Energy Expenditure and Maximum Life Span

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Introduction

The energy per mass unit (the specific energy) dissipated by an animal during its lifetime is approximately species independent for a large group of animals (see e.g. refs 1 and 2). This remarkable fact can be formulated as follows:

$$T \times SMR = \text{constant}$$

where the product of the maximum life span (T) and the specific metabolic rate (SMR) is approximately a constant. Given the preceding equation and the importance of energy metabolism to an individual it seems apparent that any valid theory of aging must be capable of providing a testable molecular explanation for the relative invariance observed for this relationship. Unfortunately, most existing theories of aging are not developed in sufficient chemical detail to allow a quantitative test of the empirical observation embodied in the above equation. One theory of aging in which chemical events have been studied in sufficient detail to make quantitative discussion possible is the free radical theory of aging (see e.g. refs 3-7). In one of its versions the chemical events leading to aging are those associated with lipid peroxidation. Thus the reactions associated with lipid peroxidation can be regarded as archtype chemical events representing the more general chemical reactions usually associated with the free radical theory of aging. It is the purpose of this report to demonstrate a connection between the chemical events of lipid peroxidation and the relationship between the maximum life span and the specific metabolic rate as stated in the equation given above.

Aging theories based on the chemical reactions of lipid peroxidation assume, as do damage theories in general, that age effects observed at the level of the intact organism are the cumulative result of events occurring at the cellular and subcellular level. Since the latter assumption seems acceptable we can conveniently proceed to divide our problem into two basic parts. The first part consists of chemical events which occur at the subcellular level. The second part includes linked processes which transform the latter chemical events to effects on the organism as a whole. We will first discuss subcellular lipid peroxidation as the archtype chemical event of aging and then relate the derived results to the intact organism.

Subcellular Lipid Peroxidation Reactions

The primary damaging reactions that initiate intracellular lipid peroxidation and the reactions that comprise the chemical changes associated with lipid peroxidation are free radical reactions which involve molecular oxygen and unsaturated lipids (see e.g. ref. 6). These free radical reactions proceed in three general phases: free radical initiation, free radical propagation and free radical termination.

In the initiation phase, free radicals (R) are formed from a molecular precursor. Typical initiation reactions may be written symbolically as

$$\text{initiation} \rightarrow R \tag{1}$$

In the propagation phase of the reaction these free radicals react to produce lipid hydroperoxides (ROOH) illustrated in the following sequence of reactions:

$$R + O_2 \rightarrow RO_2 \tag{2}$$
$$RO_2 + RH \rightarrow ROOH + R \tag{3}$$

Two known radical terminating reactions are illustrated below:

$$2\ RO_2 \rightarrow \text{nonradical products} \quad (4)$$

$$RO_2 + AH \rightarrow ROOH + A \quad (5)$$

AH represents an antioxidant such as vitamin E.

A Life Span vs Energy Expenditure Equation

To a first approximation an overall measure of the effects caused by lipid peroxidation and its homolytic reaction products including damage to tissue is expressed by the oxygen consumption as given by equ. (2) (see e.g. ref. 8). Assuming this approximation it can then be shown, by solving the rate equations corresponding to reactions (1) to (5), that the damage effect is given by the following expression

$$\text{Damage} = D \times t \times \text{rate of initiation} \quad (6)$$

In this relation t is the time during which lipid peroxidation processes have been active and the quantity D is a function which depends on the rate constants for reactions (2) to (5) and concentrations of compounds involved, but not on time and rate of initiation (reaction (1)). This equation shows that the damaging effect to a cell increases linearly with time. This linear dependence is in accord with the observation that the functional capacity of many organs and tissues decreases approximately linearly with age [9]. The formation of age pigments is another example of a linear time dependent phenomenon during aging. The appearance of age pigments, or lipfuscins is generally explained as being caused by lipid peroxidation reactions (see e.g. refs 10 and 11). The concentration of these pigments increases approximately linearly with age in many cells [10, 12]. This experimental observation supports the interpretation of the above relation (eq. 6) as being a measure of damage from lipid peroxidation reactions. This relation can be applied to a cellular situation to obtain a cellular life span versus specific metabolic rate equation.

Assume that at a particular critical time $t = T_c$, the damaging effect P has reached a critical value $[P]_c$. We define this time as being that when irreversible damage to the cell has occurred causing total loss of normal biological function. The critical value, $[P]_c$, is likely to be the same for most species. The repair capacity of a cell may be different from species to species causing the net rate of damage to vary, but as far as the main biological function of the cell is concerned no large species differences exist between analogous cells in the category of animals of interest here (see e.g. ref. 13).

Equation (6) can now be rewritten, for the condition time $t = T_c$ and damage = $[P]_c$ as

$$[P]_c = D \times T_c \times \text{rate of initiation} \quad (7)$$

The quantity rate of initiation in this equation depends on free radicals available in the cell. More specifically, it depends most likely on the hydroxyl radical as the initiator of lipid peroxidation because of its extreme reactivity. It is in general assumed that the production rates of the hydroxyl radical and the superoxide radical are directly related and proportional to the amount of oxygen consumed by the cell [14]. The conclusion is therefore that the initiation rate is proportional to the rate of the oxygen consumption of the cell and therefore also the specific metabolic rate of the cell. Thus the rate of initiation can be written

$$\text{rate of initiation} = (\text{constant})\ (SMR)_{cell} \quad (8)$$

With the help of relation (8) it is now possible to express equation (7) in the following form

$$T_c \times \text{rate of initiation} = T_c\ (\text{constant})\ (SMR)_{cell} = [P]_c/D \quad (9)$$

In other words, the product of the critical time T_c, which corresponds to the maximum life span of a cell, and the specific metabolic rate of a cell $(SMR)_{cell}$ is species independent if $[P]_c$ is constant as assumed above.

The relation between maximum life span T of the intact organism and its specific metabolic rate follows from equation (9) with two additional assumptions: (a) the organism as a whole ages in proportion to the aging of its cells and (b) the total specific metabolic rate is a sum of specific metabolic rates of individual cells. A more detailed discussion of this far from trivial problem of relating cellular properties to those of tissues or intact organisms is found elsewhere (14).

Conclusion

In conclusion we have shown that a cellular theory based on the reactions of lipid peroxidation agrees quantitatively with the empirical law relating maximum life span and specific metabolic rate. No other theory of aging has been shown to be consistent with this empirical law.

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