Ultraviolet radiation triggers "Preparation for Oxidative Stress" antioxidant response in animals: similarities and interplay with other stressors

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Summary

Preparation for oxidative stress (POS), i.e., the upregulation of endogenous antioxidants, is a widespread response of animals exposed to extreme conditions. This response has been described for more than 80 animal species belonging to eight phyla during hypometabolism or situations that limit oxygen availability. The pattern of the typical POS-response, in which a mild redox imbalance triggers antioxidant adjustments that results in increased tolerance to subsequent oxidative insults, roughly follows the curve of hormetic phenomena. A similar pattern has been reported for various animal species exposed to ultraviolet (UV) radiation – these studies, on animals from six phyla, are discussed herein. In the light of the similarities in the redox-response of animals exposed to either oxygen restriction or UV radiation, we argue in this essay that UV radiation elicits a type of response that fits the POS theory. Exposure to UV radiation induces both reactive species formation and antioxidant adaptation, which is the essence of typical POS-responses. Thus, antioxidant response to UV in animals can be considered a POS-type mechanism. Moreover, considering that animals are exposed to multiple stressors simultaneously in nature, this would represent an ecologically relevant process, by which one stressor (e.g., UV or ionizing radiation) may enhance the tolerance to other. We also discuss a possible role of low doses of ionizing radiation as inductor of POS-like responses in animals.

Keywords: free radicals, hormesis, electromagnetic wavelength, terrestrial and aquatic animals.

1. Introduction

The light from the sun brings an enormous amount of energy to Earth. Although this energy is the ultimate fuel for most of the life on this planet, it can also be life's foe. Within the range of electromagnetic wavelengths, ultraviolet (UV) radiation is the one that causes most harm to animals in nature (Cockell and Blaustein, 2001). Exposure to both UV-A and UV-B is an important factor not only for terrestrial environments but also for aquatic ecosystems, where organisms are exposed to solar UV radiation in the upper photic zone or when exposed to air during low tides. In the context of aquatic environments, UV-B has received great attention in the past years, especially in regions with a thinner ozone layer (Misra et al., 2002; Häder et al., 2007); although UV-A is also likely to be important as it can penetrate deeply into the water.

Exposure to UV radiation can damage major biomolecules and cellular structures, either through direct action of UV or, indirectly, through the formation of reactive oxygen species (ROS) (Cadet et al., 2005; Agnez-Lima et al., 2012; Schuch et al., 2017). In that regard, DNA is a main target of UV radiation, generating pyrimidine dimers, strand breaks, modified bases, photo-adducts, and DNA–protein cross-links (Karentz et al., 2004; Yagura et al., 2017). Several reports indicate that UV-effects on organisms are dose and time-dependent (Chuang and Chen, 2013; Won et al., 2014; Singh et al., 2015), eliciting adaptive responses in most life forms at low doses (Dahms and Lee, 2010; Häder et al., 2015; Cadet and Davies, 2017). Therefore, our essay concentrates on the biological effects, both adaptive and deleterious, of UV exposure, with a focus on the indirect effects mediated by ROS. Furthermore, the emphasis herein will be on the "classical" antioxidant response in animals, leaving out sunscreen molecules and DNA repair systems.

2. Redox-adaptive animal response to UV radiation

Many invertebrate and vertebrate species can improve their endogenous antioxidant systems upon exposure to low doses of UV radiation. On the other hand, under high UV doses, a rampant oxidative stress condition frequently occurs. In addition to dosage, other variables might influence the outcome of UV exposure, such as the individual size, mode of life (diurnal, nocturnal, etc.) and skin/exoskeleton characteristics. Therefore, the effects of UV exposure may differ greatly between different species and how the animal's body is exposed. For example, Kim et al. (2011) reported a dose-dependent effect of UV in which low doses (0.1–0.4 J/cm^2) prompted increases in ROS formation and both glutathione (GSH) and antioxidant enzymes in rotifers *Brachionus* sp. Increased activities of several antioxidant enzymes, as well as ROS levels, were also observed for the benthic copepod

Tigriopus japonicus after exposure to UVB (1.2 and 2.4 J/cm^2) (Kim et al., 2015). Increased ROS production was accompanied by a rise in SOD activity for the copepod *Paracyclopina nana* after exposure to low UV-B dose (0.1 J/cm^2) (Won et al., 2014) (**Figure 1**). Considering the effect of the water column on the intensity of UV that actually reaches animals, some studies have analyzed UV-effects with that perspective. For instance, an overall activation of endogenous antioxidant enzymes, as well as protein carbonyls, happened in the sea urchin larvae *Tripneustes gratilla* upon exposure to natural UV in shallow (1 m), but not in deeper water (4 m) (Lister et al., 2010). For the colonies of the coral *Acropora microphthalma* (host and zooxantella), a high antioxidant status was observed in individuals collected at shallow water, whereas antioxidant levels decreased as depth increased (Shick et al., 1995). Furthermore, the effect of depth on the redox metabolism is evident in *Strongylocentrotus droembrachiensis* larvae. Sea urchin larvae exposed to UV at a 1 m depth have higher levels of SOD and DNA damage than those exposed to UV at deeper depths (Lesser et al., 2010).

The modulation of endogenous antioxidant in response to UV might be especially important for animals restricted to environments under direct solar exposition where no microhabitats with solar protection are available. This is the case of many water bodies where a number of aquatic vertebrates cannot shelter from sunlight. Indeed, tadpoles and fish (larval and adults) inhabiting shallow waters activate their endogenous antioxidants when exposed to UV. For example, *Bufo arenarum* tadpoles increase their SOD activity when exposed to UV-B sublethal doses (0.02- 0.2 J/cm^2), followed by a return to basal levels after 5 h (Herkovits et al., 2006) (**Figure 1**). A similar response – regarding SOD and catalase activities - was reported for adult zebrafish (*Brachydanio rerio*) exposed to two UV-B doses (0.32 and 4.2 J/cm^2) (Charron et al., 2000). Likewise, embryos of the salamander *Ambystoma maculatum* enhanced their SOD levels at both the protein and activity when exposed to low doses of UV radiation (0.02-3.96 J/cm^2) (Lesser et al., 2001b). Moreover, larvae of Atlantic cod (*Gadus morhua*) exposed to UV (2.3 J/cm^2) exhibited higher levels of SOD and DNA damage than control animals (Lesser et al., 2001a). Intertidal juvenile fish *Girella laevifrons* exposed to UV-B (1.04 J/cm^2) presented increases in hepatic SOD and catalase activities after 2 h (Carrasco-Malio et al., 2014). However, a longer exposure (5 h) elicited a decrease in catalase activity as well as increased lipoperoxidation and DNA damage. For *Catla catla* fish larvae, Singh et al. (2015) reported increased SOD activity and oxidative stress after UV-B exposure (0.5-2.0 J/cm^2) for 21 days. The interplay between temperature and UV has also been explored. Mosquitofish (*Gambusia holbrooki*) specimens that had been acclimatized at low temperatures are more susceptible to oxidative damage than those acclimated at high temperatures when exposed to UV radiation (Kazerouni et al., 2016). The effect of UV is expected to be more intense in small-bodied slim animals with thin teguments, such as the

examples presented above. In these cases, both invertebrates and vertebrates discussed herein presents an adaptive strategy to manage redox imbalances through activation of antioxidants. There are cases, however, where UV induces only oxidative stress, without an adaptive antioxidant response, such as in catfish *Clarias gariepinus* (Ibrahim, 2015). Much further study is needed to understand the UV action on the redox metabolism of aquatic vertebrates.

Several of the aforementioned examples on the response of endogenous antioxidants in aquatic animals exposed to UV radiation highlight the occurrence of hormetic biphasic response (i.e., low doses stimulate antioxidants and potentially increase fitness, whereas high doses inhibit antioxidants and have deleterious effects). This biphasic-pattern has also works for land animals. For example, mRNA expression of many antioxidant enzymes is stimulated by UV-A exposure (1.1 J/cm^2) in the moth *Helicoverpa armigera*. Longer irradiation times decreases GSH:GSSG ratio, indicating that UV-A induces redox imbalance (Wang et al., 2012). In a study with the ear-cutting caterpillar *Mythimna separata*, low UV-A dose (1.2 J/cm^2) increased the activity of several antioxidant enzymes after 60 min. On the other hand, longer exposures (90–120 min) reduced the activity of antioxidant enzymes, leading to high levels of oxidative stress markers (Ali et al., 2016). Similarly, *Spodoptera litura* moths exposed to UV-B (1.08 J/cm^2) for 1 h increased the activities of several antioxidant enzymes. When UV exposure was extended to 2 h (2.16 J/cm^2), the antioxidant enzymes returned to basal levels or decreased (Karthi et al., 2014). In the case of earthworms *Amynthas gracilis*, a low UV-B dose (0.05 J/cm^2) prompted an increase in catalase activity. At a higher dose (0.3 J/cm^2), however, there was a decrease in glutathione peroxidase and catalase activities and an increase in lipid peroxidation (Singh et al., 2015). (**Figure 1**). Thus, these studies with terrestrial and aquatic animals indicate that the response of endogenous antioxidants, as well as the degree of oxidative stress, presents an overall dose-dependent response within a limited range, leading to UV radiation adaptive responses under low doses and deleterious outcomes in higher doses.

3. The POS adaptive theory

The pattern observed in the response of endogenous antioxidants to UV radiation exposure is reminiscent of the biochemical adaptations reported for many animal species challenged by extreme environments. These challenges include freezing-cold, oxygen depletion, and recovery from these conditions. Such conditions may change cyclically or abruptly in natural habitats (Welker et al., 2013). The activation of endogenous antioxidants under these situations was first reported in 1993 in garter snakes (Hermes-Lima and Storey 1993) and named “Preparation for Oxidative Stress” (POS) (Hermes-Lima et al., 1998), whereby a small-scale redox imbalance induces a physiological antioxidant

response, setting the animal to deal with subsequent, more severe, oxidative stress (Hermes-Lima et al., 2015; Giraud-Billoud et al., 2019). More than a hundred studies confirmed that POS occurs in many animal species in the following stress-situations: hypoxia/anoxia, severe dehydration, freezing, estivation, hyposaline stress and air-exposure of water-breathing animals (Giraud-Billoud et al., 2019). In total, such a POS-response was identified in 83 species from 8 different animal phyla, including vertebrates and invertebrates (Moreira et al., 2016, 2017). In animals under hypoxia, where POS has been most studied, it is one component of a set of physiological/biochemical adaptive responses that allows organisms to cope with low oxygen levels. These include: (i) the arrest of most transcriptional and translational activity, (ii) depression of metabolic rate, (iii) re-wiring of energy metabolism pathways toward fermentative routes, (iv) activation of mechanisms involved in both macromolecular repair and detoxification of cellular-derived oxidants (Krivoruchko ans Storey, 2015; Storey, 2015; Biggar and Storey, 2018). Importantly, the transient upregulation of the antioxidant defense system is a hallmark of many organisms that tolerate hypoxic stresses, as it is crucial to deal with reoxygenation. Elucidating the exact molecular mechanisms that trigger POS is an active topic of research, but, only recently, it was proposed that the biochemical patterns we call POS are brought about by an increase in ROS levels (Hermes-Lima et al., 2015). Such increase in ROS levels (which may happen during hypoxia, for example) may activate redox-sensitive transcription factors, such as FoxOs, NF-κB, and Nrf2, promoting the expression of antioxidants (**Figure 2**). In addition, posttranslational modifications on antioxidant enzymes by kinases and phosphatases may also contribute to the expression of the POS phenotype (Rashkov et al., 2016; Oliveira et al., 2018). It seems certain that many organisms exposed to mild sublethal stress conditions trigger a response that is protective against stronger subsequent challenges, typical of hormetic outputs (Costantini, 2014a). In fact, POS has strong similarities with the hormetic responses (Oliveira et al., 2018).

4. Redox-adaptive response to UV radiation as POS

In the present article, we argue that the antioxidant adaptation in response to UV radiation should be considered a new type of POS-response. Considering the discussion above, it is possible to draw some parallels between the response of animals' endogenous antioxidant systems to low oxygen stresses and to UV radiation exposure. These parallels come from the observations that exposure to low doses of UV radiation can increase ROS production and stimulate the antioxidant system, which is the essence of the typical POS response (for example, POS response in hypoxia) (**Figure 2**). Such up regulation of antioxidants should increase the animals' capacity to deal with subsequent exposures

to higher dosages of UV radiation. Although the patterns of antioxidant response to hypoxia and UV exposure are alike, whether they share the same molecular mechanisms is still an open question.

The currently proposed biochemical mechanism for POS in animals exposed to hypoxic stress relies on the increase in ROS production during oxygen deprivation (Hermes-Lima et al., 2015). It is well known that ROS activate redox-sensitive transcription factors, as well as protein kinase pathways (Oliveira et al., 2018). Some of these transcription factors, notably Nrf2, can stimulate the expression of endogenous antioxidants (Espinosa-Diez et al., 2015; Klotz et al., 2015). Like hypoxia, UV radiation also increases both ROS production (Liu et al., 2016; Jeayeng et al., 2017; Schuch et al., 2017), and the levels of endogenous antioxidants (Liu et al., 2011). Hence, the evidence strongly suggests the involvement of redox-sensitive transcription factors, such as Nrf2, in the UV adaptive-response (**Figure 2**). Indeed, the role of Nrf2 and its related genes has been demonstrated *in vitro* by studies using dermal cells and fibroblasts (Schafer et al., 2010; Schafer and Werner 2015), but not in the animal cases reported herein (**Section 2**). Thus, the pathways underlying the redox-response to UV and hypoxia seem to converge to the same set of cellular responses, both showing the POS pattern.

There are, however, some differences between the antioxidant response to UV radiation exposure and, for exampl e, hypoxia. One of the most relevant difference is the fact that the POS response to UV radiation is not necessarily accompanied by metabolic depression – a highly relevant adaptive factor for hypoxia tolerance, which also happens under estivation, severe dehydration and freezing exposure (Hermes-Lima et al., 2015). Despite their differences, there are striking parallels in the pattern of redox-response the animals show under those conditions. One of these is the involvement of transcription factor Nrf2 as a key molecular component of the antioxidant adaptive response (**Figure 2**). In the currently accepted cases of POS, we can identify typical hormetic patterns (Oliveira et al., 2018), in which an earlier and mild oxidative stress increases the animals' capacity to deal with a subsequent and more severe stress. This same POS/hormetic pattern is described herein in 17 animal species from six phyla (**Section 2**).

Although an adaptive redox-response to UV radiation can be induced in the laboratory, it is a challenge to identify ecological scenarios in which this POS-response may be important. For example, in tropical marine environments, the diversity of invertebrates exposed to direct UV is immense and totally depend on the ecophysiological mechanisms to respond to the UV excess. In this sense, the work by Lister et al. (2010) with *T. gratilla* larvae in the Cook Islands could be viewed as ecologically relevant for POS response in nature. These larvae are routinely exposed to varying levels of UV radiation in marine environments. There was an upregulation of antioxidant systems in shallow depth; such process in larval states constitutes an important investment for the animal fitness because

198 minimize long-term effects such as oxidative DNA damage (Lister et al., 2010). Moreover, the range
199 of tolerance to direct solar UV radiation is one of the limiting factors defining which habitats a species
200 can inhabit, especially for sessile animals or those that do not present behavioral adaptations associated
201 with differential use of microenvironments (Zagarese & Williamson, 1994). Within communities, both
202 the UV radiation dose and the exposure time are important factors whose differential effects on each
203 species shape the structure of the communities (Williamson et al., 2001; Yang et al., 2017). In that
204 regard, the role of UV on animal homeostasis and adaptation can be more complex than its isolated
205 direct effect on organisms; UV might have transgenerational effects and synergistic interactions with
206 other environmental stressors. For example, UV radiation not only cause a POS-type adaptive response
207 in individuals directly exposed to it (Kazerouni et al., 2016) but also in their offspring (Kazerouni et
208 al., 2017). Moreover, under natural conditions, the exposure to both solar UV radiation and aerial
209 exposure induced the activation of antioxidant systems in intertidal mussels *Brachidontes solisianus*
210 (Moreira et al. 2017).
211
212 **5. Ionizing radiation and POS**
213 Gamma and X rays are forms of ionizing radiation characterized by their smaller wavelengths,
214 and higher frequency and energy than UV. We expect them to also elicit a protective response that may
215 fit into the POS theory. Such response was first shown over a century ago, when low dose X-ray
216 radiation increased lifespan in flour beetles (Davey, 1917). Additionally, this protection allowed the
217 beetles to tolerate lethal amounts of radiation when given as smaller doses daily (Davey, 1919).
218 Predating the concepts of oxidative stress and hormesis, it is clear that Davey was aware of the
219 protective nature of low dose ionizing radiation (Calabrese, 2013). The bulk of the work on the
220 protective effects of X-ray radiation has been carried out in insects because of their importance as
221 agricultural pests and medical research models. Lifespan extensions related to low dose gamma or X-
222 ray exposure have been recorded in flies, mosquitoes, moths, crickets, wasps, and beetles (Calabrese,
223 2013). Beyond reporting longer-lived animals, longevity increases in flies only occur when associated
224 with starvation conditions (Lamb, 1964), suggesting that the mechanism behind this benefit is
225 connected to mitochondrial function and energetics.
226 Mechanistically, little is known about how gamma and X-rays increase lifespan. However,
227 performance improvements following low dose and high dose exposures seem to work differently.
228 Higher doses of ionizing radiation lead to increased longevity in insects, especially in females, mostly
229 due to a decreased in reproductive output or sterility (López-Martínez and Hahn 2014; López-Martínez
230 et al., 2014). Sterility triggers a life history trade-off where energy normally allocated for reproduction

now goes towards immunity and defense (Stearns, 1989). Conversely, low dose radiation and its protective phenomena are in line with our POS expectations; an adaptive protective antioxidant response. Mechanistic work with *Drosophila melanogaster* shows that activity and lifespan were shortened in flies with mutations to apoptosis, DNA repair, antioxidant defense, and heat shock protein genes (Moskalev et al., 2006; Moskalev et al., 2009). Mutants for apoptosis and antioxidant genes were the most affected, indicating that the benefit conferred by low-dose gamma rays is connected to a decreased in oxidative stress with the strongest benefit seen in early life exposure (Moskalev, 2007). Antioxidant enzymes and genes involved in oxidative stress responses were expressed in response to low-dose gamma irradiation connected with lifespan extension and the authors propose that the mechanism for low-dose ionizing radiation protection is the activation of oxidative stress defense mechanisms (Seong et al., 2011), which goes to the heart of the POS theory (Giraud-Billoud et al., 2019). *In vitro* and *in vivo* evidence in mammalian cells show lower levels of DNA damage following low dose radiation treatment (Vijayalaxmi et al., 2014). All this work suggests that hormetic effects associated with low-dose gamma and X rays are likely rooted in the POS theory, as some of the mechanism known indicates a key role for antioxidant protection and heat shock proteins - two sets of genes that are crucial in the POS framework.

6. Conclusions

Finally, the molecular similarity between the responses to UV radiation (and ionizing radiation) and other POS conditions may also expand the ecological relevance of POS phenotypes. It implies a possible interaction between, for example, UV radiation and hypoxia – where UV radiation pre-exposure could set up preparation for hypoxic stress (or vice-versa). This would be similar to what has been reported for other hormetic phenomena, where “stress X” sets up animals for tolerance to “stress Y” (Costantini, 2014b; López-Martínez and Hahn, 2014; Espinosa-Diez et al., 2015). This has been verified in the case of pre-exposure of multiple species of fruit flies and moths to hypoxia causing beneficial outcomes for ionizing radiation exposure (Robinson 1975, Nestel et al. 2007, López-Martínez and Hahn, 2012; López-Martínez and Hahn, 2014; López-Martínez et al., 2014). Considering that animals may be subjected to multiple stressors simultaneously, the interplay between UV/ionizing radiation and hypoxia, for instance, should affect and modulate the POS-response in nature.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

MG, DCM and MHL worked on the concept of UV redox-adaptation response as being part of the overall POS strategy. MG, MM, MFC, JMCF and MHL contributed with key examples of UV-related studies. GLM contributed with discussions on ionizing radiation. MM and DCM produced the artwork. MG, DCM, GLM, MFC, JMCF, and MHL drafted the manuscript, which was reviewed and approved by all authors.

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References

Agnez-Lima, L.F., Melo, J. T. A., Silva, A. E., Oliveira, A. H. S., Timoteo, A. R. S., Lima-Bessa, K. M., Martinez, G.R., Medeiros, M. H., Di Mascio, P., Galhardo, R. S., Menck, C. F. M., 2012. DNA damage by singlet oxygen and cellular protective mechanisms. *Mutation Research/Reviews in Mutation Research, 751*(1), 15–28. doi.org/10.1016/j.mrrev.2011.12.005

Ali, A., Rashid, M. A., Huang, Q. Y., Lei, C. L., 2017. Influence of UV-A radiation on oxidative stress and antioxidant enzymes in *Mythimna separata* (Lepidoptera: Noctuidae). *Environmental Science and Pollution Research, 24*(9), 8392–8398. doi.org/10.1007/s11356-017-8514-7

Beak, S. M., Lee, Y. S., Kim, J. A., 2004. NADPH oxidase and cyclooxygenase mediate the ultraviolet B-induced generation of reactive oxygen species and activation of nuclear factor-κB in HaCaT human keratinocytes. *Biochimie, 86*: 425–429. doi.org/10.1016/j.biochi.2004.06.010

Biggar, K. K., Storey, K. B., 2018. Functional impact of microRNA regulation in models of extreme stress adaptation. *Journal of Molecular Cell Biology, 10*(2), 93–101. doi.org/10.1093/jmcb/mjx053

Cadet, J., Davies, K. J. A., 2017. Oxidative DNA damage & repair: An introduction. *Free Radical Biology and Medicine, 107*, 2–12. doi.org/10.1016/j.freeradbiomed.2017.03.030

294 Cadet, J., Sage, E., Douki, T., 2005. Ultraviolet radiation-mediated damage to cellular DNA.
295 *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 571*(1), 3–17.
296 doi.org/10.1016/j.mrfmmm.2004.09.012.

297 Calabrese, E. J., 2013. Low doses of radiation can enhance insect lifespans. *Biogerontolog*y, 14 (4),
298 365-381. doi 10.1007/s10522-013-9436-5

299 Carrasco-Malio, A., Díaz, M., Mella, M., Montoya, M. J., Miranda, A., Landaeta, M. F., Sánchez, G.,
300 Hidalgo, M. E., 2014. Are the intertidal fish highly resistant to UV-B radiation? A study based
301 on oxidative stress in *Girella laevifrons* (Kyphosidae). *Ecotoxicology and Environmental Safety,*
302 *100*, 93–98. doi.org/10.1016/j.ecoenv.2013.07.030

303 Charron, R. A., Fenwick, J. C., Lean, D. R., Moon, T. W., 2000. Ultraviolet-B radiation effects on
304 antioxidant status and survival in the zebrafish, *Brachydanio rerio*. *Photochemistry and*
305 *Photobiology 72(3)*:327-33. doi.org/10.1562/0031-8655(2000)0720327UBREOA2.0.CO2

306 Chuang, S. C., Chen, J. H., 2013. Photooxidation and antioxidant responses in the earthworm
307 *Amynthas gracilis* exposed to environmental levels of ultraviolet B radiation. *Comparative*
308 *Biochemistry and Physiology Part A: Molecular & Integrative Physiology, 164*(3), 429–437.
309 doi.org/10.1016/j.cbpa.2012.11.006

310 Cockell, C., Blaustein, A. R., 2001. Ecosystems, Evolution, and Ultraviolet Radiation. New York,
311 Springer-Verlag.

312 Costantini, D., 2014a. *Oxidative Stress and Hormesis in Evolutionary Ecology and Physiology.*
313 Berlin, Heidelberg: Springer-Verlag.

314 Costantini, D., 2014b. Does hormesis foster organism resistance to extreme events? *Frontiers in*
315 *Ecology and the Environment, 12*(4), 209–210. doi.org/10.1890/14.WB.005

316 Dahms, H. U., Lee, J. S., 2010. UV radiation in marine ectotherms: Molecular effects and responses.
317 *Aquatic Toxicology, 97*(1), 3–14. doi.org/10.1016/j.aquatox.2009.12.002

318 Davey, W. P., 1917. The effect of X-rays on the length of life of *Tribolium confusum. Journal of*
319 *Experimental Zoology* 22(3), 573–592.

320 Davey, W. P., 1919. Prolongation of life of *Tribolium confusum* apparently due to small doses of X-
321 rays. *Journal of Experimental Zoology*, 28 (3), 447-458.

322 Espinosa-Diez, C., Miguel, V., Mennerich, D., Kietzmann, T., Sánchez-Pérez, P., Cadenas, S.,
323 Lamas, S., 2015. Antioxidant responses and cellular adjustments to oxidative stress. *Redox*
324 *Biology, 6*, 183–197. doi.org/10.1016/j.redox.2015.07.008

325 Giraud-Billoud, M., Rivera-Ingraham, G. A., Moreira, D. C., Burmester, T., Castro-Vazquez, A.,
326 Carvajalino-Fernández, J. M., Dafre, A., Niu, C., Tremblay, N., Paital, B., Rosa, R., Storey, J.
327 M., Vega, I. A., Zhang, W., Yepiz-Plascencia, G., Zenteno-Savin, T., Storey, K. B., Hermes-
328 Lima, M., 2019. Twenty years of the 'Preparation for Oxidative Stress' (POS) theory:
329 Ecophysiological advantages and molecular strategies. *Comparative Biochemistry and*
330 *Physiology A*, 234, 36–49. doi.org/10.1016/j.cbpa.2019.04.004

Häder, D. P., Kumar, H. D., Smith, R. C., Worrest, R. C., 2007. Effects of solar UV radiation on aquatic ecosystems and interactions with climate change. Photochemical & Photobiological *Sciences, 6*(3), 267–285. doi.org/10.1039/B700020K

Häder, D. P., Williamson, C. E., Wängberg, S. Â., Rautio, M., Rose, K. C., Gao, K., Helbing, E. W., Sinha, R. P., Worrest, T., 2015. Effects of UV radiation on aquatic ecosystems and interactions with other environmental factors. *Photochemical and Photobiological Sciences, 14*(1), 108–126. doi.org/10.1039/C4PP90035A

Herkovits, J., D'Eramo, J. L, Fridman, O., 2006. The effect of UV-B radiation on Bufo arenarum embryos survival and superoxide dismutase activity. *International Journal of Environmental Research and Public Health*, *3*(1), 43–47. doi.org/10.3390/ijerph2006030006

Hermes-Lima, M., Moreira, D. C., Rivera-Ingraham, G. A., Giraud-Billoud, M., Genaro-Mattos, T. C., Campos, É. G., 2015. Preparation for oxidative stress under hypoxia and metabolic depression: Revisiting the proposal two decades later. *Free Radical Biology and Medicine, 89*, 1122–1143. doi.org/10.1016/j.freeradbiomed.2015.07.156

Hermes-Lima, M., Storey, K. B., 1993. Antioxidant defenses in the tolerance of freezing and anoxia by garter snakes. *American Journal of Physiology, 265*, R646–652. doi.org/10.1152/ajpregu.1993.265.3.R646

Hermes-Lima, M., Storey, J. M., Storey, K. B., 1998. Antioxidant defenses and metabolic depression. The hypothesis of preparation for oxidative stress in land snails. *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology, 120*(3), 437–448. doi.org/10.1016/S0305-0491(98)10053-6

Ibrahim, A.T.A., 2015. Negative impacts of ultraviolet-A radiation on antioxidant and oxidative stress biomarkers of African catfish *Clarias gariepinus*. *Photochemical &Photobiological Sciences*, 14, 1337-1345. doi.org/10.1039/c5pp00112a

Jeayeng, S., Wongkajornsilp, A., Slominski, A. T., Jirawatnotai, S., Sampattavanich, S., Panich, U., 2017. Nrf2 in keratinocytes modulates UVB-induced DNA damage and apoptosis in melanocytes through MAPK signaling. *Free Radical Biology and Medicine, 108*, 918–928. doi.org/10.1016/j.freeradbiomed.2017.05.009

Karentz, D., Bosch, I., Mitchell, D. M., 2004. Limited effects of Antarctic ozone depletion on sea urchin development. *Marine Biology, 145*(2), 277–292. doi.org/10.1007/s00227-004-1310-1.

Kharty, S., Sankari, R., Shivakumar, M. S., 2014. Ultraviolet-B light induced oxidative stress: Effects on antioxidant response of *Spodoptera litura*. *Journal of Photochemistry and Photobiology B, 135*, 1–6. doi.org/10.1016/j.jphotobiol.2014.04.008

Kazerouni, E. G., Franklin, C. E., Seebacher, F. 2016. UV-B radiation interacts with temperature to determine animal performance. *Functional Ecology*, *30*(4), 584-595. doi.org/10.1111/1365-2435.12520

Kazerouni, E. G., Franklin, C. E., Seebacher, F. 2017. Parental exposure modulates the effects of UV-B on offspring in guppies. *Functional Ecology*, *31*(5), 1082-1090. doi.org/10.1111/1365-2435.12817

Kim, B. M., Rhee, J. S., Lee, K. W., Kim, M. J., Shin, K. H., Lee, S. J., Lee, Y. M., Lee, J. S., 2015. UV-B radiation-induced oxidative stress and p38 signaling pathway involvement in the benthic copepod Tigriopus japonicus. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 167*, 15–23. doi.org/10.1016/j.cbpc.2014.08.003

Kim, R. O., Rhee, J. S., Won, E. J., Lee, K. W., Kang, C. M., Lee, Y. M., Lee, J. S., 2011. Ultraviolet B retards growth, induces oxidative stress, and modulates DNA repair-related gene and heat shock protein gene expression in the monogonont rotifer, Brachionus sp. *Aquatic Toxicology (Amsterdam, Netherlands), 101*(3–4), 529–539. doi.org/10.1016/j.aquatox.2010.12.005.

Klotz, L. O., Sánchez-Ramos, C., Prieto-Arroyo, I., Urbánek, P., Steinbrenner, H., Monsalve, M., 2015. Redox regulation of FoxO transcription factors. *Redox Biology, 6*, 51–72. doi.org/10.1016/j.redox.2015.06.019

Krivoruchko, A., & Storey, K. B., 2015. Turtle anoxia tolerance: Biochemistry and gene regulation. *Biochimica et Biophysica Acta, 1850*(6), 1188–1196. doi.org/10.1016/j.bbagen.2015.02.001

Lamb, M. J., 1964. The effects of radiation on the longevity of female *Drosophila subobscura*. *Journal of Insect Physiology, 10*, 487–497. doi: https://doi.org/10.1016/0022-1910(64)90072-1

Lesser, M. P., Farrell, J. H., Walker, C. W. 2001a. Oxidative stress, DNA damage and p53 expression in the larvae of Atlantic cod (*Gadus morhua*) exposed to ultraviolet (290–400 nm) radiation. *Journal of Experimental Biology*, *204*(1), 157-164.

Lesser, M. P., Turtle, S. L., Farrell, J. H., Walker, C. W. 2001b. Exposure to ultraviolet radiation (290-400 nm) causes oxidative stress, DNA damage, and expression of p53/p73 in laboratory experiments on embryos of the spotted salamander, *Ambystoma maculatum*. *Physiological and Biochemical Zoology*, *74(5)*, 733-741. doi.org/10.1086/322931

Lesser, M. P. 2010. Depth-dependent effects of ultraviolet radiation on survivorship, oxidative stress and DNA damage in sea urchin (*Strongylocentrotus droebachiensis*) embryos from the Gulf of Maine. *Photochemistry and Photobiology*, *86*(2), 382-388. doi.org/10.1111/j.1751-1097.2009.00671.x

Lister, K. N., Lamare, M. D., Burritt, D. J., 2010. Oxidative Damage in Response to Natural Levels of UV-B Radiation in Larvae of the Tropical Sea Urchin *Tripneustes gratilla*. *Photochemistry and Photobiology, 86*(5), 1091–1098. doi.org/10.1111/j.1751-1097.2010.00779.x

Liu, C., Vojnovic, D., Kochevar, I. E., Jurkunas, U. V., 2016. UV-A Irradiation Activates Nrf2-Regulated Antioxidant Defense and Induces p53/Caspase3-Dependent Apoptosis in Corneal Endothelial Cells. *Investigative Ophthalmology & Visual Science, 57*, 2319–2327. doi.org/10.1167/iovs.16-19097

Liu, Y., Chan, F., Sun, H., Yan, J., Fan, D., Zhao, D., An, J., Zhou, D., 2011. Resveratrol protects human keratinocytes HaCaT cells from UVA-induced oxidative stress damage by downregulating Keap1 expression. *European Journal of Pharmacology, 650*, 130–137. doi.org/10.1016/j.ejphar.2010.10.009

López-Martínez, G., Hahn, D. A., 2012. Short-term anoxic conditioning hormesis boosts antioxidant defenses, lowers oxidative damage following irradiation and enhances male sexual performance

409 in the Caribbean fruit fly, *Anastrepha suspensa. Journal of Experimental Biology*, 215: 2150-
410 2161. doi: 10.1242/jeb.065631

411 López-Martínez, G., Hahn, D. A., 2014. Early life hormetic treatments decrease irradiation-induced
412 oxidative damage, increase longevity, and enhance sexual performance during old age in the
413 Caribbean fruit fly. *Plos One, 9*(1):e88128. doi.org/10.1371/journal.pone.0088128

414 López-Martínez, G., Carpenter, J. E., Hight, S. D., Hahn, D. A. 2014. Low-oxygen atmospheric
415 treatment improves the performance of irradiation-sterilized male cactus moths used in SIT.
416 *Journal of Economic Entomology*, 107 (1), 185-197. doi: http://dx.doi.org/10.1603/EC13370

417 Masaki, H., Izutsu, Y., Yahagi, S., Okano, Y., 2009. Reactive oxygen species in HaCaT
418 keratinocytes after UVB irradiation are triggered by intracellular Ca2+ levels. *Journal of*
419 *Investigative Dermatology Symposium Proceedings 14*(1)50–52.
420 doi.org/10.1038/jidsymp.2009.12

421 Misra, R. B., Babu, G. S., Ray, R. S., Hans, R. K., 2002. Tubifex: A Sensitive Model for UV-B-
422 Induced Phototoxicity. *Ecotoxicology and Environmental Safety, 52*(3), 288–295.
423 doi.org/10.1006/eesa.2002.2184

424 Moreira, D. C., Oliveira, M. F., Liz-Guimarães, L., Diniz-Rojas, N., Campos, É. G., Hermes-Lima,
425 M., 2017. Current Trends and Research Challenges Regarding "Preparation for Oxidative
426 Stress". *Frontiers in Physiology, 8*: 702. doi.org/10.3389/fphys.2017.00702

427 Moreira, D.C., Venancio, L. P. R., Sabino, M. A. C. T., Hermes-Lima, M., 2016. How widespread is
428 preparation for oxidative stress in the animal kingdom?. *Comparative Biochemistry and*
429 *Physiology Part A: Molecular & Integrative Physiology, 200*, 64–78.
430 doi.org/10.1016/j.cbpa.2016.01.023

431 Moskalev, A., 2007. Radiation-induced life span alteration of *Drosophila* lines with genotype
432 differences. *Biogerontology*, 8, 499–504. doi: 10.1007/s10522-007-9090-x

433 Moskalev, A. A., Yazkiv, A. S., Zainullin, V. G., 2006. Effect of low-dose irradiation on the lifespan
434 in various strains of *Drosophila melanogaster*. *Russian Journal of Genetics*, 42(6), 628–635. doi:
435 https://doi.org/10.1134/S102279540606007X

436 Moskalev, A., Shaposhnikov, M., Turysheva, E., 2009. Life span alteration after irradiation in
437 *Drosophila melanogaster* strains with mutation of Hsf and Hsps. *Biogerontology*, 10, 3–11. doi:
438 10.1007/s10522-008-9147-5
439
440 Nestel, D., Nemny-Lavy, E., Islam, S. M., Wornoayporn, V. & Caceres, C. , 2007.
441 Effects of pre-irradiation conditioning of medfly pupae (Diptera: Tephritidae): hypoxia
442 and quality of sterile males. *Florida Entomologist.* 90, 80-87.
443
444 Oliveira, M. F., Geihs, M. A., França, T. F. A., Moreira, D. C., Hermes-Lima, M., 2018. Is
445 "Preparation for Oxidative Stress" a Case of Physiological Conditioning Hormesis? *Frontiers in*
446 *Physiology, 9*: 945. doi.org/10.3389/fphys.2018.00945
447

448 Rashkov, P., Barrett, I. P., Beardmore, R. E., Bendtsen, C., Gudelj, I., 2016. Kinase Inhibition Leads
449 to Hormesis in a Dual Phosphorylation-Dephosphorylation Cycle. *PLOS Computational Biology*,
450 12(11), e1005216. doi.org/10.1371/journal.pcbi.1005216
451
452 Robinson, A. S., 1975. Influence of anoxia during gamma irradiation on the fertility and
453 competitiveness of the adult male codling moth, *Laspeyresia pomonella* (L.).
454 Radiation Research, 61: 526-534.
455
456 Schäfer, M., Dütsch, S., Keller, U. auf dem, Navid, F., Schwarz, A., Johnson, D. A., Johnson, J. A.,
457 Werner, S., 2010. Nrf2 establishes a glutathione-mediated gradient of UVB cytoprotection in the
458 epidermis. *Genes & Development, 24*(10), 1045–1058. doi.org/10.1101/gad.568810

459 Schäfer, M., Werner, S., 2015. Nrf2 - A regulator of keratinocyte redox signaling. *Free Radical*
460 *Biology and Medicine. 88*, 243–252. doi.org/10.1016/j.freeradbiomed.2015.04.018

461 Schuch, A. P., Moreno, N. C., Schuch, N. J., Menck, C. F. M. Garcia, C. C. M., 2017. Sunlight
462 damage to cellular DNA: Focus on oxidatively generated lesions. *Free Radical Biology and*
463 *Medicine, 107*, 110–124. doi.org/10.1016/j.freeradbiomed.2017.01.029

464 Seong, K. M., Kim, C. S., Seo, S-W., Jeon, H. Y., Lee, B-S., Nam, S. Y., Yang, K. H., Kim, J-Y.,
465 Kim, C. S., Min, K-J., Jin, Y-W., 2011. Genome-wide analysis of low-dose irradiated male
466 *Drosophila melanogaster* with extended longevity. *Biogerontology*, 12, 93–107. Doi:
467 10.1007/s10522-010-9295-2

468 Shick, J. M., Lesser, M. P., Dunlap, W. C., Stochaj, W. R., Chalker, B. E., Won, J. W. 1995. Depth-
469 dependent responses to solar ultraviolet radiation and oxidative stress in the zooxanthellate coral
470 *Acropora microphthalma*. *Marine Biology*, *122*(1), 41-51. doi.org/10.1007/BF00349276

471 Singh, M. K., Sharma, J. G., & Chakrabarti, R., 2015. Simulation study of natural UV-B radiation on
472 *Catla catla* and its impact on physiology, oxidative stress, Hsp 70 and DNA fragmentation.
473 *Journal of Photochemistry and Photobiology B: Biology, 149*, 156–163.
474 doi.org/10.1016/j.jphotobiol.2015.05.019.

475 Stearns, S. C., 1989. Trade-offs in life-history evolution. *Functional Ecology*, 3, 259-268.

476 Storey, K. B., 2015. Regulation of hypometabolism: insights into epigenetic controls. *Journal of*
477 *Experimental Biology, 218*(1), 150–159. doi.org/10.1242/jeb.106369

478 Wang, Y., Wang, L., Zhu, Z., Ma, W., Lei, C., 2012. The molecular characterization of antioxidant
479 enzyme genes in *Helicoverpa armigera* adults and their involvement in response to ultraviolet-A
480 stress. *Journal of Insect Physiology, 58*(9), 1250–1258. doi.org/10.1016/j.jinsphys.2012.06.012

481 Vijayalaxmi, Cao, Y., Scarfi, M. R., 2014. Adaptive response in mammalian cells exposed to non-
482 ionizing radiofrequency fields: a review and gaps in knowledge. Mutation Research, 760, 36045.
483 doi: 10.1016/j.mrrev.2014.02.002

484 Welker, A. F., Moreira, D. C., Campos, É. G., Hermes-Lima, M., 2013. Role of redox metabolism for
485 adaptation of aquatic animals to drastic changes in oxygen availability. *Comparative*
486 *Biochemistry and Physiology Part A: Molecular & Integrative Physiology, 165*(4), 384–404.
487 doi.org/10.1016/j.cbpa.2013.04.003

Williamson, C. E., Olson, O. G., Lott, S. E., Walker, N. D., Engstrom, D. R., Hargreaves, B. R., 2001. Ultraviolet radiation and zooplankton community structure following deglaciation in glacier bay, Alaska. *Ecology, 82*(6), 1748–1760. doi. *10.2307/2679815*

Won, E. J., Lee, Y., Han, J., Hwang, U. K., Shin, K. H., Park, H. G., Lee, J. S., 2014. Effects of UV radiation on hatching, lipid peroxidation, and fatty acid composition in the copepod *Paracyclopina nana*. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 165*, 60–66. doi.org/10.1016/j.cbpc.2014.06.001

Yagura, T., Schuch, A. P., Garcia, C. C. M., Rocha, C. R. R., Moreno, N. C., Angeli, J. P. F., Mendes, D., Severino, D., Bianchini Sanchez, A., Di Mascio, P., Medeiros M. H. G., Menck, C. F. M., 2017. Direct participation of DNA in the formation of singlet oxygen and base damage under UVA irradiation. *Free Radical Biology and Medicine, 108*, 86–93. doi.org/10.1016/j.freeradbiomed.2017.03.018

Yang, Y., Niu, K., Hu, Z., Niklas, K. J., Sun, S., 2017. Linking species performance to community structure as affected by UV-B radiation: an attenuation experiment. *Journal of Plant Ecology, 11*(2), 286–296. doi:10.1093/jpe/rtx001

Zagarese, H. E., Williamson, C. E., 1994. Modeling the impacts of UV-B radiation on ecological interactions in freshwater and marine ecosystems. In R.H. Biggs & M. B. E. Joyner (Eds.), *Stratospheric ozone depletion/UV-B radiation in the biosphere* (pp. 315–328). New York, NY: Springer-Verlag.

Figure Captions.

Figure 1. Schematic alterations in the redox metabolism in various animal species in response to UV radiation. It depicts 12 animal species, from 6 different phyla, responding to UV according the following variables: (i) levels/activity of endogenous antioxidants (GSH and antioxidant enzymes), (ii) ROS formation and (iii) and markers of oxidative stress (lipid peroxidation, protein carbonyl or DNA damage) (see **Section 2** in the main text). The figure shows only variables that increased under UV radiation.

Figure 2. Animals' redox-response to UV irradiation shares many similarities with responses to other POS-inducing conditions. The scheme shows an illustration of the convergence of redox-responses to low doses of UV irradiation and hypoxia exposure, a classical POS-inducing condition. There is accumulating evidence that hypoxia changes the redox state of mitochondria, increasing mitochondrial ROS production. This may trigger, in hypoxic-tolerant animals, a series of biochemical responses that increase the activity of the endogenous antioxidant system, either by acting upon existing enzymes through post-translational modifications (such as phosphorylation; or by inducing the synthesis of new antioxidant enzymes via activation of redox-sensitive transcription factors, such as Nrf2 (Hermes-Lima et al., 2015; Giraud-Billoud et al., 2019). This increase in antioxidant defenses helps the animal to cope with the subsequent, more severe redox stress of reoxygenation, thus creating the POS pattern (Moreira et al., 2017). UV irradiation induces ROS formation by completely different mechanisms than the ones in hypoxia, such as generation of singlet oxygen by DNA and other chromophores excited by UV-A (Yagura et al., 2017) or by UV-B-induced activation of ROS-generating enzymes, such as NADPH oxidase and cyclooxygenases (Beak et al., 2004; Masaki et al., 2009; Schuch et al., 2017). Thus, low doses of UV radiation can boost antioxidant defenses and help animals to cope with subsequent exposures to higher doses of UV.