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THE HORMETIC EFFECTS OF HYPERGRAVITY ON LONGEVITY AND AGING

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□ This paper reviews the literature on the effects of hypergravity (HG, gravity levels higher than 1g, the terrestrial gravity) on longevity and aging. The different studies showed that life-long exposures to high gravity levels decreased longevity and accelerated the age-related decline observed on some physiological and behavioral variables. In contrast, chronic exposure to HG increased resistance to heat in young and middle-aged *Drosophila melanogaster*. A short exposure to HG at the beginning of adult life increased male longevity and delayed behavioral aging in *D. melanogaster*. All these results show that HG acts as a hormetic factor. Long exposures to HG have deleterious effects on longevity and aging, whereas short exposures have beneficial effects. Some potential mechanisms of action of the beneficial effects of HG are also reviewed here. However, the ones tested so far (heat shock proteins and antioxidant defense) have proven unable to explain the hormetic effects of HG and their mechanisms of action are still unknown.

Keywords: Hypergravity; Longevity; Aging; Metabolism; Stress

1. INTRODUCTION

Gravity level has been one of the few constant environmental parameters on Earth (at least on land) over geological times, let alone over an individual's life. Organisms have therefore probably developed a strong adaptation to it. Given this predictable nature, the effects of gravity level changes have almost not been studied (*e.g.,* Wunder, 1955 for an early example). Nevertheless, a change in gravity probably induces response mechanisms from the organism and studying this phenomenon is potentially informative. This became particularly relevant with the first manned space missions, when a decrease in muscle mass and a pronounced decalcification were observed in organisms subjected to microgravity (gravity very close to 0g: 10^{-3}, 10^{-4}g). These changes being similar to what happens during aging, it was then thought that gravity could modulate aging. Microgravity effects on aging have not been studied further at the time because of the technical difficulties and high costs of organizing long enough space missions (Le Bourg, 1999 for a review). The means used to simulate microgravity on Earth (drop tubes, weightlessness towers or parabolic flights) preclude long exposures to microgravity, making them unsuitable for aging studies.

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In contrast, it is very easy to simulate hypergravity (HG, gravity levels higher than 1g, the terrestrial gravity) by keeping organisms in a centrifuge, as long as required. The gravity levels used will depend on the size of the organism: small animals such as fruit flies will withstand higher levels than bigger animals, rodents for instance (Frolkis *et al.*, 1997). Few teams have undertaken studies of the effects of HG on aging. Beginning in the 1960's, a group of gerontologists working for the NASA focused on the physiological and biochemical changes in rats kept in HG (Miquel and Economos, 1982). They stopped this project in the early 1980's. Since then, the effects of HG on longevity and aging have been studied by others using the fruit fly *Drosophila melanogaster*. As a matter of fact, HG is a useful tool to test some theories of aging. For instance, the rate-of-living theory (Pearl, 1928) negatively links longevity to metabolic rate; later the free radicals theory of aging (Harman, 1956) provided a molecular explanation for this relation. How can HG put these theories to the test?

HG increases weight, since the latter is the product of the mass by the gravity level, probably increasing as a result the metabolic needs of the organism (It must absorb more energy). This increased need probably results in a higher metabolism. According to the rate-of-living theory, this high metabolism should curtail longevity.

In the present paper, I will review the studies investigating the metabolic changes in HG, the effects of HG on longevity and aging and if they support the theories. Then, I will provide evidence that, contrarily to the theory, HG can have beneficial effects on longevity and aging: HG is a hormetic factor. Finally, I will review the literature on the studies of the mechanisms of action of the hormetic effects of HG.

2. HG AND METABOLISM

Pitts *et al.* (1975) showed that rats centrifuged at 2.76 or 3.18g lost mass during the first week of exposure. Then, their mass increased, but without reaching its initial level. The mass loss was roughly proportional to the gravity level. The authors concluded that these rats used their fat reserves to cope with higher metabolic needs. Diaphragms of rats exposed to a chronic centrifugation (2.76 and 4.15g) exhibited a higher, though not significant, glucose uptake and a significantly higher glucose use (Daligcon and Oyama, 1975). This result supports the increase of metabolism in HG. Furthermore, when the rats were transferred to 1g, the glucose uptake and use became undistinguishable from the controls. Oyama (1982) reported that the size and mass of rats and dogs in HG (from 1 to 4.17g) decreased, but their food intake and metabolic rate increased. These effects have also been observed by Economos *et al.* (1982) in rats kept at 3.14g. In the same way, Thorling and Fredens (1995) reported a lower mass in rats kept in HG (from 1 to 2.5g) and a regain of their mass when placed again at terrestrial gravity.

In *Paramecium tetraurelia* (Richoilley *et al.*, 1988), an exposure to HG (from 1.8 to 20g) decreased their cellular proliferation, proportionally to the gravity level. This study also supports an increase of metabolism in HG.

In *D. melanogaster*, no study has directly measured metabolism in HG. However, indirect measurements were performed. Lints and Le Bourg (1989) studied the fecundity of flies kept at different gravity levels (up to 5g). The total number of eggs laid by females in HG was lower and their peak of fecundity delayed. The length of reproductive and post-reproductive periods was not affected. These results can be explained by a different dispatch of available energy between maintenance and reproduction (trade-off, Stearns, 1992). To withstand a higher metabolic demand, females decrease their fecundity. The delay of the day of the peak of fecundity can be due to the fact that the females have to first adapt to HG, and then can invest in their reproduction. These results are similar to what was observed in flies subjected to under-nutrition (David *et al.*, 1971): lower total fecundity and peak of fecundity disappearing under severe under-nutrition conditions. Organisms submitted to a high metabolic demand do not have enough energy available to maximize both their maintenance and reproduction. Le Bourg and Lints (1989a) also studied viability of *Drosophila* eggs in HG (3 and 5g). When the mothers were kept at 1g and the eggs transferred in HG, the viability was only slightly changed. This can be explained by the fact that eggs can allocate all the available energy to their development. In contrast, when mothers were kept in HG, the eggs they laid were less able to develop into adults, but still 75% of them developed normally at 5g. This probably means that HG-kept females have to invest more energy into their maintenance and allocate less energy into their eggs.

It can be concluded from these various studies that HG increases metabolism.

3. LIFE-LONG EXPOSURE TO HG

3.1 HG and longevity

According to the rate-of-living theory, since HG increases metabolism, it should decrease longevity, proportionally to the gravity level.

In rodents, Oyama (1982) found a slight decrease of longevity in rats kept at 4.1g. Earlier (Oyama, 1971), he had not observed an effect of a 3.5g gravity level on the longevity of female rats. In the same way, rats kept at 3.14g did not show a significant decrease in longevity (Economos *et al.*, 1982) and lower gravity levels (1.14 and 1.47g) did not alter longevity (Ishay and Barr-Nea, 1976).

In *D. melanogaster*, a study (Le Bourg and Lints, 1989b) measured longevity at different gravity levels in male and female virgin flies, raised on two different media (one less nutritious than the other). As expected,

flies did not live as long on the less nutritious food. However, this effect was not enhanced by gravity: there was no clear effect of HG up to 4g. At 5g, flies had a shorter life span, but still reaching 45 days for average life span. In a following study, higher gravity levels were used (up to 7.38g, Lints *et al.*, 1993) and showed the same tendency: no effect of HG before 4g and even at 7.38g, the average life span still was 40 days. This weak effect of HG was observed both in virgin and mated flies, the latter exhibiting a lower longevity at all gravity levels.

It can be concluded from these different studies, that HG does not have the strong negative effect on longevity expected from the rate-of-living theory. It seems that organisms are able to implement mechanisms to ensure a normal longevity.

3.2 HG and aging

In HG, organisms might age faster, even if they do not have a reduced longevity. In order to test this hypothesis, it is necessary to follow variables that change with the age of the organism and to compare their changes in 1g and HG-kept organisms.

Doing so, Economos *et al.* (1982) reported a faster decline with age of the number of mitochondria in the heart of rats kept in HG compared with the controls, suggesting a faster aging in HG, at least on this variable.

Behavioral variables can also be used to assess the aging process in HG. For instance, climbing activity (the ability of a fly to climb along the vertical wall of a vial) declined with age and this decline was faster in flies kept in HG (Le Bourg and Lints, 1992a). In the same way, flies released in the center of an arena without visual clues displayed linear patterns of movement when young, then more and more sinuous paths when getting old. These sinuous paths appeared in younger flies when they were kept in HG (Le Bourg and Lints, 1992b). The spontaneous locomotor activity also decreased with age in flies and it decreased to a greater extent at 5g than at 1 and 3g (Le Bourg and Lints, 1992c). All these studies seem to suggest that aging is accelerated in HG.

However, other results shed another light on the effect of HG. For instance, the detection threshold to sucrose increased in old flies (they can detect only higher concentrations) but HG had no effect on the change of this variable with age (Le Bourg, 1996). We also investigated the effect of HG on memory and learning capacities in flies by studying the conditioned suppression and habituation of the proboscis extension response (Minois and Le Bourg, 1997). Middle-aged and old flies were impaired in the acquisition of these tasks. Surprisingly, a negative effect of HG was observed only in young flies, HG having no effect at older ages. It appears from the second series of studies that defining HG only as an accelerator of the aging process is too restrictive.

This led us to put forward the hypothesis that HG is actually a stress. Stress is defined here as all external and internal insults encountered by an organism, with which it must cope through an adaptive response. It had been observed that mostly old animals seemed to suffer from HG exposure probably because resistance to stress decreases with age (*e.g.*, Service *et al.*, 1985).

Exposure to a stress has two implications by which we can test whether HG is a stress. The first implication is that an exposure to a non-lethal stress can increase resistance to other stresses: the acclimation phenomenon (*e.g.*, Krebs and Loeschcke, 1994). We studied the resistance to several stresses in flies of different ages kept in HG (Le Bourg and Minois, 1997; Minois and Le Bourg, 1999). For the four stresses studied (starvation, desiccation, cold and heat), we found a decreased resistance with age, except for starvation resistance in females between young and middle age. In contrast, HG did not have the same effect on the resistance to these various stresses. Starvation and desiccation resistances slightly decreased at 5g, compared with 1 and 3g. This decrease was mainly due to old animals of both sexes and middle-aged females for desiccation resistance. The results of starvation resistance were explained by the variation of the lipid content of the flies with age and gravity, the flies most affected by HG being the ones with the lower lipid content. HG had no effect on cold resistance (percentage of survivors after a - 20°C exposure). In contrast, an exposure to HG strongly increased resistance to heat (survival time at 37°C) in young and middle-aged flies (Le Bourg and Minois, 1997).

HG can thus trigger acclimation, acting like a stress.

4. SHORT EXPOSURE TO HG

4.1 HG and longevity

The second implication of a stress is that a short exposure to a non-lethal stress can have beneficial effects on longevity (Minois, 2000; Minois and Rattan, 2003). For instance, low doses of irradiation increase longevity in *D. melanogaster* (Lamb, 1964), *Musca domestica* (Allen and Sohal, 1982) and mice (Caratero *et al.*, 1998). A short exposure to heat increases longevity in the nematode worm *Caenorhabditis elegans* (Lithgow *et al.*, 1995), *D. melanogaster* (Khazaeli *et al.*, 1997; Minois *et al.*, 2001; Minois and Vaynberg, 2002) as well as the replicative lifespan of the yeast *Saccharomyces cerevisiae* (Shama *et al.*, 1998).

We thus decided to study whether a short exposure to HG could increase flies longevity. We found that subjecting virgin flies for 2 weeks at the beginning of their adult life to 3 or 5g increased longevity in males compared with flies always kept at 1g (Le Bourg and Minois, 1997). This short exposure to HG had no effect on female longevity. This lack of effect of mild stress in females has often been reported. HG can thus be

considered as a hormetic factor, decreasing longevity as a result of long exposures and increasing longevity in case of short exposure. A more detailed study was later carried out to better define in what range HG has beneficial effects on longevity (Le Bourg *et al.*, 2000). An exposure shorter than 2 weeks did not increase longevity and already a 3-week exposure triggered a lower increase in longevity. If the 2-week exposure was broken up in 3 periods of 4 days in HG alternated with periods of 3 days at 1g, longevity was not increased. In one of the experiments, flies were raised either in group or individually. Flies kept individually lived longer but the rearing conditions did not change the effect of gravity. The only noticeable difference was that a 25-day exposure to HG still increased longevity in males individually kept. It seems from this study that the length of exposure to HG is an important factor for triggering a hormetic effect. In contrast, the same study showed that the level of gravity did not affect the longevity increase: a 2-week exposure to HG increased longevity to the same extent between 2.58 and 7.38g.

A recent work (Le Bourg *et al.*, 2004) further showed that the longevity increase after 2 weeks in HG was not observed in mated flies, contrarily to what was reported in virgin flies (Le Bourg and Minois, 1997), and when the flies were kept at 30°C (instead of the standard 25°C) after their exposure to HG. HG increased longevity only when flies were not subjected to rearing conditions decreasing longevity (mating and high temperature in these experiments).

4.2 HG and aging

The goal of gerontology should not be only to increase longevity, but to postpone aging, leading to organisms able to delay the negative effects of aging at very old ages. Hormesis will be useful if it is shown to confer global beneficial effects on aging.

We have seen in section 3.2 that HG increased resistance to heat. We then wanted to know if and how long after a short exposure to HG, flies would stay more resistant to heat when transferred back to 1g (Minois *et al.*, 1999). Flies of both sexes were kept at 3 or 5g for 2 weeks at the beginning of their adult life and then transferred to 1g. Their survival time at 37°C was measured at the removal from the centrifuge and then twice a week for the subsequent 2 weeks. As expected, flies kept at 3 or 5g were more resistant to heat just after their exposure to HG than flies always kept at 1g. Interestingly, flies exposed to HG stayed more resistant to heat for the 2 weeks after the end of the exposure during which the experiment was done: HG has long-lasting beneficial effects on resistance to heat.

We also wanted to know if a short exposure to HG could delay the impairment observed with age on behavioral variables. The same 2-week exposure at 3 or 5g was used and activity (spontaneous locomotor activity, patterns of movement and climbing activity) was measured as a func-

tion of age from the removal from HG (Le Bourg and Minois, 1999). All the variables measured showed that flies were doing worse when getting old. HG-kept flies had worse scores on removal from the centrifuge than flies kept at 1g. In contrast, later in life, flies kept shortly in HG when young obtained similar or better scores on the variables measured. This indicates that a short exposure to HG helped the flies to behaviorally age more slowly.

However, a short exposure to HG does not always protect organisms. For instance, exposure to non-lethal heat shocks decreased climbing activity, spontaneous locomotor activity and the acquisition of a learning task in flies (Le Bourg *et al.*, 2004). A short exposure to HG at young age did not protect the flies against these deleterious effects of heat shocks. Still, although the heat shocks used were not lethal, they decreased the subsequent longevity of flies, and flies kept in HG when young did not exhibit this decreased longevity.

5. MECHANISMS OF ACTION OF MILD STRESS IN GENERAL AND HG IN PARTICULAR

The mechanisms whereby mild stresses increase longevity are largely unknown at present. But several hypotheses can be and have been formulated. Researchers interested in this field favor two of them.

The first one is the regulation of metabolism. It is known that metabolic regulation is a large part of the response to stress. Therefore, metabolic regulation is one of the possible mechanisms used by organisms subjected to mild stresses, that can lead to their extended longevity. The long term effects of metabolic regulation may be explained in accordance with the disposable soma theory (Kirkwood, 1993). The organism regulates its metabolism to allocate more energy to its maintenance and survival during and probably for a limited period after the stress. This higher investment in its maintenance may allow this organism to live longer after the exposure to mild stress. However, metabolic regulation is unlikely to explain the beneficial effects of HG. Although the organisms under HG seem to allocate more energy to their own maintenance than to their reproduction (Lints and Le Bourg, 1989), the whole metabolism is increased in HG. Organisms in HG cannot regulate their metabolism in the way expected by the hypothesis.

The second hypothesis refers to the involvement of protection and repair mechanisms. Actually, exposure to many stresses share a common consequence: the induction of heat shock proteins (hsps), after heat (e.g., Fleming *et al.*, 1988), cold (Matz *et al.*, 1996), physical activity (Kregel and Moseley, 1996) for instance. These hsps are induced to protect cellular components as well as to allow a better degradation of damaged proteins during stress. Other stresses, not yet known to increase longevity, induce hsps (*e.g.*, magnetic fields, Goodman and Blank, 1998;

pressure shock treatment, Tamura *et al.*, 1998; psychological stress, Isosaki and Nakashima, 1998). I thus decided to investigate whether the induction of hsp70 (the most important hsp in *D. melanogaster*) could explain the hormetic effects of HG (Minois *et al.*, 1999). Contrarily to the hypothesis, exposure to gravity levels that increased longevity did not induce hsp70. No induction of hsp70 in HG was also observed in a strain of transgenic flies that can overexpress the inducible form of hsp70 (Le Bourg *et al.*, 2002). It has to be noted that these transgenic flies did not exhibit a longer longevity and reduced decline of climbing activity with age after a 2-week exposure to HG, further ruling out the direct involvement of hsps in the hormetic effects of HG. In contrast, when flies exposed for 2 weeks to HG were later subjected to a heat shock, they expressed more hsp70 than flies always kept at 1g during the heat shock. This latter result explains why HG-kept flies were more resistant to heat (Minois *et al.*, 1999; Le Bourg *et al.*, 2002).

Heat shock proteins are not the only protection mechanism of organisms subjected to stress. Exposure to HG could induce other repair mechanisms to trigger its hormetic effects. Since HG increases metabolism, probably generating more oxidative damage as a result, the modulation of antioxidant enzymes in HG is an appealing hypothesis to explain the hormetic effects of HG. To test it, Le Bourg and Fournier (2004) measured the activities of the two main antioxidant enzymes, catalase and superoxide dismutase, as a function of age and gravity. Flies were kept for 2 weeks at the beginning of their adult life at 3 or 5g, then transferred to 1g, or always kept at 1g. Enzyme activities were measured in flies that were 2-week (at the removal from HG), 4-week and 6-week old. The results showed that activities tended to decrease with age for both enzymes, although not significantly for catalase. The exposure to HG had no effect on the activities of the two enzymes. The regulation of antioxidant defenses thus did not explain the hormetic effects of HG. The mechanisms of action of HG remain so far unknown.

6. CONCLUSION

I have reviewed in this paper the studies of the effects of HG on longevity and aging. Importantly, the synthesis of these publications shows that HG can be added to the list of hormetic factors. Long exposures to HG have deleterious effects on longevity and aging, whereas short exposures have beneficial effects. However, HG is not a hormetic factor in the common sense of the definition (Calabrese and Baldwin, 2001). As a matter of fact, HG is not always deleterious at high doses. We have seen that gravity levels have to be high to begin decreasing longevity. A life-long exposure to HG does not have any effect on several variables studied. In the same way, low doses of HG have beneficial effects under restricted conditions. We have seen that HG can trigger beneficial

effects only when organisms were kept thereafter in optimal conditions for longevity and aging.

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