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A role for leptin-regulated neurocircuitry in subordination stress☆

Jonathan N. Flak *

Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

HIGHLIGHTS

- VBS produces distinct physiological and behavioral dysfunction primarily in subordinates.
- Leptin is dysregulated both during and post-vbs primarily in subordinates.
- Leptin-regulated neurocircuits control physiological and behavioral function dysregulated in individuals that experience the VBS.
- Leptin-regulated neurocircuts could be sites to better understand the consequences of social subordination.

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ABSTRACT

The visible burrow system produces a distinct combination of psychological and metabolic stress on, primarily, subordinate individuals that results in pronounced physiologic and behavioral dysfunction. However, the mechanisms underlying the consequences of chronic subordination stress are largely unknown. The simplest mechanistic explanation is that adaptations within brain systems with overlapping functions of both psychological and metabolic control provide immediate benefits that result in lasting susceptibility to diseases, disorders, and increased mortality rates in subordinates. Circuits regulated by leptin adapt to fluctuating levels of energy storage, such that the loss of leptin action within leptin-regulated neurocircuitry results in dysfunction in physiologic and behavioral systems implicated in the consequences of chronic social subordination. Thus, leptin-regulated neurocircuitry may provide a window into understanding the consequences of social subordination stress. This review examines the neural systems of leptin physiology implicated in social subordination stress: energy balance, motivation, HPA axis, and glycemic control.

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1. Introduction

I first met Randall Sakai, while interviewing in the neuroscience graduate program at the University of Cincinnati. Having already interviewed at several institutions, I was familiar with uncomfortable and awkward interactions with faculty members; some test your

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* Department of Internal Medicine, University of Michigan, 1000 Wall Street, 6442 Brehm Tower, Ann Arbor, MI 48105, USA.
E-mail address: jflak@med.umich.edu.

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knowledge and know-how and others boast about their research interests and accomplishments. However, the interview with Randall was *different*. As was his style, he nonchalantly brought up completely random topics with little to no relevance to the interview in rapid succession. Then, he asked me about the investigators that I had interviewed with at other institutions and responded that they all weren't good fits. He even wanted to call some of them on the spot and talk to them about me. I declined, thinking he was joking around, but he may not have been; Randall often phoned anyone at any time for any reason at the drop of a hat. He didn't possess the same kind of boundaries that many have, which made him such a magnetic person and so skilled at connecting others throughout the scientific community.

I feel extremely honored to be considered a member of "Team Sakai," although I wasn't an official trainee of Randall. I learned a great deal from Randall and the rest of the Sakai lab, and I am forever grateful for all of the memorable experiences. Most notably in my mind, he regularly invited me to his lab parties, a critical period of development in my graduate career; these parties were a site of intense discussion about science, success in academia, and rigorous scientific examination. He regularly invited faculty and visiting scientists, which were great opportunities to connect with the scientific community. These experiences were opportunities for development both socially and scientifically, and he made these efforts even though he would not get any professional credit for my potential success. And I am not unique with having this reception. Randall was extremely gracious with his time, resources, and connections for many scientists, both aspiring and established alike. He worked hard to promote and provide opportunities to scientists of all levels, including graduate students, post docs, and young investigators that weren't even in his lab; he believed that this was the most important part of his job and I, as well as many others, am very grateful for it.

2. The visible burrow system

The interview weekend in Cincinnati featured a royal introduction to the visible burrow system (VBS). VBS demonstrations were a regular part of meeting with Randall because he was very proud of the system that he set up and, of course, the work that came from the VBS.

The VBS was originally developed in the 1980′s by Robert and Caroline Blanchard at the University of Hawaii to study rodent behavior in a more naturalistic environment compared to common laboratory rat cages [1]. By connecting clear plexiglas tubes to open, opaque chambers, the Blanchard lab was able to simulate the underground burrows that wild rats live in and observe animal behavior throughout the day. Cameras were later installed for the continuous recorded observation of animal behavior. For a typical VBS experiment, the experimenter introduced 4 male and 2 female rats to the VBS; a dominance male hierarchy formed within the first few days (1 dominant and 3 subordinate male rats). Dominants displayed offensive or aggressive behaviors, while subordinate males displayed defensive or submissive behaviors. Due to the extreme stress while in the VBS, all rats displayed hallmarks of chronic stress, but 7/12 subordinates died within four months that lead to shortened future experimental runs of the VBS [2].

While a postdoctoral fellow with Bruce McEwen at Rockefeller University, Randall initiated collaboration with the Blanchard lab that continued for many years to study the neural and physiologic consequences of sustained chronic and unpredictable stress using the VBS. They discovered that subordinates exhibit elevated glucocorticoid levels that persist hours following removal from the VBS and diminished hypothalamo pituitary adrenal axis (HPA) responses to novel stress [3–5], which together indicate significant dysfunction in stress responding. These changes in HPA axis regulation were associated with dysfunctions within stress-related brain systems: lower type I and type II glucocorticoid receptors in the hippocampus, lower corticotropin releasing hormone (CRH) mRNA per cell in the paraventricular nucleus of the hypothalamus (PVH) and central nucleus of the amygdala, and remodeling of hippocampal apical dendrites [5–7].

Later on at the University of Cincinnati, Randall used the VBS to study the effect of social subordination on metabolic disorders. Chronic subordination stress elevated circulating glucocorticoid and decreased testosterone levels [3–5,8–10]; Randall thought that this combination of endocrine disruptions would predispose subordinates to the metabolic syndrome during the recovery period from the VBS. During VBS exposure, subordinates rapidly lost approximately 15% of their body weight that endured throughout periods in the VBS [3,4,10]. Dominants also lost a smaller but still significant amount of body weight, especially compared to unstressed control rats that typically gain weight [3,4,10]. Despite the common loss in body weight between dominants and subordinates, subordinates lost both adipose and lean tissues, while dominants only lost adipose tissue [9]. On closer inspection, the subordinates exhibited a higher percentage of visceral fat than dominants during recovery from the VBS [10], suggesting that subordinates may be more susceptible to diabetes, obesity, and cardiovascular disease due to the proportion and location of the preserved mass. Similar to changes in body composition, leptin and insulin levels dropped in subordinates, and this reduction was less dramatic in the dominants [9]. In parallel with endocrine and body weight changes following VBS exposure, both dominants and subordinates reduced food intake following introduction to the VBS, coincident with the changes in body weight [11,12]; however, dominants quickly recovered basal food intake levels, but subordinates reduced the number and size of meals throughout VBS exposure [12]. Together, these results indicate that the VBS inflicts constant energy deficiency that may be the cause of the significant repercussions throughout metabolic systems post-VBS.

In order to re-establish energy homeostasis after being in chronic negative energy balance while in the VBS, subordinates displayed excessive hyperphagia once singly housed and removed from stress during recovery from the VBS [10]. However, dominants and subordinates didn't recover body weight in the same way. Subordinates only gained adiposity, whereas dominants regained both lean and adipose tissue [10]. In addition to increased proportion of adipose tissue, subordinates developed hyperinsulinemia and hyperleptinemia [10], mirroring development of the metabolic syndrome in humans and supporting the original hypothesis. Since weight-matched and food-matched controls do not display increased proportion of adipose deposition and endocrine disruption [7], metabolic effects were not merely due to weight cycling, but were in fact due to unique factors to the experience of chronic subordination stress.

Thus, the VBS produces a distinct combination of psychological and metabolic stress on, primarily, subordinates that predisposes the individual to the metabolic syndrome. In addition to the potentially deleterious effects of chronic subordination stress, these adaptations may also prepare the individual for future periods of extreme psychological and metabolic stress, such as VBS exposure. For example, supplemental adipose tissue can be more easily utilized for energy during emergency situations (e.g. exercise, fight or flight) than lean tissue. VBS-exposed, especially subordinates, are commonly unable to obtain food, are injured, or escaping danger that necessitate energy from stores. The simplest mechanistic explanation is that chronic subordination stress initiates adaptations within brain systems that control both psychological and metabolic function, and that these short term benefits result in lingering susceptibility to disease and disorder. It is well established that the activity of leptin-regulated circuits shifts according to energy storage levels, which rapidly change during periods of prolonged subordination stress. Additionally, brain regions that contain leptin-responsive neurons adapt to chronic periods of stress [13–15] and can control responses to stress [16–18]. In further support of this connection, the Sakai lab previously reported that subordinates exhibited lower levels of leptin post-VBS and hyperleptinemia following recovery [10] that potentially dysregulate the circuitry by which leptin acts on both immediately during and post-VBS. This review will examine the function and organization of leptin-regulated neurocircuits that pertain to the plethora of effects of subordination stress on food intake,

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