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COMPLEX SYSTEMS BIOPHYSICS

Modeling the Entire Human Mortality Curve: A Regulatory Model of Aging

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Abstract—Modeling of the human aging process was performed based on the relationship between overall viability and the processes of growth and self-renewal of tissues, which is presumably regulated by the centers of the vegetative brain. The presence of two regulatory centers, which stimulate and inhibit such growth, as well as the spontaneous degradation of the cells in those centers at different rates, allowed us to simulate the periods of growth, retardation, and decrease of the rate of the growth or self-renewal of tissues. The resulting curve corresponds to the real entire mortality intensity curve for populations, which is known to best describe the growth and aging processes. Such a correspondence between the model and the mortality curve, which is usually described by the Gompertz formula only for the middle part of the curve, was obtained for the first time. The model complies with the regulatory theory of aging and connects aging processes with the processes of regulation of growth and tissue self-renewal.

Keywords: development, aging, mortality, aging models, tissue growth

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Researchers have proposed many models of aging; thus far, the best and most practically used is the phenomenological model of B. Gompertz (B. Gompertz, 1825), which describes the age-related mortality of populations [1]. However, this model describes only middle-aged mortality (a monotonous exponential increase in mortality) and is not capable of modeling the initial and final forms of the real mortality curve of humans and mammals. It also does not have a clear biological meaning, i.e., associations with specific physiological mechanisms.

The aim of this work was to build an aging model that describes all the stages of the real human mortality curve and connects aging and mortality with the main life processes, that is, growth and self-renewal of tissues.

METHODS

We used differential equations for this modeling, which were simulated on a computer and displayed in graph form constructed in Excel.

To compare the model with the real mortality curve, optimal countries were chosen during the periods of the most favorable historical conditions, in order to minimize the influence of external factors on the mortality curve. Mortality rates were calculated. Mortality data for different countries were taken on the public website http://www.mortality.org, which reflects the dynamics of mortality for 40 countries over two and a half centuries. We used the mortality rate, since this indicator is considered by gerontologists as being optimal for describing changes in the aging rate with age.

RESULTS AND DISCUSSION

The model is based on the concepts of the relationship of aging with the processes of growth and development and self-renewal of its tissues as the main force of vitality opposing aging [2–7]; it combines the theory of stochastic damage and regulatory theory of aging [2–4, 6–14].

The model is based on the following simplest assumptions, which have clear biological meaning:

—the growth and self-renewal of the body is controlled by two types of interacting regulatory cells (stimulatory and inhibitory, such as the central regulation of hormones by the hypothalamus and pituitary gland) with different rates of spontaneous death;

—vitality is equivalent to the rate of tissue self-renewal due to mechanisms of cell growth and division;

—mortality is considered as the inverse of vitality.

Based on these assumptions, it is possible to explain both the regulation of the growth of a living

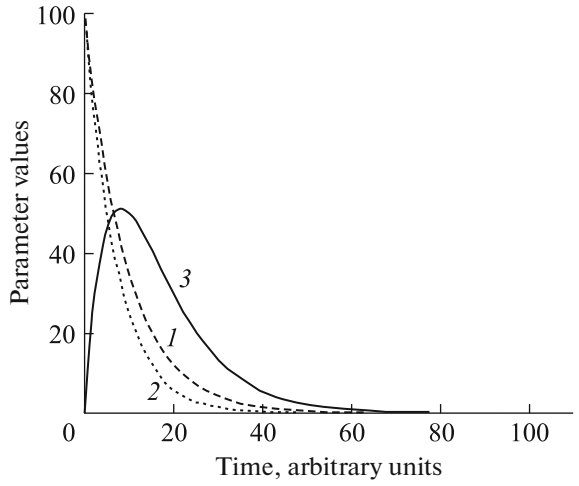

Fig. 1. A model of regulatory aging as age-related tissue dystrophy with a change in cell growth regulation. The y-axis represents parameter values, the x-axis is the time in arbitrary units: (*1*) number of stimulator cells (*h*) for the initial $h = 100$ with the spontaneous death of 10% of the cells per time unit; (*2*) number of inhibitor cells (*s*) for the initial $s = 100$ with the spontaneous death of 13% cells per time unit; (*3*) the content of the final regulatory *F* factor ($F = h - s$), with the proportionality coefficient 5*F*.

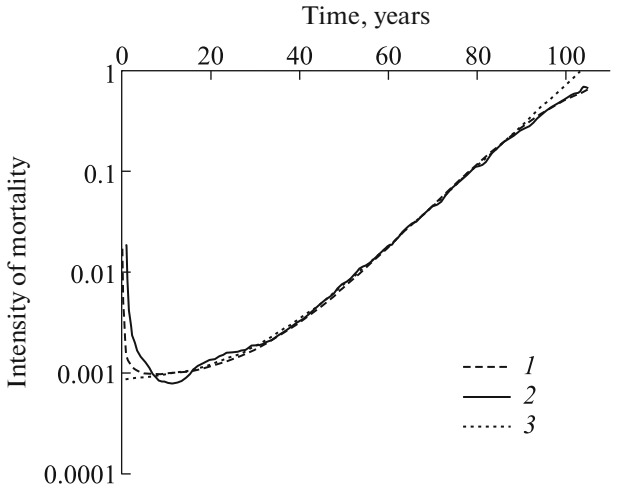

Fig. 2. A mathematical model of the regulatory theory of mortality and the actual intensity of mortality in Australia (1940). The x-axis is the time in years, the y-axis is the intensity of mortality (on a logarithmic scale): (*1*) the estimated mortality rate according to the proposed model with the coefficients indicated in the text; (*2*) the real mortality rate (data are presented on the website http://www.mortality.org, 11/15/2019); (*3*) graph according to the Gompertz formula: $m = 7.95\text{E}{-4} + 6.13\text{E}{-5}\exp(9.37\text{E}{-2}t)$.

system and the cessation of this development at the correct time with subsequent spontaneous aging.

Given the above assumptions, the age-related dynamics of regulatory cells can be described by a system of two simple linear differential equations used to describe any stochastic decay processes of elements (for example, radioactive decay occurs according to the same fundamental mechanisms and general causes and laws):

$$\begin{aligned} dh/dt &= -k_h h, \\ ds/dt &= -k_s s, \end{aligned} \tag{1}$$

where h and s are the numbers of stimulatory (helper) and inhibitory (suppressor) cells, accordingly and k_h and k_s are coefficients of probabilistic death intensity for the corresponding cell types.

Based on the simplest assumption that the production of a certain final regulatory factor F in the body is proportional to the difference between the number of stimulatory and inhibitory cells, we obtain the ratio:

$$F = k_f(h - s) + C, \tag{2}$$

where k_f is a coefficient and C is a constant.

If we consider the regulatory factor as the main factor of viability that provides the integral functioning of the body as a system, in particular, tissue regeneration, then we can assume that the F value characterizes the viability of the organism and in the simplest case is proportional to it. Then, for mortality, as for the reciprocal of vitality, we obtain the expression:

$$m = k_m(1/F), \tag{3}$$

where k_m is a proportionality coefficient.

For the practical purposes of computer simulation, the following quantitative coefficients were used: $m = 1/(F \times 375 + C)$; with $C = 1$; $k_h = 0.1$; $k_s = 0.13$. To consider mortality from external causes that always affect the mortality rate of the population, a constant A, which is 0.0007 for the selected country, was added.

If we assume that inhibitory cells are dying faster with age (their function is exhausted by the period of development: their death during the period of rapid growth of the body, when the tissue mass increases by more than an order of magnitude in comparison with the body weight at birth, serves to inhibit stimulatory effects), then the obtained equations can provide the dynamics of the modeled variables and show very good qualitative agreement with the real human mortality curve (Figs. 1 and 2).

Unlike the first purely stochastic mechanism of death of viable elements of the body as a whole, which allows modeling only the middle part of the mortality curve using the Gompertz equation, this model reflects all parts of the true mortality curve: a high initial mortality rate with a subsequent decrease and some minimum during the growth period, a subsequent exponential increase in mortality during the main period of life, and a slight decrease in the oldest ages.

To compare the model with the real mortality curve, several countries were selected during periods of relatively favorable historical conditions (Australia, Denmark, Canada, the Netherlands and others in 1910–1940, as well as in 1950). Figure 2 shows, as an

example, graphs for Australia (1940): a real graph of the mortality rate, a calculated graph using the Gompertz formula (which deviates from the real graph in the initial and final parts), and a calculated graph according to our formula, which matches the real curve in the best way in all age intervals (correlation coefficient $r = 0.999$).

The qualitative correspondence of the model with the actual demographic curves of mortality intensity is the result of modeling; it is adequate to the task, which is primarily biological. The real morphological substrate (parameters h and s cells) of the described mechanism may be regulatory non-dividing hypothalamic cells that produce tissue growth regulation factors; for peripheral mechanisms, this may be various somatic cells that grow and self-renew via division.

Some mechanisms of somatic cell growth regulation can play a special role: some types of T-lymphocytes regulate growth of somatic cells rather than immunity; these, in our opinion, can constitute a separate special immune system for controlling somatic cell growth [2–4] and their age-related immunodeficiency may underlie the immune theory of aging [2].

All this may indicate the decisive role of regulatory processes for human aging. The long-known effects of hypophysectomy on age-related involution of the thymus [15] and the developed methods of transplantation of cerebral embryonic tissue [5] allow one to influence the restoration of depleted regulatory programs in old animals. One alternative is methods of pharmacological or physiotherapeutic activation of the corresponding nuclei of the hypothalamus, as well as the creation of new functional regulatory centers and pacemakers, including using (auto) psychotherapeutic techniques, and hypnosis. At the level of peripheral mechanisms, the most promising ones are immunopharmacological agents that affect lymphocytes, which are somatic cell growth regulators, as well as growth factors isolated from the blood of young growing animals; the number of such factors decreases markedly with age [2, 16].

CONCLUSIONS

A mathematical model of the regulatory mechanism of aging has been developed, with a description of the entire human mortality curve and a clear biological interpretation related to the concept of aging as a stage of growth and development. The model is based on the interaction of stimulatory and inhibitory types of autonomic centers of regulation of brain regulatory cells that influence the growth of tissues of the brain, with different rates of spontaneous death, which allows us to simulate the periods of growth, its completion, and the aging process. Mortality is considered as the inverse of viability and viability is assumed to be proportional to the rate of cell growth as the basis for tissue self-renewal.

For the first time, the proposed regulatory aging model allows us to describe the characteristic changes in the initial, middle, and final parts of the human mortality curve simultaneously, which coincide with the real picture, and can be physiologically interpreted.

The model indicates the possible important role of regulatory mechanisms of reducin tissue self-renewal (cell division) with age during the aging of humans and animals.

Since regulatory influences, unlike stochastic mechanisms, are easily amenable to external control influences, this opens up fundamentally new possibilities for producing a radical effect on the aging of humans and mammals.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This work does not contain a description of any research using humans and animals as objects.

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