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IT IS TIME TO THOROUGHLY STUDY THE EFFECTS OF MILD STRESS IN RODENTS, BUT ALSO IN HUMAN BEINGS

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□ Many experiments on the effect of mild stress on aging have been done in invertebrates, but not in mammals. Using mild stress to improve healthspan seems to be possible, because the few studies on humans which have been published appear to be promising. Particularly, one may wonder whether heat shocks could be of some use in therapy or as an integrated part of daily life of elderly people. However, the top priority is probably to study more thoroughly the effects of mild stress in rodents, and not only in invertebrates.

Key words:mild stress, invertebrates, mammals, human beings, aging, therapy

1. THE NEXT STEP OF THE STUDY OF HORMESIS: PERFORMING MORE EXPERIMENTS IN RODENTS

One of the most important problems in life sciences is trying to extrapolate to human beings the conclusions of experiments carried out with model organisms, such as rodents or invertebrates. For instance, dietary restriction can increase longevity in rodents and in some invertebrate species (Bertrand *et al.* 1999), but there is a debate regarding its effect in human beings (see issue 3, volume 6 of Biogerontology). Similarly, it seems clear that FOXO transcription factors can modulate longevity in invertebrates, particularly in *Caenorhabditis elegans* (*e.g.* Henderson *et al.* 2006), but it is not so sure in humans since such a modulation is observed in German centenarians but not in French ones (Flachsbart *et al.* 2009).

Regarding hormesis, it cannot be concluded from studies in invertebrates showing that mild stress can increase longevity and delay aging that similar effects would be observed in mammals and human beings. Studies of mild stress in mammals are not numerous (Le Bourg 2009) and we have to imagine new experiments to know whether mild stress could be used to modulate aging in human beings, because most studies are currently done with invertebrates, mainly *Drosophila melanogaster* and *C. elegans*. It seems that only one study of the effect of cold stress on longevity and aging has been done in rats: a cold stress nonsignificantly increased longevity, decreased the incidence of sarcomas and carcinomas but increased vascular pathologies (Holloszy and Smith 1986). Indeed,

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gathering more results on the effects of cold in rodents would be of interest. The same could be said regarding the effect of short hyperthermias, but hypergravity, a mild stress with positive effects in flies, is known to have severe negative effects in rodents (Le Bourg 2008).

2. USING MILD STRESS IN HUMAN BEINGS?

Before thinking to use mild stress in human beings, we have to consider that a mild stress could have positive effects for some individuals but negative ones for others. For instance, in *C. elegans,* heat shock can increase the lifespan of some animals and reduce that of other ones. A short heat shock increases lifespan of most of the animals and the negative effect is negligeable, but this negative effect becomes more important when the duration of the heat shock increases (Wu *et al.* 2008). It is useless to say that using mild stress in human beings requires that it does not put at risk some individuals. Therefore, the problem of heterogeneity in populations has to be taken into account: a stress could be mild at young age but more severe in elderly people and, among them, even more deleterious for some persons.

Concerning the use of hormesis in people, it is necessary to separate the possible effects of mild stress in two different categories: the effects on pathology and those on the aging process.

2.1. Mild stress as a help to fight some pathologies: an example in cardiology

Patients with a low body mass-index and a high activity level have a lower mortality after a heart attack than other patients and this mortality can be still lowered if they have suffered before their heart attack from preinfarction angina (Abete and Rengo 2008). In a way, preinfarction angina has similar effects to those of ischemic preconditioning in rats. Ischemic preconditioning is a brief episode of ischemia-reperfusion of the heart which reduces the adverse consequences of a severe ischemia. Therefore, ischemic preconditioning in rats can be considered as a mild stress with hormetic effects. The positive effect of ischemic preconditioning has been reported to decrease with age (Abete and Rengo 2008; but see however Dai *et al.* 2009), but it is possible to restore its effect by subjecting old animals to a combination of exercise and dietary restriction (Abete *et al.* 2005).

Could we imagine to subject young and old patients to a mild stress in order to minimize the negative after-effects of cardiac surgery? For instance, could a brief heat shock of the heart prepare to the more severe stress of cardiac surgery? We may imagine that such a brief heat shock (or another mild stress) would induce the synthesis of heat-shock proteins (Leppä and Sistonen 1997; Frier and Locke 2005), which could help the

heart to recover after the surgical operation. Obviously, it would probably not be a good idea to subject a patient suffering from cardiac problems to a brief episode of ischemia-reperfusion, as it is done in isolated hearts of rats subjected to ischemic perconditioning.

2.2. Using mild stress to improve health at old age

In a parallel effort to studies in rodents, one may wonder whether studies of people living for extended periods in harsh conditions could be useful. For instance, do cosmonauts who have lived in microgravity in the Soviet/Russian Mir and Saliouts spacecrafts suffer more or less than other people from age-linked pathologies? Soviet/Russian cosmonauts are rather numerous and the time they have spent in microgravity can extend from a few days to many months, which could provide a way to know the effect of the duration of the microgravity stress. However, it is clear enough that selecting a control group would not be an easy task, because cosmonauts are a highly selected group and cannot be compared to the general population. Could similar studies of people who have lived in Antartic scientific stations also be done?

However, such studies — if they really could be performed — cannot replace experimental studies of mild stress in human beings. Studying the effect of cold exposure could be useful if studies in rodents would report positive effects of cold stress. Similarly, the study of short heat shocks could be performed, since it has been reported that sauna therapy improves cardiac function and clinical symptoms of patients with chronic heart failure, and also decreases body weight and fat of obese patients (Biro *et al.* 2003). It has also been shown that a short hyperthermia can prevent the activation of proinflammatory genes in human cells (for other hormetic effects, see Rattan 2008): could we imagine to subject the joints of elderly people to regular short heat shocks to delay an age-linked pathology, such as arthritis (Markovic and Stuhlmeier 2006)?

Even if mild stress would improve aging in human beings, it may be argued that there is hardly a chance that people would accept to be subjected regularly to a mild stress, say exposure to a cold or hot temperature. Except in countries where, for instance, using sauna is an old habit, exposure to mild stress would thus probably be confined to patients for whom such an exposure is expected to provide an immediate health benefit (see Markovic and Stuhlmeier 2006). However, we cannot exclude that the use of sauna could become very common in developed countries if people were convinced that it can improve daily life at old age. After all, during the last decades, many fitness centers were built when people realized that regular exercise is good for health.

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3. CONCLUSIONS

Will mild stress be used one day as a therapy for elderly people or as an integrated part of daily life? It is too early to provide any answer. It is however time to perform experiments in mammals to get a chance to know the answer to this question. These experiments, in addition to those carried out in invertebrates, are the obvious next step of hormesis studies. The few results on hormesis in rodents lead to the conclusion that studying more thoroughly the effects of cold and heat shocks is probably the highest priority on the agenda. I hope that colleagues working with rodents will consider the matter and provide us with new results.

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