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Longevity and aging. Role of free radicals and xanthine oxidase. A review☆

Longévité et vieillissement. Rôle des radicaux libres et de la xanthine oxydase. Une revue

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ABSTRACT

Longevity and aging are differently regulated. Longevity has an important part of genetic determinants, aging is essentially post-genetic. Among the genes involved in longevity determination, sirtuins, activated also by calorie restriction and some others as the TOR pathway, attracted special interest after the insulin–IGF pathway first shown to regulate longevity in model organisms. For most of these genes, postponement of life-threatening diseases is the basis of their action which never exceeds about 35% of all determinants, in humans. Among the post-genetic mechanisms responsible for age-related decline of function, free radicals attracted early interest as well as the Maillard reaction, generating also free radicals. Most attempts to remediate to free radical damage failed however, although different scavenger mechanisms and protective substances are present in the organism. Synthetic protectors were also tested without success. The only example of a successful treatment of a free radical mediated pathology is the case of xanthine oxidase, involved in cardiovascular pathology, essentially during the ischemia-reperfusion process. Its inhibition by allopurinol is currently used to fight this deadly syndrome.

Mots clés :
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RÉSUMÉ

La longévité et le vieillissement sont sous le contrôle de mécanismes différents. La régulation de la longévité comporte un facteur génétique important, le vieillissement est essentiellement le résultat de mécanismes post-génétiques. Pour la longévité, des voies génétiques, sous le contrôle des sirtuines et la voie TOR ont attiré l'attention, après celle de l'insuline–IGF testée chez des animaux modèles, les premiers, les sirtuines, responsables de l'effet de la restriction calorique (CR). Parmi les mécanismes impliqués dans le déclin des fonctions avec l'âge, les radicaux libres et la réaction de Maillard se sont révélés importants. Bien que l'on dispose de capteurs de radicaux libres efficaces, leur effet protecteur ne s'est pas révélé suffisant pour prévenir leur nocivité. Le cas de la xanthine oxydase représente une exception intéressante car elle est impliquée dans le syndrome d'ischémie-reperfusion au cours des maladies cardiovasculaires. L'allopurinol, l'inhibiteur de la xanthine oxydase s'est révélé efficace pour le traitement de ce syndrome.

1. Introduction

Although frequently confused, mechanisms involved in longevity determination and in age-dependent decline of functions are different. Longevity determinants have an important part of genetic control although environmental factors play also an important role. Age-dependent decline of functions is essentially

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due to post-genetic mechanisms. This problem will be discussed first in some detail. Among the agents considered playing an important role in age-dependent decline of functions, free radicals, or better reactive oxygen and nitrogen species (ROS, NOS) play an important role. The organism is provided by intrinsic defense mechanisms which apparently are insufficient to ensure adequate protection. Pharmacological research yielded a number of efficient drugs, which however also failed to protect against ROS- and RNS-produced damage [1]. One exception stands out in this hopeless fight against these chemical pathogens, the ischemia-reperfusion syndrome involved in cardiovascular pathology which is efficiently counteracted by treatment with a xanthine oxidase (XO) inhibitor, allopurinol. Some details on this success story will also be described in this review.

2. Longevity

Striving for an increased longevity is as old as humanity as shown, among others, by the early recording of persons having reached an exceptional high age, as for example the pharaoh Ramses II with his 92 years, more than two millennia before present [2]. The Bible presents also several prophets and wise patriarchs having reached exceptionally old age. Plinius the elder in his treatise of Natural History [3] devoted a chapter (in vol. 3) to discuss this issue. One of the first, he shed doubt on several of the above mentioned exaggerations of exceptional old age. Closer to us, in the second half of the 19th century, Brown-Sequard (1817–1897), MD, PhD, who taught also at Harvard, was appointed professor at the College de France and carried out self-experiments to test the possibility to increase age expectancy with preserved sexual vigor. He prepared animal (dog and guinea pig) testicular extracts, their injection increased his sexual vigor (he was then 72 years old). This was criticized in recent times because of the water insolubility of testosterone. This criticism ignored however the details of the method used by Brown-Sequard. His testicular extracts could well contain testosterone in suspension or adsorbed to lipoprotein particles, no fast centrifugation was then available. His work on "glands" justifies the proposition to consider him as one of the founders of endocrinology [4]. This strive for efficient prolongation of life expectancy produced one of the confirmed methods to reach this goal, by calorie restriction, originally described by McCay on rats [5], reproduced on several animal models, yeast, flatworm (*Caenorhabditis elegans*), drosophila and also mice ([6] for review). The original work of Len Guarente provided evidence showing that calorie restriction acts through the activation of genes of the sirtuin family [7,8]. Other experiments provided evidence for an important role of genes belonging to the TOR pathway [9]. The first genetic pathway explored essentially in model organisms was the insulin–IGF triggered metabolic pathway shown to control longevity when inhibited [10]. A large number of publications testify for the interest of the genetic approach of longevity. Nevertheless, estimates by several authors put the role of genetic effects on longevity between 5 and 35% of total affects. One important reason for this caveat is the fact that identical twins raised apart have widely different life spans. Much can be found on this interesting study, started in Minnesota in ref. [11]. One of the arguments against a strong genetic effect is the important role of natural selection for longevity. Selection did only indirectly act on longevity by reinforcing protective mechanisms [12]. Evolution cares mainly for efficient, rapid reproduction in order to preserve the species (ref. [13], for more information). There is however an indirect argument which has to be considered. Every species has a different genome and a relatively well-defined maximal life span. Some examples are shown in Table 1 [14]. On the contrary, some genotypes increase the risk of life-threatening diseases, as for instance the $\varepsilon_4/\varepsilon_4$ genotype for apolipoprotein E which produces an accelerated atherosclerosis with increased severity and frequent fatal issue [15] (for review). Another argument in favor of the importance of environmental factors for longevity determination is the progressive increase of average life expectancy over centuries with a recent upswing (Fig. 1) [16]. Successive increases can be traced to progress in hygiene and in medical research. One consequence of this rapid recent increase is the flourishing of books and reviews promising continued rapid increase of human life expectancy reaching 150 or even 200 years. These forecasts are in sharp contradiction with statistics on centenarians (Table 2) and supercentenarians (over 110 years). These statistics show that although the number of centenarians is progressing indeed, only a small fraction of them (from 0.15 to 0.35%) become supercentenarians [16]. The steady increase of the senior population, essentially in countries with advanced hygiene, did however transform the age-pyramides into haystacks.

Table 1
Longevity of some animal species.

1. Arthropods	4–20 years
2. Mice	2–3
3. Rats	4–5
4. Dogs	15–20
5. Elephants	−60
6. Chimpanzee	−60
7. Man	100–120
8. Turtle (Galapagos)	−120
9. Sturgeon	−120

From ref. [14].

Some scientists hoped to remediate this situation by testing CR on humans. Roy Walford, an eminent immunologist and aging-researcher in L.A. was among them, but his tentatives failed. This could be foreseen for historic-physiological reasons. Mankind spent most of its time since its emergence during evolution by fighting for food. Its exceptional abundance was considered as one of the enviable promises of "Paradise". This ancestral fight for survival did certainly imprint its effect on the human genome. One remarkable example can be seen in the Museum for Aborigenes in Adelaide, Australia, presenting a man and woman, sitting back against back in a desert to improve their chance to grasp an insect or other sand-dwelling animal to get fed. This hypothesis was further strengthened by the recent conclusion of a remarkable experiment initiated by George Roth and his team at the NIA of NIH. They imposed on primates, macaques calorie restriction for a long period. The recent report from the team who took over this experiment when G. Roth retired, stated that there was no promising sign of extended life span, although all indicators of a better health condition did improve [17]. As the health conditions of these animals at NIA were optimal, CR could not do too much for further improve it, extending longevity.

For these reasons, the best hope to increase healthy life span if not longevity remains with drugs tested as stimulators of genes as Sirtuins, shown to be involved in life span extension in animal experiments. Such drugs, starting with resveratrol are on the market and widely used by "anti-aging medicine". Their action is essentially on the epigenetic level and concerns mostly their capacity to postpone fatal pathologies [12] (Table 3).

3. Aging

Aging can be defined as the functional, structural, morphological modifications observed between birth and death, starting right after reaching the end of development, although some put it immediately after birth. Its most important feature is the differential decline of functions at varying rates from relatively fast for elastic functions to quite slow as nervous conductivity, as if the organism would age in