intake and adiposity [28]. Two bouts of VBS social stress result in alterations of adipose tissue distribution in SUB rats. Partitions of adipose tissue distribution are commonly separated into two general groups. First there is the abdominal, which contains the visceral and intra-abdominal adipose depot compartments. Second is subcutaneous adipose tissue depots which represents the higher percent of total adiposity. When compared with control (CON) or DOM rats, SUBs have a redistribution of lipid stores from the subcutaneous to the visceral depot [28]. Therefore, lipid storage gets redirected from the subcutaneous area between muscle and hypodermis to the visceral depot in the intra-abdominal cavity where it accumulates among various organs like the liver. This is similar to stress-induced redistribution of adipose tissue in humans.

4. Stress and visceral adiposity

The relation between stress and abdominal adipose distribution is well characterized in humans. Björntorp was among the first to

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