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HORMESIS AND TRADE-OFFS: A COMMENT

Éric Le Bourg □ Université Paul-Sabatier, Centre de Recherche sur la Cognition Animale, UMR CNRS 5169, 118 route de Narbonne, 31062 Toulouse cedex 9, France

Suresh I. S. Rattan □ Department of Molecular Biology and Genetics, Aarhus University, Gustav Wieds Vej 10C, DK8000 Aarhus – C, Denmark

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Single or multiple exposures to mild stress at younger ages often have positive health beneficial effects throughout life, indicating that rescue systems turned on at a young age can be effective even in old age (e.g. Le Bourg 2011). This seems to be at variance with the notion of the so-called trade-offs that due to a limitation of resources it is impossible for an organism to increase all aspects of fitness (see for example, Stearns 2000). Recently, this view has again been raised in an article by McClure *et al.* (2014), published in *Evolution*. These authors have reported that *Drosophila melanogaster* flies challenged by a pretreatment with dead spores of the fungus *Metarhizium robertsii* lived longer, survived better under heat stress, and had a higher fecundity. Thus, these flies displayed the well-established phenomenon of physiological hormesis (for hormesis terminology, see for example Calabrese *et al.* 2007; Wiegant 2014). However, McClure *et al.* (2014) also showed that the pretreatment by dead fungal spores decreased by 10% the survival time of the flies after infection by live spores of the same fungus, and concluded that "when it occurs, hormesis leads to trade-offs with other fitness traits" and that, if applied to human patients, "the consequences of hormetic treatments for infected patients could be dire". Thus, the balance of positive and negative effects of hormesis on fitness traits could be definitely on the negative side, precluding relying on hormesis in therapy or health maintenance and improvement.

In our opinion, this viewpoint is not completely accurate because several other studies performed with flies and other systems show that a mild stress can have positive, negative or no effects on fitness-related traits. For instance, Lints and Le Bourg (1989) showed that female *D. melanogaster* flies living continuously in hypergravity had a lower and

Address correspondence to Éric Le Bourg, Université Paul-Sabatier, Centre de Recherche sur la Cognition Animale, UMR CNRS 5169, 118 route de Narbonne, 31062 Toulouse cedex 9, France; Email : eric.le-bourg@univ-tlse3.fr

delayed peak of egg-laying, but the total fecundity remained roughly the same. Similarly, Hercus *et al.* (2003) showed that four rounds of exposure to mild heat stress, which increased the average and maximum lifespan of *D. melanogaster* and their resistance to heat, slightly reduced egg-laying (about 5%). Growing in hypergravity or having parents living in hypergravity slightly decreased viability of the larvae (Le Bourg and Lints 1989) but, by contrast, living in hypergravity for two weeks, a treatment known to increase longevity of males and resistance to heat in both sexes, had no effect on the number of females inseminated by males (Le Bourg, unpublished results). Regarding resistance to infection by the entomopathogenic fungus *Beauveria bassiana*, two mild stresses had no effect on post-infection lifespan (hypergravity and heat, Le Bourg *et al.* 2009), while a pretreatment by cold increased survival in males and had no clear effect in females (e.g. Le Bourg *et al.* 2009), the result of males being opposite to that of McClure *et al.* (2014) on immunity.

Therefore, these results on traits linked to fitness in a direct (fecundity and viability) or in an indirect way (survival to fungal infection, possibly encountered in the wild) show that mild stresses can have either positive, slightly negative or no effects on these traits. The negative effects, using dead spores of a fungus as a mild stress, reported by McClure *et al.* (2014), do not pose a serious challenge to the application of hormesis for human health and longevity. However, by pointing out the possible interactive, counteractive or synergistic effects of hormetic interventions, these authors surely address an important aspect of physiological hormesis.

Indeed, not all mild stresses increase lifespan and resistance to severe stresses (Lagisz *et al.* 2013), because the effects on longevity can be sex-specific and mild stresses can decrease resistance to starvation (Le Bourg 2009). Therefore, using hormesis as a possible therapy or a preventive strategy requires, as for any new therapy, testing whether any deleterious consequences of the pretreatment do exist. To give an example in mammals, subjecting a pig to a pretreatment with 250 ppm of carbon monoxide (1000 ppm is lethal) before cardiopulmonary bypass decreases the number of defibrillations necessary to restart the heart (2 vs 6) and prevents cardiac edema (Lavitrano *et al.* 2004). Obviously, it is necessary to rule out possible deleterious effects of this pretreatment before routinely using it in human cardiac surgery. Other studies have shown that mild stress can mitigate the effects of cardiac and cerebral ischemia (reviews in Simm and Horstkorte 2014; Béjot and Garnier 2014).

Since a wide variety of mild stresses, including exercise, have been shown to have health beneficial hormetic effects in various species, including mammals, there is a definitive hope that new strategies relying on hormetic effects could be used either as preventive or as therapeutic in human beings (reviews in Rattan and Le Bourg 2014, but see also, Pardon 2010; Sørensen *et al.* 2010). It seems that the balance between positive and possible negative effects of mild stress is clearly on the positive side, and any trade-offs in fitness are specific to the general health, robustness and resilience of the body.

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