Stress and glucocorticoid modulation of feeding and metabolism

G. Balsevich[a,*], A. Abizaid[b], A. Chen[c], I.N. Karatsoreos[d], M.V. Schmidt[c]

[a] Hotchkiss Brain Institute, University of Calgary, 3330 Hospital Dr NW, Calgary, AB, T2N 4N1, Canada
[b] Institute of Neuroscience, Carleton University, 1125 Colonel By Drive, Ottawa, ON, K1S 5B6, Canada
[c] Department of Stress Neurobiology and Neurogenetics, Max Planck Institute of Psychiatry, Kraepelinstrasse 2 – 10, Munich, 80804, Germany
[d] Department of Integrative Physiology and Neuroscience, Washington State University, 1815 Ferdinand's Lane, Pullman, WA, 99164, United States

A B S T R A C T

This perspective highlights research presented as part of the symposium entitled, "Stress and Glucocorticoid Modulation of Feeding and Metabolism" at the 2018 Neurobiology of Stress Workshop held in Banff, AB, Canada. The symposium comprised five researchers at different career stages who each study different aspects of the interaction between the stress response and metabolic control. Their collective results reveal the complexity of this relationship in terms of behavioural and physiological outcomes. Their work emphasizes the need to consider the level of interaction (cellular, tissue, systems) as well as the timing and context in which the interaction is studied. Rather than a comprehensive review on the work presented at the Symposium, here we discuss recurring themes that emerged at the biennial workshop, which address new avenues of research that will drive the field forward.

1. Introduction

Energy homeostasis encompasses both energy intake and energy expenditure. Energy expenditure is further divided into basal thermogenesis, physical activity-related thermogenesis, and adaptive thermogenesis. While basal thermogenesis (referring to the energy required for core body functions) is relatively fixed, adaptive thermogenesis (referring to heat production in response to cold (non-shivering thermogenesis) and food intake (diet-induced thermogenesis) is highly variable. Interestingly, stress is able to affect both energy expenditure and energy intake. The net effects of stress can either lead to body weight gain or body weight loss. In fact, a prominent hypothesis suggests that stress either causes weight gain or loss depending on whether stress promotes hyperphagia and adaptive thermogenesis or rather hypophagia (Razzoli and Bartolomucci, 2016). The complexity of this interaction relates to the multitude of stress and metabolic signals that reciprocally regulate the stress response and energy balance in a regional-, temporal, and functional-dependent manner.

Acute and chronic stress exposure elicit physiological and behavioural responses that significantly modify energy balance. Both neural and neuroendocrine systems are recruited in order to maintain and reinstate homeostasis following stress exposure (reviewed in Ulrich-Lai and Herman (2009)). For example, in response to a stressor (defined as any perceived challenge or threat to homeostasis), the sympatho adrenomedullary axis represents the immediate 'fight or flight' response, leading to the release of catecholamines and the subsequent mobilization of energy stores among other physiological changes.

Reflex parasympathetic activation generally opposes sympathetic actions to terminate the short-lived neural response. Activation of the hypothalamic-pituitary-adrenal (HPA) axis, represents the neuroendocrine arm of the stress response, leading to the release of glucocorticoids. Glucocorticoids in turn are powerful regulators of whole body energy and glucose metabolism. Glucocorticoids signal through the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), members of the superfamily of nuclear receptors. Not only do glucocorticoids mediate negative feedback on the HPA axis, but they also mobilize glucose to fuel the energy demands of the stress response and furthermore promote energy storage, feeding, and weight gain. The effects of glucocorticoids on energy balance are exemplified in Cushing's syndrome, a pathophysiological state defined by hypercortisolemia, in which central obesity is one of the classic features (Lacroix et al., 2015). Nevertheless, many pathways, in addition to the autonomic nervous system and the HPA axis, connect stress and metabolic regulation. Notably, the gastric peptide ghrelin, a well-known orexigenic signal that acts within the hypothalamus to stimulate food intake, is released in response to acute stress and is elevated in response to chronic stress (Lutter et al., 2008; Asakawa et al., 2001; Kristensson et al., 2006). In fact, it has been shown that ghrelin and its receptor, growth hormone secretagogue receptor (GHSR), are required for chronic social stress-induced body weight gain and feeding responses in mice (Patterson et al., 2013a). Moreover, ghrelin has been shown to suppress anxiety-like and depressive-like behaviours in mice (Lutter et al., 2008).

Over the past few decades, a myriad of additional hormone, peptide,

lipid, and neurotransmitter signals that lie at the interface between stress and metabolic regulation have been identified (for an extensive review, refer to (Ulrich-Lai and Ryan, 2014)). Nevertheless, there are still many gaps remaining regarding their mechanism of action and their own regulation. Furthermore, individual differences in susceptibility to stress-induced metabolic outcomes are at best, poorly understood. In this Symposium, five researchers presented their research findings, shedding light on such ambiguities linking stress, metabolic regulation, weight gain, and eating disorders. Although their work comprised distinct models and approaches, their collective findings revealed important similarities and differences in the biology of stress regulation and energy metabolism, which depend on both genetic and environmental factors. In the following sections, we discuss recurring themes that emerged at the Symposium, which highlight the current state of the field and address new avenues of research that the authors believe will advance the field.

1.1. Location, location, location

The stress response is a coordinated physiological response to threatening stimuli involving nearly every organ system and tissue. Likewise, energy homeostasis requires the cooperation of peripheral and central mechanisms. Therefore, when we study the global effects of stress on metabolic regulation we are examining the collective regulation at multiple tissue levels across multiple functional domains. The role of different stress/metabolic signals at various tissue levels, across distinct brain regions, and at a cellular level is only now being systematically investigated. For example, the GR is expressed across nearly all tissue types, which allow glucocorticoids to regulate broad physiological functions, including development, metabolism, and the immune response. Research has shown that in adipose tissue, GRs regulate lipolysis and adipogenesis (Seckl et al., 2004). Moreover, adipocyte-specific GR deletion increases HPA axis activity, stress reactivity and protects against diet-induced obesity (de Kloet et al., 2015), exemplifying a fat-to-brain regulatory network that not only affects metabolic parameters, but also the stress response.

In this Symposium, Mathias Schmidt presented data demonstrating that a regulator of the GR, FK506 binding protein 51 (FKBP51), likewise plays an important role in both whole body energy metabolism and the stress response. FKBP51 is an important negative regulator of the GR, and consequently the stress response (Ratajczak et al., 2015). Global knockout mice present improved stress-coping behaviours and are also resistant to diet-induced obesity (Hartmann et al., 2012; Touma et al., 2011; Balsevich et al., 2017). However, most recently tissue/region-specific roles of FKBP51 have been identified in the fat, muscle, and amygdala where FKBP51 is involved in adaptive thermogenesis (Stechschulte et al., 2016), glucose homeostasis (Balsevich et al., 2017), and anxiety-related behaviours (Hartmann et al., 2015), respectively. It is intriguing that FKBP51 was found not only to interact with the GR-HSP90 complex, but also with various other intracellular proteins in a tissue-specific manner. For example, the interaction of FKBP51 with Akt2-AS160 in muscle is essential for its function in modulating insulin signaling and glucose homeostasis (14). Therefore, FKBP51 is one example where the cellular context dictates the signaling mechanisms involved and ultimately the functional output. Through these versatile actions, interventions targeting FKBP51 at specific tissues holds promise for diverse stress-related disorders (Gaali et al., 2015; Schmidt et al., 2012). In the future, it will be important to study the role of various stress-related molecules and signaling mechanisms at the individual tissue level in order to improve our understanding of disease mechanisms and to potentially pave the way for tissue-specific interventional strategies with fewer side effects.

1.2. Vulnerability is in the genes

Although many individuals experience stressful life events, only a

fraction of individuals develop stress-induced metabolic disorders, such as obesity and type II diabetes. In fact, when confronted with stress, some individuals gain weight, whereas others lose weight (Kivimaki et al., 2006; Dallman, 2010). It is believed that an individual's response to stress is moderated by genetic variants and the specific environmental context. Genome wide association studies and candidate gene approaches have identified genetic susceptibility chromosomal loci for both stress-related psychiatric disorders and metabolic diseases. However, few studies have looked at genetic variants at the interface between stress and metabolic regulation. Identifying genetic polymorphisms that predispose individuals to stress-induced weight gain or weight loss will not only help our understanding of the disease mechanism, but will also potentially lead to personalized medicine.

Given the important roles of the glucocorticoid and the ghrelin signaling pathways in the regulation of the stress response and energy metabolism, it is not surprising that genetic variants within each pathway have been associated with obesity, stress-related mental disorders, or both (Gueorguiev and Korbonits, 2013; van Rossum and Lamberts, 2004; Derijk and de Kloet, 2008). Interestingly, both pathways are known to interact with the endocannabinoid system in order to exert their many effects (Schroeder et al., 2018; Edwards and Abizaid, 2016). For example, Matthew Hill's lab has shown that intact endocannabinoids signaling is required for glucocorticoid-mediated metabolic outcomes (Bowles et al., 2015). Indeed genetic variants within the endocannabinoid system have likewise been associated with obesity and stress-related psychiatric disorders (Hillard et al., 2012; Di Marzo, 2008). In fact, there is a common variant in the human gene for fatty acid amide hydrolase (FAAH) (1000 Genomes Project Consortium et al., 2012), the primary enzyme responsible for the inactivation of the endocannabinoid N-arachidonoylethanolamide (AEA), that has been associated with both the stress response and energy metabolism. This variant (FAAH C385A, rs324420) reduces FAAH expression and increases AEA signaling (Sipe et al., 2002; Chiang et al., 2004). Importantly, reduced stress reactivity (Gunduz-Cinar et al., 2012) and increased body mass index (Sipe et al., 2005; Monteleone et al., 2008; Durand et al., 2008; Zhang et al., 2009; de Luis et al., 2010) have been associated with the low-expressing FAAH variant (A-allele). In this Symposium, Georgia Balsevich demonstrated that the FAAH C385A indeed alters leptin sensitivity and subsequent leptin-dependent metabolic effects in a FAAH C385A knock-in (KI) mouse model that recapitulates the common human FAAH mutation (Balsevich et al., 2018). Given the known role of the endocannabinoid system in both the stress response and energy balance, it will be important to determine whether genetic variants within the endocannabinoid system influence metabolic outcomes resulting from stress exposure. Likewise, additional genetic variants predicting metabolic outcomes resulting after stress exposure must be identified in order to understand individual susceptibility to stress-related weight gain and metabolic problems.

Besides changes in DNA sequence, environmental factors are able to change levels of gene expression through epigenetic mechanisms. MicroRNAs (miRNAs), a class of non-coding RNAs, are one way by which environmental factors alter gene expression in order to impact physiology and behaviour. It is reported that any given miRNA can post-transcriptionally regulate hundreds of downstream targets (Issler and Chen, 2015). Indeed dysregulation of miRNAs in different tissues have been reported in association with obesity (Iacomino and Siani, 2017) and stress-related psychiatric disorders (Issler and Chen, 2015). Yet few studies have examined miRNAs at the intersection between stress and metabolism. One transgenerational study reported that the delivery of sperm miRNA from stressed males into non-stressed oocytes parallels the effects of stress on glucose metabolism (Gapp et al., 2014). At this Symposium, Alon Chen presented data demonstrating the importance of miRNAs in the regulation of stress-related eating disorders. Specifically, prenatal stress exposure increases the expression of a specific miRNA (miR-340), whose expression level predicts individual vulnerability to activity-based anorexia (ABA) in mice (Schroeder et al.,

2018). Furthermore, in a separate study, his lab showed that increased maternal corticotropin-releasing factor (CRF) levels during late gestation (a model of chronic stress), predisposes female offspring to the development of binge eating-like behaviour, which coincides with hypomethylation of hypothalamic miR-1a and ultimately the downstream dysregulation of the melanocortin system (Schroeder et al., 2017). The study of miRNAs in stress-related energy metabolism should continue to be studied across different stress models, examining broader metabolic readouts.

1.3. The nature of stressors

Similar to humans, animal models often present variable and even opposite body weight phenotypes when confronted with chronic stress. Such variability persists even when genetic background is held constant using inbred mouse lines, indicating that genetic factors do not exclusively determine the metabolic outcomes arising from chronic stress. The variability has partly been attributed to differences in the types of stressors. For example, whereas chronic psychosocial stress models (i.e. chronic social defeat stress, CSDS) promote hyperphagia and increased body weight gain (Bhatnagar and Vining, 2003; Bartolomucci et al., 2009; Moles et al., 2006), chronic unpredictable stress and repetitive daily restraint stress favor hypophagia and decreased body weight gain (Michel et al., 2005; Kim et al., 2003; Weninger et al., 1999). Interestingly, both CSDS and chronic unpredictable stress increase circulating ghrelin levels, and ghrelin receptor knockout mice are protected from the stress-induced metabolic responses in either model, despite diverging (model-dependent) metabolic outcomes (Patterson et al., 2010, 2013a). The effects of ghrelin receptor ablation across stress models may be attributed to the activation of ghrelin receptors in different brain regions, a phenomenon that is responsible for the diverging effects of ghrelin on sexual motivation (Hyland et al., 2018).

To complicate matters further, the dietary condition also affects the net outcome of chronic stress models. When fed a high fat diet (HFD, itself considered a metabolic stressor), chronic psychosocial stress no longer leads to body weight gain but rather results in body weight loss (Balsevich et al., 2014; Finger et al., 2011, 2012). In agreement, work from Alfonso Abizaid shows that when you give 4h access to HFD throughout CSDS, stressed-exposed mice lower their intake of HFD in favor of the chow diet, whereas control mice continue to favor HFD (Patterson et al., 2013b). Mechanistically, the shift towards chow diet (with higher relative carbohydrate content) in response to chronic stress is likely attributed to elevated levels of glucocorticoids and ghrelin, both of which favor carbohydrate utilization as an energy source (Tschöp et al., 2000; Wang and Harris, 2015). In fact, it is possible that ghrelin favours carbohydrate utilization in spite of reduced caloric intake and body weight during chronic unpredictable stress, as stressed mice do not show a reduction in their adipose stores (Patterson et al., 2010). During CSDS, WT mice increase their respiratory exchange ratios (RER) (i.e. carbohydrate utilization) and accumulate adipose depots whereas GHSR KO mice do not show changes in RER and show adipose tissue depletion (Kristensson et al., 2006). As such, ghrelin may be critical in the metabolic adaptations required to meet stressful events, and these events may be independent of food intake. Taken together, it is clear that different stressors result in different metabolic outcomes, which is analogous to the situation in humans. It is thus important to study metabolic responses to different stress modalities (psychosocial stress, dietary stress, inflammatory stress, etc.) that humans commonly encounter in order to better understand the complexity of the interaction between stress and metabolic processes.

1.4. Sex matters

Currently there is underrepresentation of female studies at both the preclinical and clinical level. Yet sex differences are an important

consideration when examining the relationship between stress and metabolism. Indeed males and females show differences in susceptibility to stress-related disease. In humans, females are more vulnerable to stress-induced anxiety and depression (Bale and Epperson, 2015) whereas males are more vulnerable to the metabolic consequences of peripheral glucocorticoid actions, including visceral adiposity, hyperglycemia, and hyperinsulinemia (Bourke et al., 2012). Indeed sex-specific activation of the HPA axis exists. In the dexamethasone suppression-CRF stimulation test, which examines HPA axis functionality, females show an accentuated HPA axis response compared to males (Kudielka and Kirschbaum, 2005; Kunugi et al., 2006). There are multiple factors likely contributing to sex differences in stress-mediated metabolic dysfunction that can begin as early as the in utero stage. To this point, the earlier example that prenatal stress exposure regulates the expression of miR-340, which in turn determines the vulnerability to ABA (Iacomino and Siani, 2017), is in fact sex-dependent. Specifically, prenatal stress exposure decreases placental miR-340 exclusively in females to levels observed within male placentas. Interestingly, there is also a sex difference in the vulnerability to ABA with females showing an increased risk to develop this disorder. In fact, in this study prenatal stress exposure actually protected females from developing ABA, which agrees with the sexually dimorphic regulation of miR-340 by prenatal stress. Nevertheless, it is quite surprising that prenatal stress protected against ABA since many studies have found that early life stress is rather a risk factor for eating disorders (Favaro et al., 2003; Boersma et al., 2016). The discrepancies between these studies may be due to the exact timing of the stress exposure. It will be important for future studies to determine the sex-dependent effects of stress exposure throughout the lifespan on various metabolic outcomes.

1.5. Timing is everything

We have discussed the importance of genetics, sex, and type of stressor for the resulting outcome of stress exposure on metabolic outcomes. However, it is equally important to consider the timing of the stressor. For example, ghrelin receptor knockout mice are protected against HFD-induced body weight gain when diet exposure begins early in life (post-weaning) (Zigman et al., 2005). By contrast, ghrelin receptor ablation does not protect against HFD-induced weight gain during adulthood (16 weeks) (Sun et al., 2008). In the activity-induced anorexia model, prenatal stress exposure during the last week of gestation increases the susceptibility to ABA (Boersma et al., 2016), whereas prenatal stress exposure throughout the entire gestational period protects mice from developing ABA (Schroeder et al., 2018). These are just a few examples of how the timing of the stress exposure determines the ultimate outcome. Despite appreciating the importance of timing, the exact underlying mechanisms contributing to the diverging outcomes are poorly understood. Of course there are critical developmental windows, where exposure to challenging situations influence maturational processes and thus, may have enduring effects in the nervous and endocrine systems (Danese and McEwen, 2012). We now recognize that in utero, childhood, and adolescence represent vulnerable developmental periods to adverse experiences that can have time-period specific and lasting influences on physiological and emotional health over the lifespan. However, whether the exact timing of early life stress exposure predicts future stress-mediated metabolic outcomes (weight gain/loss, stress-mediated protection/vulnerability to eating disorders, etc.) is unknown. Indeed the outcome of adult stress exposure will depend on the particular social and physical environment, genotype, and previous lifetime experiences (Nederhof and Schmidt, 2012), and it is therefore important to identify interacting mediators that predict the consequences of stress exposure at distinct life stages.

While developmental timescales are clearly important in understanding the effects of stress on metabolic function, it is also important to think about time, in particular the body's daily clock, as a modulator of stress effects. Over the past 100 years, our modern industrialized

society, from electric lighting to a 24/7 "always on" economy, has gradually degraded the links between the solar day and our endogenous circadian (daily) clock. There is a body of experimental evidence demonstrating that circadian disruption parallels the physiological and behavioural effects of chronic stress (McEwen and Karatsoreos, 2015; Landgraf et al., 2014). Indeed both glucocorticoids and ghrelin present circadian rhythms that can be disrupted by circadian desynchronization (Bodosi et al., 2004; Oster et al., 2006). Many other signaling molecules that lie at the interface between stress and metabolic regulation, such as leptin and cytokines, likewise possess circadian rhythmicity (Bodosi et al., 2004; Nakao, 2014). Therefore, it is important to understand the physiological consequences of circadian disruption. Ilia Karatsoreos has shown that a disrupted circadian period of 20-h light/dark cycles (T20) accelerates weight gain and the development of obesity in mice (Karatsoreos et al., 2011). In addition to metabolic dysregulation, this model of circadian disruption further leads to changes in prefrontal cortical morphology and cognitive rigidity, again paralleling the effects of chronic stress. Intriguingly, these effects seem to occur without hypercortisolemia or grossly disrupted HPA function, suggesting that while circadian disruption mirrors chronic stress effects, it may do so by acting on common downstream processes. The T20 model does not attempt to directly relate to a specific human condition. Rather, the goal of this model is to drive desynchronization between the endogenous circadian oscillator and the environmental light-dark cycle. Many human laboratory studies use altered period cycles, including T20, to drive circadian and sleep desynchronization, thus this model allows for a potential way to link both human and non-human animal studies. Finally, altered periods are used in specific work environments. For instance, the US Navy has used the "five and dime" watch schedule (5 h on duty, 10hrs off duty) for decades. However, recent naval accidents has led to the Navy introducing more "circadian friendly" work schedules given the potential links between circadian/sleep desynchronization, fatigue, and cognitive dysfunction. It will be imperative to understand the underlying mechanisms that contribute to the effects of circadian disruption, including which pathways are affected (central, peripheral oscillators). Moreover, it is important to understand whether circadian disruption alters the vulnerability to other stress exposures, including metabolic stressors (diet) as well as psychosocial stressors.

Thus, time becomes a key variable to consider, both in the context of lifecourse exposures to stressors, but also in the context of a key system the body and brain use to anticipate and cope with changes in the environment. Both of these timescales align with the concept of allostasis, the ability to maintain stability over time through changes, and allostatic load, the progressive and cumulative wear and tear on allostatic systems resulting from an imbalance in the mediators (e.g. glucocorticoids) in order to adapt to stressors (McEwen and Wingfield, 2003). It is important to consider that insults occurring at different developmental times, or which disrupt timing systems that help organisms adapt, can impact allostatic load, thereby contributing to increased vulnerability to other insults, such as the ones discussed earlier in this summary.

2. Conclusion

This research symposium emphasized the intricacies involved in the relationship between stress and metabolic regulation. Each researcher used different models to explore diverse mechanisms that contribute to the interaction between stress and metabolism. Taken together, it is clear that the type of stress model dictates the metabolic outcomes (Fig. 1). Future studies should choose ecologically relevant models that translate to human stress exposures. Nevertheless, the cumulative work shed light on shared interests within the field, which we have attempted to highlight here. Moving forward, there are several questions that need to be addressed, including, but not limited to, the following examples.

- Where do various signaling molecules act to modify energy
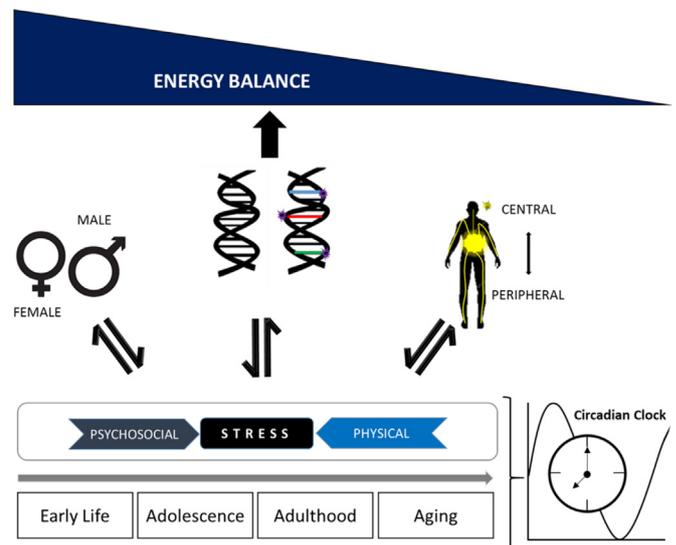
Fig. 1. The effects of stress across lifespan on energy balance depend on multiple factors including type of stressor, sex, genetics, timing (developmental stage and circadian clock), and tissue/cell-specific activation of signaling cascades.

expenditure, feeding, and energy storage in response to stress? How do peripheral and central factors interact to drive stress- and metabolic responses (brain-body interactions, looking beyond the gut-brain axis)?
- What genetic and epigenetic markers determine individual metabolic responses to stress? What are the specific factors that determine whether an individual gains weight or loses weight in response to stress?
- Is the type of stressor (including dietary challenge) important for the bi-directional effects of stress on body weight and food intake? What mechanisms mediate this?
- What mechanisms are responsible for the diverging effects of stress exposure between males and females (HPA axis, stress hormones, etc)?
- How does the timing of a stress exposure affect the risk of developing metabolic disorders, including diet-induced obesity, binge eating, and anorexia nervosa? Are there developmental time windows that predict stress-induced weight gain versus loss, or stress-mediated protection versus susceptibility to eating disorders?

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2019.100171.

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