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Hypothalamus as a Possible Modulator of the Rates of Development and Aging of Mammals

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Abstract—The review analyzes the information concerning the possibility to delay aging by slowing down development. It is supposed that the rates of development and aging of mammals are modulated by the circadian rhythm generated by the suprachiasmatic nuclei of the hypothalamus. Reversible arrest of growth in certain mammal species can be triggered by enhanced somatostatin synthesis with an inhibition of growth hormone, thyroid-stimulating hormone, and melatonin and with a loss of circadian function in the suprachiasmatic nucleus of the hypothalamus.

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INTRODUCTION

There are two explanations in the modern biology for the aging phenomenon.

One considers aging as a phenomenon inevitably intrinsic to all live organisms and based on the stochastic process of their wearing and an increase of entropy.

The alternative groups of theories considers aging as an evolutionary phenomenon. To explain how the aging program has arisen in the course of evolution is quite a challenging problem. Actually, death of an organism makes impossible its reproduction and thus reduces the probability that its genes will distribute over the population. It can thus be concluded that natural selection should favor the distribution of longevity genes which allow one to leave more descendants. Nevertheless, increasing lifespan slows down generation change, and, as a consequence, the evolution process. Therefore, the populations of short-living organisms in changing habitat conditions can get an essential preference over ling-living species due to fast accumulation of traits favoring the adaptability of species forming these populations [1].

The first of the hypotheses postulating programmed aging and death was that of the German scientist August Weismann. He suggested that there is a mechanism developed by natural selection and funcioning to eliminate "imperfect" species and release of resources and life space for descendants [2].

Finch [3] recognizes three types of senescence: rapid senescence, gradual senescence, and negligible senescence. The minimum necessary criteria for a species to be related to the third category are the lack of age-related mortality enhancement after sexual maturation, reproduction retardation, and reduction of a number of physiological parameters [4].

One of the arguments in favor of the concept of programmed senescence is the existence of organisms with negligible senescence. Negligible senescence (according to the definition) is characterized by a lack of principal signs of senescence, i.e. organisms with negligible senescence are in essence unaging. But, if there are aging and unaging organisms, then at least one of these groups would has arisen in the course of natural selection. Since unaging organisms occur preferentially among lowly organized forms, whereas aging ones, among highly organized forms, then the suggestion that aging arose during evolution and is a program (like all other stages of individual development) in nature, look fairly reasonable. Many plants are able for clonal reproduction over thousands of years [5]. Among animals there are also numerous species (actinias, sea urchins, molluscs, fish, tortoises) [6] in which no signs of aging were found, and their natural death is caused by their too large size (as a

consequence of continuous growth), which adversely affects adaptability [7].

Considering ontogenesis as a recapitulation of phylogenesis, viz. repetition of the stages of evolution of a biologic species (Muller–Haeckel biogenetic law), we can suggest that evolution has simply "not written" a genetic program for later stages of development of such organisms.

A further argument in favor of the theory of programmed aging is provided by manifestations of pathological aging known in medicine as child progeria or Hutchinson–Gilford syndrome. In these cases, death of age-related diseases (sarcopenia, osteoporosis, atherosclerosis, myocarial infarction, diabetes, malignant tumors, dystrophic processes in teeth, hairs, and nails) occurs before sexual maturation [8].

The concept of programmed death (phenoptosis) was developed by the Russian Academician V.P. Skulachev [9]. According to this concept, phenoptosis relates to deaths resulting from the activation of the corresponding genetic program. Examples of phenoptosis are provided by the programmed suicide of bacteria, fungi (yeast), higher plants (agava, bamboo, many cereals), septic shock in animals, and death of salmon fish and freshwater eel after spawning [10].

Phenoptosis could appear in the course of evolution as a means to protect a population from species with damaged genomes, since such species are potentially dangerous and can inflict an irreversible damage to the population. The phenoptosis program could be formed via selection of species capable of better protecting their genome from damage [9, 10].

Skulachev postulated the "samurai law of biology" (it is better to die than to be wrong), whose essence consists in that the multilevel biologic systems are extremely complex and, therefore, their higher level systems should be protected from mistakes arising in lower level systems by self-liquidation of the latter, and suggested gradual aging to be considered as a form of phenoptosis [10].

Retardation of Individual Development as a Factor of a "Delay" of Aging

In 1976, Libbert first demonstrated the possibility of cancelling the programmed death of an organism. He described an experiment with *Agave mexicana*, in which the species lifespan could be extended ten times [11]. Agave lives 10 years, and at the last year of life it flowers, fruits, and dies. Removal of a floral shoot every time before flowering resulted in that the plant lived the whole century. A biennial *Hyoscianus niger* can vegetate many years, provided one, maintaining a uniformly high temperature, does not allow it to flower [12]. The *Margaritifera margaritifera* pearle shell maggot parasitic on gills, is able to prevent death of salmon fish after spawning [13]. Death of *Octopus filosus* after laying eggs can be prevented by the removal of both optic glands [14]. Female *Anquilla anquilla* that reside in isolated ponds and are not involved in reproduction live many tens of years and reach a maximum size for this species. It is a female freshwater eel was included in the Guinness Book of Records as the oldest fish (88 years).

Retarded ontogenesis can also prolong life by "delaying" aging, since the phenoptosis program under normal conditions is switched only after the organism has reached a definite stage of development. A decrease of internal temperature in poikilothermal organisms (whose body temperature depends on the surrounding temperature) much extends their lifespan [15]. Retardation of individual development can be associated not only with temperature, but also with other factors, such as population density, availability of food, involvement in reproduction, etc. [16, 18, 19].

Growth is one of the components of individual development of an organism, and, therefore, reversible growth retardation (arrest) in most cases can serve as a marker of retarded ontogenesis.

Reversible growth arrest is fairly common in the nature: blastogenic diapausing (i.e. dormant) early embryo of gemmate primitive modular multicellular animals (sponges, coelenterates); spores of bacteria and animalculines (cellular formations with one or several tight shells resistant to various unfavorable exposures); dormant periods of higher plants and their seeds, associated with unfavorable seasonal phenomena; duapause (latent perios) in insects. Many mammal and bird species feature a duapause at early stages of embryogenesis.

Growth retardation is sometimes observed in fish not invloved in reproduction. This phenomenon has been studied in detail on an example of clownfish (*Amphiprion ocellaris*). Young clownfishes drops from the plankton on reefs to shelter under actinias. The biggest fish in the group becomes a female and the second biggest becomes a male. Other fishes remain sexually immature and experience growth retardation.

If the female dies, then the male fast turns to be a male, and the one next in size compensates its growth retardation, matures as a male, and replaces the previous male [17].

We observed reversible growth retardation in young *Vipera nikolski*. These snakes are born in Mid-Dnepr Region (Ukraine) from late August to mid-September and have a well-developed yolk sac. In captivity at 22–25ºC they tend to reject food and undergo growth retardation the first few months after birth. At the same time, cooling to 8–10°C for two weeks induces feed activity and growth. Similar growth retardation accompanied by food rejection we observed at our laboratory in young *Elaphe schrenckii*.

Reversible growth arrest in the euthermy state (a continuously high body temperature is a norm in mammals) was observed in boreal species of small mammals with a short lifespan, such as field mice or shrewmice, which are not hibernants (winter-sleeping animals).

Alternative ways (trajectories) of development in the *Clethrionomys glareolus* population were described by Olenev et al. [18, 19]. The first development trajectory is characterized by a single-phase growth and a short (less than one year) lifespan. Animals born in spring and summer reproduced in the current reproductive season and are almost completely eliminated from the population by the end of the season. The second development trajectory realized in a part of young species under unfavorable conditions (winter, drought) can be considered as reversible growth arrest. The animals feature a low stress reactivity and a high resistance to unfavorable factors. The mean lifespans in representatives of two cohorts (fast and retarded developments) differ about three times [19], providing evidence for the concept that the retardation of ontogenesis favors a "delay" of aging.

The alternative (second) development trajectory prevails in certain populations of common shrew (*Sorex araneus*). Young representatives of this species exhibit a long growth delay and reach sexual maturation as late as spring of the next year. Their transition of the "winter" state is accompanied by a decrease in body size and weight, including brain weight [20].

One more example of the variability of development rate is provided by edible dormous (*Glis glis*), a small rodent of the dormous (*Gliridae)* family. This species occupies a large areal including almost entire Europe and adjacent territories (Caucasis, Asia Minor, Kopet Dagh) [21]. Edible dormice are obligate hibernates with a long (up to 8 months a year) winter sleeping [21, 22]. Current year's young edible dormice stop to grow short before they fall into hibernation. Reversible growth retardation in these species can be prolonged for an indefinite period of time (in out experiments, more than 1.5 years) in the euthermy state [23, 24]. Since over the entire growth retardation period the animals preserve all traits characteristic of the juvenile stage of development (size, type of hair coat not changing on molting), we can speak here about a reversible arrest of "ontogenesis clocks" in these animals or about "freezing" of the biologic age (Fig. 1).

Fig. 1. Two trajectories of indiviual development of edible dormice (animals of the same age): (left) continuous development an (right) reversible growth arrest.

Winter-sleeping mammals in the pre-hibernation period undergo expressed perturbation of physiological and endocrine body functions, including inhibition of the production the growth hormone melatonin, thyroid-stimulating hormone (TSH), and somatotropic hormone (STH), decrease in cell proliferation, changes in the immune system (seasonal thymus involution), and general metabolism inhibition [25].

The growth arrest in young mammals results, in our opinion, from combined inhibition of the production of TSH, STH, and melatonin. Probably, the key factor favoring this state is the enhancement of somatostatin synthesis in the hypothalamus under deteriorated exogenous conditions. Evidence for this suggestion is provided from the high concentration of somatostatin in the hypothalamus of winter-sleeping mammals in the hibernation period, reported by certain researchers [26].

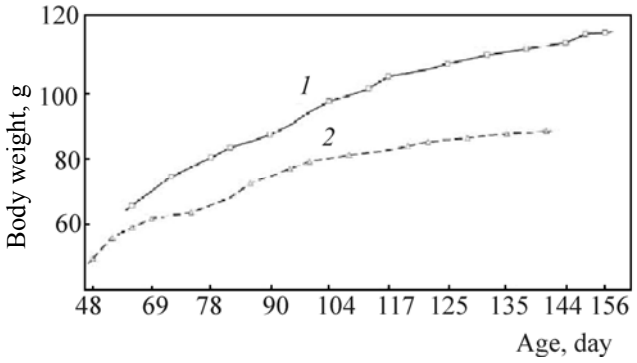


Fig. 2. Growth curves of golden hamsters in the (*1*) control and (*2*) experimental groups (mean body weight, $p < 0.001$).

Somatostatin (SST) exists in two biologically active forms: SST-14 (14 amino acids) and SST-28 (28 amino acids). Being a neuromediator, somatostatin is synthesized by somatostatin neurons localized both in different compartments of brain and in peripheral nerve fibers. As a hormonally active peptide , it is also synthesized by *Langergance* islets of pancreas and in the small intestine.

Somatostatin synthesized in the hypothalamus inhibits secretion of the somatotropin-releasing factor and also TSH and STH secretion by the adenohypophysis. Somatostatin also inhibits secretion of various hormonally active peptides: insulin, glucagon, gastrin, cholescystokinin, vasoactive intestinal peptide, insulin-like growth factor 1 (IGF-1), and serotonin. By inhibiting serotonin synthesis, somatostatin affects melatonin secretion and by inhibiting release of IGF-1, somatostatin affects cell proliferation [27–29].

Somatostatin function is mediated by at least six subtypes of receptors (sst1, sst2A, sst2B, sst3, sst4, and sst5). Somatostatin receptors are localized in many organs (brain, gastrointestinal tract, pancreas, liver, spleen, lung, heart, adrenals, placenta) and cells (pancreatic α, β, or δ-cells, immune-cempetent cells) [30, 31].

The properties of somatostatin and its receptors allow the somatostatin complex to be considered as a key factor controlling growth and rate of individual development of vertebrate animals.

Based on our [24] and published data [18, 19] we can suggest that the reversible growth arrest in mammals is triggered by enhanced somatostatin synthesis mainly induced by various exogenous factors: duration of photoperiod, light intensity and temperature, availability of food, and population density. A high light intensity may favor growth retardation, since, on the one hand, it enhances sensitivity to photoperiod and, on the other, inhibits melatonin synthesis.

In [24] we showed that the state of growth retardation can be exited in various conditions (hibernation, light deprivation, or indefitine light conditions) by different scenarios: within several days or with a latent period of up to two months [24]. It is suggested that increased concentration of melatonin in blood serum is a common key factor of termination of reversible growth retardation (in winter-sleeping mammls, the concentration of melatonin increases jumpwise during their periodic wakenings) [32, 33].

In [24] we gave to the reversible arrest of development in mammals the name neobiosis. What are the evolutionary prerequisites of this phenomenon? In our opinion, the rate of ontogenesis reaches a maximum at optimal (for a specific organism) exogenous parameters, including physical, chemical, and biological factors. A deviation of these parameters from optimal retards development and increases mortality associated with adaptability attenuation rather than with age. The retardation of ontogenesis in deteriorated exogenous conditions is the main prerequisite for neobiosis.

Neobiosis may arise in two independent ways (both in short-living nonhibernating species and in hibernants). In the first case, the retardation of the development of a part of young species in a population over the course of a prolonged unfavorable period can enhance their total adaptability due to that they both spend less energy and “succeed” to take part in spring reproduction. In the second case, the deceleration of ontogenesis favors more efficient use of resources and preparation to hibernation. As a result, the process of natural selection forms, over a fairly short time, a genotype maintaining reversible growth arrest.

Modeling Reversible Growth Arrest

We performed an experiment with golden hamsters (*Mesocricetus auratus*), the aim of which was to compare the growth rates of the animals in comfort and extreme conditions. Golden hamsters are facultative hibernants with a short lifespan. The reproductive aging of female species occurs at about a year age [34]. In natural species sites (the Near East; this species is presently considered as virtually epiobiotic) long droughts are not infrequent; in this connection we

suggested that golden hamsters are quite flexible in controlling the rate of their individual development.

Young (1.5 months) wildtype golden hamsters were obtained from a private breeding facility (Kiev) in October 2008. The experimental group (98 animals) was placed in a climatic chamber, each animal was kept in an individual cage 250×250 mm, made of a zinc-plated steel caging with a 10-mm spacing. Starting on October, 28 the temperature in the chamber was gradually lowered from 22 to 13°C. The illumination at the cage level at the gackgroun at the background of a short light day was maintained at 500–1000 lx, humidity 80%. After 2.5 months the climatic regime in the chamber was changed: The temperature was raised to 25ºC, and the light day was prolonged to 16 h. The control group (30 animals) was kept under natural light conditions (window light, 200–700 lx), temperature 22–24°C, humidity 40–60%.

Hamsters had a free access to food. The diet was water-free and comprised apples, carrot, and a mixture of cereals (50% oat and 50% wheat) and protein granules [Nutra Nuggets Professional for Cats, 32% protein, 21% fat, 3% carbohydrates (fiber), ash 5.5%, humidity 10%].

Each week control and experimental animals were weighed. The resulting data revealed an expressed growth retardation in experimental animals kept in unfavorable exogenous conditions (Fig. 2).

However, growth retardation in this case was irreversible, as judged from the fact that after the re-establishment of a favorable climatic regime in the chamber no growth resumption was observed, and the final size of animals in the experimental group proved to be much smaller (the mean body weight in a 6-month age was 93.01±1.85 g in the experimental group and 123.63±4.62 g in the control group, $p < 0{,}001$).

Thus, attempted reproduction of reverseble growth arrest in golden humsters proved to be not completely successful (by stopping growth, we failed to stop development). The irreversible growth arrest in golder humsters in our experiment may point to an important role of circadian (daily) clockes of the suprachiasmatic nuclei of the hypothalamus as a component of the mechanism of control of the biologic time in mammals.

Modulating the Rate of Individual Development by Biorhythms

The individual development of an organism can be considered as a complex of epigenetically induced changes. The rate of these changes devends on a great variety of factors: rate of biochemical reactions, temperature, quantitative and qualitative components of the internal medium, and external conditions. Biologic rhythms, too, are epigenetically induced but periodic changes of an organism and its functions. From this it follows that the rate of inividual development can, in principle, be modulated by biorhythms.

There are a lot of species giving examples of biorhythm-modulated development rates. Thus, the growth of most trees in the moderate climatic zone does not occur continuously and alternates with vegetative dormancy periods. Annual grasses grow intensively until reproduction, whereas bulb plants with a seasonal rthythm of vegetation need a few year to reach the flowering phase. In certain cases, the character of biorhythm-related development can be affected. An example is provided by the jarovization of winter cereals by cooling their seeds, as a result of which these plants, under conditions of a short light day, develop continuously, without winter delay.

The aforesaid allows us to postulate basic principles of the modulation of development rate by biorhythms: (1) modulation of the rate of individual development of an organism by development rate by biorhythms stabilizes development rates; and (2) development processes can be slowed down when the “biologic clocks” slow down (prolongation of the rhythm phase), or, vice versa, occur continuously (at a maximum rate) when the biorhytm is eliminated (the rhythm phase is zero).

Development as a complex of epigenetically induced changes in characteristic of not only an organism as a whole, but also of its constituent parts, viz. cells, tissues, and organs. Therefore, different tissues and organs in the same organism can have their own biorhytms, and, therewith, the rate of development of some tissue or organ can essentially affect the rate of development of both other tissues and the whole organism.

The principal role the neuroendocrine system plays in development and aging processes was first mentioned by Dilman [35–37]. According to the evolutionary theory of aging, the key role in the triggering and realization of aging mechanisms belongs to the cetral nervous system, pituitary–hypothalamic complex, and, primarily, hypothalamus (a change in its sensitivity to homeostatic signals). How the program of changing the sensitivity of hypothalamus can be realized?

Hypothalamus is a polymorphous structure comprising more than 30 main groups of cells (nuclei) with different functions [38]. In our opinin, each specialized cell group has is specific development scenario inclusing a definite scheme (succession) and complex of changes. This is changes in hypotalamic cells whoch is reposible for regulatory parameters of the hypothalamus. Therewith, the hypothalamus– organism interrelationships can be built no only by a hierarchical from-top-to-bottom principle, but also by a democratic from-bottom-to-top one (i.e. the organism, too, can affect the regulatory parameters of the hypothalamus). One of the most functionally important functions of the hypothalamus are the suprachiasmatic nuclei which are a leader of the circadian system of the organism [39].

We consider the suprachiasmatic nuclei as a pacemaker for the cyclic changes that occur in separate hypotalamic structures and controls in this way the rates of development aging of mammals.

Convincing evidence for the circadian control of the biologic time was obtained for the estrous cycles in rodents and humans [40]. The duration of separate phases of the seasonal cycle in mammls, too, can be controlled by the circadian or circannual "clocks."

The circannual rhythms probably function to accurately distribute seasonal functions in time, thus providing a sufficient intertia of physiological control systems and attenuating the impact of exogenous factors on the seasonal rhythm. If this is the case, we can suggest that the circannual rhythms control to the greatest extent the seasonal activity of species which have to exactly follow the time schedule of seasonal functions. Actually, evidence for this suggestion is provided by the results of comparative research on closely related species.

The circannual rhythms of body weight and hibernation in *Citellus* ground squirrels are under the most rigid endogenous control in the *Citellus lateralis* obligately hibernating species inhabitating in boreal regions (snowy winter and short warm summer). At constant photoperiod and remperature, these rhythms are maintained without decay over at least five cycles. Other related species inhabitating in drier regions are less sensitive to such endogenous rhythms. Under stable conditions, their body weight and hibernation rhythms tend to decay (for example, in *C. mohavenis*) or even disappear over the first cycle (for example, in *C. tereticaudus*). Pengelley and Kelly [41] note that the circannular rhythm is an excellent adaptive tool for *Citellus lateralis* inhabitating in a climatically severe and regularly changing medium, where "for survival, an animal needs that each event of its lifecycle occurs at a stricly definite time."

The time period between falling in hibernation and initiation of mating in female edible dormice is about 270 days irrespective of the population (Nothern or Southern) these animals belong to, and, therewith, the time of estrus depends on the time of falling in hibernation (Fig. 3). We drew this conclusion having analyzed the data of Milazzo et al. [42] and our own unpublished observations. The above regularity points to the fact that the reproduction of dormice is rigidly tied to autumn, a period which is favorable in terms of the availability of food (ripening of oak fruits and beech nuts). The "stop clock" state developeing before hibernation can reset the circadian timer in dormice at the beginning of hibernation.

Comparing the role of hibernation in reptils and mammals in their reproductive cycle, we came to a conclusion that the duration of hibernation, as a factor triggering reproduction, is more essential for mammals. The breeding of most reptil species living in a moderate climate zone involves an artificial wintering which is much shorter (up to 1 month) compared with natural hibernation terms [43]. At the same time, for example, bobak marmots (*Marmota bobac*) are unable to reproduce without hibernation, and require a full-scale hibernation of which they go out spontaneously without any external stimulation [44].

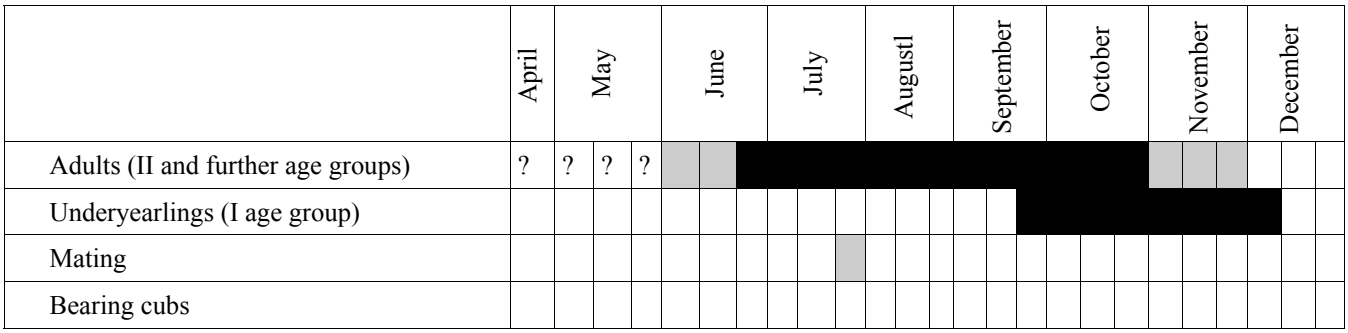
The above data show that mammals have a fairly perfect mechanism for controlling the biologic time, which can, even in the hypothermia state, almost exactly reflect the real (astronomic) time. Since the circadian rhythm generated by the suprachiasmatic nuclei of the hypothalamus is subject to temperature compensation [45], then the suprachiasmatic nuclei may, in principle, well play the role of such clocks.

However, we still have insufficient evidence for the modulation of circannual rhythms by circadian rhythms. Attempts of experimental substantiation of this model gave umbiguous results (ground squirrels with damaged suprachiasmatic nuclei of the hypothalamus lost, in part, the annual hibernation rhythm) [46, 47].

"Correct" Stoppage of Circadian Clocks

Revel et al. [48] showed that certain hibernants (for example *Cricetus cricetus*) lose the circadian function

(a)



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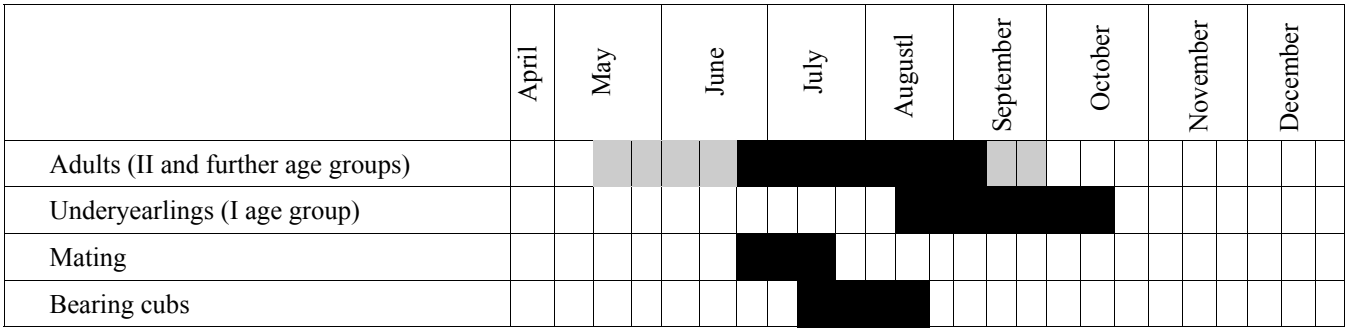

Fig. 3. Circannual activity and reproduction rhythms in edible dormice: (a) Sicily, Madonie Regional Park and (b) Ukraine, Cherkassy Region, Cold Ravine. (Gray fields) Start and end of acive periods, and (black fields) activity and reproduction peaks.

of the suprachiasmatic nuclei of the hypothalamus during hibernation. At the background of a high metabolic activity of the suprachiasmatic nuclei in the hypothermia conditions, they observed a paradoxical pattern of clock gene expression levels: continuously high Per1, continuously low Per2, and intermediate (also continuous) Bmal1. Low and high expression levels were observed for Avp and c-Fos, respectively. The transcription level of the enzyme arylalkylamino-*N*-acetyltransferase, responsible for melatonin synthesis, was continuously high, and the content of this enzyme in blood plasma was low (the blood level of this enzyme sharply increased after awaikening). The authors of [48] consider that the circadian clocks stop as the body temperature falls below a certain level. At the same time, there are certain mammal species whose hibernation occurs at fairly high temperatures. Madagaskar pygmy mouse lemur (*Cheirogaleus medius*) hibernates in tree holes for seven months, and, therewith, its body temperature can increase up to 30°C and even higher [49]. Lemurs, like Arctic hibernants, periodically wake up. Edible dormice whose areal includes also subtropics (Sicily) successfully hibernate at temperatures of up to 18°C [50].

Certain mammals (wing-handed, rodents) feature a seasonal or constant heterothermicity, when animals stay in the torpor state in that period of day, when their activity is suppressed. As shown by Herwig et al. [51] on an example of Siberian hamster (*Phodopus sungorus*), the molecular mechanisms of circadian clocks continue to function in these animals when they are in the hypothermy state. Apparently, the stop clock in the hibernatin period is an adaptive temperature-independent tool required to avoid daily periodical awaikenings. In this connection, the daily circadian hypothermy periods can hardly be considered as an analogy of hibernation, since the long winter hibernation is likely to be underlain by an inhibition of the circadian rhythm of the suprachiasmatic nuclei of the hypothalamus.

Probably, a “correct” stoppage of circadian clocks at a preserved activity forms an important consituent part of reversible growth arrest, and, therewith, loss of the circadian function (but with the preservation of a

constant electrical activity of neurons) of the suprachiasmatic nuclei takes place at a increased somatostatin level in mammalian hypothalamus.

In this connection, it makes sense to perform the research described in [48] on dormice in their prehibernation period.

CONCLUSIONS

We consider that the gradual aging program in most mammals and humans is one of the forms of phenoptosis (programmed aging) implemented by the neuroendocrinal system. Therewith, the rates of individual development can be modulated by the circadian rhythm generated by the suprachiasmatic nuclei of the hypothalamus. The development of the circadian control mechanism in the predecessors of mammals might serve as an important prerequisite of their homoiothermicity (independence of body temperature of environmental temperature) in the framework of the resistence strategy which stabilizes the rate of animal development at a varied body temperature. By contrast, the tolerance strategy proved unfavorable, since a decrease of the metabolism level decreased the rate of reproduction without prolonging the lifespan.

Research on the mechanism of modulating the rate of mammalian development by circadian rhythm can reveal approaches to delaying human aging.

By destroying the suprachiasmatic nuclei and introducing somatostatin analogs one can try to model neobiosis—reversible growth arrest—in laboratory animals (this method is unacceptable for humans). To develop a procedure for "freezing" the biologic age in humans, one should explore the mechanism of a "correct" stoppage of circadian rhythm (on an example of edible dormice) and to model it (probably, by artificial electrical simulation of the suprachiasmatic nuclei area).

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