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Review

Stress revisited: A critical evaluation of the stress concept

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ABSTRACT

With the steadily increasing number of publications in the field of stress research it has become evident that the conventional usage of the stress concept bears considerable problems. The use of the term 'stress' to conditions ranging from even the mildest challenging stimulation to severely aversive conditions, is in our view inappropriate. Review of the literature reveals that the physiological 'stress' response to appetitive, rewarding stimuli that are often not considered to be stressors can be as large as the response to negative stimuli. Analysis of the physiological response during exercise supports the view that the magnitude of the neuroendocrine response reflects the metabolic and physiological demands required for behavioural activity. We propose that the term 'stress' should be restricted to conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability. Physiologically, stress seems to be characterized by either the absence of an anticipatory response (unpredictable) or a reduced recovery (uncontrollable) of the neuroendocrine reaction. The consequences of this restricted definition for stress research and the interpretation of results in terms of the adaptive and/or maladaptive nature of the response are discussed.

Contents

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1. Introduction

The present paper is the result of a workshop on conceptual issues in stress research held in spring 2009 in Göttingen (Germany), organized by Eberhard Fuchs and Jaap Koolhaas. The workshop brought together a number of scientists that are actively involved in preclinical stress research. They intensively discussed the current use of the stress concept in various scientific disciplines and the lack of consistency of scientific results across laboratories and stress models. The group felt it important to revitalize the view that stress should be considered as a cognitive perception of uncontrollability and/or unpredictability that is expressed in a physiological and behavioural response. Moreover, one needs to be aware that the reverse is not always true: the physiological response by itself does not necessarily always indicate a state of stress. We propose that the use of the terms 'stress' and 'stressor' should be restricted to conditions and stimuli where predictability and controllability are at stake; unpredictability being characterized by the absence of an anticipatory response and loss of control being reflected by a delayed recovery of the response and the presence of a typical neuroendocrine profile. This definition will be discussed in the following sections and we argue that this more narrow definition will avoid confusion with normal physiological reactions that are mandatory to support behaviour.

The concept of stress has been subject of scientific debate ever since its first use in physiological and biomedical research by Selye (1950). Stress was originally defined as the non-specific response of the body to any noxious stimulus. Later, the concept was refined by distinguishing between 'stressor' and 'stress response'. A stressor is considered a stimulus that threatens homeostasis and the stress response is the reaction of the organism aimed to regain homeostasis (Chrousos, 2009). The term "homeostasis" was originally coined by Cannon (1932). In his work, he conceived that many physiological variables such as blood pressure, blood glucose and intracellular osmolarity have a certain preferred set-point and that a deviation of this set-point is counteracted by physiological responses which are aimed at restoring the optimal level. Several authors have emphasized the ambiguity and circularity of the definition of stress in terms of a threat to homeostasis in general (Levine and Ursin, 1991; McEwen, 1998; Day, 2005; Levine, 2005; Romero et al., 2009). Virtually all activities of an organism directly or indirectly concern the defense of homeostasis. Hence, the definition of stress as a threat to homeostasis is almost meaningless and needs critical consideration in the light of the current knowledge of the systems involved.

Levine and Ursin (1991) emphasize the view that stress should be considered as a process that includes the stimulus, the perceptual processing of this input and the behavioural and physiological output (Levine, 2005). Many studies seem to neglect the aspect of cognitive, higher level cortical processing of information leading to the risk of circular reasoning. In fact, many studies interpret the presence of a stress response as an indicator of stress exposure, without an independent definition of either the stressor or the stress response (Armario, 2006). Conversely, other studies define their stimulus as aversive, often from an anthropomorphic line of reasoning, and interpret the response as a stress response. Hence, there is a need for indices that allow an answer to the question whether a stimulus is indeed perceived as a stressor in the sense that it is considered as a serious threat to homeostasis and thus to physical and psychological health.

Apart from this definition problem, there is the question of the adaptive and/or maladaptive nature of the stress response. In the formulation of the General Adaptation Syndrome (GAS), Selye (1936, 1950) has emphasized the adaptive nature of the stress response. Only after prolonged exposure to stressors might adaptation fail and the organism reach a phase of exhaustion with adverse consequences. Research has always struggled with this dual nature of the stress response. The terms 'distress' and 'eustress' were introduced by Selye in 1976 to distinguish between the maladaptive and the adaptive consequences of the stress response, respectively (Selye, 1976). Despite the fact that several authors have emphasized both the adaptive and maladaptive aspects of the stress response (McEwen and Wingfield, 2003; de Kloet et al., 2005; Korte et al., 2005; Dallman, 2007), it appears to be extremely difficult to dissociate these two sides of the coin. This may lead to a certain degree of interpretation bias of the experimental results in either the maladaptive or adaptive direction.

In the present paper, we will argue that the stress terminology should be limited to uncontrollability and/or unpredictability of stimuli. To illustrate this, we want to follow a less biased line of reasoning by starting from the wide range of both causal and supporting physiological processes required for the performance of behaviour.

2. Physiological support of behaviour

The hypothalamic pituitary adrenocortical (HPA) axis and the sympathetic adrenomedullary (SAM) system are generally considered to be the two key players in the stress response. These systems are well recognized to have a main role in energy mobilization and redistribution of e.g. oxygen and nutrients to active organs and tissues, a metabolic function that goes beyond stress *per se*. Therefore, from a more neutral point of view, one might say that both the HPA and the SAM system have a crucial function in the metabolic and cardiovascular preparation of the body to perform behaviour (Sapolsky et al., 2000). These two master systems can be considered as integrated communication systems aimed to coordinate and synchronize the peripheral physiology at the level of cells, tissues and organs in interaction with the environment. Metabolically more demanding behaviour will be accompanied by a higher activation. To illustrate this point, we will compare the HPA axis activity during several types of behaviours, some of which are not generally thought of in the context of stress. The HPA axis activation of rats in response to aversive (painful) stimuli as well as appetitive (rewarding stimuli) is summarized in Fig. 1, expressed as area under the curve for plasma corticosterone. Although there may be species and/or strain differences in the magnitude of these responses, it is clear that a stress-related framework of interpretation fails to explain the activation of the HPA axis shown in Fig. 1. Appetitive and rewarding situations such as sexual behaviour (Bronson and Desjardins, 1982; Woodson et al., 2003; Bonilla-Jaime et al., 2006) and winning a social interaction elicit HPA responses that are similar in magnitude as highly aversive situations like social defeat.

In many cases, the magnitude of the response seems to be a direct reflection of the behavioural activity and hence of the metabolic requirements of activated tissues. It is important to notice that the stimulus that triggers the behaviour may not necessarily present a direct challenge to homeostasis. Behaviour and hence the physiological response can be self-initiated or be trig-

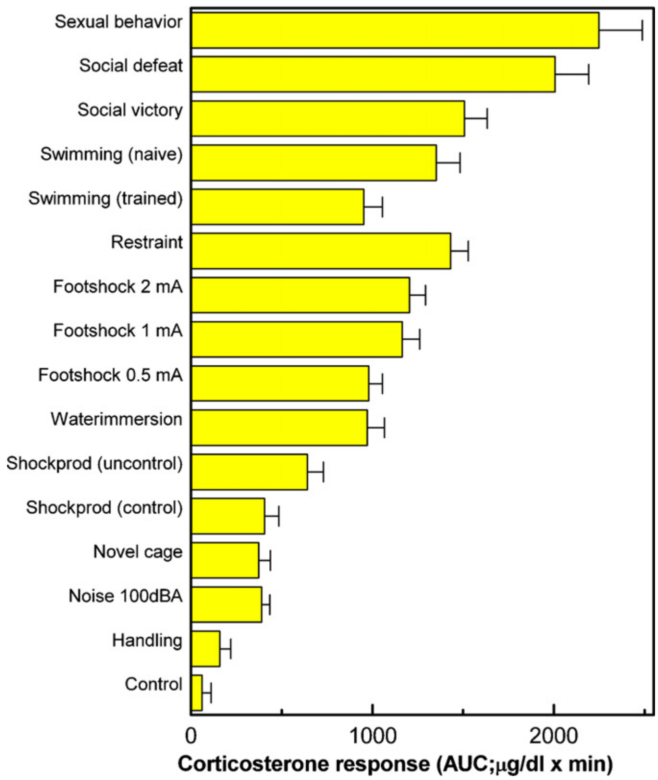

Fig. 1. Plasma corticosterone responses of adult male Wistar rats to different test conditions, quantified as total area under the response curve (AUC). Each test consisted of a standardized series of baseline samples and a 15 min exposure to the stimulus followed by a recovery phase for the remaining hour. The control condition is based on a home cage sample taken halfway through the active period. Blood samples were collected via a permanently implanted jugular vein canula (Koolhaas et al., 1997).

gered in anticipation of homeostatic needs, or may occur in reaction to a threat to homeostasis.

The notion that many appetitive and aversive stimuli may activate both the HPA and the SAM system has long been recognized. Indeed, Hennessy and Levine (1979) considered this system as a component of the general arousal system. We prefer to see arousal as an important physiological prerequisite in support of behaviour and the preparation thereof (see also Pfaff et al., 2008). The degree of activation may be a direct reflection of the amount of physical activity and of the accompanying metabolic demands.

In our opinion, the physiological reactions that are a prerequisite of any behaviour should not be called “stress” nor should arousal be used as synonymous of “stress”. Nevertheless, intuitively several situations such as social defeat can be considered as serious stressors. What then is the difference between appetitive situations like victory or sexual activity on the one hand and strongly aversive situations like social defeat on the other hand if the magnitude of the physiological response does not discriminate between the two? In other words, when is a stimulus a stressor and what makes a response a stress response?

3. Controllability and predictability

The terms controllability and predictability are central in the definition of a stressor. These terms date back to a series of experiments by Weiss (1972) in the early seventies of the last century. Using a well-validated stress paradigm, the author concluded that it is not the physical nature of an aversive stimulus that induces pathology such as stomach wall erosions but rather the degree in which the stimulus can be predicted and controlled. Although the concept of controllability and predictability has strongly contributed to the present insights in stress physiology and the development of stress-related pathology, there are two problems with this hypothesis. First, there is a lot of evidence from the human literature that it is not the actual control that counts, but the perceived control (Salvador, 2005). For preclinical research this means that stimuli that are considered as stressors from the anthropomorphic point of view may not necessarily be stressors from the animal point of view. Second, controllability and predictability are generally operationally defined as binary factors, i.e. full control or complete absence of control often using strongly aversive stimuli. However, in everyday life situations controllability is graded from absolute control, via threat to control to loss of control. For example, a dominant male rat may have full control in a stable social environment, but only partial control or may experience threat to control in socially unstable conditions (Ely and Henry, 1978; Manuck et al., 1983; Sapolsky, 1995; Fokkema et al., 1995). The graded degree of controllability and predictability in the development of stress-related pathology requires further attention. Moreover, the biology of the species and the natural adaptive capacity and defense repertoire (see also Section 6) offers a range of situations that can be used to design experiments with a more refined gradation of stressors and a higher ecological validity. For example, one may use predictability and controllability over food availability or the workload to obtain that food as stressor. After all, the controllability and predictability of food availability and the effort to obtain food are crucial to survival and part of everyday life in nature. Along these lines, de Boer et al. (1990) demonstrated the importance of controllability and predictability for HPA axis and SAM activation in an experiment on food availability. Jugular vein-cannulated rats were trained to lever press for food and the availability of that food was signaled by the introduction of the (retractable) levers into their home cage. This paradigm allows the analysis of the physiological response in relation to the predictability and controllability of food availability. The corticosterone response in a condition where bar pressing delivered food and a situation of extinction where lever pressing no longer resulted in receiving food pellets is shown in Fig. 2. Both conditions showed a strong anticipatory corticosterone response. However, in the food reward condition, the corticosterone concentrations rapidly decline, but they remain high in the non-reward condition (Fig. 2, lower panel). Moreover, in the SAM response there is a clear dissociation between adrenaline and noradrenaline. After a small anticipatory response, noradrenaline rises strongly in the reward condition only. This is consistent with the general view that plasma noradrenaline is closely associated with physical activity (Christensen and Galbo, 1983). Adrenaline on the other hand shows a rise in the non-reward condition only, suggesting that it is closely associated with uncontrollability. These experiments lead to three important conclusions. First, organisms prepare physiologically in anticipation of expected events (Ferrari et al., 2003). Hence, an unpredictable situation should be characterized by the absence of an anticipatory response. This has to be kept in mind in particular in experiments using frequent/repeated exposure to stressors. Second, it may be the downward slope of the HPA response (or the recovery to baseline) rather than the peak of the response that dissociates a controllable from an uncontrollable condition. Third, in the SAM system, plasma adrenaline in particular seems to be associated with the uncontrollable condition.

Let us consider in more detail the hypothesis that a stressor can be distinguished from a normal controllable situation by the recovery of the physiological response rather than the magnitude of the response. Early experiments by Schuurman (1981) already showed in male rats that the main difference in the corticosterone response to either winning or losing a social interaction is the speed of recovery of the response (Fig. 3). This also holds for the SAM response and blood pressure, and heart rate responses during winning and losing

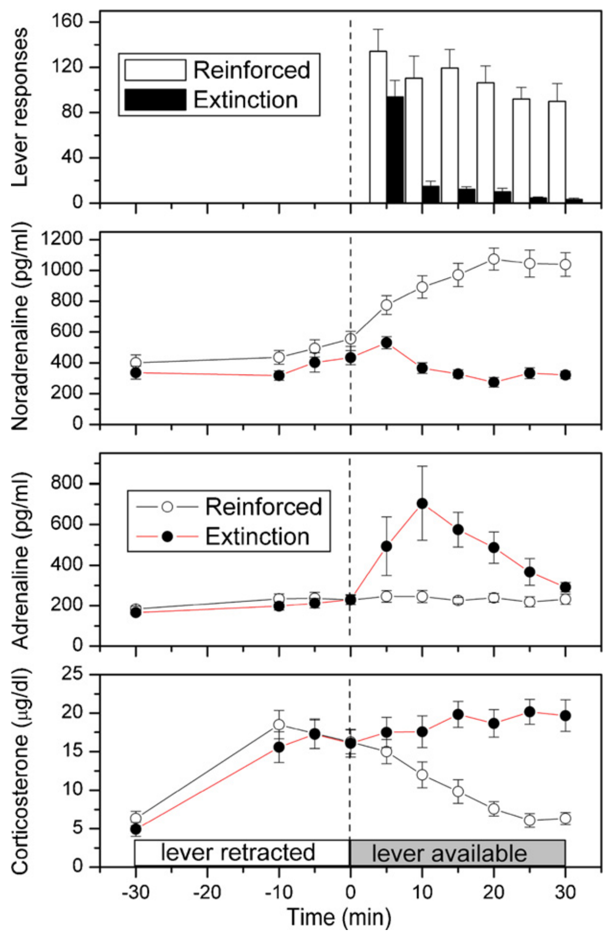

Fig. 2. Behavioural and physiological measures obtained in male rats in an operant conditioning paradigm. Rats were trained to obtain food by pressing a lever. In the experiment, well trained rats were suddenly put in extinction, i.e. lever presses are no longer reinforced. Blood samples were collected via a permanently implanted jugular vein canula (de Boer et al., 1990).

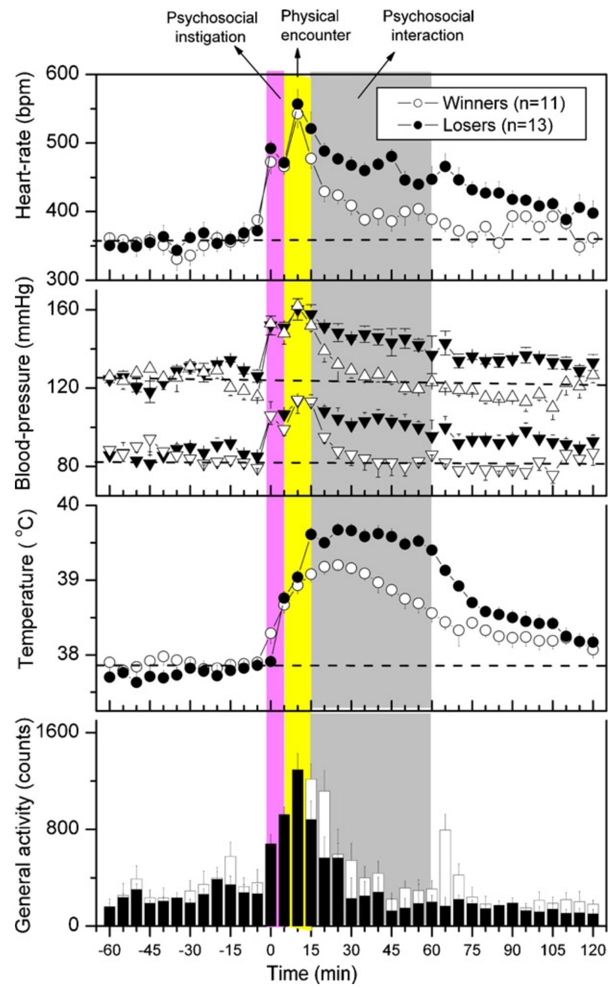

Fig. 4. Changes in heart rate, blood pressure and core body temperature in male rats during winning or losing a social interaction in a resident intruder paradigm. The animals were provided with permanently implanted radiotelemetry transmitters.

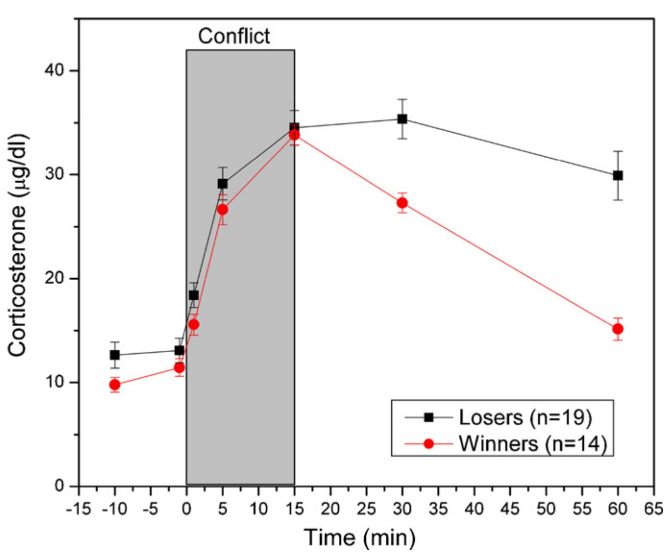

Fig. 3. Time course of plasma corticosterone concentration in male rats that either win or lose a social confrontation in a resident intruder paradigm. Blood samples were collected via a permanently implanted jugular vein canula.

a social interaction (Fig. 4). Here too, the main difference between the appetitive and rewarding condition of winning and the aversive condition of defeat is in the recovery of elevated levels to baseline values, the downward slope of the response (Fish et al., 2005). When fighting dyads are only physically separated after repetitive fights, cardiovascular adaptation does occur neither in winners nor in losers (Bartolomucci et al., 2003). The physical separation seems to create an uncontrollable situation for both animals because the winner is unable to exclude the defeated animal and the loser is unable to escape from the winner.

While the peak of the response (Figs. 3 and 4) may be considered as physiological support for the actual or anticipated physical activity involved in the conflict, it is unlikely that the difference in recovery is due to a difference in behavioural activity since during the recovery phase, the stimulus animal is absent and the test animal generally rests quietly in its cage. The need to focus on the recovery of the response is consistent with the experiments by Garcia and colleagues. They observed that the speed of recovery of the HPA response to immobilization stress depends on previous experience (Garcia et al., 2000). A single pre-exposure to immobilization stress strongly enhanced the speed of recovery. This relation with previous stress experience may also be interpreted in terms of increased predictability and controllability.

The downward slope of the sympathetic response is likely to reflect the return of parasympathetic tone concomitantly with the fading of sympathetic activation. The mechanisms underlying the

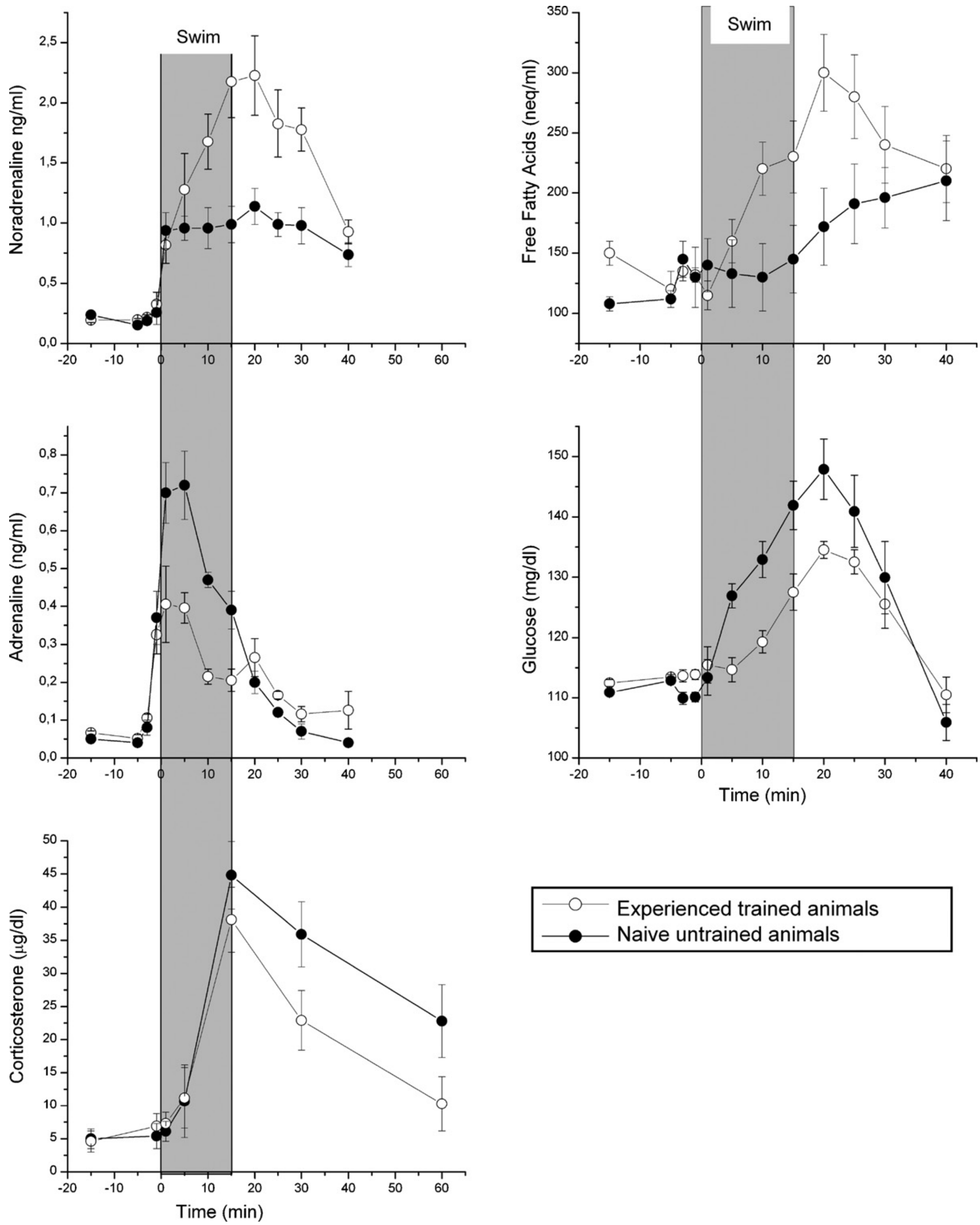

Fig. 5. Plasma neuroendocrine responses of naïve and experienced male rats during physical exercise. Blood samples were collected via a permanently implanted jugular vein canula. Exercise consisted of 15 min swimming against a counter current in lukewarm water (Scheurink et al., 1999).

change in autonomic balance during the recovery phase are largely unknown. Recent evidence suggests that the speed of recovery of the HPA axis response is determined by a delayed onset of negative feedback control mechanisms. This delayed onset includes a fast non-genomic action of glucocorticoids on neuronal excitability mediated by both mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (de Kloet et al., 2008). It is suggested that the stressful nature of a stimulus acts in particular through this fast glucocorticoid action. However, a study by Arnhold et al. (2009) suggests that the parasympathetic nervous system might be involved in the recovery of the HPA response as well. Similar to the controllable and uncontrollable food availability mentioned above (de Boer et al., 1990), these authors described a rapid decline of plasma corticosterone concentrations in thirsty rats during drinking. This rapid decline in HPA axis activity could be prevented by subdiaphragmatic vagotomy (Arnhold et al., 2009).

We conclude that the use of the terms ‘stress’ and ‘stressor’ should be restricted to conditions and stimuli where predictability and controllability are at stake. Unpredictability is characterized by the absence of an anticipatory response. Loss of control may be reflected by a delayed recovery of the response and the presence of an adrenaline response. This more narrow definition will avoid confusion with normal physiological reactions that are mandatory to support behaviour.

4. Frequency and predictability of stressors

The chronic character of stressors is generally considered an important factor in the development of various forms of stress-related pathology. In view of the discussion above on predictability and controllability, frequency and duration of stressors are a matter of concern. After all, with repeated exposure to a stimulus, predictability may increase and increased control cannot be excluded as well. Many chronic stress models use in fact a series of intermittent acute aversive stimuli of variable duration [e.g. the chronic mild stress protocol (Willner, 2005)]. It is quite conceivable that stimuli, which, according to our definition were stressors in the beginning of the experiment, may not be perceived as stressors anymore after a while (e.g. Martinez et al., 1998). The implication of this view is that behavioural and physiological changes observed in such a chronic intermittent paradigm must be interpreted as adaptation rather than pathology. The recent observation that exposure to a predictable mild 'stress' paradigm changes behaviour and physiology in opposite direction as chronic unpredictable 'stress' is consistent with this view (Parihar et al., 2009).

The gradual decline of the magnitude of the physiological response with repeated exposures to stressors/stimuli is well known. This decline is generally interpreted as habituation. However, Grissom and Bhatnagar (2009) argue that the decline of the HPA response with repeated exposures to the stimulus reflects a higher order adaptive process and thus an elaborate central nervous interpretation (processing) by the individual that leads to increased predictability and control over the challenging situation. Here, the role of the medial prefrontal cortex, especially the infralimbic region, that plays a role in stress controllability (Amat et al., 2005) and that exerts an inhibitory influence on emotional responsiveness as observed during extinction of conditioned fear, warrants further investigation (Sotres-Bayon and Quirk, 2010).

An example of the adaptive nature of the changes in physiological responses with repeated exposure to the same stressor is given in Fig. 5. This figure shows the plasma catecholamines adrenaline and noradrenaline, free fatty acid (FFA) and corticosterone levels in a forced swim experiment in male rats. The amount of physical activity was standardized throughout the experiment to 15 min of swimming against a counter current. When rats are forced to swim for the first time, there is a strong rise in adrenaline that is reduced by 50% in rats tested after repeated swimming trials. The opposite is shown for the noradrenaline response; after repeated exposures the response is significantly increased. These alterations are accompanied by changes in the mobilization of energy substrates. With repeated experiences, the metabolism shifts from glucose to fatty acids (Scheurink et al., 1999). According to the views of sports physiology (Holloszy et al., 1998), this can be considered as an example of an adaptive process. In the naïve animal, the stimulus can be considered as unpredictable and uncontrollable, because a laboratory-bred rat has never been exposed to a swimming pool before. Consequently, the animal responds with a strong adrenaline response and a metabolic overshoot in the form of glucose mobilization. After repeated exposures, the magnitude of sympathetic response seems to become tuned to the mere metabolic demands of swimming for 15 min. Also, the magnitude of the corticosterone response is reduced in the experienced animals. Moreover, analysis of the speed of recovery of the response reveals a significantly more rapid decline in the experienced animals ($p = 0.02$). This is consistent with the view that the situation has become controllable and

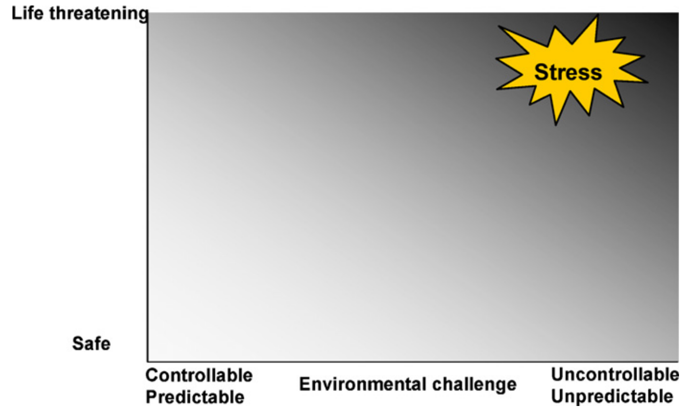

Fig. 6. Graphic presentation of the relationship between the controllability and predictability of environmental challenges and the life threatening nature of these challenges. The term "stress" should be restricted to conditions depicted in the right top corner of the graph. The lower left corner belongs to the realm of the physiological support of behaviour.

therefore, the stimulus may no longer be perceived by the animal as a stressor. In fact, after a while the animals appear to like swimming and often jump into the water from the waiting platform before the actual start of the experiment. This is consistent with the notion that water is an important component of the natural habitat of the Norway rat in which swimming is a part of every day life. Although there is a difference in the speed of recovery of the corticosterone response, it is important to notice that swim experiments are not very suitable for an accurate analysis of the recovery. This is due to the fact that the animals will show a lot of grooming behaviour to reorganize and clean their wet coats.

It is surprising that the factor of predictability in terms of outcome expectancy has not played a more prominent role in the design of stress experiments so far; although it is addressed in newer theoretical approaches (see e.g. Eriksen et al., 2005). Intuitively, one may expect the largest behavioural and physiological impact when an originally fully predictable and seemingly controllable situation suddenly deteriorates and becomes unpredictable and uncontrollable. Indeed, predictability implies that the response of the organism depends on previous experience. An indication that this might be true is given in an experiment in which animals were socially defeated after they had already ten winning experiences (Meerlo et al., 1999). A single social defeat in these experienced winners had a long-lasting impact on their circadian amplitude of heart rate, body temperature and physical activity, in only part of the animals, indicating individual differences in stress susceptibility. Similarly, losing territory ownership and lowering in social rank has been demonstrated to exert greater immune-suppressing effects than social subordination in itself in a mouse model of chronic subordination stress (Bartolomucci, 2007).

5. Stressor intensity

Apart from being qualitatively defined as an uncontrollable and/or unpredictable stimulus, a stressor has a quantitative dimension as well. An individual's interpretation of a situation and its reaction may vary from full control to only partial or complete loss of control. Moreover, a stressor may be mild in terms of its potential consequences or it may be life-threatening. Of course, a traumatic event that is life-threatening can be regarded as an unpredictable and uncontrollable situation. In theory, this leads to a three-dimensional constellation in which controllability and predictability form two dimensions and the third dimension is stressor intensity. However, because controllability and predictability are not fully independent, these two dimensions are combined in Fig. 6.

This figure depicts a graded relationship between the degree of uncontrollability/unpredictability and the life-threatening nature of the situation. The lower part of the *Y*-axis indicates the 'safe' condition where the organism is free from any environmental challenges, e.g. a clear and fully accepted position in the social hierarchy, presence of sufficient social support, freely available food, etc. As argued before, the term 'stress' should be restricted to conditions depicted in the right top corner of the graph, for example an unstable social hierarchy, social outcast, limited access to food or resources (e.g. Bohus et al., 1991; Sapolsky, 1995; Bartolomucci, 2007).

Also in the situation of a traumatic life event, the subjective perception of the event seems to contribute to the severity of its consequences. For example in humans, a traumatic-like event will trigger post-traumatic stress disorder (PTSD) only in about 20–30% of the individuals, despite a similar uncontrollable, unpredictable and potentially life-threatening situation (Breslau, 2001). Similar percentages were obtained in a rat model of PTSD (Cohen et al., 2004). This again demonstrates that the subjective perception and subsequent central nervous processing of information on e.g. a cognitive rational versus emotional level will additionally determine the severity of a stressor and its potential pathological consequences. As argued above, the speed of recovery of the HPA and the SAM response as well as adrenaline may be used as indices to determine whether a certain stimulus is perceived as stressor by the individual.

6. Homeostasis, allostasis, regulatory range and adaptive capacity

Many of the issues addressed above have been discussed by McEwen in his seminal work on allostasis (McEwen and Stellar, 1993; McEwen, 1998; McEwen and Wingfield, 2003). Allostasis is defined as the process of achieving stability through change in anticipation of physiological requirements (Sterling and Eyer, 1988). Organisms can maintain stability by changing set-points of homeostatic mechanisms; the same idea was already included in the original definition of homeostasis by Cannon (1932). Since physiological parameters fluctuate within certain ranges that are further affected by oscillating circadian and seasonal changes (e.g. acclimation), the classical homeostatic theory of biological systems according to which physiological processes, when perturbated readjust to maintain 'constancy' does not hold (Stiedl et al., 2004). The brain plays a central role in the regulation of allostasis. Allostasis involves mechanisms that change the controlled physiological variable by predicting what level will be needed to meet anticipated demand (Koob and Le Moal, 2001). Natural selection has sculpted physiology and behaviour to meet the most likely environmental demands plus a modest safety margin. Thus, allostasis considers a physiological response not as an attempt to defend a set-point, but rather as a response to some prediction. After all, it is much more cost-efficient to prevent errors than to correct them. This is clearly demonstrated by the swim test data presented in Fig. 5, in which the physiological response changes with repeated experience. A better prediction of the demands shifts the integrated response. Indeed, mediators of allostasis (e.g. adrenal hormones, neurotransmitters, cytokines, etc.) act on receptors in various tissues and organs to produce changes that are adaptive to behaviour, metabolism, immune system and cardiovascular system in the short term. A state of chronic deviation of the regulatory system from its normal (homeostatic) operating level is called allostatic state (Koob and Le Moal, 2001).

Recently, a refinement to the allostasis concept has been formulated by Romero et al. (2009) in their reactive scope model. From an evolutionary point of view, not only species, but also individuals of a given species are optimized to survive in a species-specific habitat and an ecological niche. This implies that species and individuals have a certain range of environmental conditions within which regulating processes operate adequately without requiring adaptive changes. We will call this range of environmental conditions the regulatory range. These environmental conditions may include a temperature range, a range of food availability or a range of social instability. The regulatory range should be distinguished from adaptive capacity. The distinction between regulatory range and adaptive capacity can be illustrated by considering the response of an organism to an environment of food shortage that gets gradually colder. The adaptive capacity includes behavioural responses such as migration in anticipation of a seasonal drop in temperature and food shortage, building a nest to reduce energy expenditure, food hoarding, etc. A physiological response may include changes in cardiovascular physiology and metabolism. At the level of the brain, some species such as groundhogs have the capacity to change the set-point of body temperature regulation and metabolism and go into torpor (Heldmaier et al., 2004). Thus, the full adaptive capacity includes mechanisms at the level of the brain, peripheral physiology and behaviour. In a fully fit and healthy organism this set of mechanisms is optimized for a range of environmental conditions (regulatory range). However, there are many conditions that may reduce the actual adaptive capacity of an individual. For example, when an individual has been unable to build up sufficient adipose tissue due to food shortage, or has insufficient nest building material, its capacity to cope with a freezing temperature is reduced. In these situations, despite an individual being within his normal regulatory range, its adaptive capacity might be reduced and the stimulus will be perceived as a stressor, thus inducing a stress response, in agreement with our definition.

This distinction between regulatory range and adaptive capacity is depicted in Fig. 7A. The exact shape of the curve within the regulatory range depends on conditions such as circadian and seasonal rhythms, previous experience, general physical condition, age, gender, etc. (Wingfield, 2008). Environmental conditions that exceed the adaptive capacity result in failure to mount an adequate response or in failure of shutting off the physiological response when the challenge is over.

The distinction between regulatory range and adaptive capacity implies that a stressor might affect either the adaptive capacity (Fig. 7B) or the regulatory range (Fig. 7C). A reduced adaptive capacity as indicated in Fig. 7B implies that stimulus intensities that were originally not perceived as stressors and allowed a normal physiological and behavioural adaptive response (Fig. 7A) are now perceived as uncontrollable. Alternatively, a shift of the regulatory range of the organism (Fig. 7C) implies that conditions that were originally perceived as a stressor are now fully controllable and predictable.

It is important to realize that the concept of regulatory range has not only a quantitative character, but includes a qualitative aspect as well. In other words, individuals may differ qualitatively in the way they deal with environmental challenges. Studies in a wide variety of species show that even within a particular species, individuals may differ in their coping style (Koolhaas et al., 1999). Recent ecological evidence shows that these coping styles are in fact individual adaptations to different environmental conditions. This individual variation in coping style within a species has fitness value and apparently protects the species against fluctuations in the environment (Sih et al., 2004; Dingemanse et al., 2004). For example, proactive coping individuals are adapted to stable, predictable environments, whereas reactive coping individuals do better in an unpredictable environment. Hence, in terms of the conceptual model presented above one has to consider the possibility that individuals may have different regulatory ranges. This implies that a stimulus that is perceived as a stressor by one individual may not

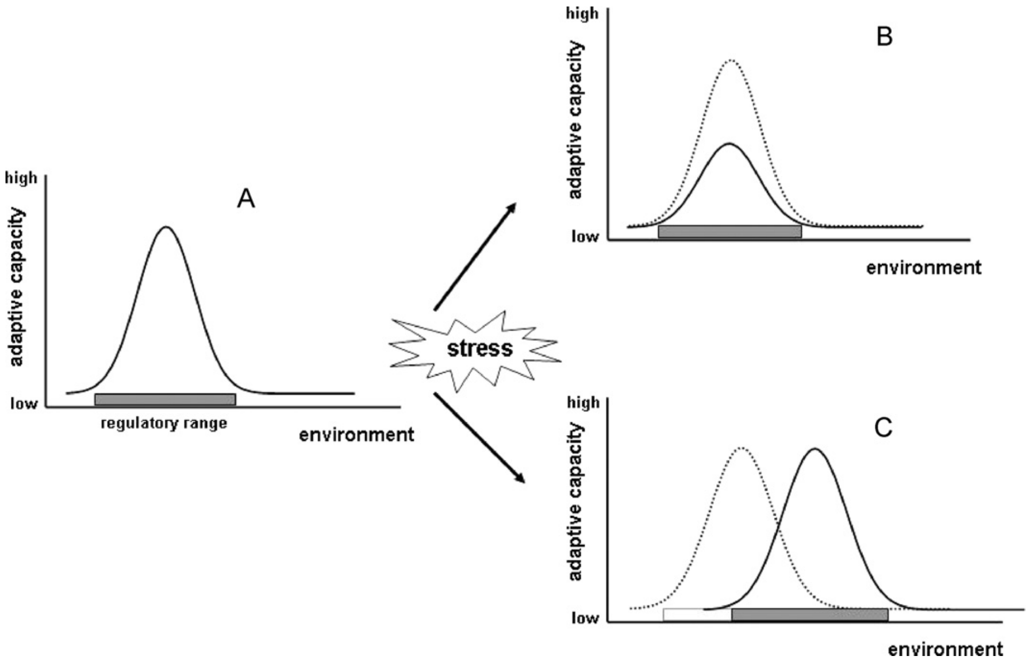

Fig. 7. Schematic presentation of the concepts of regulatory range and adaptive capacity (A) and the two alternative ways in which a stressor might affect an organism. The *X*-axis represents the characteristics of the environment such as ambient temperature, food density or stability of the social structure. (B) shows that stress reduces adaptive capacity (solid line) compared to the original capacity (stippled line). (C) depicts a situation where stress induces a shift in the regulatory range of the organism while the adaptive capacity remains the same as in (A).

necessarily be a stressor for another individual of the same species and living in the same environment as well. Thus, the term regulatory range refers to the theoretically maximum range of conditions that a fit and healthy organism can cope with. Adaptive capacity is the remaining capacity given environmental constraints and the wear and tear of homeostatic processes.

Taken together, this conceptual framework leads to the following definition of a stressor: a stressor is a stimulus or environmental condition in which the response demands exceed the adaptive capacity of the organism. Demands that fall within the adaptive capacity belong to the realm of the normal physiology of behaviour and therefore should not be regarded as stressors.

7. Consequences

7.1. Regulatory range and adaptive capacity

The restricted and refined definition of stress and the distinction between regulatory range and adaptive capacity has a number of consequences regarding the design and interpretation of experiments. The bottom line of many, if not all stress experiments is that a stimulus changes the organism. This change may occur at various levels of organization from behavioural to physiological. In view of the distinction between regulatory range and adaptive capacity, such a change may now be interpreted in two directions. As argued above (Fig. 7), it may either present a change in adaptive capacity or a shift in regulatory range. While most results of stress research have been interpreted in terms of adaptive capacity, i.e. disease vulnerability, interpretations in terms of regulatory range have hardly been considered. This is important in particular for developmental studies aimed at the consequences of perinatal or adolescent stress for vulnerability to stressful experiences later in life. Indeed, several studies indicate that the prenatal and neonatal (maternal) environment prepares the organism for environmental conditions it may have to cope with in adulthood (Kaiser and Sachser, 2005; Champagne et al., 2008). This has been summarized as the predictive adaptation hypothesis and implies in our terminology that the prenatal/neonatal environment determines the regulatory range. Similar views are currently developed on the importance of individual phenotypical variation and phenotypic plasticity in the ecology and evolutionary biology of a species (Stamps and Groothuis, 2010). In the same line of reasoning, recent studies in humans indicate that genetic and developmental processes as well as their interactions determine the regulatory range, rather than the adaptive capacity (Belsky et al., 2009). An interpretation in terms of regulatory range is also consistent with the match–mismatch hypothesis (Gluckman et al., 2007). This hypothesis is based on recent evidence that early maternal environment seems to prepare the regulatory range of offspring for the conditions it may meet in adulthood. When the adult environment matches the early prediction, the organism is fine. However, when the early prediction was wrong, there is a mismatch between the regulatory range and the actual environment, leading to a frequent exposure to environmental stimuli outside the regulatory range. Unfortunately, perinatal and adolescent stress research usually does not meet our more strict definition of stress. It is conceivable that the controllability and predictability of stimuli are an important developmental determinant for the adult capacity to cope with environmental demands. In addition, an answer to this question would require probing the regulatory range by testing adult animals in a broad range of challenging conditions. When stressed animals perform better than controls in certain tests and worse than controls in other tests, this would favor a regulatory range interpretation. An example of this is given in a recent study in mice by Heiming and co-workers. They showed that mice that were raised in a threatening social environment performed significantly better as adults when confronted with threatening social situations than animals that were raised in a stable social environment (Heiming et al., 2009).

7.2. Adaptation, maladaptation and pathology

Implicit in the interpretation of many stress experiments is that the observed changes somehow contribute to the development of pathology. However, in view of the conceptual issues discussed

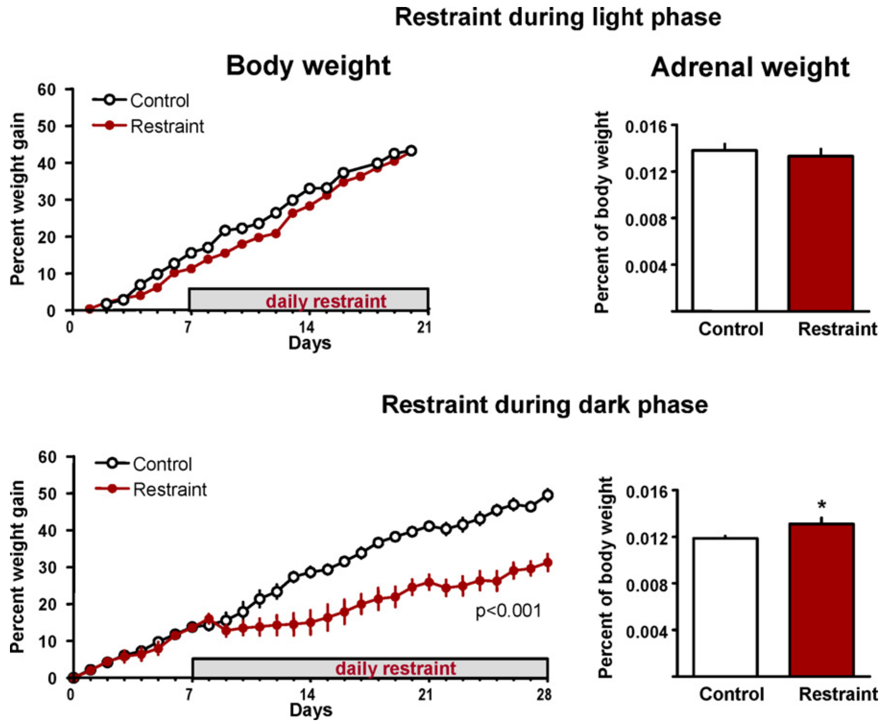

Fig. 8. Effects of daily immobilization in adult male rats: animals were either immobilized during the light phase (resting period, top row) or during the dark phase (activity period, bottom row). Please note that in the animals that are repeatedly restrained during their activity period there is a strong, non-habituating metabolic reaction represented by reduced body weight gain. Moreover, at the end of the experiment, adrenal weight is significantly increased in the animals that were restrained during their activity period indicating HPA axis activation.

above, one should be able to make more specific predictions. First, controllable and predictable stimuli that trigger behaviour and the accompanying physiological responses are unlikely to contribute to pathological alterations (or reduced adaptive capacity according to our definition). As argued above they should not be considered as stressors despite the sometimes extremely strong HPA and SAM responses. It is tempting to consider the possibility that these controllable stimuli may even enhance adaptive capacity by promoting response optimization based on experience. Second, uncontrollable and unpredictable stimuli, i.e. stressors in our strict sense, will either affect the adaptive capacity or shift the regulatory range. It is important to notice that the adaptive or maladaptive nature of such a change will of course depend on the subsequent environmental demands. An individual is still all right when the environmental demand does not exceed the reduced adaptive capacity. Only under conditions of a mismatch between demands and adaptive capacity, i.e. continuous uncontrollable and or unpredictable conditions, pathology may develop.

7.3. Experimental approaches

The concept outlined above has several consequences for experimental approaches in research on stress and adaptation. In particular, some commonly used animal models of chronic stress may be models of adaptation rather than models of stress-related pathology. At best, these paradigms may result in reduced adaptive capacity or may cause a shift in regulatory range. This holds for example for chronic mild stress models in which animals are exposed to daily changing non-life threatening conditions such as a wet bedding, tilted cage, or reduced ambient temperature (Willner, 2005). The same may also hold for repeated restraint (immobilization) experiments in view of the strong decline of the physiological response upon its repetition (Grissom et al., 2008). When rats are daily immobilized during the dark phase, which is their activity period, their body weight gain will be dramatically reduced; whereas immobilization during the light phase (resting period) has no significant effect on body weight (Fig. 8). In other words, it seems that for rats being restrained during the activity phase is stressful whereas being restrained during the resting period requires just some adaptation processes with no apparent functional consequences. In view of the ecology of the Norway rat, this may not be surprising as in nature the species hides in a narrow burrow system during their resting phase. It is comprehensible that being restrained during the resting period is less challenging than being restrained during the activity period. If our current line of reasoning is correct we would expect that exposure to restraint in the light phase differs from restraint in the dark phase in the speed of recovery of the HPA and SAM responses and the magnitude of the adrenaline response, in particular after repeated exposures.

It is an old observation that the behavioural or physiological data derived from 'stress experiments' depend very much on possibly small details in the experimental setups. For example in subordinate male tree shrews, the presence of a dominant male might impair memory or even enhance it, depending on the frequency of and the time intervals between previous negative experiences with the dominant opponent (Ohl and Fuchs, 1998; Bartolomucci et al., 2002). According to the present definition, the individual with the higher social rank might be a stressor in one context but only a stimulus in another context.

Ethological aspects such as the natural social system of a species also have to be considered. For example, it has been shown in male rats that chronic social defeat has detectable central nervous effects but only when the animals were isolated from their conspecifics after the social defeats (Isovich et al., 2001). In their natural social environment, male rats obviously have to adapt to the aversive experience of social defeat. However, the combination of being defeated and socially isolated is stressful for them (Ruis et al., 1999). The important contribution of social support has also been shown by counteracting the development of depressive-like behaviour in rats subjected to social defeat (Von Frijtag et al., 2000).

Natural surroundings of an animal normally provide many challenges, such as unknown smells, confrontations with other animals or humans, temperature changes, etc., which all evoke physiological responses and experience-dependent adjustments. In the laboratory, however, animals that are not part of an experimental procedure are often fully deprived of such stimuli (e.g. mice in individually ventilated micro-isolator-cages). When these individuals are first confronted with an unknown stimulus (e.g. the experimenter) they may show a pronounced (exaggerated) physiological/behavioural reaction that might be mistakenly interpreted as the desired stress response.

8. Concluding remarks

The use of the terms controllability and predictability emphasizes the importance to consider the cognitive, perceptual aspects of stress in addition to the behavioural and physiological responses. These terms imply that animals have some kind of internal representation of the outside world and this representation may change by learning and memory processes. Due to its general role in the metabolic support of behaviour, the mere presence of a neuroendocrine response is not sufficient to label it as stress nor is it indicative of the presence of a stressor as is nicely illustrated in a learning and memory experiment by Woodson and colleagues. Here, either predator exposure or exposure to a receptive female was used to activate the HPA axis in male rats. Despite a similar degree of activation of the HPA axis, predator exposure did impair hippocampus-dependent working memory, whereas exposure to a receptive female did not. In other words, only the predator exposure may have been perceived as a stressor (Woodson et al., 2003).

Since we cannot monitor *in vivo* the internal representation of perception in animals, we have to rely on a more subtle and detailed analysis of the consequent behavioural and physiological responses. The present line of reasoning shows that the measurement of the stress response should not only consider the magnitude of the response, but should focus in particular on the speed of recovery and the anticipatory response. This may hold for the SAM system as well as the HPA axis. Hence, a more detailed analysis of the time course of both SAM and HPA activity may allow a conclusion on the nature of the stimulus or condition in terms of its controllability and predictability.

The experimental approach towards stress-related pathology might gain a lot by more carefully exploiting the concept of predictability. Traditionally, experiments use naïve animals and often use stimuli that bear no relationship with the biology and every day life of the species. To further increase the face validity of the animal models, it would be wise to use stressors with a certain degree of ecological validity. These stressors somehow challenge the natural defense mechanisms and hence call upon the adaptive capacity of the animal. We would like to emphasize the word "natural", because it means that on the basis of the specific evolutionary biology of the species, one expects the animal to have an adequate answer to a given challenge (regulatory range). Moreover, it might be more fruitful to experimentally manipulate predictability by changing a predictable and fully controllable situation suddenly to unpredictable and/or uncontrollable. Our current refined definition of stress may help to move towards a more subtle understanding of the factors and processes underlying the development of stress-related pathology. Rather than pushing the animal towards its physiological limits, it might be far more informative to explore the natural factors that determine and modulate the individual regulatory range and adaptive capacity. These factors may include not only functional genetic variation, but also perinatal and adult experience and individual differences in subjective cognitive perception of given situations. Furthermore, adaptation based on prior experience and repeated exposure indicates adjustment of responses to necessary demands. Based on this argumentation, it is essential to delineate and differentiate functional (autonomic, behavioural and endocrine) adjustments in response to ecologically relevant challenges in the normal life of an individual from failures to adjust to uncontrollable, life-threatening conditions, i.e. stressors, having potentially maladaptive consequences.

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