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Review

Importance of the glucocorticoid stress response in a changing world: Theory, hypotheses and perspectives

Frédéric Angelier [a,*], John C. Wingfield [b]

[a] Centre d'Etudes Biologiques de Chizé, CNRS, 79360 Villiers en Bois, France
[b] Department of Neurobiology, Physiology and Behavior, University of California, One Shields Avenue, Davis, CA 95616, USA

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ABSTRACT

In this perspective paper, we emphasize the importance that integrative mechanisms, and especially the GC (glucocorticoid) stress response, can play in the ability of vertebrates to cope with ongoing global change. The GC stress response is an essential mediator of allostasis (i.e., the responses of an organism to a perturbation) that aims at maintaining stability (homeostasis) despite changing conditions. The GC stress response is a complex mechanism that depends on several physiological components and aims at promoting immediate survival at the expense of other life-history components (e.g., reproduction) when a labile perturbation factor (LPF) occurs. Importantly, this mechanism is somewhat flexible and its degree of activation can be adjusted to the fitness costs and benefits that result from the GC stress response. Therefore, this GC stress response mediates life-history decisions and is involved in the regulation of important life-history trade-offs. By inducing abrupt and rapid changes in the regime of LPFs, we believe that global change can affect the efficiency of the GC stress response to maintain homeostasis and to appropriately regulate these trades-offs. This dysfunction may result in an important mismatch between new LPFs and the associated GC stress response and, thus, in the inability of vertebrates to cope with a changing world. In that context, it is essential to better understand how the GC stress response can be adjusted to new LPFs through micro-evolution, phenotypic plasticity and phenotypic flexibility (habituation and sensitization). This paper sets up a theoretical framework, hypotheses and new perspectives that will allow testing and better understanding how the GC stress response can help or constrain individuals, populations and species to adjust to ongoing global change.

1. Living in a changing world: a whole new range of perturbations

During the last century, climate change and the exponential growth of the world human population have rapidly and deeply modified the ecological characteristics of worldwide ecosystems (Steffen et al., 2004; Williams and Jackson, 2007). These changes mainly resulted from several anthropogenic activities such as habitat destruction and fragmentation, changes in climatic characteristics, human disturbance, pollution and introduction of species in specific environments (Brook et al., 2003). All these changes have definitely modified the relationship between vertebrate populations and their environment. Therefore, global change may compromise the ability of individuals to survive and reproduce properly in their new changing environment and it could cause the decline and the extinction of a large percentage of vertebrate species (Pounds et al., 2006; Thomas et al., 2004). One of the major challenges for ecologists is now to predict whether vertebrates will be able to adjust well and fast enough to these ongoing changes (Visser, 2008).

Numerous studies have investigated how these changes have affected vertebrate populations during the last decades and, interestingly, they have reported a large heterogeneity among species and even populations (Menzel et al., 2006). Some of them have dramatically declined, whereas others have not been affected or, surprisingly, have even benefited from these changes (Davey et al., 2012; Julliard et al., 2003). For instance, specialist species have overall been declining and have been replaced by generalist species that have extended their geographical range (Clavel et al., 2010), confirming that all species and populations differ in their ability to cope with a new and a changing environment. Although these studies have improved our understanding of the influence of global change on vertebrates, it may still be difficult to reliably and accurately predict how species and populations will be affected by changes that have not occurred yet because demographic responses to environmental changes are complex, non-linear and,

* Corresponding author. Fax: +33 (0)5 49 09 65 26.
E-mail address: angelier@cebc.cnrs.fr (F. Angelier).

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therefore, cannot be totally extrapolated from demographic responses to current or past changes.

In that respect, using an integrative and functional approach can help to understand what drives the ability of vertebrates to cope with a changing environment. This approach has recently received an increasing attention from ecologists and several studies have investigated how global change could disrupt the ability of vertebrates to cope with their environment (Visser et al., 2010; Wingfield et al., 2008). It has been demonstrated that rigid physiological mechanisms can result in mismatches between energetic needs (ex: energy-demanding reproduction) and energetic availability (ex: food) in vertebrates (Dawson, 2008; Pörtner and Farrell, 2008; Visser, 2008; Wingfield, 2008). For instance, physiological mechanisms relying on photoperiodic cues can trigger individuals to start breeding, migrating or molting at a time when energetic conditions are overall reduced by global changes and, therefore, cannot support such activities (Visser et al., 2010). Most of these proximate studies have focused on overall changes in seasonal energetic conditions whereas the importance of unpredictable, abrupt and deleterious events (i.e., stressors) has to our knowledge received less attention (Wingfield, 2008; Wingfield et al., 2011). However, global changes are known to confront vertebrates with a new range of stressful situations (e.g., new predators or diseases, extreme climatic events, disturbance, etc., i.e. labile perturbation factors (LPF) *sensu* (Wingfield, 2003; Wingfield et al., 2011). Therefore, in this perspective paper, we aim to highlight the importance of studying the integrative physiological mechanisms that govern the ability of vertebrates to cope with these new stressful situations.

2. Integrative physiological mechanisms orchestrate an organism's response to changes

In vertebrates, allostasis – the response of an organism to a perturbation and its effort to maintain stability (homeostasis) despite changing conditions (McEwen and Wingfield, 2003) – is mainly mediated by a few major physiological mechanisms (e.g., central nervous, endocrine or immune system (Romero et al., 2009). These integrative mechanisms act on several traits to mediate an integrated and appropriate response of the whole organism to a specific environmental stimulus. These mechanisms are definitely pleiotropic, meaning that they simultaneously activate multiple physiological or behavioral traits while inhibiting several others (Hau, 2007; Ricklefs and Wikelski, 2002). By doing so, they mediate the ability of individuals to cope with ongoing global change (Wingfield, 2008; Wingfield et al., 2011).

Because of their integrative role, these mechanisms are crucial to explore when focusing on the ability of individuals to cope with environmental challenges (allostasis and reactive scope, (McEwen and Wingfield, 2003; Romero et al., 2009; Wingfield et al., 2011). These mechanisms are somewhat complex and, for example, the reactive scope model proposes that the mediators of these central mechanisms have various effects on the organism depending on their concentrations (Romero et al., 2009). To briefly sum up their general functioning, a stimulus triggers a biological signal through its perception by the organism (Fig. 1). This signal is then transduced by an integrative organ or tissue into a computed signal that is then transferred through various mechanisms (e.g., nervous or endocrine system, etc.) to other cells, tissues or organs (Fig. 1). In turn, this triggers a biological response (reactive scope, Romero et al., 2009) that is designed to help the organism to react appropriately to the given stimulus (Wingfield, 2003, 2005) (Fig. 1). Finally, this biological response is turned off when the stimulus is not perceived anymore, or is deemed non-threatening.

These mechanisms have been selected through evolution to mediate responses that optimize the fitness of individuals when specific environmental challenges occur (Hau, 2007; Ricklefs and Wikelski, 2002). Despite their obvious importance in terms of allostasis and reactive scope, these integrative systems could also appear as constraints for individuals in the context of rapid environmental changes (Dawson, 2008; Pörtner and Farrell, 2008; Visser, 2008; Wingfield, 2008). New stimuli, i.e., totally novel stimuli (ex: introduction of a new predator), or stimuli that occur out of the range of the individual's experience that has been selected for, could trigger an inappropriate or/and ineffective response, leading to a mismatch between the perturbation and the biological response with major fitness costs for the individual.

Such mismatches could be triggered by different non-mutually exclusive dysfunctions: an inappropriate perception of the perturbation (dysfunction 1, Fig. 1); an inappropriate integration of the information by the central mechanism (dysfunction 2, Fig. 1); an inappropriate response of the target cells/tissues/organs (dysfunction 3, Fig. 1). An inappropriate response of the target cells/tissues/organs could happen if these cells/tissues/organs operate in a reaction norm – the range of phenotypic possibilities – that does not allow coping effectively with the new perturbation. For instance, the introduction of a novel predator could lead to population extinction (e.g., the case of apteral birds that could not cope with the introduction of new predators because they did not have an appropriate locomotion system to flee from the new predators, (Roberts and Solow, 2003)). Despite this possibility, the most likely causes of an ineffective or inappropriate response to new perturbations are probably either an inappropriate perception of the perturbation or an inappropriate integration of the information by central mechanisms (dysfunctions 1 and 2). Although the dysfunction 1 could be, at least partly, investigated through behavioral studies, studying the dysfunction 2 will require much more invasive laboratory investigation that cannot be conducted on wild populations of vertebrates. Interestingly, for both of these dysfunctions, the mismatch between the perturbation and the biological response should result in inappropriate signals being transferred

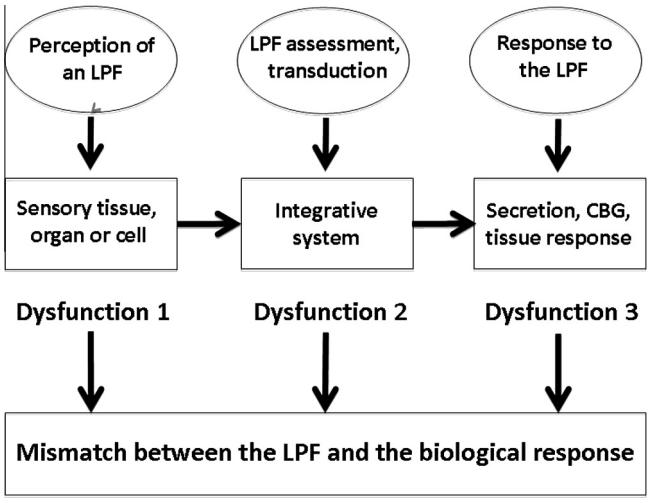

Fig. 1. General functioning of the biological response to a labile perturbation factor (LPF, *sensu* Wingfield , 2003). The LPF is first perceived by specific sensory organs, tissues or cells. This leads to a signal that is then computed by an integrative organ, tissue or cell that assesses the threat that the LPF represents. Finally, this integrative system activates specific organs, tissues or cells and this triggers a biological response that is supposed to help the organism to react appropriately to the LPF. Environmental changes may lead to changes in the LPF characteristics (intensity, frequency and type of LPF) and the ability of the organism to cope with such new situations may be impaired by dysfunctions that occur at the perception, integration or response level. This may lead to a mismatch between the new LPF situation and the biological response (reactive scope) of the organism to it.

from the central integrative system to target cells/tissues/organs. Therefore, studying the mediators of these signals could definitely help us understand when individuals can (or cannot) adjust to ongoing environmental changes.

3. New perturbations, life-history trade-offs and the glucocorticoid (GC) stress response

3.1. LPF and the trade-off between the risk of short-term mortality and long-term fitness costs

In a context of global change, new LPFs will set-up important constraints on individuals. These LPFs are life-threatening for individuals since they compromise immediate or short-term survival (e.g., predator attack or food shortage) but, as new resource-demanding events, they will also create or exacerbate some life-history trade-offs. Actually, individuals will have to allocate some of their resources – energy and time – to cope with the LPF and these resources will not then be available for other life-history components that are directly related to reproduction or long-term survival and, therefore, fitness (e.g., reproductive effort, growth, moult, immunocompetence, protection against oxidative damage, etc.). Through evolution, individuals have been selected to optimize their fitness by balancing the risk of immediate mortality due to a given LPF and the long-term fitness cost of a specific life-history decision. Therefore, this selection has certainly acted on the integrative mechanisms that mediate these life-history decisions in order to adjust them to the LPFs that individuals are likely to encounter during their life (i.e., reaction norm of LPF).

When focusing on the ability or the inability of individuals and species to cope with the new LPFs originating from global change, the GC stress response deserves specific attention (among all integrative mechanisms) for three main reasons. First, the GC stress response aims at mediating rapid behavioral and physiological modifications that benefit to immediate survival – i.e., that allow the organism to cope with the LPF (Landys et al., 2006; Romero, 2004; Sapolsky et al., 2000; Wingfield et al., 1998, 2011; Wingfield, 2003). Second, the GC stress response is flexible in intensity and duration and can be down-regulated when the benefits of mounting a strong GC stress response are outweighed by the long-term fitness costs of bearing elevated GC levels (Wingfield and Sapolsky, 2003). Thus, the modulation of the GC stress response aims at mediating life-history decisions by reorganizing the allocation of resources – time and energy – between immediate survival and other life-history components when a LPF occurs (Wingfield and Sapolsky, 2003). Finally, the GC stress response is at least partially heritable and, therefore, selection is likely to act on this mechanism in order to optimize individual's fitness (Angelier et al., 2011; Evans et al., 2006; Satterlee and Johnson, 1988).

3.2. The GC stress response: a complex mechanism to promote homeostasis

GCs are secreted quickly by the adrenal glands – within a few minutes – after the perception of the stressor. In response to the stressor, the Hypothalamus–Pituitary–Adrenal (HPA) axis is activated and this results in an increase in plasma GC concentrations that reach maximum levels 30 min to 1 h or so after the stressor was first perceived by the organism (Romero, 2002; Wingfield et al., 1992). When the stressor stops, plasma GC levels decrease as they are being metabolized. Concomitantly, elevated plasma GC levels activate a negative feedback that reduces the amount of GC being secreted by the adrenal glands (Romero, 2004). The action of GC on cells, tissues and organs is mediated through its binding to two kinds of receptors that have very different affinities for GC (Landys et al., 2006; Romero, 2004). This is essential to consider since it means that GC can have totally different actions on physiological and behavioral components depending on the amount of GC that is available to the cells/tissues/organs. At low GC levels, binding only occurs by receptors that have a high-affinity to GC (type 1 receptor, mineralocorticoid receptor). On the other hand, at elevated GC levels, these type 1 receptors are saturated and GCs start binding to another type of receptor that has low affinity for GC (type 2 receptors) that are only saturated at higher circulating levels of GCs. In addition, most of GCs are bound to a binding globulin in the blood and it is thought that only unbound GC can enter cells and bind to receptors and mediate biological effects (Breuner and Orchinik, 2001, 2002; Breuner, 2013; Malisch and Breuner, 2010). All these components – GC levels, receptors density and location, binding globulin levels, clearance rate of GC – are known to vary seasonally and in relation to several ecological and physiological variables (Breuner, 2013; Breuner et al., 2003; Romero, 2002). Therefore, the biological effects of GC depend on complex interactions between GC secretion, type 1 and type 2 receptor numbers and locations, binding globulin concentrations and clearance rate of GC in the blood (Wingfield, 2012). This complexity may explain why the actions of GC on physiology and behavior do not always appear consistent and depend on the individual state (e.g., body condition) and the environmental context (Wingfield et al., 2013). In the rest of this paper, the GC stress response will refer to all these complex interrelated components of reactive scope and not just plasma GC levels.

Because excellent reviews have previously exhaustively described the actions of GCs on physiology and behaviors (Landys et al., 2006; Romero, 2004; Sapolsky et al., 2000; Wingfield, 1994; Wingfield et al., 1998), we will only briefly summarize how GCs can help the organism to cope with a LPF. Overall, the cumulative actions of GC aims at restoring homeostasis and, thus, energy balance of individuals by acting on metabolism, food intake and by regulating several resource demanding activities or physiological processes (Landys et al., 2006; McEwen and Wingfield, 2003; Romero, 2002; Sapolsky et al., 2000). At first, GCs sustain daily and seasonal demands such as reproduction, migration and daily routines of energy balance. This role of GCs is primarily mediated through the binding of GC to type 1 receptor and regulated by small to moderate variation of GC levels. However, the actions of GC are totally different when GC levels reach intermediate to elevated GC levels, i.e. when the GC stress response is activated through binding to type 2 receptors (Landys et al., 2006; Romero, 2004). In this case, GCs have stimulatory effects on behaviors and physiological processes that will help individuals to maintain their energy balance despite challenging conditions (i.e., LPFs). For example, elevated GC levels can stimulate locomotor and foraging activities allowing the individual to escape the area where the LPF occurs (Breuner and Hahn, 2003) or to increase its energy intake in order to maintain its energy balance (Angelier et al., 2007d, 2009a; Astheimer et al. 1992). Similarly, elevated GC levels stimulate protein and fat catabolism in order to provide energy to sustain demanding processes that allow the individual to survive the LPF (Landys et al., 2006; Sapolsky et al., 2000). In addition, GCs have inhibitory effects on several resource-demanding activities that do not benefit the immediate maintenance of energy balance. For instance, GCs have inhibitory actions on other endocrine axes (e.g., prolactin secretion; Angelier et al., 2009b), resulting in reduced sexual, territorial or parental activities (Wingfield and Sapolsky, 2003). These effects are likely to become greater as the GC stress response becomes more marked. For example, moderately elevated GC levels reduce reproductive activities to some extent whereas reproduction is totally suppressed when very elevated GC levels are reached (Angelier et al., 2007c, 2009a; Ouyang et al., 2012; Silverin, 1986; Spée et al., 2010; Wingfield et al.,

1998). When the GC stress response reaches an upper threshold value, often modeled as the cumulative energy levels available as food in the environment and stored energy reserves such as fat, above which allostatic overload type 1 is reached, an emergency life-history stage is activated and all the resources available are redirected towards immediate survival (McEwen and Wingfield, 2003; Wingfield et al., 1998).

3.3. Effective and ineffective GC stress responses

For a given LPF, it is theoretically possible to identify the most effective GC stress response as the intensity and duration of a response that will balance the risk of immediate or short-term mortality, and the long-term fitness costs of bearing elevated GC levels to maximize the individual's fitness (Fig. 2A). Therefore, an ineffective stress response could be defined as a response that entails either a too high risk of immediate or short-term mortality (under-reaction to stress) or too severe long-term fitness costs (over-reaction to stress). In the case of an over-reaction to stress, there is no benefit of mounting such a strong GC stress response and the GC stress response should be suppressed to enhance individual's fitness (critical adaptive value of the GC stress response, (Jacobs, 1996; Wingfield et al., 2011). In other words, the GC stress response is ineffective if it is out of the range needed to re-establish homeostasis when a specific LPF occurs (*sensu* the reactive scope model, (Romero et al., 2009). Obviously and importantly, a given GC stress response can be effective to cope with a specific LPF but not necessarily another type of LPF (Fig. 2B). This also emphasizes that individuals need to be able to effectively perceive and assess the threat of a given LPF and to show enough flexibility in the intensity and duration of the GC stress response to adjust to the range of LPFs that occurs in their environment (i.e., reaction norm of the GC stress response to LPFs).

4. Need to adjust the GC stress response in a changing environment?

Because the GC stress response helps an organism to get the best of a bad situation when a LPF occurs (Landys et al., 2006; Sapolsky et al., 2000; Wingfield, 2003; Wingfield et al., 1998), one can logically expect that this mechanism should play a major role in the ability of individuals to cope with a new regime of LPFs that results from global change (Wingfield, 2008; Wingfield et al., 2011). In the following paragraphs, we describe three different non-mutually exclusive scenarios about the rapid and intense changes in the regime of LPFs that are likely to occur with global change. For each of these scenarios, our goal is to raise hypotheses to understand what could be the consequences of such changes on the efficiency of the GC stress response to cope with LPFs.

4.1. First scenario: new types of LPF

It is expected that global change will induce a shift in the regime of LPFs. Individuals could have to cope with new and unknown LPFs whereas old and known LPFs may not even occur anymore (Fig. 3A). This could result in a mismatch between the LPF and the associated intensity and duration of the GC stress response. When a new LPF is perceived, the organism may initiate a GC response that is adjusted to the old and known LPF because it is perceived the most similar to the new one. While this GC stress response would definitely optimize the organism's fitness if the old LPF had occurred, it may not when the new LPF occurs (Fig. 3A). Under this scenario, individuals would therefore face new situations for which the intensity and duration of the GC stress response may not be appropriate anymore. These new situations may result from a new type of LPF that are totally unknown for the individual but also from an increased intensity and/or duration of a known LPF. In this later case, the individual would have to cope with a higher allostatic load than expected and its GC stress response may not be appropriate anymore to deal with this increased intensity or/and duration of the LPF. The most extreme situations would be for the organism to perceive a new non-threatening event as being a LPF, or a new LPF as being not threatening. In these two examples, the GC stress response would be totally ineffective. In addition to this problem of inappropriate perception of the new LPF, it is also possible that the organism could not express a GC stress response that would allow it to cope efficiently with the new LPF. In other words, some components of the GC stress response would need to be modified. This may involve some or all parts of the GC stress response (intensity, rapidity and duration of GC secretion, binding globulin levels, receptor locations and densities – type 1 and/or type 2 – and clearance rate, (Wingfield, 2012; Wingfield et al., 2013). Such a mismatch would result in dramatic fitness costs because the balance between the costs and the benefits of the GC stress response would not be optimized to the new situation (Fig. 1A). To cope with new types of LPFs, the perception of the LPF and the GC stress response itself may consequently need to be adjusted to the new LPF in a way that limits these fit-

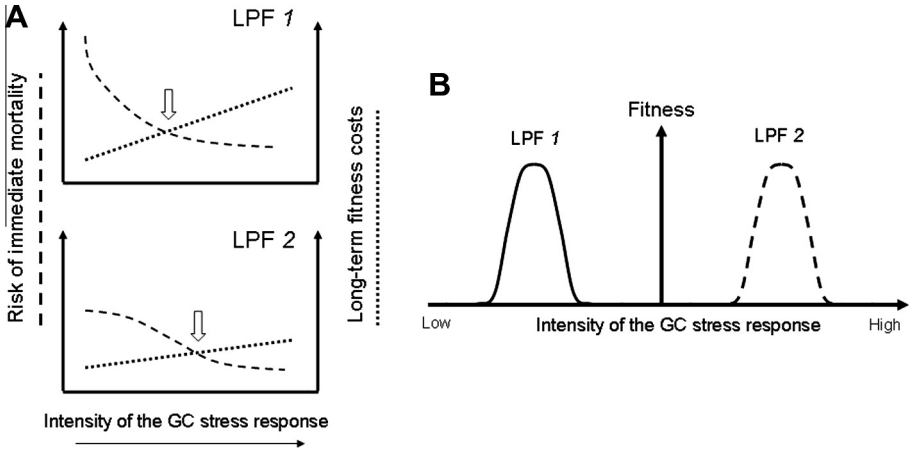

Fig. 2. The GC stress response: a mechanism to maximize fitness when LPFs occur. When a LPF occurs, a GC stress response is activated to promote immediate or short-term survival. Depending on its intensity, this GC stress response also accrues long-term fitness costs and, therefore, for a given LPF, the most effective GC stress response can theoretically be identified as the response that maximizes the individual's fitness (i.e., that balances the risk of immediate or short-term mortality and the long-term fitness costs of bearing elevated GC levels). Two different LPFs – LPF 1 and LPF 2 – can represent different risk of immediate mortality and can be associated with different long-term fitness costs (A). The most effective GC stress response maximizing the individual's fitness –represented with a white arrow (A) – will not be similar for both LPFs (B).

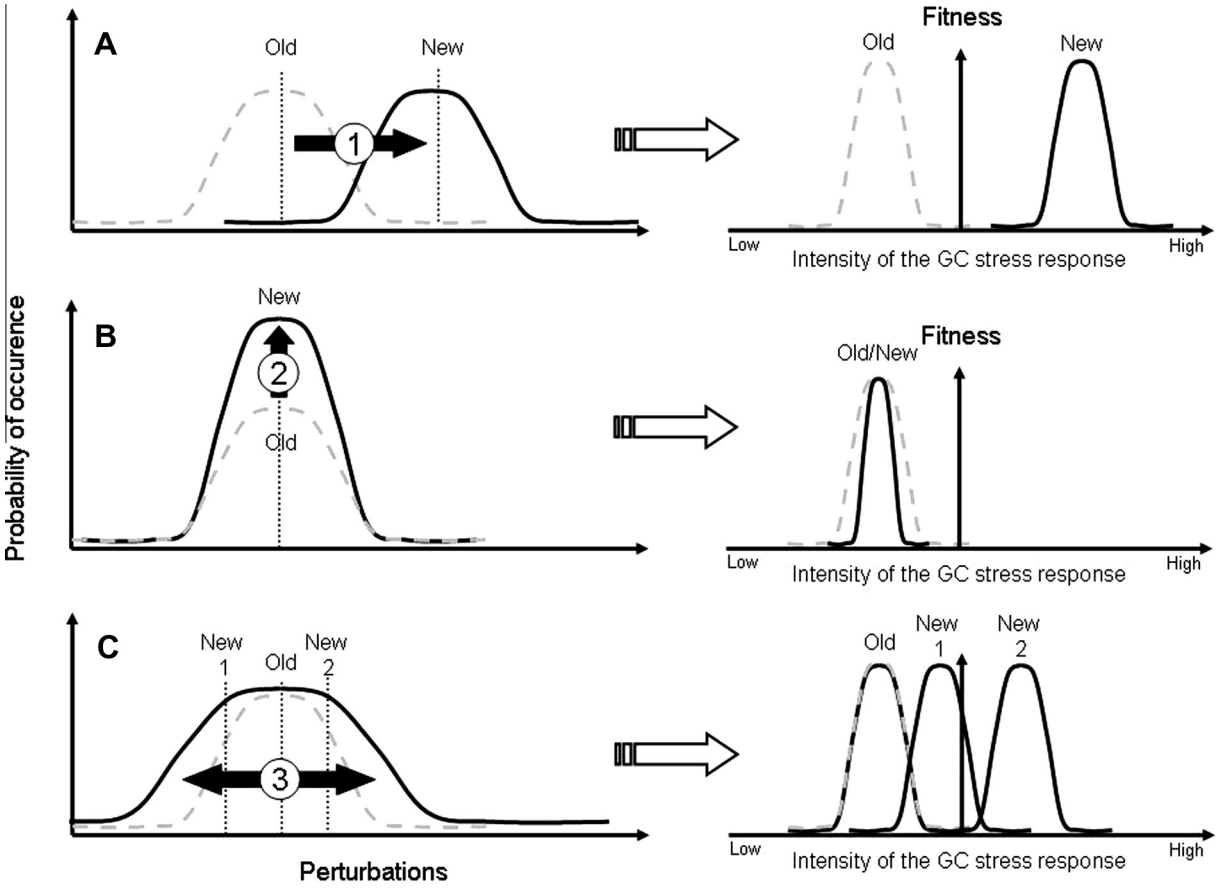

Fig. 3. Environmental changes may lead to a mismatch between the GC stress response and the new LPF situations. On the left panels, 'New' and 'Old' respectively represent the old and new LPFs. On the right panels, 'New' and 'Old' respectively represent the optimal GC stress responses under the old and the new LPF situation. (A) *Scenario 1*: Individuals have to cope with new types of LPFs: the probability of occurrence of the old LPF decreases whereas the probability of occurrence of the new LPF increases. Under this scenario, fitness would be optimized by a different GC stress response and not anymore by the old GC stress response. (B) *Scenario 2*: Individuals have to cope with an increased frequency of an existing LPF ('old'). Under this scenario, the individuals that mount a non-optimal stress response to this LPF will be likely to pay greater fitness costs while this perturbation becomes more frequent. (C) *Scenario 3*: Individuals have to cope with numerous LPFs (old – 'old' – and new – 'new 1' and 'new 2' – ones). Under this scenario, individuals would need to increase their ability to differentiate various LPFs but also to mount LPF-specific GC stress responses that optimize their fitness under different LPFs (old and new ones).

ness costs. If the new LPF was simply a change in allostatic load, then the adjustment of the duration and intensity of the GC response to a new threat would be relatively easy to accommodate. However, if the new LPF involves appropriate perception and processing of that information then adjustment of the GC response would require some form of learning or even micro-evolution to optimize the response.

4.2. Second scenario: increased frequency of LPFs

In a context of global change, it is also expected that the frequency of existing LPFs will increase (Fig. 3B). This could be linked for instance with an increased risk of predator attacks, a higher frequency of food shortage or an increased frequency of inclement weather (Wingfield, 2008; Wingfield et al., 2011). The GC stress response aims at promoting immediate survival in response to LPFs (McEwen and Wingfield, 2003; Wingfield, 2003; Wingfield et al., 1998) and the degree of activation, intensity and duration of this response (allostatic load) helps individuals to balance the costs, such as abandoned reproduction, and benefits such as improved immediate survival, of coping with the LPF. Consequently, we can posit the hypothesis that being able to mount an appropriate stress response will become more and more important while the frequency of LPFs increases. Indeed, the individuals that mount a non-optimal stress response to a specific LPF should pay greater fitness costs when this perturbation becomes more and more frequent (Fig. 3B). However, it is important to note that, under this scenario, individuals will have to deal with a LPF they are used to – only the frequency of this LPF increases – and they do not have to adjust the GC stress response to a new totally unknown LPF (Fig. 1B). Although individuals with a non-optimal GC stress response may have coped with this LPF because of its low frequency, they may need to modify their GC stress response under this scenario since their fitness will now strongly depend on their ability to appropriately cope with this LPF, which becomes very frequent.

4.3. Third scenario: a wider range of LPFs

It is predicted that global change will result in greater environmental stochasticity because of increased frequency, intensity and duration of LPFs as well as new types of LPFs. Consequently, new LPFs will occur while old LPFs remain. In the context of global change, individuals should therefore have to cope with a wider spectrum of LPFs (Fig. 3C). For example, this may mean that individuals will have to cope with both extreme cold temperature and extreme warm temperature over their annual life cycle or with an increased community of predators with various predation techniques. Under these scenarios, individuals would need to increase their ability to differentiate various LPFs and to mount LPF-specific GC stress responses that optimize their fitness under different LPFs.

This implies that organisms would need to identify reliable cues to perceive appropriately old and new LPFs without confounding them. This also means that individuals would have to develop a high flexibility in their GC stress response integrating control of secretion of GCs with mechanisms of transport in blood to responsiveness of target tissues such as increasing sensitivity of some and decreasing sensitivity of others (Wingfield, 2012; Wingfield et al., 2013). Depending on the balance between the risk of immediate mortality and the long-term costs of having elevated GC levels, the GC stress response may need to be very weak when some LPFs occur but very strong when others occur. As explained in the first scenario, it means that the GC stress response may need to be modified to go beyond the range that normally exists in this specific individual or even in this specific species. This would imply some important changes in some or all of the components of the GC stress response (GC secretion, binding globulin, receptor locations and densities – type 1 and/or type 2 – and clearance rate).

5. How could the GC stress response be adjusted to new LPFs?

In all the scenarios that are presented in the previous section, the abrupt and intense changes in the regime of LPFs resulting from global change may mean that the GC stress response is not optimized to cope with the new LPF situation. It is currently clear that the GC stress response is flexible and can be modified but how it is responsive to new unknown LPFs remains to be clarified. We present here three general mechanisms that would allow individuals and populations adjusting their GC stress response to the new situation.

5.1. Micro-evolution

One of the first obvious processes that can adjust the GC stress response of a population to a new LPF situation is micro-evolution (Fig. 4). This mechanism acts by selecting individuals that have the most appropriate GC stress response to the new LPF situation. Actually, a proportion of the population will show a GC stress response that is not adjusted to the new LPF situation. These individuals will obviously accrue very high fitness costs – immediate mortality, low reproductive output and/or long-term survival costs – and they will be selected against in the population. Supposing that the GC stress response is heritable (Angelier et al., 2011; Evans et al., 2006; Satterlee and Johnson, 1988), the population will quickly be only composed of individuals that show a GC stress response adjusted to the new LPF situation.

In a few situations, this process may not be sufficient to maintain a population when a shift in the regime of LPF occurs. If no individual within the population is able to mount a GC stress response that is adjusted well enough to the new LPF situation, the whole population will then experience very high fitness costs and the population may disappear. This means that only the populations with a high inter-individual variability of GC stress responses may be able to persist through such a micro-evolution process. Interestingly, this idea is supported by a recent study that reported a very high inter-individual variation in the GC stress response in populations of white-crowned sparrows that were able to invade a new habitat (Addis et al., 2011). It also means that populations may not be able to cope with abrupt changes in frequency, intensity and duration of LPFs that confront all individuals of a population to LPFs they can't cope with. Second, this micro-evolution process will definitely result in a reduction of the number of individuals being able to contribute to reproduction and future generations. Therefore, the effective population size may reach a low number which would not be large enough to sustain the existence of the population in the long term (i.e., the extinction risk of the population would become very high). This situation may be especially true for long-lived species that show a very protracted generation time (low reproductive output). Here again, the fate of the population will depend on the number of individuals that are initially able to cope with the new LPF situation.

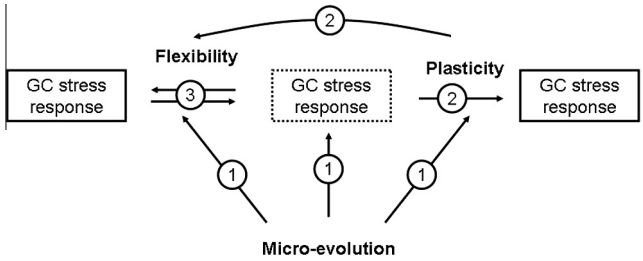

Fig. 4. The GC stress response can be adjusted to new LPF situations through different processes. "GC stress response" surrounded by a dotted line and by a solid line respectively represents the initial and the modified/adjusted GC stress response. (1) *Micro-evolution*: individuals with the most appropriate GC stress response have a higher fitness and are therefore selected; (2) *Phenotypic plasticity*: ecological or physiological processes, such as developmental conditions and maternal effects, lead to irreversible modifications of the GC stress response; (3) *Phenotypic flexibility*: Individuals can get adjusted to new LPF situations through reversible modifications of their GC stress response (i.e., habituation and sensitization to new LPF situations). Phenotypic plasticity may subsequently affect the ability of individuals to reversibly adjust their GC stress response to new LPF situations (i.e., flexibility). Micro-evolution can act directly on the GC stress response but also on the plasticity and the flexibility of the GC stress response. Numbers in the figure refer to these three processes (1: micro-evolution, 2: phenotypic plasticity, 3: phenotypic flexibility).

5.2. Phenotypic plasticity

In common language, plasticity could be defined as a process that modifies something without the possibility for it to return to its previous form. Therefore, we define here phenotypic plasticity as ecological or physiological processes that lead to irreversible modifications of the phenotype of an organism and, in our topic of interest, into irreversible modifications of the GC stress response (Fig. 4). Most of this plasticity is likely to happen during the development when the GC stress response is being shaped by developmental conditions and maternal effects (Love et al, 2013). Indeed, it is now very well-documented that prenatal and early life events can affect the development of the whole HPA axis and are associated with specific GC stress response later in life (e.g., Love and Williams, 2008; Wada et al., 2009). For instance, Sheriff et al. (2010) showed that a high predation risk during the gestation of a prey species (snow hare) induced a persistent increased responsiveness of the HPA axis in their progeny (i.e., a strong GC stress response). However, this plasticity can also happen later in life and induce irreversible modifications of the GC stress response (ex: modification of the HPA system in relation with senescence (Goutte et al., 2010). In some situations, phenotypic plasticity – during the development phase or later in life - could help individuals to adjust to new LPF situation if they orientate the phenotype of individuals in an appropriate way. For instance, challenging developmental conditions affect the development of the GC stress response system and this can adjust it to the challenging environmental conditions that the organism is likely to encounter after development (Love et al., 2013; Monaghan, 2008). In snow hares, an increased responsiveness of the HPA axis could benefit to offspring under a context of high predation risk because of the positive effect of the GC stress response on immediate survival (Sheriff and Love, 2012).

However, there is still much debate onto what extent phenotypic plasticity and irreversible modifications of the GC stress re-

sponse help individuals to cope with new LPF situations (Monaghan, 2008; Sheriff and Love, 2012). Indeed, these irreversible modifications appear very often detrimental to individuals rather than beneficial. For instance, poor developmental conditions can induce an inappropriate development of the GC stress response, which often result in poor performances. Going back to the snow hare case, Sheriff & Love (Sheriff and Love, 2012) suggest that, under a context of low predation risk, an increased responsiveness of the HPA axis in the progeny could be maladaptive because a strong GC stress response would be associated with poor reproductive performances and overall a poor fitness. Similarly, during adulthood, the senescence of the HPA axis can lead to irreversible modifications of the GC stress response that does obviously not help individuals to cope better with LPFs (e.g., ineffective regulation of GC stress levels (Angelier et al., 2006, 2007a; Goutte et al., 2010). Even if this plasticity aims at adjusting the GC stress response to specific environmental conditions, it may also become a constraint in a changing world where the stochasticity of environmental conditions is expected to increase (rapid succession of contrasted extreme environmental conditions). Under this scenario, the GC stress response may be shaped by specific environmental conditions that won't occur during the life of the organism and it would create/exacerbate a mismatch between the GC stress response and the environmental conditions that individuals encounter later during their life.

Therefore, this mechanism may help individuals to cope with ongoing change to a certain extent but plasticity may also become ineffective in the context of global change or may even appear as a constraint rather than a coping mechanism. It is also important to note that micro-evolution could act on the plasticity of the GC stress response (rather than on the GC stress response itself) to help individuals and populations to cope with new regimes of LPFs (Fig. 4).

5.3. Phenotypic flexibility

Contrary to plasticity, elasticity could be defined as a process that modifies something with the possibility for it to return to its previous form. Therefore, we define here phenotypic flexibility as ecological or physiological processes that lead to reversible modifications of the phenotype of an organism (Piersma and Drent, 2003; Piersma and Van Gils, 2011) and, in our topic of interest, into reversible modifications of the GC stress response (Fig. 4). This flexibility appears essential for individuals to cope with a new regime of LPFs because it will allow an individual to adjust its GC stress response to a new LPF situation and, therefore, to optimize its life-history decisions and its fitness in a changing world. Importantly and contrary to phenotypic plasticity, such flexibility allows individuals to constantly adjust – back and forth – their GC stress response to new situations (Piersma and Drent, 2003; Piersma and Van Gils, 2011). It is entirely possible that this may be the major mechanism to help individuals cope with stochastic regimes of LPFs.

The GC stress response is likely to be modified and may thus be adjusted to new LPF situations through two major processes: habituation and/or sensitization (Berger et al., 2007; Cyr and Romero, 2009; Rödl et al., 2007; Romero and Wikelski, 2002; Wilcoxen et al., 2011). Indeed, in some situations, the GC stress response may be initially too strong or too weak and not well adjusted to the new LPF situation. Such a mismatch leads therefore to elevated fitness costs (too weak GC stress response, high risk of immediate mortality; too strong GC stress response, long-term fitness costs such as reduced reproductive performances). After having experienced the new LPF situation a few times, habituation and/or sensitization may occur and respectively allow individuals to dampen or exacerbate their GC stress response. These two processes may appropriately adjust the GC stress response to the new LPF situation and, therefore, may minimize the risk of immediate mortality while limiting the fitness costs of bearing elevated GC levels. In other words, these two processes may avoid individual over-reaction or under-reaction to a new LPF situation and, thus, allow individuals to adopt the best life-history strategy when such a situation occurs. For instance, Rödl et al. (2007) showed in marine iguanas (*Amblyrhynchus cristatus*) that a GC stress response to experimental chasing is absent in naive animals, but is quickly restored with experience suggesting that sensitization may allow these iguanas to cope with new LPFs. Importantly, Romero and Wikelski (2002) found that marine iguanas can on the opposite attenuate their GC stress response in response to non-threatening tourist-related disturbance, allowing them to cope with a new type of LPF (i.e., habituation). This suggests that these habituation and sensitization processes are not irreversible and can adjust the GC stress response back and forth to allow individuals to cope with a range of LPFs.

This flexibility of the GC stress response obviously depends on the range of GC stress responses that individuals can develop and, therefore, depends on the HPA axis and its regulation (receptors, binding globulins, etc., (Landys et al., 2006; Romero, 2004). The GC stress response is definitely flexible since many studies have shown that, for instance, the GC stress response varies according to individual state or environmental conditions (Addis et al., 2011; Angelier et al., 2013; Goutte et al., 2010; Horton and Holberton, 2010). However, the ability of individuals to show flexibility in their GC stress response has rarely been studied. In addition, the flexibility of the GC stress response also depends on the ability of individuals to effectively perceive and assess the actual threat that is associated with a new LPF situation. Consequently, cognitive processes, memory and learning capacities are likely to also play a major role in these habituation and sensitization processes. Importantly, some of these processes may also be irreversible (e.g., post-traumatic disorder and definitive modification of the HPA system) and this suggests that sensitization and habituation may also be involved in phenotypic plasticity.

In some situations, phenotypic flexibility may not be sufficient to allow individuals to survive changes in their experience of LPFs. Habituation and sensitization may need time to occur since individuals need to encounter the new LPF situation at least once to adjust their GC stress response to it. For example, sensitization may not have time to occur if the first exposure to the new LPF is associated with a very high probability of immediate mortality. Obviously, micro-evolution can affect this flexibility of the GC stress response through the selection of individuals showing an appropriate flexibility of their stress response (Fig. 4). Similarly, phenotypic plasticity can determine the range of GC stress responses that individuals can show through irreversible modification of some or all components of the GC stress response (Fig. 4). Therefore, phenotypic plasticity could determine how flexible the GC stress response is.

6. New LPF situation and heterogeneity in the GC stress response

When a LPF occurs, all individuals do not necessarily adopt the same strategy to cope with it and these differences can be related to contrasted GC stress responses among individuals. Because the GC stress response is likely to play a major role in the ability of individuals to cope with new LPF situations, this inter-individual variability in the GC stress response means that different individuals may react very differently to new LPF situations and, therefore, it is likely that a new LPF situation won't have the same impact on all individuals.

When a specific LPF occurs, individuals are supposed to mount a GC stress response that will optimize their fitness by balancing the risk of immediate mortality and the long-term fitness costs of mounting a GC stress response (Lendvai et al., 2007; Lendvai and Chastel, 2008, 2010; Wingfield and Sapolsky, 2003; Wingfield et al., 1995). A given LPF does not represent the same risk of immediate mortality for all individuals and a specific GC stress response does not necessarily accrue the same fitness costs for all individuals. For instance, food shortage entails higher survival costs for subordinate individuals that do not have much access to food relatively to dominant individuals in a passerine species, the white-throated sparrow, *zonotrichia albicollis* (Piper and Wiley, 1990). Therefore, a specific GC stress response may not accrue the same risk of immediate mortality for subordinates and dominants because their fitness would probably be optimized by a different GC stress response (Wingfield and Sapolsky, 2003). These inter-individual differences in benefits could ultimately explain why the GC stress response varies so much between individuals (Cockrem, 2013; Cockrem and Silverin, 2002; Ouyang et al., 2011). When a new LPF situation occurs, individuals may mount an inappropriate GC stress response because they do not assess appropriately the threat that this new situation represents (i.e., perception, transduction and response – the three earlier scenarios). Interestingly, this mismatch between the new LPF situation and the GC stress response may be more exacerbated for some individuals than others because of the inter-individual variability in the GC stress response that results from genetic factors (Angelier et al., 2011; Evans et al., 2006; Satterlee and Johnson, 1988) or from different individual states (e.g., habitat quality, (Marra and Holberton, 1998); body condition, (Angelier et al., 2013; Lynn et al., 2003); parasite load, (Raouf et al., 2006); social status, (Poisbleau et al., 2005); experience (Angelier et al., 2006, 2007a), etc.). When facing a new LPF situation, the GC stress response of some individuals may therefore be better tuned to appropriately balance the risk of immediate mortality and the long-term fitness costs associated with the GC stress response than the GC stress response of others.

6.1. Age and the GC stress response in breeders: an example

In vertebrates, young breeders usually show a stronger GC stress response than older ones (Angelier et al., 2007b; Goutte et al., 2010; Heidinger et al., 2006; Wilcoxen et al., 2011) and this has been interpreted as a higher parental investment in older birds. As individuals age, their future breeding opportunities become lower. Therefore, the value of their current reproduction becomes high relative to the value of future reproduction and survival, and their GC stress response is attenuated to ensure that reproduction is not inhibited. In this way they avoid the long-term fitness costs of the GC stress response (Wingfield and Sapolsky, 2003) (Fig. 5A).

In a context of global change, this inter-individual variability may be crucial to consider because it means that individuals of different ages will probably react very differently to new LPF situations. Actually, it is likely that young birds will also show a stronger GC stress response than older individuals when confronted to a new LPF situation (Angelier et al., 2007b; Goutte et al., 2010; Heidinger et al., 2006; Wilcoxen et al., 2011) and this can result in different scenarios depending on the actual threat that the new LPF situation represents. If this new LPF entails a high risk of immediate mortality, young individuals may cope with it better than older individuals because their strong GC stress response will make them more likely to survive the new LPF situation than older individuals with a weaker GC stress response (Fig. 5B). On the other hand, older individuals may cope with this new LPF situation better than young individuals if this LPF only represents a minor threat to their immediate survival: older individuals with a weak GC stress response will be likely to survive this new LPF situation as will younger ones but, contrary to young individuals, older individuals will not accrue the high long-term fitness costs associated with the activation of a strong GC stress response (e.g., inhibition of reproduction, (Wingfield and Sapolsky, 2003) (Fig. 5C)).

6.2. Different levels of heterogeneity in the GC stress response

The GC stress response is a flexible multi-components mechanism that shows a high inter-individual but also intra-individual variability (Angelier et al., 2011; Bokony et al., 2009; Cockrem, 2013; Cockrem and Silverin, 2002; Hau et al., 2010; Wada et al., 2006; Wingfield et al., 1995). Indeed, the GC stress response depends on when it occurs since daily and seasonal variations in the GC stress response have been well-documented (Romero, 2002; Wingfield and Romero, 2001). In addition, the GC stress response also varies with the state of the individual (e.g., body condition, (Lynn et al., 2003); age, (Goutte et al., 2010; Heidinger et al., 2006; Wilcoxen et al., 2011), social status, (Poisbleau et al., 2005) and with life-history stages (Romero, 2002). For example, individuals in poor condition usually have a stronger GC stress response than individuals in good body condition (Angelier et al., 2013). All these variations in the GC stress response are thought to be linked to various life-history strategies that optimize individual's fitness under specific circumstances (Wingfield and Sapolsky, 2003). The same reasoning could apply to populations and species. Different populations of the same species sometimes show contrasted GC stress responses and these can be related to different life-history strategies. For instance, two populations of willow tits living at different latitudes show different GC stress responses and this difference has been related to the length of the breeding season and to different costs of abandoning reproduction for these two populations (Silverin et al., 1997). In addition, comparative and experimental studies have also shown that different species showing contrasted life-history strategies differ in their GC stress response (Angelier et al., 2011; Bokony et al., 2009; Hau et al., 2010; Wada et al., 2006; Wingfield and Romero, 2001; Wingfield et al., 1995). For instance, short-lived species with only a few breeding opportunities show a weaker GC stress response than long-lived species because the value of their current reproduction is high relatively to the value of future reproduction and survival (Bokony et al., 2009; Hau et al., 2010).

Obviously, this theory does not mean that individuals, populations and species won't be able to adjust to new LPF situation through the processes we described earlier (micro-evolution, phenotypic plasticity and phenotypic elasticity) but it suggests that all individuals, populations and species won't be able to equally cope with a new LPF situation. Indeed, the GC stress response and its sources of variation provide an exciting functional basis to raise hypotheses that may allow better understanding how global change and modifications of LPF situations affect different species, populations and individuals. It may also provide us with a physiological tool to better assess when an individual or a species is the most at risk of being unable to cope with a given new LPF situation during its life-history cycle (conservation physiology Cockrem, 2005).

7. Conclusion and perspectives

In this perspective paper, we aimed at emphasizing the importance that integrative mechanisms, and especially the GC stress response, can play in the ability of vertebrates to cope with ongoing global change. The GC stress response is a complex mechanism that depends on several physiological components (GC secretion,

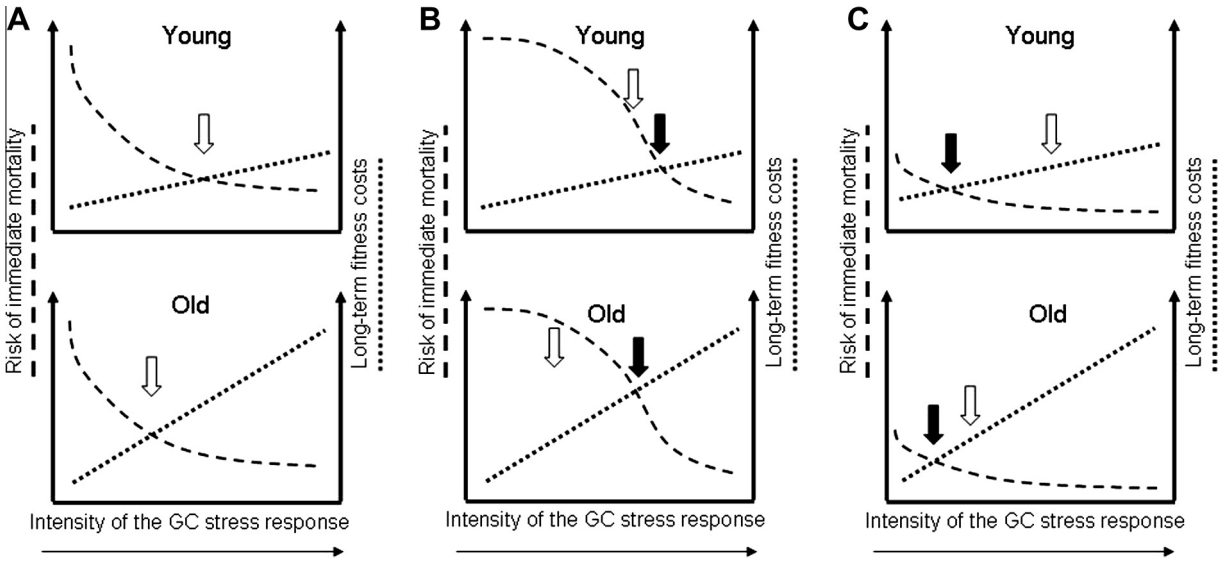

Fig. 5. Heterogeneity in the GC stress response and changes in the LPF situation. (A) All individuals do not accrue the same long-term fitness costs when a specific LPF occurs. For instance, some individuals (old) may entail higher long-term fitness costs than others (young) when activating an intense GC stress response. Therefore, old and young individuals may differ in their optimal GC stress response (white arrows). (B and C) When a new LPF situation occurs, a mismatch may appear between the GC stress response and the new LPF situation: Individuals may mount a GC stress response that would be adjusted to a specific known LPF (white arrow) whereas another GC stress response would be required to effectively cope with this new LPF situation (black arrow). Importantly, this mismatch and the related fitness costs may be more important for some individuals than others depending on their original optimal GC stress response. (B) When the risk of immediate mortality of the new LPF is increased relatively to that of the original LPF, the mismatch and the fitness costs may be especially important for individuals with a weak GC stress response (old individuals). (C) When the risk of mortality of the new LPF is reduced relatively to that of the original LPF, the mismatch and the fitness costs may be especially important for individuals with a strong GC stress response (young individuals).

binding globulin, receptors, etc. (Wingfield, 2012; Wingfield et al., 2013) and aims at promoting immediate survival when a LPF occurs. It is a somewhat flexible mechanism of which the degree of activation can be adjusted to the fitness costs and benefits that result from the GC stress response. Therefore, this stress response mediates life-history decisions and is involved in the regulation of important life-history trade-offs (Lendvai et al., 2007; Lendvai and Chastel, 2008, 2010; Wingfield and Sapolsky, 2003). By inducing abrupt and rapid changes in the regime of LPFs, we believe that global change can affect the efficiency of the GC stress response to maintain homeostasis and to appropriately regulate these trade-offs. This paper sets up a theoretical framework, hypotheses and new perspectives that will allow testing and better understanding how this mechanism can help or constrain species to adjust to ongoing global change.

Several topics need to be further investigated in order to better understand the role that the GC stress response plays in the ability of individuals, populations and species to cope with new LPF situations. First, only a few studies have explored how the GC stress response varies according to various LPFs and to the threat they represent for the organism. Second, it remains unclear to what extent new LPF situations can compromise the ability of the GC stress response to optimize an individual's fitness. Indeed, there is still much debate about the actual ability of the GC stress response to promote immediate survival (Breuner et al., 2008) and we need to further investigate the benefits and costs of various intensities of the GC stress response when different LPFs occur (see Angelier et al., 2009c for an example; (Bonier et al., 2009)). Third, it is crucial to investigate to what extent and how quickly the GC stress response can be adjusted to new LPF situations through micro-evolution, phenotypic plasticity and phenotypic flexibility. Specifically, more studies need not only to investigate how developmental conditions, maternal effects and environmental factors can modify the GC stress response but also to assess to what extent these modifications are adaptive and help individuals to cope with LPFs. Importantly, phenotypic flexibility has been rarely studied and, although we know that sensitization and habituation to new LPF situations occur (Cyr and Romero, 2009; Rödl et al., 2007; Romero and Wikelski, 2002; Walker et al., 2005), only a few studies have investigated these processes and their characteristics are not well known. Finally, we need to better document intra-individual, inter-individual and inter-species heterogeneity in the GC stress response and the causes of these variations to better understand what individuals/species are more at risk in case of abrupt and rapid changes in the regime of LPFs. All these questions need to be investigated by focusing on the multiple physiological components that constitute the GC stress response. So far, most studies have only examined absolute GC levels (baseline and maximal) and only a few have considered other components such as GC receptors, binding globulins, the termination of the GC stress response or the kinetics of this stress response. In that context, it will be critical to conduct more manipulations of the intensity, and duration of the GC stress response through implants of GCs and blockers under various environmental scenarios. This will allow better understanding whether experimentally shifted GC responses result in higher immediate risk of mortality, higher long-term fitness costs and, thus, to better understand the role that this mechanism plays in the ability of individuals, populations and species to cope with global change.

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