Hormones and Behavior 55 (2009) 375–389

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review

The reactive scope model — A new model integrating homeostasis, allostasis, and stress

L. Michael Romero *, Molly J. Dickens, Nicole E. Cyr

Department of Biology, Tufts University, Medford, MA 02155, USA

ARTICLE INFO

Article history:
Received 18 July 2008
Revised 2 December 2008
Accepted 11 December 2008
Available online 20 January 2009

Keywords:
Stress
Allostasis
Glucocorticoids
Fight-or-flight
Homeostasis

ABSTRACT

Allostasis, the concept of maintaining stability through change, has been proposed as a term and a model to replace the ambiguous term of stress, the concept of adequately or inadequately coping with threatening or unpredictable environmental stimuli. However, both the term allostasis and its underlying model have generated criticism. Here we propose the Reactive Scope Model, an alternate graphical model that builds on the strengths of allostasis and traditional concepts of stress yet addresses many of the criticisms. The basic model proposes divergent effects in four ranges for the concentrations or levels of various physiological mediators involved in responding to stress. (1) Predictive Homeostasis is the range encompassing circadian and seasonal variation — the concentrations/levels needed to respond to predictable environmental changes. (2) Reactive Homeostasis is the range of the mediator needed to respond to unpredictable or threatening environmental changes. Together, Predictive and Reactive Homeostasis comprise the normal reactive scope of the mediator for that individual. Concentrations/levels above the Reactive Homeostasis range is (3) Homeostatic Overload, and concentrations/levels below the Predictive Homeostasis range is (4) Homeostatic Failure. These two ranges represent concentrations/levels with pathological effects and are not compatible with long-term (Homeostatic Overload) or short-term (Homeostatic Failure) health. Wear and tear is the concept that there is a cost to maintaining physiological systems in the Reactive Homeostasis range, so that over time these systems gradually lose their ability to counteract threatening and unpredictable stimuli. Wear and tear can be modeled by a decrease in the threshold between Reactive Homeostasis and Homeostatic Overload, i.e. a decrease in reactive scope. This basic model can then be modified by altering the threshold between Reactive Homeostasis and Homeostatic Overload to help understand how an individual's response to environmental stressors can differ depending upon factors such as prior stressors, dominance status, and early life experience. We illustrate the benefits of the Reactive Scope Model and contrast it with the traditional model and with allostasis in the context of chronic malnutrition, changes in social status, and changes in stress responses due to early life experiences. The Reactive Scope Model, as an extension of allostasis, should be useful to both biomedical researchers studying laboratory animals and humans, as well as ecologists studying stress in free-living animals.

Contents

* Corresponding author. Fax: +1 617 627 3805.
E-mail address: Michael.romero@tufts.edu (L.M. Romero).

0018-506X/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.yhbeh.2008.12.009

Introduction

Nearly from the introduction of the concept of stress by Cannon (1932) and Selye (1946), there have been attempts to narrow the concept and make the definition more precise (Levine, 2005). Much of the dissatisfaction in existing definitions originates from two problems. The first is that the term "stress" has come to encompass three related concepts — those stimuli (both internal and external) that cause stress, the emergency physiological and behavioral responses activated in response to those stimuli, and the pathological consequences of over-stimulation of the emergency responses (Le Moal, 2007; Romero, 2004). Part of the problem of defining "stress" is addressed by referring to the stimuli as stressors, the emergency responses as the stress response, and the over-stimulation of the emergency responses as chronic stress. Chronic stress is then associated with an increased risk of stress-related disease and pathology. However, most uses of the word "stress" remain ambiguous. The second dissatisfaction derives from an inability to rigorously define these three concepts. When is a stimulus a stressor? In many instances, a stressor is defined as a stimulus that initiates a stress response. But what behavioral and physiological responses are stress responses? A typical answer is that a physiological or behavioral response is considered a stress response if it is initiated in response to a stressor. These definitions are clearly circular, and the problem is compounded when trying to determine when a presumably beneficial stress response becomes pathological. The most common attempt to resolve this dilemma has been to define stressors as stimuli that disrupt or threaten to disrupt homeostasis (e.g. Chrousos and Gold, 1992), but the concept of homeostasis has its own limitations (Schulkin, 2003). A more successful definition, and the one most widely used currently, is that unpredictable and/or uncontrollable stimuli are stressors (Levine and Ursin, 1991).

The most recent attempt to redefine stress was the introduction of the concept of allostasis (Sterling and Eyer, 1988) and specifically the melding of biomedical and ecological research in the Allostasis Model as proposed by McEwen and Wingfield (2003b). Although allostasis has been applied in a number of biomedical contexts, the McEwen and Wingfield (2003b) paper was the first, and remains one of the few, attempts to use allostasis to connect biomedical and ecological data. Consequently, we will focus much of our discussion on that specific formulation of allostasis. To summarize McEwen and Wingfield's conceptualization, allostasis is the process of maintaining stability (homeostasis) through change in both environmental stimuli and physiological mechanisms. Allostasis then accounts for daily and seasonal physiological adjustments (termed allostatic state) that maintain physiological parameters, such as blood glucose, within narrow life-sustaining ranges. With these definitions, homeostasis refers to the maintenance of these physiological parameters, whereas allostasis refers to the physiological mechanisms that maintain that homeostasis (via allostatic mediators). As a consequence, there is a difference between the physiological variables that are kept constant and those mediators that vary in order to maintain constancy. However, environmental changes, such as storms or winter conditions, and life-history changes, such as pregnancy, could make the animal work harder to maintain stability of these physiological parameters. Importantly, environmental and life-history changes can be additive so that an animal would have to work even harder if there were multiple changes, such as a storm occurring during pregnancy. McEwen and Wingfield termed this increase in workload allostatic load and proposed that allostatic load could be measured with overall energy expenditure. McEwen and Wingfield then identified two instances where an animal could get into physiological trouble. The first they termed allostatic overload Type I which occurs when the animal's energy demand for maintaining homeostasis exceeds the energy the animal can obtain from its environment. Allostatic overload Type I then initiates an emergency life-history stage whereby the animal adjusts its behavior and physiology to decrease allostatic load. The second they termed allostatic overload Type II, which occurs when allostatic load is too high for too long. As a consequence, the prolonged activation of the physiological systems that mediate allostasis starts to create pathological problems themselves, despite the presence of adequate energy. Building on Sterling and Eyer's (1988) allostasis concept, McEwen and Wingfield proposed that allostasis, allostatic load, and allostatic overload could provide a framework for understanding how an animal copes with unpredictable challenges, and the framework can be tested rigorously by evaluating energy budgets. The Allostatic Model would then replace the concept of stress.

Allostasis was conceived originally in the biomedical setting specifically to apply to human health. The concept has great promise in understanding some human diseases and is currently a leading model for understanding the etiology of diseases such as diabetes, obesity, depression and drug addiction. However, since none of these diseases is likely to be important for wild animals attempting to survive in their natural habitats, it is still debated whether the allostasis concept is successful when applied to more ethologically, as compared to biomedically, relevant phenomena. There are a number of strengths and weaknesses (see below) of the allostasis model and a strengthened biological foundation might help make the model applicable to more than one species (humans) or to other species in only specific contexts (such as zoo animals). What follows is a new graphical model that builds on the strengths of the allostasis concept while addressing its weaknesses. Our hope is that this new formulation will better integrate the biomedical and ethological concepts of homeostasis, allostasis, and stress in a way that will be useful heuristically and empirically to both communities.

We specifically chose a top-down approach to creating this graphical model by incorporating whole-animal responses to stressors without requiring detailed physiological mechanisms. Our goal is to create a comprehensive framework for stress by focusing only on how an individual animal responds to survive in the short term and how these adaptive acute responses can become pathological if sustained. We then identify mechanisms that could underlie these responses. This is more typical of an ecological approach to addressing a physiological problem. In contrast, the typical biomedical approach has been to understand the mechanistic responses and then to integrate all the mechanisms to build an understanding of how and why the organism responds the way it does. This bottom-up, or reductionist, approach of generating a comprehensive theory of stress has been conspicuously unsuccessful. For example, it has been over 60 years since Selye (1946) identified glucocorticoids as a prime mediator of coping with stressors and yet we still do not fully know how glucocorticoids help an animal survive a stressor. Our hope is that framing our graphical model in a top-down approach, as did McEwen and Wingfield (2003b) in formulating their Allostasis Model, will prove more successful.

Our first task was to identify the strengths of McEwen and Wingfield's Allostasis Model so that these features could be

incorporated into the new framework, as well as to identify weaknesses that could be profitably changed. The following descriptions are brief and are not intended to provide a synthesis and/or resolution to the current homeostasis vs. allostasis debate.

Strengths of allostasis

Perhaps the strongest impetus for proposing the concept of allostasis was the perception that the term homeostasis was too restrictive (Sterling and Eyer, 1988). Although there is some debate, there is evidence that both Cannon (1932) and Selye (1971) considered homeostasis to refer to the maintenance of physiological variables within very narrow ranges (reviewed by Schulkin, 2003). One result was the description of homeostatic regulation via the metaphor of a set point — a self-limiting process involving negative feedback. Although many modern physiologists and endocrinologists use a more expansive definition of homeostasis that incorporates both circadian and circannual rhythms (i.e. changing set points), this usage is not universal. By defining allostasis as "constancy through change," the concept of allostasis incorporates circadian, circannual, and other life-history changes and emphasizes their importance in maintaining the animal's internal balance. In other words, a regulatory system can operate at both elevated and reduced levels, termed allostatic states (Koob and Le Moal, 2001; McEwen and Wingfield, 2003b). We consider that, regardless of the nomenclature, incorporating the idea that physiological parameters change over time is a major strength of the Allostasis Model.

We consider the second major strength to be the formulation of allostatic load. This innovative concept starts to model the wear and tear on individuals coping with repeated stressors and can indicate how prepared the individual is to cope with future stressors (e.g. McEwen and Seeman, 1999). Wear and tear is the concept that there is a cost to maintaining physiological systems, and is discussed below in detail. Several indices, such as blood pressure and cholesterol, have been proposed for measuring allostatic load in humans (e.g. Seeman et al., 2001). McEwen and Wingfield (2003b) further proposed the use of energy as both an underlying mechanism and a universal metric for allostatic load. Using energy in this manner allowed for integrating diverse physiological responses so that they could be compared in terms of their effects on the animal. Although there may be drawbacks to using energy as a universal metric (see below), it provided, for the first time, a way to predict whether a specific stressor (or series of stressors) would either initiate a stress response or result in the symptoms of chronic stress. The use of energy seems especially useful in ecology studies and there are examples where using energy and allostatic load can help explain empirical data (e.g. Goymann and Wingfield, 2004; Romero et al., 2000; Romero and Wikelski, 2001).

The concept of allostatic overload provides a third strength by proposing a threshold for when accumulated allostatic load turns into allostatic overload (Goldstein and McEwen, 2002). This threshold allows testable predictions for two related phenomena. First, we can now predict when normal adaptive responses will become insufficient and require new, stronger responses to counteract the stressor. Second, we can now predict when adaptive responses will fail and result in stress-related disease. Thus, the ability of the Allostasis Model to generate testable predictions is an important theoretical advance.

Weaknesses of allostasis

There are several weaknesses to the concept of allostasis as it is presented in McEwen and Wingfield (2003b). The first is that energy input and expenditure are too variable and poorly understood to use as a simple measure of allostatic load (Walsberg, 2003). Walsberg (2003) points out that consumption and use of energy (the animal's energy budget) is heavily dependent upon the time frame over which the measurements are made. The shorter the time frame the more variable the energy budget, which makes it more difficult to discern which changes in energy use result from normal consumption (allostasis) and which contribute to increased expenditures (allostatic load). This problem is exacerbated when comparing across taxa. Walsberg suggested that whether energy use contributes to allostatic load might be very different in small endotherms with limited storage capacities in relation to high rates of energy consumption, compared to an ectotherm that might subsist for months between meals. Walsberg also highlighted the importance of different contexts in energy use. Animals might profitably alter the rate rather than the amount of energy consumption during different life-history stages, which he argues would again make it difficult to use energy consumption to assess allostatic load. It is also clear that not all energy mobilization is equivalent. For example, the problems of acidosis and potential cell damage (allostatic overload) that can accompany glycolysis or gluconeogenesis (conversion of protein to glucose) are not present when converting glycogen to glucose.

Furthermore, although McEwen and Wingfield (2003a) recognized that their model may have relied too heavily on a connection between glucocorticoids and energy specifically, their model assumes researchers are measuring glucocorticoids and not energy expenditure directly (2003b). However, recent work from our lab indicates that the connection between corticosteroids, presumed to be one of the prime mediators of energy balance during stress, and glucose regulation is not as well understood as once thought. Starting from the earliest studies (e.g. Munck and Koritz, 1962), corticosteroids were known to increase blood glucose levels. These data were the foundation for claims that glucocorticoids were mobilizing energy (specifically glucose) to cope with a stressor (Sapolsky et al., 2000). However, virtually all work in this area has been performed on fasted animals and it is unlikely that all, or even most, animals are fasting when exposed to a stressor in a natural context. When similar studies are performed on fed animals (e.g. Remage-Healey and Romero, 2001), corticosteroids are ineffective at altering blood glucose concentrations. Much of the allure of the Allostasis Model might decrease if glucocorticoids only have a short-term impact on energy mobilization under the narrow context of fasting.

In addition, not all stress responses appear to culminate in measurable energy expenditure. For example, if robust sympathetic and behavioral responses to moderate psychological stressors are not sustained for sufficient time, they fail to incur significant energy consumption when compared to the 24 h energy budget (Cyr et al., 2008). This is likely to be true of many behavioral responses to stressors — at least in the short term, behavioral responses will be sufficiently inexpensive to initiate that they are essentially cost-free in the context of normal daily/weekly energy budgets. As an example, if an animal freezes in the presence of a predator, overall energy expenditure may actually decrease (i.e. it is no longer active). Consequently, a highly-relevant behavioral stress response becomes essentially invisible to the Allostasis Model.

It has also become clear that a fair amount of the criticism of allostasis is due to the term itself, not the underlying concepts. As mentioned above, many physiologists and endocrinologists have had little difficulty using a definition of homeostasis that includes circadian and circannual changes. These researchers emphasize parts of Cannon's writings that seem to include circadian and seasonal changes. For instance, Cannon (1932: pg. 24) states: "The coordinated physiological processes which maintain most of the steady states in the organism are so complex and so peculiar to living beings – involving, as they may, the brain and nerves, the heart, lungs, kidneys and spleen, all working cooperatively – that I have suggested a special designation for these states, *homeostasis*. The word does not imply something set and immobile, a stagnation. It means a condition — a condition which may vary, but which is relatively constant." Although allostasis may emphasize these concepts by more explicitly separating those physiological variables that are kept constant (e.g. pH, oxygen

tension, body temperature for homeotherms) and those mediators that actively maintain that constancy (e.g. glucocorticoids, epinephrine, cytokines), for many researchers the new term of allostasis is irrelevant at best, and at worst adds to the confusion surrounding the definition of stress (Dallman, 2003).

There are also a number of concepts that typically are included when discussing stress that the current allostatic model does not adequately address. There are numerous early developmental effects (reviewed by Caldji et al., 2001) that clearly alter an individual's responses to stressors later in life. These changes are believed to be mediated through neural (e.g. Kapoor et al., 2006) and epigenetic (e.g. Szyf et al., 2005) mechanisms that are not easily explained using an energy-based model. Early life history is an important component to allostatic state and allostatic load in formulations of allostasis addressing biomedical issues (e.g. McEwen, 1998a), but it is not clear how to incorporate developmental effects into McEwen and Wingfield's Allostatic Model that attempts to encompass ecological data using energy. Similarly, adaptation leading to changes in evolutionary fitness, concepts of great concern to ecologists (e.g. Hadany et al., 2006), is difficult to fit within the Allostatic Model because individual variation – the grist of evolutionary change – is at best only implicitly addressed in the model.

Another weakness of the allostasis model is the heavy reliance on glucocorticoid effects. Catecholamine responses via the sympathetic nervous system, or the fight-or-flight response, are major parts of an integrated response to stressors (e.g. Reeder and Kramer, 2005). These rapid changes may not involve long-term expenditures of energy, and therefore are difficult to include in an energy-based model. In fact, both Type I and Type II allostatic overload essentially model responses to long-term, relatively constant (i.e. chronic), stressors. Examples provided by McEwen and Wingfield include bad weather, habitat changes, parasite loads, social status, social conflict, low socio-economic status, and obesity. Missing from this list are short-term responses mediated by the sympathetic nervous system, such as predator attacks (e.g. Sapolsky et al., 2000; Steen et al., 1988).

Finally, behavioral and cognitive responses are difficult to fit into the Allostasis Model. They often cost little energy (see above) and yet are fundamental to our understanding of stress. Day (2005) argues that allostasis provides little help in understanding how the brain distinguishes stressful from nonstressful stimuli, nor does it provide a framework for identifying which are the important neural circuits underlying these behavioral and cognitive responses. Ideally, a theoretical framework of stress would be able to encompass these concepts.

The basic model

Our goal was to generate a new model by modifying the Allostatic Model to ensure that we kept its strengths and avoided as many of the weaknesses as possible. The result was the basic model presented in Fig. 1A, which depicts a graph of the level of some physiological mediator over time. These physiological mediators are specifically the homeostatic mediators discussed by McEwen (2003) and McEwen and Wingfield (2003b). These include changes in behavior, changes in the central nervous system, mediators of immune function, mediators of the hypothalamic-pituitary-adrenal axis, and changes in cardiovascular function (Table 1) and will be discussed in more detail below.

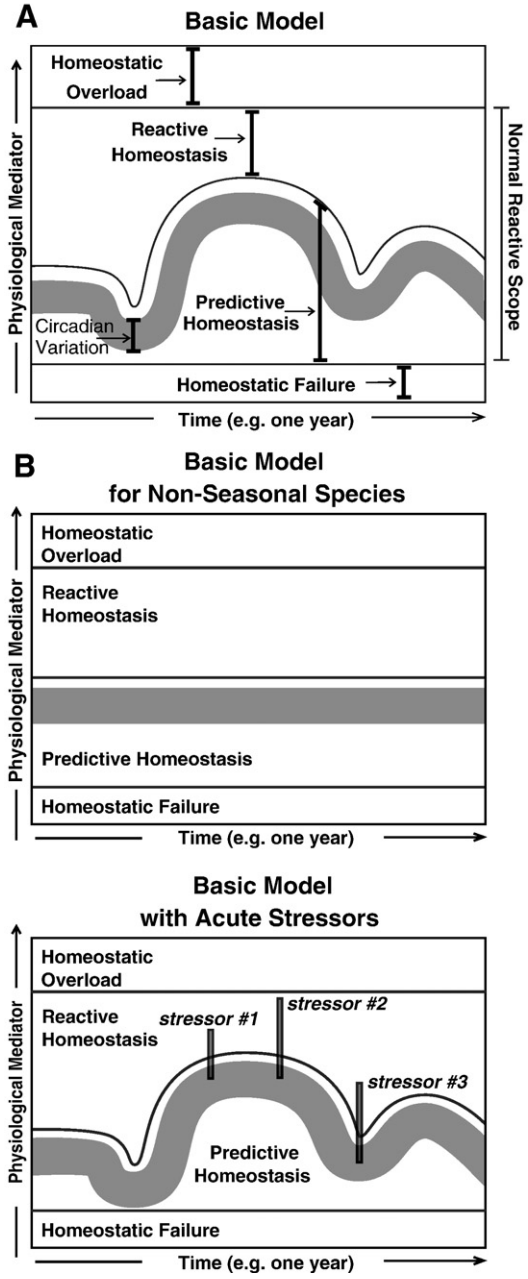

Fig. 1. (A) Graphical model of the concentrations of different physiological mediators on the *y*-axis vs. time. The range of concentrations or levels of physiological mediators is broken into 4 ranges. The lowest range depicts concentrations/levels that are too low to maintain homeostasis and is termed Homeostatic Failure. The minimum required concentration/level forms a threshold that does not change over time. Above this threshold is the Predictive Homeostasis range that varies according to predictable life-history changes. The circadian variation in concentrations/levels is depicted as a gray bar (with the bottom being the circadian nadir and the top being the circadian peak). The range of Predictive Homeostasis varies depending upon life-history demands, and thus changes seasonally. The Predictive Range extends slightly above the circadian peak in each season to encompass predictable daily events such as foraging. Above the Predictive Homeostasis range is the Reactive Homeostasis range, which represents concentrations/levels of the physiological mediator necessary to maintain homeostasis following an unpredictable event that threatens homeostasis. The Predictive and Reactive Homeostasis ranges form the normal reactive scope for that physiological mediator. The upper limit to the Reactive Homeostasis range is the concentration/level where the mediator itself starts to cause damage, and the range above this threshold is termed Homeostatic Overload. The threshold between Reactive Homeostasis and Homeostatic Overload is presumed to not change on a daily or seasonal basis. (B) A simplified version of the graphical model presented in A in a nonseasonal species such as humans. (C) A graphical depiction of the response to stressors. Each vertical line represents both a rapid spike of the mediator into the Reactive Homeostasis range in order to maintain homeostasis in the face of a stressor and a rapid decrease in the mediator once the stressor has ended. Stressor #2 is a stronger stressor than #1 and thus requires a stronger response to maintain homeostasis. Stressors #2 and #3 are of equivalent strength, but occur at different times of year. Consequently, the mediator is at different concentrations/levels in the Predictive Homeostasis range so that stressor #3 is less likely to elicit a response from the mediator that extends into the Homeostatic Overload range.

Table 1

Physiological system	Physiological mediator	Predictive homeostasis range	Reactive homeostasis range	Homeostatic overload range	Homeostatic failure range
Immune	Prostaglandin T-cell activation Antibody titers Cytokines	Seasonal ability to fight infection	Mobilization of immune system	Autoimmune Immunosuppression	Immune failure
HPA	Glucocorticoids ACTH	Seasonal life-history needs a. Energetic needs b. Behavioral needs c. Preparative needs	Inhibit immune system Energy mobilization Change behavior Inhibit reproduction Inhibit growth	Immunosuppression Diabetes Muscle breakdown Reproductive suppression Decreased survival	Energy dysregulation Water balance failure Catecholamine insufficiency Decreased survival
Cardiovascular (catecholamines)	Heart rate Heart rate variability Blood pressure	Life-history energy needs	Fight-or-flight Energy mobilization	Hypertension Myocardial infarction Muscle breakdown	Hypotension Lethargy Decreased survival
Behavior	Foraging/feeding Locomotion Migration Conspecific aggression	Life-history changes: a. Energy needs b. Energy availability c. Predator presence d. Mate access	Fleeing behavior Freezing behavior Increase/decrease foraging Increase food intake Increase vigilance Conspecific fighting	Tonic immobility Obesity Anxiety Fear Violence	
Central nervous system	Neurogenesis Dendritic arborization Neurotransmitter concentrations Cytokines	Life-history changes in neural networks Learning and memory	Increase neurotransmission (titers or receptors) Increase learning and memory	Neuronal atrophy/death Depression Decrease learning and memory	Post traumatic stress disorder

Most studies measure only one of these mediators at a time and the concentration or level of each mediator can be placed on the *y*-axis. However, we intend that only one mediator is placed on the *y*-axis at a time, so that different mediators would require different versions of the basic model.

The values of a mediator are presumed to exist in four general ranges. The first is the range of Predictive Homeostasis, which consists of the normal circadian and seasonal range for the physiological mediator (this includes ranges for species that show no apparent seasonal rhythms). This term is borrowed from Moore-Ede (1986) and specifically refers to the range of values that encompasses responses initiated in anticipation of predictably timed challenges. In other words, Predictive Homeostasis is the adjustable range of responses to ultimate predictive cues such as photoperiod. In our model, the gray area represents circadian variation that is driven by predictable daily changes in light and dark. Furthermore, that gray area changes over the course of the year to reflect seasonal variation resulting from predictable changes normally driven by changes in photoperiod. Using the "set point" metaphor often used to explain homeostasis, the Predictive Homeostasis range can be thought of as the range of homeostatic set points. As an example, glucocorticoid concentrations show changes in daily set points due to a circadian rhythm (Dallman et al., 1987) and changes in seasonal set points due to the natural progression of life-history stages such as breeding (Romero, 2002). Of course, species vary in the degree of seasonality they show, but even in non-seasonal species (Fig. 1B), such as humans, Predictive Homeostasis can vary with life-history changes such as pregnancy. For those species, Fig. 1A might represent a female mammal that undergoes pregnancy, whereas Fig. 1B might represent a male mammal.

The second general range is Reactive Homeostasis, which consists of increases above the normal circadian range that serve to reestablish homeostasis. This term is also borrowed from Moore-Ede (1986) and specifically refers to the range of levels of the physiological mediator that is needed to counteract unpredictable changes in the environment. Mediator concentrations or levels in the range of Reactive Homeostasis are required to either maintain or return the body to homeostasis. This is the range of responses introduced by Cannon (1932) and Selye (1946) and popularly referred to as the stress response. In our graphical depiction, the Reactive Homeostasis range is presumed to begin at concentrations slightly above the circadian peak for that time of year, and so closely matches the seasonal variation in the Predictive Homeostasis range. The beginning of the Reactive Homeostasis Range is not equivalent to the circadian peak since there can be some increases in the physiological mediator that correspond to normal daily activities, such as foraging, that are predictable (or using other terminology, the circadian peak would correspond to the resting metabolic rate, and the threshold between Predictive and Reactive Homeostasis would correspond to the active metabolic rate).

The combination of Predictive and Reactive Homeostasis ranges will establish the normal reactive scope for the individual and is the basis for our naming this new graphical model the Reactive Scope Model. The normal reactive scope defines the physiological constraints of a healthy animal. When a physiological mediator cannot be maintained within the normal reactive scope, i.e. it is below the lower limit of Predictive Homeostasis, the normal physiological processes that the mediator regulates cannot be maintained and death usually rapidly follows. Examples would be the death that occurs after removal of glucocorticoids through adrenalectomy (Darlington et al., 1990) or from an inability to maintain blood pressure. We refer to this range as Homeostatic Failure. In the basic Reactive Scope Model (Fig. 1) we presume that the minimum concentration/level of a physiological mediator required to maintain homeostasis constitutes a threshold. We are not aware of any data indicating that the minimum concentration or level of a mediator necessary to sustain life changes daily or seasonally, so we represent this threshold as constant over time.

Above the upper end of the Reactive Homeostatic range, when a physiological mediator exceeds the normal reactive scope (i.e. exceeds the upper limit of Reactive Homeostasis), the animal enters a pathological state. We call this range Homeostatic Overload. The physiological mediator can enter Homeostatic Overload, but cannot be maintained in this range without the mediator causing physiological disruption itself. Essentially, when the physiological mediator enters the Homeostatic Overload range, the mediator itself becomes a problem (hence, pathological). An example is the long-term behavioral and cardiovascular responses to stressors that result in cardiovascular disease (Sapolsky, 2001). In general, these problems do not result in immediate death, but can cause disease over time that could eventually result in death. Consequently, Homeostatic Overload

is different from Homeostatic Failure. Similar to Homeostatic Failure, however, we presume that there is a threshold between Reactive Homeostasis and Homeostatic Overload. Once again, we are unaware of any data suggesting that the pathology-inducing concentration or level of a mediator varies systematically in a circadian or seasonal manner, so we represent the threshold as constant over time. However, unlike the threshold for Homeostatic Failure, the threshold for Homeostatic Overload, and thus the normal reactive scope, can differ between individuals and within a single individual in response to certain stimuli (see below).

The nomenclature for these four ranges (see Table 2) is different from and expanded from the terms proposed by McEwen and Wingfield (2003b). Although allostasis forms the central foundation of the Reactive Scope model, there are significant-enough differences to preclude using the allostasis nomenclature. We believe that to use the allostasis terminology, and yet subtly alter the meaning, would breed confusion in much the same way confusion now surrounds the use of the term stress. Allostasis is often described differently in different publications, but a restrictive definition of allostasis would correspond to the Predictive Homeostasis range of our model, whereas a broader definition of allostasis would correspond to the combined Predictive and Reactive Homeostatic ranges. The boundary between Predictive and Reactive Homeostatic ranges approximately corresponds to E_I defined by McEwen and Wingfield (2003b) as the amount of energy an animal needs for basic maintenance and successful foraging under ideal conditions, although our framework no longer relies upon energy as a metric.

Also note that our framework borrows heavily from a model discussed for several years by Wingfield and collaborators where they define three levels for hormones: level A being constitutive levels; level B being regulated predictive levels; and level C being regulated facultative levels (e.g. Landys et al., 2006; Wingfield et al., 1997). Our boundary between Homeostatic Failure and Predictive Homeostasis corresponds to Wingfield et al.'s level A, the Predictive Homeostasis range corresponds to level B, and the Reactive Homeostasis range corresponds to level C. In addition, Reactive Homeostasis corresponds to the Emergency Life History Stage (e.g. Wingfield et al., 1998), so the theoretical work for this concept also can be applied to our graphical model (Table 2).

Once this basic graphical model has been defined, it is easy to see how we can represent acute responses to stressors. A rapid spike moves the level of the physiological mediator out of the Predictive Homeostasis range and into the Reactive Homeostasis range (Fig. 1C). This spike could be in response to an actual change in homeostasis or in anticipation of a change in homeostasis. The mediator then either counteracts the effect of the stressor or allows the impact of the stressor to be avoided, followed by a quick return to the Predictive Homeostasis range. Importantly, responses *in anticipation* of a stressor, an important concept in the psychology of stress, will evoke the same response as an actual stressor — the two are not distinguishable. Both are represented as spikes into the Reactive Homeostasis range. Throughout the response, the mediator remains within the normal reactive scope. Furthermore, a mediator can vary in the magnitude of its responses to different stressors and still remain within the Reactive Homeostasis range (stressors #1 and #2 in Fig. 1C). However, even an equivalent response to a stressor, if occurring at different times of year (stressors #2 and #3 in Fig. 1C, which are equivalent but occur at different times), can differ dramatically in how closely that response comes to the range of Homeostatic Overload. Therefore, the move into the Reactive Homeostasis range (the stress response) at each life-history stage, with each stage having its own predictable demands resulting in different ranges of Predictable Homeostasis, will have different consequences even though the response of the mediator may appear equivalent. Consequently, our model is functionally equivalent to the McEwen and Wingfield (2003b) allostasis model in that it predicts that animals will be more resistant to entering Homeostatic Overload (allostatic overload) at some times of the year. In the Allostasis Model, animals would be more resistant when their energy requirements are lowest, and in our model animals would be more resistant when the daily and seasonal variation of the physiological mediator is at its nadir (these times might coincide).

Table 2

Term	Definition	Source	Similar but not identical terms
Physiological Mediators	Processes (e.g. hormones, cytokines, cardiovascular regulation, etc.) involved in maintaining physiological variables in a constant state	Incorporated from the Allostatic Model	Homeostatic Mediators Allostatic Mediators Stress Response
Predictive Homeostasis	Normal circadian and seasonal range of a mediator that encompasses adjustments to cope with predictable challenges from the environment	Term originally proposed by Moore-Ede (1986)	Allostatic State Level B sensu Wingfield et al.
Reactive Homeostasis	Range of a mediator needed to reestablish homeostasis after an unpredictable challenge from the environment	Term originally proposed by Moore-Ede (1986)	Stress Response Allostatic Load Emergency Life History Stage Level C sensu Wingfield et al.
Homeostatic Overload	Range of a mediator where the mediator itself begins to disrupt normal function	Direct corollary to Allostatic Overload	Allostatic Overload Chronic Stress
Homeostatic Failure	Range of a mediator that is insufficient to maintain normal physiological function to sustain life		< Level A sensu Wingfield et al.
Reactive Scope	Range of a mediator as defined by the normal physiological constraints of a healthy animal	Inspired by the ecological concept of "Reaction Norm" — the range of phenotypic possibilities in a species	Allostatic State
Wear and Tear	The cost of maintaining physiological mediators	Direct corollary to Allostatic Load	Allostatic Load

Physiological mediators

Over the past few decades, there has been a general, although not complete, consensus on the physiological mediators involved in returning an animal to homeostasis in response to unpredictable environmental stimuli. These mediators have been called many things, including homeostatic mediators (Dallman, 2003), allostatic mediators (McEwen, 2003), and even more generically, the stress response (Sapolsky et al., 2000). Table 1 lists the five major systems generally considered to be involved in the stress response and examples of their common mediators. Table 1 is not intended to be exhaustive in its list of mediators, but instead presents examples of mediators that have been studied and that could be used as the *y*-axis in our model, depending upon what is being measured. There has been significant recent work on understanding the functioning of many of these mediators in the context of allostasis. For example, seasonal variation can occur in immune function (Nelson et al., 2002), hypothalamic-pituitary-adrenal (HPA) function (Romero, 2002), and the size of dendritic trees in hippocampal neurons (Popov and Bocharova, 1992; Popov et al., 1992); all of which can be understood as physiological processes and all of which can be modeled easily as forming a Predictive Homeostatic range. In each case, different seasons and different life-history stages have different demands and different risks. Preparing physiologically for those predictable changes in demands and risks is what creates a varying range for Predictive Homeostasis.

Furthermore, the entire field of stress research has been dedicated to understanding how short-term (acute) increases in these mediators help to counteract stressors (the Reactive Homeostatic range), how chronic increases can lead to problems including disease (Homeostatic Overload), and how lack of these mediators can lead to homeostasis failure. An important concept is that these mediators play central roles in both successful adaptation and pathophysiology. Common examples of the physiological consequences of mediators being in each of these ranges are also given in Table 1. Again, it is not our intention in this table to provide a summary of all that is known about why these mediators vary daily or seasonally (Predictive Homeostasis), what their physiological effects are in the various ranges, or how they act on multiple systems concurrently. We fully recognize that Table 1 is simplistic; it ignores extensive cross-talk between these systems and fails to indicate the non-linear nature of their interactions. In addition, the consequences of being in Homeostatic Overload may not be death per se, but instead the expression of pathology and disease (important for biomedical researchers) that increase vulnerability and, therefore, could eventually result in death (important for ecologists). Instead, our intention is to provide examples of how what is currently known about stress physiology can be incorporated into the Reactive Scope Model.

Modeling "wear and tear" (or allostatic load)

Allostatic load, the concept that at certain times an animal has to work harder (i.e. expend more energy) to maintain homeostasis, has arguably been the most important conceptual advance of the Allostatic Model (e.g. Korte et al., 2005). Although allostatic load is normally used to refer to cumulative or sustained changes in mediator function due to genetic predispositions, previous history, lifestyle, etc. (McEwen, 1998a), allostatic load also can be interpreted as the ease with which an animal can maintain its mediators in the Reactive Homeostasis range. Maintaining mediators in the Reactive Homeostasis range incurs a cost, either through direct energy consumption or through lost opportunities to perform other tasks such as basic tissue maintenance. Costs increase the longer the mediator continues to stay in the Reactive Homeostasis range and with the frequency that the mediator enters the Reactive Homeostasis range. We propose that "wear and tear" would be a good term for the accumulation of this cost. Note that the concept of wear and tear is different than the concept of pathology. In the later, the mediators themselves are causing damage to the animal, whereas in the former the likelihood of the mediator causing pathology increases.

Wear and tear on the animal can be represented by a gradual decrease in the ability of the animal to cope. As the animal continues to respond to a stressor, and the mediator continues to enter the range of Reactive Homeostasis, the ability of that response to counteract the stressor diminishes. For example, the longer an animal secretes glucocorticoids, the greater the impact on the immune system, which leads to a greater susceptibility to infections (Spencer et al., 2001). At some point, the elevated glucocorticoids will cross a threshold and start to create problems themselves — they have moved from the Reactive Homeostasis range to the Homeostatic Overload range, even though their concentrations may not have changed. In this example, elevated glucocorticoids created wear and tear on the immune system, and consequently decreased the animal's ability to cope. In other words, there are two ways to enter Homeostatic Overload: the concentration or level of the mediator extends beyond the normal reactive scope; or the concentration or level of the mediator remains in the Reactive Homeostasis range for an extended period. The later scenario can be modeled graphically by a gradual decrease in the threshold between the Reactive Homeostasis range and the Homeostatic Overload range. This is an alternative way to express the concepts encompassed by allostatic load. However, for the concept of wear and tear to have anything other than a heuristic value, there must be a physiological mechanism that can produce a gradual decrease in an animal's capacity to cope. In Fig. 2 we propose such a physiological mechanism.

All physiological mediators are under the control of their own regulators. Heart rate, for example, is under the control of two primary regulators — vagal input that decreases heart rate and sympathetic input that increases heart rate (Bohus and Koolhaas, 1993; Perini and Veicsteinas, 2003). Although many mediators are under the control of multiple regulators, Fig. 2 presents a generic mediator under the control of a positive regulator (A) and a negative regulator (B). The normal concentration ranges for the pair of regulators is the normal reactive scope for the system.

When the physiological mediator is in the Predictive Homeostasis range, the concentrations of regulators A and B are balanced so that the physiological mediator is maintained at a stable level (Fig. 2A). When the mediator concentration needs to be maintained in the Reactive Homeostasis range (i.e. a long-term, rather than an acute response), regulator A is altered (e.g. shifting the physiological effect curve to the left generates a greater effect at lower concentrations) so that it drives the concentrations of the physiological mediator up (Fig. 2B). Once the stressor has passed, regulator A can return to its original efficacy, thereby shifting the physiological effect curve to the right, restoring the physiological mediator to its original concentration.

If, however, regulator A continues in it's altered state, regulator B could also change (e.g. shifting its physiological effect curve to the left) in order to restore the physiological mediator to its original concentration (Fig. 2C). Note that as far as restoring the concentrations of the physiological mediator, a decrease in the efficacy of regulator A and an increase in the efficacy of regulator B are functionally equivalent (at least in this simple two-regulator system). The second response (Fig. 2C), however, pushes the system closer to the limits of the normal reactive scope of the system, and would thus make the system more likely to exceed the reactive scope (i.e. enter Homeostatic Overload) if a robust increase in regulator A were required in the future. This increased propensity to exceed the normal reactive scope is what we define as "wear and tear" and this mechanism can provide the physiological foundation for the differences between Reactive Homeostasis and Homeostatic Overload.

We can illustrate this point with the following metaphor. A children's see-saw can be perfectly balanced by two mice or by two

elephants, but the see-saw is going to wear out a lot faster with the elephants. With the elephants, the dynamic range (reactive scope) of the mediator is narrower because the system is less capable of absorbing more weight.

Keeping this underlying mechanism in mind, "wear and tear," or allostatic load, can easily be modeled graphically by a lower border between Reactive Homeostasis and Homeostatic Overload in the basic Reactive Scope Model (Fig. 1A). The closer regulators A and B are to their limits, the less "buffer" there is before the system goes into overload, meaning that there is a decrease in the animal's capacity to cope. In essence, the longer a physiological mediator remains in the Reactive Homeostasis range, the more disrupted the functioning of the underlying regulators becomes. "Wear and tear," however, is a dynamic process. When the animal is required to respond to repeated stressors, a decrease in the Homeostatic Overload threshold begins and continues until the repeated stressors end (Fig. 3A). In other words, the Reactive Homeostasis range narrows because the animal is less capable of adequately coping. Importantly, a narrowing reactive scope does not mean that the animal is in trouble and has entered Homeostatic Overload, just that it has become more vulnerable to entering Homeostatic Overload.

Consider the following financial metaphor. A financial emergency can be dealt with easily by removing money from savings. This does not create long-term problems as long as the financial emergency is not sustained or future financial emergencies do not occur too frequently, but it does decrease the ability to cope with a future emergency. This corresponds to an animal's short-term acute stress response modeled in Fig. 1C. If, however, a person experiences either sustained or frequent emergencies, they quickly deplete their savings and face financial ruin. For an animal, the counterpart for the depletion of savings is McEwen and Wingfield's allostatic load, and the counterpart to financial ruin is McEwen and Wingfield's allostatic overload (either Type I or Type II). Applying this metaphor to our model, the decrease in the threshold between Reactive Homeostasis and Homeostatic Overload is akin to the individual removing money from its savings and thus becoming more vulnerable to future financial crises. If the stressors end before the decrease in the Homeostatic Overload threshold becomes lower than the stress response, then the animal recovers and the Homeostatic Overload threshold returns to its original state. If, however, the stressors continue after the Homeostatic Overload threshold becomes lower than the stress response (Fig. 3A), then the animal enters Homeostatic Overload and the consequences summarized in Table 1 begin to occur. This would be akin to the individual requiring more money than is currently in its financial savings.

Modeling wear and tear, or allostatic load, as a decrease in Homeostatic Overload threshold immediately suggests some complications and some questions. For example, even if this is a good way to graphically model wear and tear, why choose that specific slope for the decline of the Homeostatic Overload threshold? Would it vary between species, or individuals? We have two responses. First, we believe that there is heuristic value in modeling wear and tear in this manner because it illustrates why equivalent stress responses might be adaptive early but cause problems later. It also illustrates why animals will be more resistant to stress-linked pathologies during some life-history stages compared to others. This concept is central to the Allostatic Model (McEwen, 1998b, 2000) and is retained here. Second, the specific slope we selected was for demonstrative purposes, but we anticipate that the actual slope of the decrease can be determined empirically. Since the boundary between Reactive Homeostasis and Homeostatic Overload is equivalent to the peak of the normal reactive scope, the peak

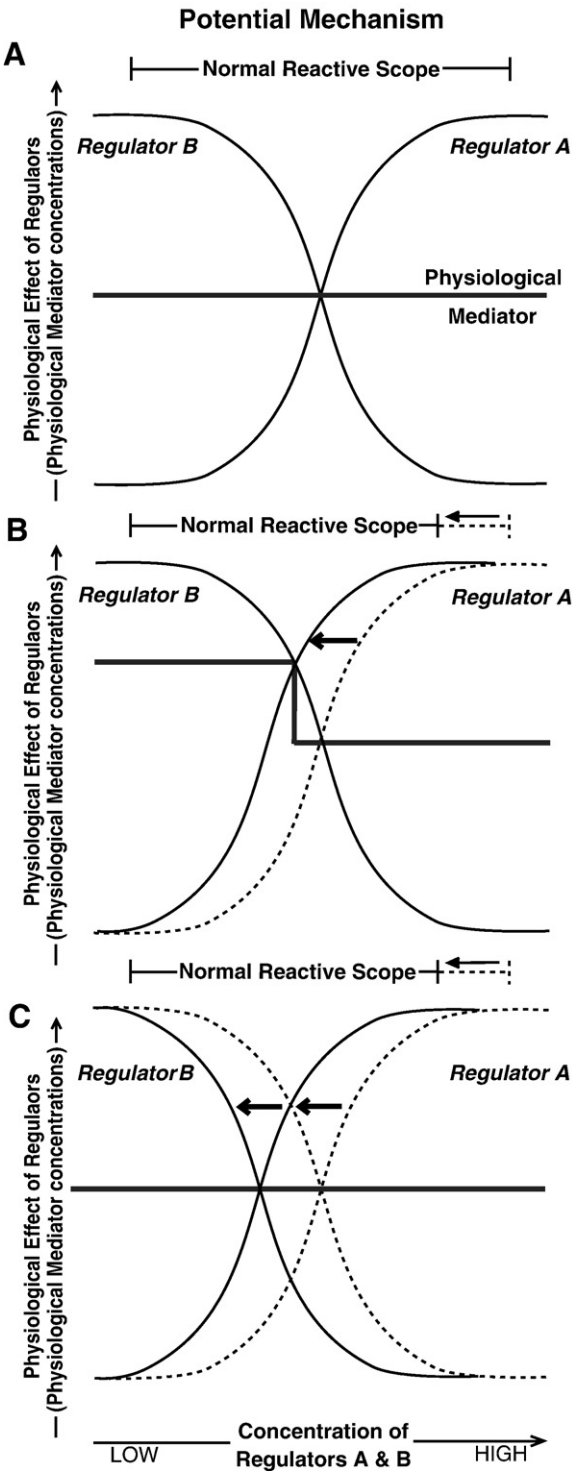

Fig. 2. (A) The concentration/level of the physiological mediator (*y*-axis) depends upon the interaction between the concentrations/levels of a positive Regulator A and a negative Regulator B (*x*-axis). Normal fluctuations of the concentration/level of the mediator (represented by horizontal line) are regulated by changes in the concentrations of both regulators. The *y*-axis can also be thought of as the effectiveness of Regulators A and B in driving the concentration/level of the physiological mediator. The normal reactive scope for the system is determined by the dose–response curves of the two regulators. (B) Long-term increases in the efficacy of Regulator A causes a left-shift in the dose response curve (Regulator A becomes more effective at smaller concentrations/levels). This results in a shift in the balance between Regulators A and B and a long-term increase in the concentration/level of the physiological mediator (represented by horizontal lines). (C) The original concentration/level of the physiological mediator can be restored by an equivalent increase in the efficacy of Regulator B resulting in a left-shift of Regulator B's dose–response curve. In this case, however, the normal reactive scope of the system has narrowed. Note that a similar narrowing of the normal reactive scope would occur if there where a decrease in the efficacies of Regulators A and B (right-shifts to the dose–response curves).

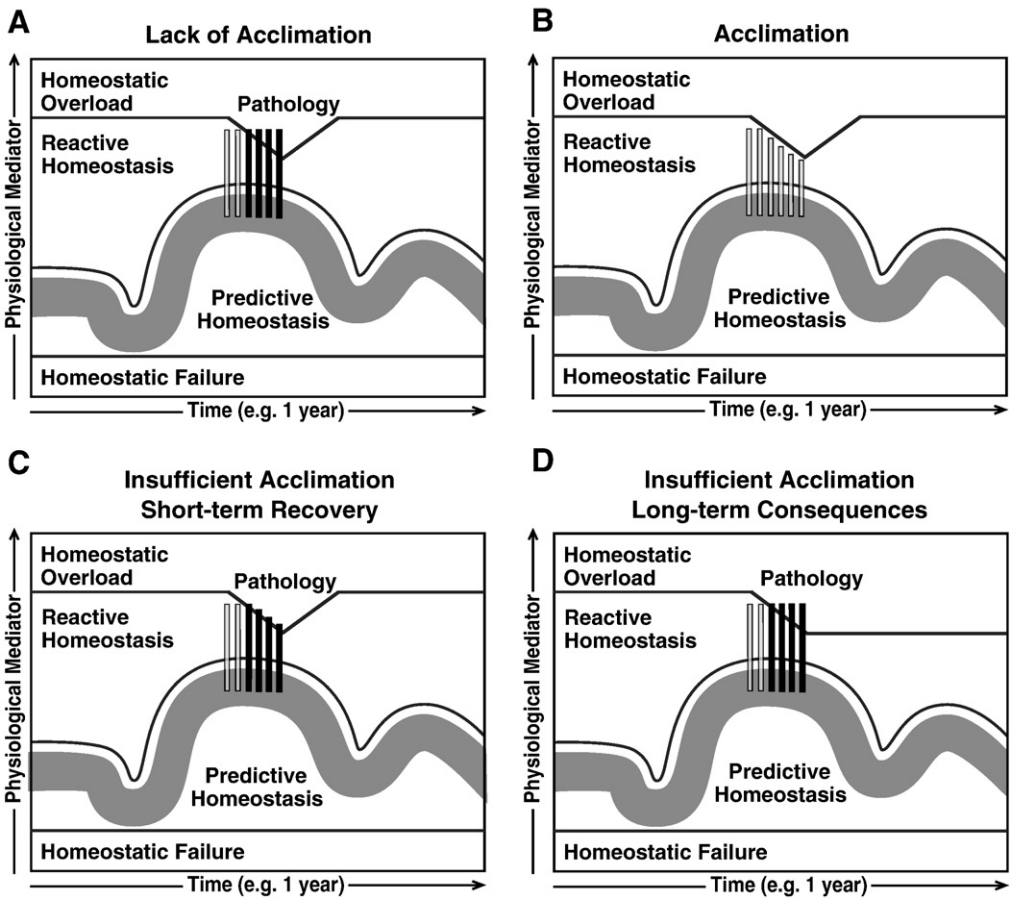

Fig. 3. Impact of repeated stressors on "wear and tear" as depicted by a progressive decrease in the threshold between Reactive Homeostasis and Homeostatic Overload. Each vertical line represents a short-term increase followed by a rapid recovery of the physiological mediator in response to a stressor. Lighter lines represent increases in the concentration/level of the physiological mediator that remain in the Reactive Homeostasis range and darker lines represent increases that extend into the Homeostatic Overload range. (A) Repeated responses to stressors initiate a progressive decrease in the threshold between Reactive Homeostasis and Homeostatic Overload. This graphically models "wear and tear" with a progressive decrease in the ability of the physiological mediator to successfully counteract the stressor without the mediator itself causing problems. When the increases in the mediator extend above the adjusted threshold, pathology resulting from the physiological mediator results. Once the stressors end, the threshold between Reactive Homeostasis and Homeostatic Overload recovers (i.e. "wear and tear" is repaired). (B) The animal acclimates, or habituates, to a repeated stressor so that the response of the physiological mediator to the stressor decreases over time. Even though "wear and tear" continues to occur, the responses never cross the threshold into Homeostatic Overload and pathology does not develop. The accumulated "wear and tear" is then repaired once the stressors end (the threshold between Reactive Homeostasis and Homeostatic Overload returns to its previous concentration/level). (C) As in panel B, the animal acclimates to the repeated stressors, but this acclimation is insufficient to prevent concentrations/levels from entering Homeostatic Overload and pathology due to the physiological mediator develops. The threshold recovers to its original concentration/level once the stressors end. (D) As in panel A, repeated stressors create "wear and tear" and the concentrations/levels of the physiological regulator eventually extend into the Homeostatic Overload range. In this case, once the stressors end the "wear and tear" becomes permanent and the threshold between Reactive Homeostasis and Homeostatic Overload does not recover. The physiological mediator's responses to the stressors have created a permanent decrease in the normal reactive scope of the mediator.

physiological response in a young, healthy, naïve animal should provide the level of the homeostatic mediator that is the limit to Reactive Homeostasis. This is because the level of the threshold is determined by the underlying reactive scope of the regulators in Fig. 2. Then if a light to moderate stressor is applied repeatedly to the animal for a short period, acclimation should occur and the magnitude of the response to the stressor will decrease (Fig. 3B). As long as Homeostatic Overload does not occur (i.e. none of the symptoms from Table 1 occur), the acclimation over time should result in the slope of the line. The slope of this line undoubtedly will differ depending upon the physiological mediator and the species, but at least in principle, the rate of wear and tear on the organism can be determined empirically.

Fig. 3B indicates successful acclimation to repeated stressors. The animal adjusts its stress responses to prevent entering into Homeostatic Overload even though the repeated increases of the mediator into the Reactive Homeostasis range cause wear and tear. Acclimation, however, might be insufficient, leading to the animal entering Homeostatic Overload (Fig. 3C). Fig. 3C, however, models a situation in which even though the animal has entered Homeostatic Overload, when the stressors cease the animal can recover to its original physiological state. In other words, the period of the repeated stressors initiates the symptoms of Homeostatic Overload from Table 1, but the animal suffers no long-term detriments. To return to the financial saving metaphor, even though the animal exhausted its savings, once the stressors cease the animal begins to rebuild those savings.

Notice that both Figs. 3B and C accumulate wear and tear, or allostatic load. However, in the first case the animal successfully acclimates and in the second Homeostatic Overload occurs. The difference between the two responses could derive from either a difference in the severity of the repeated stressor (the more severe stressors being depicted in Fig. 3C) or in the time between stressors (with the more frequent stressors being depicted in Fig. 3C).

In contrast, there are situations where a period in Homeostatic Overload causes permanent changes to the animal's physiology. The animal cannot recover to its original physiological state, even though the stressors have ended and the animal did not die. This can be shown in our graphical modeled by a permanent change in the boundary between the Reactive Homeostasis range and the Homeostatic Overload range (Fig. 3D). Two examples illustrate the

difference between Figs. 3A and D. The first comes from studies of the central nervous system. Repeated stressors can cause remodeling of dendritic processes of neurons and a change in synapse densities, but this process does not necessarily result in the death of these neurons (e.g. Stewart et al., 2005). In contrast, neurons are also known to die during chronic stress (Sapolsky, 1992). Once the stressors end, if neurons are not killed the neuronal remodeling can be reversed so that changes are not permanent (Fig. 3A), but if neurons are killed then the long-term functioning of the brain has changed (Fig. 3D). The second example comes from ecology. Snowshoe hares undergo significant multi-generational population cycles driven primarily by reciprocal changes in predator densities (Boonstra et al., 1998). When population numbers are at their peak, predator pressure becomes intense and population numbers begin to decline. Surviving hares show all the symptoms of Homeostatic Overload (Boonstra et al., 1998) and this intense predation pressure is modeled by Fig. 3A or C. Once the predators disappear, however (primarily due to overexploitation of prey), hares during the nadir of the population cycle show compromised responses to stressors and decreased reproductive potential (Boonstra et al., 1998). This would be the situation modeled in Fig. 3D. Even though predation risk (i.e. the stressor) had ended, there were permanent changes in the subsequent physiology (e.g. reproductive potential) that affected both parent and offspring so that it took several generations to reverse. In conclusion, multiple repeated stressors can have short-term or long-term effects on physiology and both responses can be incorporated in the Reactive Scope model.

Graphically modeling the impact of prolonged stress responses

In their 2003 paper, McEwen and Wingfield (2003b) distinguished between two types of allostatic overload — Type I and Type II. Much of

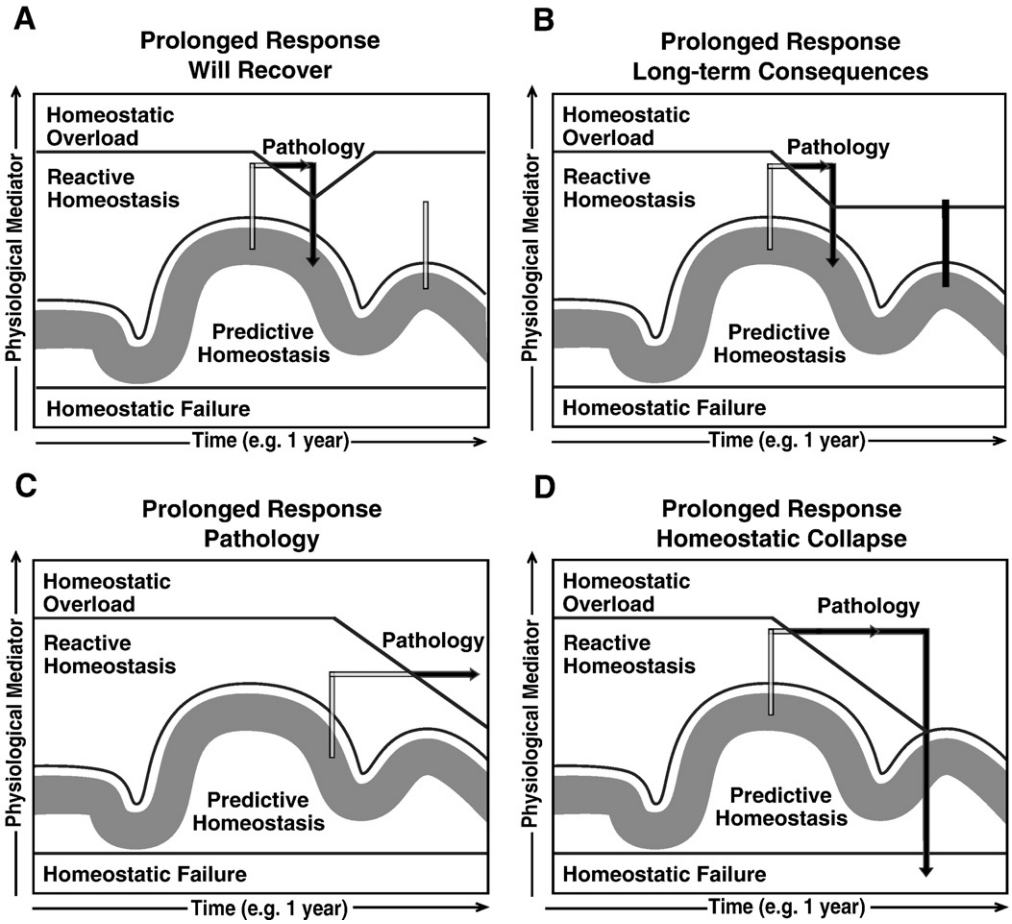

Fig. 4. Impact of prolonged stressors on "wear and tear" as depicted by a progressive decrease in the threshold between Reactive Homeostasis and Homeostatic Overload. Each vertical line represents a short-term increase followed by a rapid recovery of the physiological mediator in response to a stressor. Lighter lines represent increases in the concentration/level of the physiological mediator that remain in the Reactive Homeostasis range and darker lines represent increases that extend into the Homeostatic Overload range. Each initial vertical line represents an identical magnitude response to a stressor even though they are initiated at different points of the seasonal cycle. (A) A prolonged response to a stressor initiates a progressive decrease in the threshold between Reactive Homeostasis and Homeostatic Overload. This graphically models "wear and tear" with a progressive decrease in the ability of the physiological mediator to successfully counteract the stressor without the mediator itself causing problems. When the sustained increase in the concentration/level of the mediator extends above the adjusted threshold, pathology resulting from the physiological mediator results. Once the stressor ends, the mediator returns to the Predictive Homeostasis range and the threshold between Reactive Homeostasis and Homeostatic Overload recovers (i.e. "wear and tear" is repaired) so that a later response to a stressor can remain in the Reactive Homeostasis range. (B) Identical to panel A, except in this case the "wear and tear" becomes permanent and the threshold between Reactive Homeostasis and Homeostatic Overload does not recover. The physiological mediator's responses to the stressors have created a permanent decrease in the normal reactive scope of the mediator. Consequently, a later response to a stressor pushes the physiological mediator immediately into the Homeostatic Overload range. (C) Similar to panel A, but the response to a stressor occurs when the initial concentration/level of the physiological mediator is being maintained at a lower range of Predictive Homeostasis. The wider range of Reactive Homeostasis means that the response can be sustained longer, and "wear and tear" can be accumulated for a longer time, before the concentration/level crosses the threshold between Reactive Homeostasis and Homeostatic Overload and results in pathology. (D) Similar to panel C, but as the concentration/level of the physiological mediator remains in the Homeostatic Overload range it continues to accumulate "wear and tear." Once the threshold between Reactive Homeostasis and Homeostatic Overload intersects the threshold between Reactive Homeostasis and Predictive Homeostasis, the concentration/level of the physiological mediator collapses into the Homeostatic Failure range.

the concept of Type I allostatic overload, characterized by stress responses requiring more energy than is currently available in the environment, is incorporated into our model as depicted in Fig. 3. The concept of Type II allostatic overload, characterized by prolonged activation of stress responses, can also be easily incorporated. Fig. 4 shows how a prolonged response will initiate a progressive decrease in the Homeostatic Overload threshold and ultimately cross that threshold. When the stress response ends, the threshold can either recover to its original level (Fig. 4A) or result in a permanently lower threshold (Fig. 4B). The consequences of having the Homeostatic Overload threshold return to its original level (Fig. 4A) or become permanently altered (Fig. 4B) can be seen with a subsequent stress response. When the threshold is permanently lowered, a future stress response can immediately push the animal into Homeostatic Overload (Fig. 4B) whereas an equivalent stress response in an animal that recovers its threshold remains inside the Reactive Homeostasis range (Fig. 4A). Note that the graphical models for repeated stressors and a prolonged stress response are very similar. The dichotomy between Type I and Type II allostatic overload is no longer necessary.

Inherent in McEwen and Wingfield's (2003b) formulation of allostasis was the explicit incorporation of seasonal variation in an animal's susceptibility to enter Type I allostatic overload. This generated testable predictions of whether an animal was likely to show the symptoms of Homeostatic Overload described in Table 1 and constituted a significant theoretical advance. This concept is easy to incorporate into the Reactive Scope Model as well. The seasonal changes in the Predictive Homeostasis range suggest that when that range is lower, a prolonged stress response will need to be sustained for longer before the decrease in the Homeostatic Overload threshold results in the physiological mediator entering the Homeostatic Overload range (Fig. 4C). To return to the financial metaphor, the size of your savings may change over time, providing more or less of a financial buffer at different times of the year.

Note that one type of chronic stressor, lifestyle, can be easily incorporated into the Reactive Scope model using Figs. 4A–C. Lifestyle, interpreted generally as how an individual copes with its living conditions, could apply to living in poor neighborhoods, coping with agonistic and antagonistic conspecific encounters, living in a zoo, foraging in a dangerous environment, etc. Lifestyle may have a profound impact not only on perception of stressors but also anticipation of stressors. Because both scenarios, reaction to a stressor and anticipation of a stressor, shift the physiological mediators into the Reactive Homeostasis range, the constant anticipation of stressors inherent in some lifestyles will have the functional equivalent of a constant stressor. The result is what is modeled in Fig. 4.

Until now, all the above scenarios have the repeated stressor or prolonged stress response eventually ending. One prediction generated from this graphical model, however, is that as long as a prolonged stress response remains in the Homeostatic Overload range, the threshold between Reactive Homeostasis and Homeostatic Overload continues to decrease (i.e. wear and tear continues to occur, Fig. 4D). When that threshold becomes lower than the Predictive Homeostasis range, normal homeostasis cannot be maintained. Homeostatic collapse will occur and the physiological mediator will fall into the Homeostatic Failure range. Examples of homeostatic failure are included in Table 1. Our model thus provides a testable mechanism, and potentially a testable time frame, for how long a physiological mediator can remain in the Homeostatic Overload range until collapse occurs.

Comparing and contrasting the traditional, allostasis, and reactive scope models using classic stressors

A few stressors have generated enormous interest from both biomedical researchers and ecologists. Three examples of these are chronic malnutrition and/or starvation, changes in social status, and changes in stress responses due to early life experiences. Each of these has relevance to both human health and to wild animals coping with unpredictable environmental events. In this section we present a very brief and simplified description of each stressor, the body's response, and potential downstream pathologies, and then show how these responses would be interpreted by the three different models. Although much is known in the biomedical literature about the responses of many physiological mediators during these stressors, an understanding in free-living animals is just beginning. For wild animals, the best-studied physiological mediators are parts of the HPA axis. To make this section useful for both biomedical researchers and ecologists, we have focused on responses by the HPA axis.

Chronic malnutrition or starvation

Chronic malnutrition or starvation is one of the three major stressors that affect all vertebrates (inclement environmental conditions and predation attempts being the other two). It is a fairly common occurrence in the lives of free-living wild animals (Newton, 1998) and it is often argued that it was common throughout human history as well (Diamond, 1999). There generally are considered three phases of starvation that are vital for survival (Phillips, 1994) — a short phase I uses glucose metabolism, supplemented by breakdown of easily-mobilizable protein, until glucose stores are exhausted; a longer phase II shifts to fatty acid metabolism in an effort to save protein; and a final phase III relies on breakdown of essential proteins for energy after fatty acids are depleted (Cahill, 1976; Robin et al., 1987; Vleck and Vleck, 2002). The decrease in glucose use during phase II is accompanied by increased glucagon (Totzke et al., 1999) and decreased insulin levels (Cahill, 1976), while increased fatty acid metabolism results in production of ketone bodies used by tissues, especially the brain, in lieu of glucose (Owen et al., 1983). The shift from phase II to III is marked by a decrease in fatty acid oxidation (Bernard et al., 2002; Cherel and Le Maho, 1985) and appears to be regulated by corticosteroids (Challet et al., 1995; Cherel et al., 1988; Dallman et al., 1993; Le Ninan et al., 1988; Nasir et al., 1999). Phases I and II are highly adaptive in the sense that they allow the individual to cope with a lack of nutrients. Phase III, in contrast, is typified by the mediators that help regulate phases I and II beginning to break down the proteins necessary for life.

The Traditional Model of stress does a poor job of helping us predict the physiology underlying starvation. For example, the lack of food is clearly a stressor, yet glucocorticoid concentrations show only a transient rise during phase I followed by an extended period during phase II where glucocorticoid concentrations are not elevated (Dallman et al., 1999, 1993). Glucocorticoids only show a robust increase when the individual exhausts its metabolizable fat stores and enters phase III (Cherel et al., 1988). Because glucocorticoid concentrations do not rise during phase II (i.e. no stress response), the traditional model would indicate that this period is not stressful (i.e. lack of food is not a stressor). Instead, the traditional model would predict that as phase II continued and the stressor became more intense, glucocorticoids and other stress mediators would increase. The failure of this prediction highlights the insufficiency of the traditional model.

The Allostasis Model does an excellent job of helping explain starvation because it is an energy-based model. Changes in available energy from the environment is one of the explicit variables in the model and decreases are predicted either to increase allostatic load (by requiring greater foraging effort) or initiating Type I allostatic overload (when the maintenance energy exceeds available energy). However, there are several weaknesses that make it less successful than it would first appear. First, because glucocorticoid concentrations are critical markers of allostatic load, the Allostatic Model cannot explain the lack of glucocorticoid increases during phase II. Like the Traditional Model, the Allostatic Model would predict that glucocorticoid levels should rise in order to mobilize energy and mediate the increase in allostatic load. Second, the concept of allostatic load does not currently encompass differences in how that load is created.

During starvation the source of internal energy shifts from protein to fats and back to protein. Even though the individual is continually in allostatic overload and the amount of mobilized internal energy is equivalent, protein breakdown induces far more damage than does fat breakdown. The Allostatic Model cannot make this distinction. Third, the Allostatic Model cannot predict the initiation of phase III. Based upon energy budgets, the individual is in allostatic overload long before phase III is reached. Phases II and III indicate that not all allostatic overload states are equivalent, yet there is no basis for this difference in the Allostatic Model. Finally, individuals can compensate for lack of food to some extent by decreasing activity (i.e. lethargy), metabolic rate, water utilization, etc. (Cahill, 1976). The end result is a decrease in allostatic load. There is no mechanism in the Allostasis Model that can predict these compensatory changes.

The Reactive Scope Model is more successful at explaining the responses to starvation. The onset of food loss initiates the wear and tear described earlier. The individual must immediately start accessing its reserves, so the ability to cope gradually declines. We can fit this response easily into the Reactive Scope Model by having the threshold for entering Homeostatic Overload immediately start to decline (Fig. 5A). The functional result is a decrease in the range of Predictive Homeostasis, or reactive scope. Modeling starvation in this way solves many of the problems discussed earlier. First, the decrease in reactive scope can be accomplished without extending a response into the Reactive Homeostasis range. Since phase I is transitory, the decrease in reactive scope corresponds to phase II. Consequently, the Reactive Scope Model predicts that glucocorticoid concentrations will not be elevated during phase II. Second, the compensation for lack of food by decreasing activity, metabolic rate, water utilization, etc. can be modeled by shrinking the Predictive Homeostasis range (Fig. 5A). This will functionally extend the time the animal can remain in phase II. Third, the Reactive Scope Model provides a prediction of when the individual will enter phase III — when the threshold reaches the boundary between Predictive and Reactive Homeostasis ranges. This will correspond to when the mediators start to create pathology. Notice that this helps explain the differential damage caused by fat and protein metabolism. In the case of glucocorticoids, when concentrations exceed the truncated reactive scope, they will start to metabolize proteins. The resultant protein breakdown will cause the pathology of Homeostatic Overload. Finally, as discussed earlier in

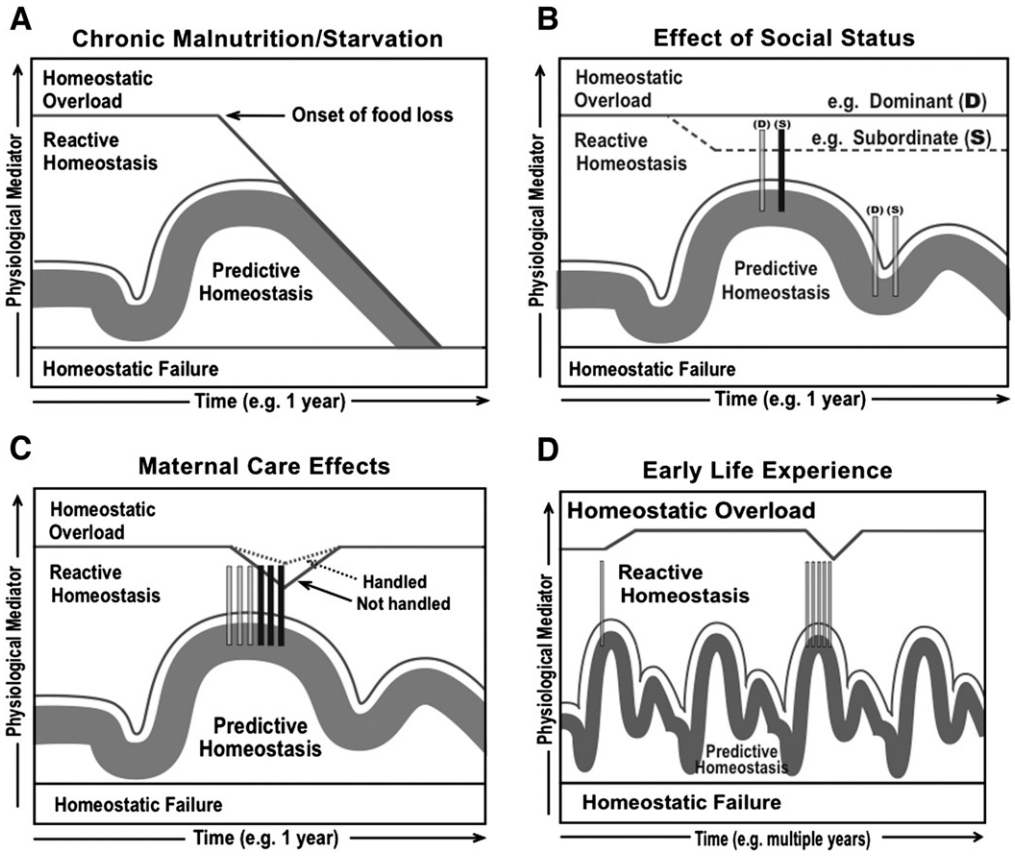

Fig. 5. Examples of modified graphical models that represent responses of physiological mediators to common stressors. A. The response to chronic malnutrition or starvation. The onset of food loss results in a progressive decrease in the threshold between Reactive Homeostasis and Homeostatic Overload, signifying a progressive decrease in the normal reactive scope and the ability to sustain a response in the Reactive Homeostasis range. The individual compensates by progressively truncating its Predictive Homeostasis range, but when "wear and tear" progresses to the point that concentrations/levels cannot be maintained in the Predictive Homeostasis range, concentrations/levels progress into the Homeostatic Failure range and death ensues. B. Social status alters the threshold between Reactive Homeostasis and Homeostatic Overload, with the subordinate having a lower threshold. Each spike represents an identical increase and a decrease in the concentration/level of the physiological mediator, a response that crosses into the Homeostatic Overload range in the subordinate but not in the dominant. Only the subordinate will show pathology. The subordinate can also be more susceptible at certain times of the year, such that when the concentration/level of the physiological mediator is at a lower part of the Predictive Homeostasis range, equivalent responses to the stressor do not cross into Homeostatic Overload. Note that in some species, the more-susceptible social status can be reversed. C. Beneficial effects of a mild handling stressor early in life in altering responses as adults can be graphically modeled by a resistance to "wear and tear," or a shallower decrease in the threshold between Reactive Homeostasis and Homeostatic Overload. The decrease in the normal reactive scope in response to stressors is shallower for the handled individual compared to a non-handled individual. Each spike represents an identical increase and a decrease in the concentration/level of the physiological mediator. The shallower decrease in the Homeostatic Overload threshold means that a similar series of stressors will enter the Homeostatic Overload range sooner in the individual not handled as a neonate. D. An alternative model for mild stressors early in life with a permanently increased threshold between Reactive Homeostasis and Homeostatic Overload. The normal reactive scope for that individual increases. Each spike represents an identical increase and a decrease in the concentration/level of the physiological mediator. The repeated spikes later in life are identical to those depicted in Fig. 3A, but in this case do not extend into the Homeostatic Overload range.

this paper, the slope of the decrease in the threshold of Homeostatic Overload can, in principle, be determined, so that the Reactive Scope Model also provides a testable prediction for when physiological mediators reach the range of Homeostatic Failure and death occurs.

Social status

Social status in humans and other animals can have a profound impact on the ability to cope with stress (Sapolsky, 2005). Which social status is more susceptible to stress is species-dependent (Creel, 2001; Goymann and Wingfield, 2004; Sapolsky, 2005). For example, in many primate dominance hierarchies, lower-ranked individuals are often harassed by higher-ranked individuals, whereas in harem species the dominant male is often continually challenged by subordinates. Social stressors provide a classic example of a situation where the individual must respond to a series of repeated stressors over time. Each stressor requires a response that includes behavioral changes, stimulation of both the sympathetic nervous system and the HPA axis, etc. The accumulation of these stress responses over time eventually leads to numerous physiological problems, including, but not limited to, hypertension, a pathogenic cholesterol profile, decreased fertility, immunosuppression, and dendritic atrophy (reviewed by Sapolsky, 2005). The expression of these pathologies is related to the frequency and intensity of the stressors.

The Traditional Model has been reasonably successful in explaining stress related to social status. Much of our framework for understanding social stress is based upon the concepts of stressors and the resultant pathology is almost the archetypal example of problems resulting from chronic stress. Furthermore, our understanding of which social interactions initiate stress responses is firmly rooted in the concepts of controllability and predictability (Sapolsky, 2005). However, there is nothing in the Traditional Model that helps us understand the progressive wear and tear in response to social stressors that makes individuals more vulnerable to stress-induced pathology. In other words, the Traditional Model does not predict how or when normal adaptive stress responses move into the realm of chronic stress, and thence to pathology. It was specifically this limitation that led many researchers to turn to the Allostasis Model (e.g. McEwen and Seeman, 1999).

The Allostatic Model has been used recently to explain why individuals are more susceptible to stress in humans of lower socio-economic status (SES) (McEwen, 2000). The use of allostasis, and specifically allostatic load, in humans was a major advancement because for the first time there were clear predictions as to which individuals would ultimately face pathological consequences for social interactions (McEwen, 2000). The sum of an individual's status on ten indices, such as systolic and diastolic blood pressure, waist–hip ratio, urinary adrenalin, noradrenalin and cortisol, and serum cholesterol, determines the accumulated allostatic load (Seeman et al., 1997) and the accumulated allostatic load is correlated with the pathological aspects of low SES. However, there are several drawbacks that prevent the Allostatic Model from providing a complete picture of social stress. Note that none of the indices are energy based, so that allostatic overload must result from Type II, not Type I, overload. Consequently, the Allostatic Model is good at showing that allostatic overload results from accumulated allostatic load, but what causes allostatic load? In other words, the Allostatic Model does not help in understanding what drives increases in systolic and diastolic blood pressure, waist–hip ratio, etc. Instead, it relies upon the Traditional Model (i.e. repeated exposure to stressors) to explain changes in allostatic parameters. Furthermore, the Allostatic Model provides little help in predicting when allostatic load will become allostatic overload.

Although low SES in human societies is very different from dominant/subordinate relationships in animal societies, Goymann and Wingfield (2004) provide the only attempt to date to apply allostasis to social stress in nonhuman species. They used energy, and thus Type I allostatic overload, to try to solve the problem of predicting whether dominants or subordinates will show higher stress-induced pathology. They showed that allostatic load is an excellent predictor of ultimate pathology. However, they encountered the same problem as the analyses of allostasis and low SES. The Traditional Model is still required to understand how allostatic load accumulates in the first place.

The Reactive Scope Model specifically addresses accumulation of wear and tear. Low SES is easily modeled in Fig. 4, where the wear and tear of the low SES lifestyle creates the reduced reactive scope that eventually results in Homeostatic Overload. Dominant/subordinate relationships can also be represented by modifying Fig. 3. Subordinate status can be indicated with a lower threshold between Reactive Homeostasis and Homeostatic Overload (Fig. 5B) in a case where the subordinate is more susceptible to social stressors than is the dominant (the thresholds can be reversed for species where the dominant is more susceptible). Differentiation of these thresholds can be extrapolated easily from Figs. 3A and D during the period when dominance is established. Establishment of the dominance relationship is often the period when social stressors are most intense (Sapolsky, 2005), thereby requiring either stronger or more frequent increases into the Reactive Homeostasis range. The threshold will be permanently reset for the individual that experiences the most intense stressors (i.e. Fig. 3D), resulting in a narrower reactive scope, but the threshold will recover for the individual that experiences the less intense stressors (i.e. Fig. 3A). The downstream consequences will be profound, even though the intense period of dominance establishment ends. This difference in thresholds means that the subordinate has less of a buffer and is more vulnerable to entering Homeostatic Overload. It is striking how closely the pathological consequences of social stress presented above (Sapolsky, 2005) match the consequences of having stress mediators in the Homeostatic Overload range as shown in Table 1. Social stressor-induced pathology ultimately results from the subordinate being more vulnerable than the dominant to multiple increases into the Reactive Homeostasis range, thereby further decreasing the threshold to Homeostatic Overload. Alternatively, an equivalent future stress response will remain within the Reactive Homeostasis range for the dominant individual, but reach into the Homeostatic Overload range in the subordinate. One prediction from the Reactive Scope model is that the subordinate will also be more vulnerable to other nonsocial stressors. Once again, the Reactive Scope Model provides a potential time-frame for when pathology will begin to appear.

Early life experience

A substantial amount of work indicates that early life experience can alter how an individual responds to stress later in life. In general, early short-term maternal separation of a neonate makes the animal less susceptible to stressors (i.e. less likely to show stress-induced pathology) as an adult (Caldji et al., 2000; Champagne et al., 2003). The basic profile of these animals is that exposure to a mild stressor as a neonate induces a reduction in hypothalamic-pituitary-adrenal (HPA) responses to stressors as an adult when compared to a non-handled cohort. However, the basal HPA physiology of handled and non-handled adults appears equivalent. These are life-long changes and the mechanism appears to involve permanent changes in the brain. For example, laboratory rodents exhibit large increases in glucocorticoid receptors in the brain (Caldji et al., 2001; McEwen et al., 1999) regulated by changes in DNA methylation that alter receptor gene transcription rates (Szyf et al., 2005). The increased receptor number then enhances the efficacy of negative feedback so that glucocorticoids are less likely to induce stress-related pathology. The ultimate environmental stimulus that appears to drive these mechanistic changes is an increase in maternal grooming (Cameron et al., 2005). Although the majority of this work has been in laboratory rodents and primates, similar changes may occur in

humans (Gunnar and Donzella, 2002). Note that the decrease in HPA responses resulting from a mild stressor as a neonate differ from increases in HPA responses resulting from more intense stressors as a neonate, such as maternal separation in laboratory rodents (reviewed by Cameron et al., 2005), maternal stress in birds (e.g. Hayward and Wingfield, 2004; Rubolini et al., 2005; Saino et al., 2005), or child abuse in human children (e.g. Tarullo and Gunnar, 2006; Teicher et al., 2006).

The Traditional Model does a very poor job helping us understand beneficial changes in HPA function resulting from a mild stressor early in life. The core concepts of the Traditional Model, stress responses initiated by lack of predictability and/or controllability and a threat to homeostasis, do not allow us to predict the existence of responses to stimuli that make an individual less vulnerable. The failure of the Traditional Model was highlighted in a recent review (Cameron et al., 2005). In fact, the Traditional Model has been so unsuccessful in providing a framework for reductions in adult vulnerabilities due to neonatal exposures that numerous researchers have resorted to invoking the concept of "eustress," a word used by Selye (1976) to highlight the positive aspects of stressors and stress responses.

The Allostasis Model, at least the formulation based upon energy, also is not successful at producing a useful framework. The life-long changes in HPA responsiveness have no obvious connection to energy. There is nothing in the Allostatic Model that could account for a long-term decrease in vulnerability to allostatic overload. There is no evidence in these individuals for changes in energy mobilization or the energy required to maintain allostasis. As a consequence, the Allostatic Model cannot predict that these individuals would be more resistant to entering Type I allostatic overload (i.e. enter a negative energy balance). Increased negative feedback might explain why individuals are resistant to Type II allostatic overload (i.e. increased glucocorticoids cause problems even though energy is plentiful), but this begs the question of how and why a decrease in HPA axis reactivity arose in the first place.

The Reactive Scope Model, on the other hand, provides a framework for understanding how a mild stressor to a neonate can result in a life-long phenotypic change. The increase in maternal grooming can alter the underlying dynamics of the regulators in Fig. 2 (e.g. by altering glucocorticoid receptor numbers), thereby making it less likely that later in life the regulators will shift (Fig. 2B). This in turn will make it less likely that a stressor experienced as an adult will decrease the reactive scope. This can be readily represented graphically with a lower slope in the decrease of the threshold between Predictive and Reactive Homeostasis upon the onset of the stressor (Fig. 5C). This makes it less likely that the individual will enter Homeostatic Overload. Alternatively, a mild stressor as a neonate can permanently elevate and reset the threshold between Reactive Homeostasis and Homeostatic Overload (Fig. 5D). This would essentially provide a larger buffer later in life, so that repeated or prolonged stress responses later in life are less likely to reach the Homeostatic Overload range. In either case, the Reactive Scope Model predicts potentially beneficial effects of mild stressors. It provides a framework for how changes occurring during development can reset an animal's reactive scope and provides a mechanism for why that resetting will result in lower vulnerability to entering Homeostatic Overload later in life.

Conclusion

Our goal in creating this graphical model was to retain the benefits of the concepts of homeostasis and allostasis while at the same time removing some of the weaknesses identified in the current formulation of allostasis. We do not see the Reactive Scope model as a rebuttal of allostasis, but rather as an extension of allostasis. We use different nomenclature to avoid confusion with previously-defined terms. We anticipate that the Reactive Scope Model will have both heuristic value in helping categorize how individual animals respond to stressors, as well as predictive value in helping formulate new hypotheses. Just like McEwen and Wingfield's (2003b) Allostasis Model, we hope that this formulation of these concepts will be of use both in understanding stress in wild animals as well as understanding stress in humans both in health and disease.

One last note: because we hope the model will be broadly applicable, we chose only three examples to illustrate how we envision the model functioning with specific species or specific diseases. We anticipate that much of this model's value will be in modifying it to accommodate the specifics of the species, the individual, or disease that is being studied, much like we did in Fig. 5.

Acknowledgments

We thank Mary Dallman, Michaela Hau, Martin Wikelski, John Wingfield, Robert Sapolsky, and four anonymous reviewers for invaluable comments on early drafts. We especially thank Robert Sapolsky for suggesting the elephant and mouse analogy. We also thank the many participants of the E-Bird collaborative network workshop on allostasis for providing the context and impetus for this work. Funding was provided by the United States National Science Foundation, both from a workshop grant through the E-Bird collaborative network (IBN-0342242 to John Wingfield) and from IOB-0542099 and DEB-0545592 to LMR.

References

Bernard, S.F., Mioskowski, E., Groscolas, R., 2002. Blockade of fatty acid oxidation mimics phase II-phase III transition in a fasting bird, the king penguin. Am. J. Physiol., Regul. Integr. Comp. Physiol. 283, R144–R152.
Bohus, B., Koolhaas, J.M., 1993. Stress and the cardiovascular system: central and peripheral physiological mechanisms. In: Stanford, S.C., et al. (Ed.), Stress: From Synapse to Syndrome. Academic Press, Boston, MA, pp. 75–117.
Boonstra, R., Hik, D., Singleton, G.P., Tinnikov, A., 1998. The impact of predator-induced stress on the snowshore hare cycle. Ecol. Monogr. 68, 371–394.
Cahill, G.F.J., 1976. Starvation in man. Clin. Endocrinol. Metab. 5, 397–415.
Caldji, C., Diorio, J., Meaney, M.J., 2000. Variations in maternal care in infancy regulate the development of stress reactivity. Biol. Psychiatry 48, 1164–1174.
Caldji, C., Liu, D., Sharma, S., Diorio, J., Francis, D., Meaney, M.J., Plotsky, P.M., 2001. Development of individual differences in behavioral and endocrine responses to stress: role of the postnatal environment. In: McEwen, B.S., Goodman, H.M. (Eds.), Handbook of Physiology; Section 7: The Endocrine System; Volume IV: Coping with the Environment: Neural and Endocrine Mechanisms. Oxford University Press, New York, pp. 271–292.
Cameron, N.M., Champagne, F.A., Parent, C., Fish, E.W., Ozaki-Kuroda, K., Meaney, M.J., 2005. The programming of individual differences in defensive responses and reproductive strategies in the rat through variations in maternal care. Neurosci. Biobehav. Rev. 29, 843–865.
Cannon, W.B., 1932. The Wisdom of the Body. W.W. Norton & Company, inc., New York.
Challet, E., le Maho, Y., Robin, J.P., Malan, A., Cherel, Y., 1995. Involvement of corticosterone in the fasting-induced rise in protein utilization and locomotor activity. Pharmacol. Biochem. Behav. 50, 405–412.
Champagne, F.A., Francis, D.D., Mar, A., Meaney, M.J., 2003. Variations in maternal care in the rat as a mediating influence for the effects of environment on development. Physiol. Behav. 79, 359–371.
Cherel, Y., Le Maho, Y., 1985. Five months of fasting in king penguin chicks: body mass loss and fuel metabolism. Am. J. Physiol., Regul. Integr. Comp. Physiol. 18, R387–R392.
Cherel, Y., Robin, J.P., Walch, O., Karmann, H., Netchitailo, P., Le Maho, Y., 1988. Fasting in king penguin. I. Hormonal and metabolic changes during breeding. Am. J. Physiol. 254, R170–177.
Chrousos, G.P., Gold, P.W., 1992. The concepts of stress and stress system disorders overview of physical and behavioral homeostasis. J. Am. Med. Assoc. 267, 1244–1252.
Creel, S., 2001. Social dominance and stress hormones. Trends Ecol. Evol. 16, 491–497.
Cyr, N.E., Wikelski, M., Romero, L.M., 2008. Increased energy expenditure but decreased stress responsiveness during molt. Physiol. Biochem. Zool. 81, 452–462.
Dallman, M.F., 2003. Stress by any other name …? Horm. Behav. 43, 18–20.
Dallman, M.F., Akana, S.F., Cascio, C.S., Darlington, D.N., Jacobson, L., Levin, N., 1987. Regulation of ACTH secretion: variations on a theme of B. Recent Prog. Horm. Res. 43, 113–173.
Dallman, M.F., Strack, A.M., Akana, S.F., Bradbury, M.J., Hanson, E.S., Scribner, K.A., Smith, M., 1993. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front. Neuroendocrinol. 14, 303–347.
Dallman, M.F., Akana, S.F., Bhatnagar, S., Bell, M.E., Choi, S., Chu, A., Horsley, C., Levin, N., Meijer, O., Soriano, L.R., Strack, A.M., Viau, V., 1999. Starvation: early signals, sensors, and sequelae. Endocrinology 140, 4015–4023.

Darlington, D.N., Chew, G., Ha, T., Keil, L.C., Dallman, M.F., 1990. Corticosterone, but not glucose, treatment enables fasted adrenalectomized rats to survive moderate hemorrhage. Endocrinology. 127, 766–772.
Day, T.A., 2005. Defining stress as a prelude to mapping its neurocircuitry: no help from allostasis. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 29, 1195.
Diamond, J., 1999. Guns, Germs, and Steel: The Fate of Human Societies. W.W. Norton & Co., New York.
Goldstein, D.S., McEwen, B., 2002. Allostasis, homeostats, and the nature of stress. Stress 5, 55–58.
Goymann, W., Wingfield, J.C., 2004. Allostatic load, social status and stress hormones: the costs of social status matter. Anim. Behav. 67, 591–602.
Gunnar, M.R., Donzella, B., 2002. Social regulation of the cortisol levels in early human development. Psychoneuroendocrinology 27, 199–220.
Hadany, L., Beker, T., Eshel, I., Feldman, M.W., 2006. Why is stress so deadly? An evolutionary perspective. Proc. R. Soc. Biol. Sci. (Series B). 273, 881–885.
Hayward, L.S., Wingfield, J.C., 2004. Maternal corticosterone is transferred to avian yolk and may alter offspring growth and adult phenotype. Gen. Comp. Endocrinol. 135, 365–371.
Kapoor, A., Dunn, E., Kostaki, A., Andrews, M.H., Matthews, S.G., 2006. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. J. Physiol. 572.
Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.
Korte, S.M., Koolhaas, J.M., Wingfield, J.C., McEwen, B.S., 2005. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci. Biobehav. Rev. 29, 3–38.
Landys, M.M., Ramenofsky, M., Wingfield, J.C., 2006. Actions of glucocorticoids at a seasonal baseline as compared to stress-related levels in the regulation of periodic life processes. Gen. Comp. Endocrinol. 148, 132–149.
Le Moal, M., 2007. Historical approach and evolution of the stress concept: a personal account. Psychoneuroendocrinology 32, S3–S9.
Le Ninan, F., Cherel, Y., Sardet, C., Le Maho, Y., 1988. Plasma hormone levels in relation to lipid and protein metabolism during prolonged fasting in king penguin chicks. Gen. Comp. Endocrinol. 71, 331–337.
Levine, S., 2005. Stress: an historical perspective. In: Steckler, T., et al. (Ed.), Handbook of Stress and the Brain. Elsevier, Amsterdam, the Netherlands, pp. 3–23.
Levine, S., Ursin, H., 1991. What is stress? In: Brown, M.R., et al. (Ed.), Stress: Neurobiology and Neuroendocrinology. Marcel Dekker, Inc., New York, pp. 3–21.
McEwen, B.S., 1998a. Protective and damaging effects of stress mediators. New Engl. J. Med. 338, 171–179.
McEwen, B.S., 1998b. Protective and damaging effects of stress. New Engl. J. Med. 338, 171–179.
McEwen, B.S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108–124.
McEwen, B.S., 2003. Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. Metabolism 52, 10–16.
McEwen, B.S., Seeman, T., 1999. Anonymous, Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load. Annals of the New York Academy of Sciences; Socioeconomic Status and Health in Industrial Nations: Social, Psychological and Biological Pathways, pp. 30–47.
McEwen, B.S., Wingfield, J.C., 2003a. Response to commentaries on the concept of allostasis. Horm. Behav. 43, 28–30.
McEwen, B.S., Wingfield, J.C., 2003b. The concept of allostasis in biology and biomedicine. Horm. Behav. 43, 2–15.
McEwen, B.S., de Leon, M.J., Lupien, S.J., Meaney, M.J., 1999. Corticosteroids, the aging brain and cognition. Trends Endocrinol. Metab. 10, 92–96.
Moore-Ede, M.C., 1986. Physiology of the circadian timing system: predictive versus reactive homeostasis. Am. J. Physiol., Regul. Integr. Comp. Physiol. 250, R735–R752.
Munck, A., Koritz, S.B., 1962. Studies on the mode of action of glucocorticoids in rats. I. Early effects of cortisol on blood glucose and on glucose entry into muscle, liver and adipose tissue. Biochim. Biophys. Acta 57.
Nasir, A., Moudgal, R.P., Singh, N.B., 1999. Involvement of corticosterone in food intake, food passage time and *in vivo* uptake of nutrients in the chicken (*Gallus domesticus*). Br. Poult. Sci. 40, 517–522.
Nelson, R.J., Demas, G.E., Klein, S.L., Kriegsfeld, L.J., 2002. Seasonal Patterns of Stress, Immune Function, and Disease. Cambridge University Press, Cambridge.
Newton, I., 1998. Population Limitation in Birds. Academic Press, Boston.
Owen, O.E., Caprio, S., Reichard Jr., G.A., Boden, G., Owen, R.S., 1983. Ketosis of starvation: a revisit and new perspectives. Clin. Endocrinol. Metab. 12, 359–379.
Perini, R., Veicsteinas, A., 2003. Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. Eur. J. Appl. Physiol. 90, 317–325.
Phillips, W.J., 1994. Starvation and survival: some military considerations. Mil. Med. 159, 513–516.
Popov, V.I., Bocharova, L.S., 1992. Hibernation-induced structural changes in synaptic contacts between mossy fibres and hippocampal pyramidal neurons. Neuroscience 48, 53–62.
Popov, V.I., Bocharova, L.S., Bragin, A.G., 1992. Repeated changes of dendritic morphology in the hippocampus of ground squirrels in the course of hibernation. Neuroscience 48, 45–51.
Reeder, D.M., Kramer, K.M., 2005. Stress in free-ranging mammals: integrating physiology, ecology, and natural history. J. Mammal. 86, 225–235.
Remage-Healey, L., Romero, L.M., 2001. Corticosterone and insulin interact to regulate glucose and triglyceride levels during stress in a bird. Am. J. Physiol., Regul. Integr. Comp. Physiol. 281, R994–R1003.
Robin, J.P., Cherel, Y., Girard, H., Geloen, A., LeMaho, Y., 1987. Uric acid and urea in relation to protein catabolism in long-term fasting geese. J. Comp. Physiol., Part B. 157, 491–499.
Romero, L.M., 2002. Seasonal changes in plasma glucocorticoid concentrations in free-living vertebrates. Gen. Comp. Endocrinol. 128, 1–24.
Romero, L.M., 2004. Physiological stress in ecology: lessons from biomedical research. Trends Ecol. Evol. 19, 249–255.
Romero, L.M., Wikelski, M., 2001. Corticosterone levels predict survival probabilities of Galápagos marine iguanas during El Niño events. Proc. Natl. Acad. Sci. U. S. A. 98, 7366–7370.
Romero, L.M., Reed, J.M., Wingfield, J.C., 2000. Effects of weather on corticosterone responses in wild free-living passerine birds. Gen. Comp. Endocrinol. 118, 113–122.
Rubolini, D., Romano, M., Boncoraglio, G., Ferrari, R.P., Martinelli, R., Galeotti, P., Fasola, M., Saino, N., 2005. Effects of elevated egg corticosterone levels on behavior, growth, and immunity of yellow-legged gull (*Larus michahellis*) chicks. Horm. Behav. 47, 592–605.
Saino, N., Romano, M., Ferrari, R.P., Martinelli, R., Moller, A.P., 2005. Stressed mothers lay eggs with high corticosterone levels which produce low-quality offspring. J. Exp. Zool. 303A, 998–1006.
Sapolsky, R.M., 1992. Stress, the Aging Brain, and the Mechanisms of Neuron Death. MIT Press, Cambridge, MA.
Sapolsky, R.M., 2001. Physiological and pathophysiological implications of social stress in mammals. In: McEwen, B.S., Goodman, H.M. (Eds.), Handbook of Physiology; Section 7: The Endocrine System; Volume IV: Coping with the Environment: Neural and Endocrine Mechanisms. Oxford University Press, New York, pp. 517–532.
Sapolsky, R.M., 2005. The influence of social hierarchy on primate health. Science 308, 648–652.
Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress-responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55–89.
Schulkin, J., 2003. Rethinking Homeostasis: Allostatic Regulation in Physiology and Pathophysiology. MIT Press, Cambridge, MA.
Seeman, T.E., Singer, B.H., Rowe, J.W., Horwitz, R.I., McEwen, B.S., 1997. Price of adaptation. Allostatic load and its health consequences. MacArthur studies of successful aging. Arch. Intern. Med. 157, 2259–2268.
Seeman, T.E., McEwen, B.S., Rowe, J.W., Singer, B.H., 2001. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc. Natl. Acad. Sci. of the U. S. A. 98, 4770–4775.
Selye, H., 1946. The general adaptation syndrome and the diseases of adaptation. Journal of Clin. Endocrinol. 6, 117–230.
Selye, H., 1971. Hormones and resistance. J. Pharm. Sci. 60, 1–28.
Selye, H., 1976. The Stress of Life. McGraw-Hill, New York.
Spencer, R.L., Kalman, B.A., Dhabhar, F.S., 2001. Role of endogenous glucocorticoids in immune system function: regulation and counterregulation. In: McEwen, B., Goodman, H.M. (Eds.), Handbook of Physiology; Section 7: The Endocrine System; Volume IV: Coping with the Environment: Neural and Endocrine Mechanisms. Oxford University Press, New York, pp. 381–423.
Steen, J.B., Gabrielsen, G.W., Kanwisher, J.W., 1988. Physiological aspects of freezing behavior in willow ptarmigan hens. Acta Physiol. Scand. 134, 299–304.
Sterling, P., Eyer, J., 1988. Allostasis a new paradigm to explain arousal pathology. In: Fisher, S., Reason, J. (Eds.), Handbook of Life Stress Cognition and Health. John Wiley and Sons, Inc., New York, pp. 629–650.
Stewart, M.G., Davies, H.A., Sandi, C., Kraev, I.V., Rogachevsky, V.V., Peddie, C.J., Rodriguez, J.J., Cordero, M.I., Donohue, H.S., Gabbott, P.L.A., Popov, V.I., 2005. Stress suppresses and learning induces plasticity in CA3 of rat hippocampus: a three-dimensional ultrastructural study of thorny excrescences and their postsynaptic densities. Neuroscience. 131, 43–54.
Szyf, M., Weaver, I.C.G., Champagne, F.A., Diorio, J., Meaney, M.J., 2005. Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. Front. Neuroendocrinol. 26, 139–162.
Tarullo, A.R., Gunnar, M.R., 2006. Child maltreatment and the developing HPA axis. Horm. Behav. 50, 632–639.
Teicher, M.H., Tomoda, A., Andersen, S.L., 2006. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? Ann. N.Y. Acad. Sci. 313–323.
Totzke, U., Hubinger, A., Korthaus, G., Bairlein, F., 1999. Fasting increases the plasma glucagon response in the migratory garden warbler (*Sylvia borin*). Gen. Comp. Endocrinol. 115, 116–121.
Vleck, C.M., Vleck, D., 2002. Physiological condition and reproductive consequences in Adelie penguins. Integr. Comp. Biol. 42, 76–83.
Walsberg, G.E., 2003. How useful is energy balance as a overall index of stress in animals? Horm. Behav. 43, 16–17.
Wingfield, J.C., Breuner, C., Jacobs, J., 1997. Corticosterone and behavioral responses to unpredictable events. In: Harvey, S., Etches, R.J. (Eds.), Perspectives in Avian Endocrinology. Journal of Endocrinology Press, Bristol, U.K., pp. 267–278.
Wingfield, J.C., Maney, D.L., Breuner, C.W., Jacobs, J.D., Lynn, S., Ramenofsky, M., Richardson, R.D., 1998. Ecological bases of hormone-behavior interactions: the "emergency life history stage". Integr. Comp. Biol. 38, 191.