ISSN 1070-3632, Russian Journal of General Chemistry, 2010, Vol. 80, No. 7, pp. 1482–1489. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © A.M. Olovnikov, 2010, published in Rossiiskii Khimicheskii Zhurnal, 2010, Vol. 53, No. 3, pp. 88–94.

How Could the Program of Aging be Arranged?

A. M. Olovnikov

Institute of Biochemical Physics of Russian Academy of Sciences, ul. Kosygina 4, Moscow, 119334 Russia
e-mail: olovnikov@dol.ru

Received June 10, 2009

Abstract—Aging could be a consequence of the programmed partial dedifferentiation of brain neurons that is performed through nonrandom losses of chronomeres–short perichromosomal DNA molecules that also participate in maintenance of cellular differentiation state. Process of their sequential losses, implementing as the "relay-race partial dedifferentiations, " serves as a basis for the activity of the lifelong brain clock that regulates a physiological age of multicellular animals. These relay-race dedifferentiations are performed in a consecutive mode by different groups of neurons during the peaks of a so called T-rhythm, whose length of period is different in various animal species.

DOI: 10.1134/S1070363210070443

INTRODUCTION

The development of an organism proceeds not only in space (formation of multi-cellular structures and their growth), but also in time (a consecutive manner of the processes of origination, maturation, and a successive aging). The organism has to possess its own clock in order to trace a timely deployment of the events of individual development in time. It is quite evident that such biological chronometer can be set in the central nervous system as an integrated centre of the organism. Because of alterations in the endocrinal system with aging, hypothalamus, being an important regulator of hypophysis and through it of other tissues, has been suggested for a role of the clock; the history and the current state of the issue is reported in [1, 2]. However, also possible is another approach to choosing a substrate for the clock. Here presented is a hypothesis, according to which evolution applies actually the whole of the brain as a bio-chronometer, rather than its small regions like hypothalamus or hypophysis, however important they might be for the endocrinal regulation.

The key mechanism which could underlie the run of the brain clock still remains elusive: how does the brain clock go, what are its main components, what force moves its fingers, how are the instructions on the flow of biological time given, and how does the clock change the activity of the organism? Understanding of these processes will help to realize why the run of a biological clock leads the organism to aging.

Hypothesis of a Relay-Race Dedifferentiation: How the Lifelong Brain Clock Works

Plausible answers to the above questions can be found within the framework of the proposed hypothesis. In outline, the essence of the hypothesis can be elucidated as follows. Let us visualize that the mammalian brain represents a transparent column. Let the column be filled with the gel, in which a platform with dye is slowly plunging, leaving a dusk trail. The lower the platform sinks to the foot of the column, the longer a dusk column of the brain cells which have lost youth becomes, and the smaller a little transparent column of the cells separated by the platform and still keeping their adolescence is getting. A part of the platform is actually played by a wave of partial de-differentiations of neurons, which slowly moves along the brain from one group of neurons to another; in other words, the wave of some alterations in their gene expression. Neurons do not turn into other types of cells in the course of partial dedifferentiations; however, their activity changes. The velocity with which the front of partial dedifferentiations mainly associated with quantitative shifts in the gene expression pattern spreads can be not strictly the same in diverse species of animals. Propagation of this front throughout the nervous system bears a stepwise nature, with certain temporal intervals. These intervals are set by a special hypothetical biorhythm, let us designate it as T-rhythm for short (from the word temporal, i.e. transient). The border between the neurons which have

been affected and not yet affected by partial dedifferentiation is likely to shift every 24 hours in the worm *C. elegans*, while in humans, a recurrent shift of the border probably occurs once a year. A partial loss of differentiation by neurons is reflected in the state of organs and tissues of the organism in whole, which are directly or indirectly innervated by these cells. On moving along non-random inter-neuronal routes, the border of times, splitting into a number of fronts scattered throughout the brain, draws, little by little like a skillful artist, ever new features on the faces of people, thus turning them into strangers for those who have not seen them for long. On passing from a columnar metaphor to putative however quite likely concrete processes, let us examine a list of the players in the scenario which nature could utilize when solving the problem under discussion.

Participants of the Eexamined Process

Small so-called perichromosomal DNA molecules holding with their ends on the body of a chromosome are presumably responsible for maintaining the differentiation of neurons. They code for regulatory RNAs which modulate the activity of chromosomal genes. In case a chronomere (perichromosomal DNA molecule located in neurons and engaged in the work of the brain clock) is lost by a postmitotic, namely no longer dividing, neuron, its chromosome genes go on doing their work; however, the level of their expression alters, thus lessening functions of the neuron and other cells subordinated to it. The totality of all perichromosomal DNA molecules of the organism (all brain chronomeres and other perichromosomal DNA of different organs) is its paragenome. The paragenome is an operative memory essential for the genome to work. Regulatory RNAs transcribed from the paragenome are liable for setting and maintaining cellular differentiations not only in neurons, but also in other multiple types of cells.

Chromosomal originals of perichromosomal DNAs lapse into silence shortly after creation of their perichromosomal copies and are no longer used by the organism. Drop in the content of the paragenome components, crucial cellular regulators, in cells (for example, in postmitotic neurons, mitotic fibroblasts, etc.) weakens homeostatic opportunities of the corresponding cells. In particular, such age-dependent changes as accumulation of mutations in a mitochondrial DNA, suppression of expression of antioxidant defense genes, accumulation of lipofuscin and other unfavorable for cells events in a senescing organism are coupled precisely with the losses in paragenome. Why such a form of the operative memory is required for the organism itself to emerge in the course of the embryonic and post-embryonic morphogenesis, what is the reason of failure in a direct usage of genome originals of the paragenome for this purpose, and whether just their perichromosomal copies are necessary for the development are the issues considered earlier [3].

Hormones, neuropeptides and neural signalling in itself are involved in formation of the above T-rhythm playing an important part in the destiny of chronomeres. Duration of the period of T-rhythm drastically differs in different species of animals (short duration of the period in short-living animals and long, in long-living ones). Duration of the period and the amplitude of T-rhythm can be set by different combinations of physiological systems of the organism and modulated by external factors, such as duration of daylight hours, seasonal prevalence, etc. A chronomere can be exposed to the so-called scrupting at a peak of the T-rhythm [3]. Scrupting is a transcription-dependent process which leads to tearing an end of the chronomere from its chromosomal docking site, on which it used to stay. Under a normal intensity of transcription (namely, in the period between peaks of the T-rhythm), a chronomere manages to hold at the docking site. However, its transcription drastically enhances at a peak of the T-rhythm, thus resulting in tearing the 5'-terminus of a chronomere's meaningful chain from the chromosome body. The process of tearing-off occurs under the influence of the transcriptional machinery operating at its maximum rate and driven by the factors of the T-rhythm at its maximum. It should also be emphasized that intensification of the chronomere transcription in neurons proceeds simultaneously with intensification of transcription of chromosomal genes as well, which for all this are not damaged mechanically since the ends of chromosomal genes are not anchored or exposed to the nuclease attack unlike the ends of a chronomere DNA. Rupture of the chronomere end from a chromosome leads to its releasing from the nuclease defense. This is why detachment of the chronomere end is immediately followed by degradation of the chronomere and, as the result of that, by a partial dedifferentiation of a corresponding neuron. This process takes quite considerable time (possibly from several hours to 24 hours) which is

spent on a gradual alteration of the level of intracellular factors which were previously controlled by a chronomere which has just vanished.

How the Wave of Neuronal Partial Dedifferentiations Moves

Why do brain neurons not dedifferentiate at a peak of the T-rhythm all at once? And why is dedifferentiation of a neuron partial rather than total? The answer is as follows. Different neurons of the brain have chronomeres of different specificities. They are able to respond to a signal of the T-rhythm (hereinafter referred to as T-signal for short) only in case of their preliminary activation (see about the conditions of activation below). Not all the components of a paragenome respond to the T-signal; this is why a neuron retains many of its functions even though it has lost its specific chronomere. Neurons are getting less efficient without chronomeres, in particular, with respect to their capability of participating directly or indirectly in implementation of neurotrophic and/or neuroendocrinal activity.

When a wave of the loss of chronomeres by neurons spreads throughout the brain at the maximums of the T-rhythm and a certain neuron loses its chronomere, this loss in itself serves a signal which makes the next neuron ready for a proper reaction to the T-signal which will come further, namely, at the next maximum of the T-rhythm (let us assume, in 24 hours in worms and in a year in humans). The matter is actually about a relay-race of losses of chronomeres which are sequentially found missing by neurons. The disappearance of a chronomere in neuron 1 is supposed to abolish the ban on a T-signal-dependent activation of the chronomere transcription in neuron 2. T-signal is incapable of intensifying transcription of a chronomere in neuron 2 before this ban has been removed. It is possible when an inhibiting signal from neuron 1 enters neuron 2; cessation of arrival of this inhibitor results in readiness of neuron 2 and its chronomere to respond to T-signal. Neuron 2, in its turn, will lose its chronomere when a recurrent T-signal comes to it later (for example, in a year). The loss of a chronomere in neuron 2 will create a prerequisite for a T-signal-depending activation of the chronomere transcription in neuron 3 and so on. It is crucially important that the term of acquisition by a successive neuron of the ability to answer the T-signal with a drastic activation of transcription of a corresponding chronomere (this term is so to say a period of creating the neuron competence) should be much longer than the short interval (probably, less than an hour) within which a peak concentration of the T-signal emerges and preserves. A period of the competence creation (in other words, creation of readiness of a successive neuron to respond to the T-signal) can, in all probability, vary from several hours to several days. This time is spent on elimination of traces of an inhibiting signal in a successive neuron, as well as on a subsequent reconfiguration of chromatin (in order to activate genes whose products assist a chronomere in responding to the T-signal with an elevated transcription). T-signal fails to act upon chronomeres which are unprepared to its influence, and this is the reason why each successive peak of the T-rhythm meets in the depths of the brain just a limited number of neurons whose chronomeres are now ready for a proper answer to the T-signal. No other but just these neurons become its "victims."

Program Against Stochastics

Groups of neurons rather than a single neuron take part in the above events. The loss of chronomeres of a certain group of neurons is an equivalent of the run of the brain clock one beat faster. However, what is important for the clock turns out to be a lessening of the neuronal activity. As long as there are few neurons, they exhaust their facilities quickly, that is, their chronomere relay-race is very short. Species with a large brain are capable of realizing a longer chronomere relay-race; this is why they have, other conditions being equal, an elongated life span. Those species whose nervous system constantly grows with the growth of the organism or efficiently regenerates have an opportunity of joining a group with a negligibly minor aging; for example, some species of tortoises and fish hardly ever senesce [4]. Due to its own changes, the brain gradually alters the pattern of an innervated by it body first for the better – during the growth and development of an organism, and then towards the aging of the organism.

If aging is a consequence of a monotonous ticking of the T-rhythm which has not ceased (though, as a matter of fact, is no longer necessary for the organism after it has attained a mature age), then it is determinism, rather than manifestation of random events. It is essential in this respect to bring up a programmed nature of aging in the same manner as a schedule of the events of a physiological maturation of all the systems of the organism is programmed. If differentiations take part in creating an organism, then

dedifferentiations, though partial, as well participate in its destruction, not at all random.

It should be noted that the issue about breaches of differentiation has time and again been discussed in the literature as a plausible cause of the cell aging. Cutler [5-7] surmises that cell dedifferentiation in the course of aging is caused by the genetic errors induced by retroviruses or by active forms of oxygen under oxidative stress, etc., and accentuates that these errors distort a true pattern of the gene expression. A breach of differentiation in this connection turns out to result from a random genetic instability, so a similar variant leaves no place for saying about the program of aging.

Within the framework of the proposed hypothesis of relay-race dedifferentiation, dedifferentiation of the brain cells is no randomness or pathology, but a programmed way of organizing the work of a biochronometer of the organism controlling development of the organism in time.

Evolution and Lifelong Brain Clock

Hormones, mediators and other factors underlying the T-rhythm are not totally identical in diverse animal species. The structural basis (namely, those centers of the nervous system and other regions of the organism which are involved into generation of the T-rhythm) is not strictly the same in different species either and can be an object of evolutionary transformations. The sense of such transformations is in modifying a value of the T-rhythm period, that is, a time interval separating its successive maxima. The longer a period within peaks of the T-rhythm is, the slower, other conditions being equal, the biological age of the organism changes. And vice versa, frequent beats of the T-rhythm accelerate the rate of the individual development. By changing the value of the T-rhythm period (due to morphophysiological transformations), biological species get a chance of adjusting their average longevity to the resources of their ecological habitat. It is known that K-strategists (these relatively large animals are notable for their care about not numerous progeny, their embryonic development proceeding not at a rapid rate, for example, elephants and humans) live relatively long and take advantage of having T-rhythms with a big value of the period. To the contrary, r-strategists (relatively small animals which are characterized by the utmost fertility and the absence of care or poorly expressed care for the progeny; their embryonic development is quite rapid and they reach puberty early, for example, drosophilae, nematodes, mice) live not long and they should have T-rhythm with short intervals. In this connection, it is pertinent to point to the peculiarities of the so-called biological time. Biological time is essentially different from physical time in an intermittent and uneven character of its run. The flux of biological time is equivalent to evolutionally programmed successive shifts of physiological ages of a developing and then senescing organism. Biological time can accelerate or slow down its run depending on the tempo at which the exhaustion of chronomeres proceeds in the organism.

Some Biological Factors Against the Background of the Lifelong Brain Clock Functioning

The average number of lifelong heartbeats in each mammal is nearly the same, with heart rate being different in different species [8]. A striking dependence has been established: the resting heart rate is inversely proportional to the lifespan of the organism [9]. Among warm-blooded animals, this rule is kept both for different species and for different individuals within a species. Large numbers of clinical observations have proved that a constantly overrated heart rate is always associated with an increased danger of an unfavorable outcome, in other words, the heart rate serves a clear and precise indicator for the cardiovascular health and, consequently, a predictor of viability of the organism. Correlation between the maximum lifespan and resting heart rate is linked with the basal metabolic rate and amortization of the cardiovascular system [9]. To the point, physical exercise, temporarily increasing the pulse, lowers heart rate which is assisted by the rise in the tone of the parasympathetic system and the drop in the tone of the sympathetic system [10]. Observations over cardio-patients regularly and moderately training for a year have demonstrated not only a drop in the percentage of unfavorable events as compared with the control, but also the maximal oxygen uptake [11]. Similar trainings normalize pressure, work of the lungs, etc. [12]. Meanwhile, the stated fact of the maximal oxygen uptake is undoubtedly at variance with the above-mentioned reverse correlation between the heart rate (this value reflects the level of the consumed oxygen) and the lifespan (if to admit that lifelong cardio-trainings could, in principle, elongate the lifespan in patients, which, as a matter of fact, could not be checked by researchers). If similar separate observations reflect some covert dependence of the lifespan on some key, crucially important factor, the level of basal metabolism can hardly be this factor.

Amortization of vessels or the heart against the background of high heart rate is unlikely to be such a factor either: both the level of the basal metabolism and the heart rate are higher in many birds as compared to mammals of the same mass, birds living much longer. Of course, there are many sources of influence on the result (efficiency of the antioxidant system, regeneration of some types of neurons in the brain, etc.). Nevertheless, one can surmise that the resting heart rate reversely correlating with the lifespan in mammals is, probably, in itself coupled with some factor which is essential for the control of an average lifespan of individuals of any species of warm-blooded mammals. This factor can be represented by an individual frequency of the T-rhythm in each biological species. Being a multiple-factor mixture of biologically active components, humoral participants of the T-rhythm are under the control of both various endocrinal glands and interplaying centers of the nervous system of an organism.

The considered way of functioning of a biochronometer, activation of the neighboring cells due to the cancel of inhibition of a certain activity, applies a principle which was experimentally detected by embryologists when researching into the phenomenon of neural induction. Neural induction is the first step in formation of the brain and the spinal marrow in higher vertebrates. It turned out that the act of switching off a certain signal way in one area of a developing brain can be used as a signal for induction of a successive specialization of cells of the nervous system. This variant of launching neural differentiations was named as default neural induction [13-15]. The data obtained on mammals testify to the same mechanism as in amphibians: neural induction starts in the absence of activating signals, with a mere cancel of an inhibiting, i.e. prohibiting, signal serving an initiating factor for it to start [16]. Large numbers of factors participating in the neural induction in an embryo have been shown to be as well responsible for an artificial neurogenesis realized on the basis of embryonic stem cells [17]. This principle (elimination of an inhibitor in favor of the next stage of development) could also be utilized in the work of chronomeres which should function exactly in cells of the brain.

In view of the above-mentioned, this principle as applied to chronomeres looks as follows: elimination through scrupting of a preceding chronomere makes it possible to organize a T-signal-dependent hyperactivation of transcription of a successive chronomere which is further eliminated in the course of scrupting as well, with such a cycle reiterating from time to time. Evolution needs selection for an appropriate length of the T-rhythm period, whose formation and regulation can involve not only biologically active and humoral factors, but also the nervous system since it can modulate the parameters of various oscillators [18]. It has been shown on the example of circadian rhythms that though alteration of the mode of illumination changes, e.g., the activity of genes in the liver in rats, denervation of the organ cancels this effect [19]. T-rhythm, being a poly-factor sign in terms of formation, does not have to exhibit maximal indices in an aged organism, in other words, the intensity of the T-signal can sufficiently decline, thus leading to a paradoxically long survival of some individuals against the background of a significant weakening of physiological indices of the organism.

As concerns various ways of forming the T-rhythm, they could be different in diverse biological species. For example, in species-super-short-livers, such as *C.elegans* (the worm stops propagating by the fourth day of a grown-up life and then weakens with each day), circadian oscillations could be widely used as a T-rhythm. On the contrary, in *H. sapience* as one of species-record-breakers in longevity among higher mammals, T-rhythm is, in all probability, a product of a very complex system of interactions, which can even comprise organs which elegant nematodes lack at all, for example, pineal gland [20]. Complication of the system organizing the structure of the T-rhythm in evolution could be targeted mainly at modifying the duration of the T-rhythm period as the most flexible and universal factor allowing a population to select an optimal species-specific lifespan when exploring new niches and on forming new species.

Thus, a chronomere relay-race of neuron dedifferentiations, which functions in accord with the principle of "dedifferentiation through elimination of a previous chronomere," could guide the development of an organism in time. A chronomere clock, whose components are distributed throughout multiple regions of the brain, sends its signals about the reached age (namely about the level of the activity of their neurons) to various organs of a body and to various departments of the brain itself, hypothalamus including. The latter takes part in integrating such signals due to its endocrinal activity; however, it is no basal or unique element of the clock controlling a physiological age of the organism. The activity of

neurons gradually losing their chronomeres changes more remarkably with time. As a population of neurons which have lost their chronomeres is getting larger in the brain, the total neuroendocrinal and neurotrophic opportunities of this interesting organ are gradually decreasing. It is the circumstance that is responsible for the phenomenon of a slow, however, without any artificial interference, inevitable process of aging. The ticking of the T-rhythm when there is no necessity in it creates the picture of a working program of self-destruction of an organism. Aging, though with manifestation of randomness (action of oxygen active forms, cross-links, etc.) and though bringing certain element of inaccuracy into the work of an organism, is nevertheless a consequence of the work of a program and nothing else. Representatives of highly organized biological species can not at the end of life get rid of the mechanisms which were necessary for creating the organism at the first half of life since evolution in no way favors the cancel of aging. As long as ticking of a lifelong chronometer is part of the developmental program, the T-rhythm turns out to kill what it bore. If the T-rhythm were stopped in due time without inflicting any harm to the organism, the program of aging would be switched off.

How is it possible to interrupt pernicious work of the process of aging? Provided there are, according to the supposition, two main working factors on the scene: paragenome and T-rhythm, one can try to act upon each of them. Decoding of the paragenome in the future would make it possible to imitate the activity of genes of the paragenome, i.e. paragenes, by introducing into the organism from the outside what it lacks with age. As concerns the other direction - influence on the functioning of T-rhythm whose special features are recorded in the brain morphophysiology and other structures of the organism, it is unreal to change them radically. Nevertheless, one can, having elucidated the detailed foundations of the T-rhythm work, try to modify pharmacologically the amplitude and/or the value of its period after all physiological systems of the organism have completely matured and are gradually starting aging.

Age-Dependent Changes of the Human Brain as a Plausible Payment for the Chronomere Clock Functioning

If the postulated successive, yet partial dedifferentiation of the brain which is utilized as a means of development really takes place, then its signs should be observed not only in a very old man, but also in a person in the prime of their life. Signs of loss of the control and dedifferentiation of neurons were noted in some pathologies [21, 22]. However, alteration of the brain should proceed without pathologies as well, merely as a charge for a normal development. Ever perfecting lifetime techniques of neurovisualization make it possible to assess current macro- and microstructural changes of the brain [23]. Neural specialization of the visual cortex area responsible for recognition of faces, location and words [24] descends with time; age-dependent changes being, probably, distributed inhomogeneously over the visual cortex [25]. Age-dependent specialization is also observed for the cognitive function of frontal lobes of the hemispheres [26]. Middle brain undergoes alterations particularly exhibiting in the loss of receptors and dopamine transporters in the course of the so-called healthy aging [27]. Signs of a regional [28] and even global tissue atrophy, generally more expressed in the frontal regions [29], exhibit in the brain of healthy adults. To the point, structural changes in the anterior part of hippocamp are insignificant. Attenuation of functional correlations of separate parts of the aging brain spreads with the age in the anterior-posterior direction, namely from forehead to occiput [30].

The total volume of the human brain keeps growing up to approximately 20 years (data [31]), reduction of the volume being remarkably expressed from nearly 30 years [32]. According to the revised data, the total volume of the brain in psychically healthy volunteers steadily declines by 0.22% a year between 20 and 80 years [33], this decline somewhat accelerating at the advanced age. The volume of the brain descends even more in those patients in whom sediments of protein substance amyloid have been found in their lifetime as an illustration of a preclinical phase of Alzheimer's disease (senile dementia): their brain volume is decreased by more than 2.5% as compared to the changes of the brain of their quite healthy peers. In healthy males at the age of between the second and the sixth decades, predominantly diminished is the volume of subcortical cores of the brain and cortical regions of the sensor-locomotive system (cerebellum, thalamus, somatosensor and motor cortex), as well as some regions of the frontal lobes of the so-called prefrontal system [34].

The portion of the so-called grey substance of the brain turned out to decrease in the beginning, followed by the decrease of the white substance [32]. Age-dependent losses of grey and white substances of the brain are most evident in the middle-temporal, parietal and frontal regions. Interestingly, fitness diminishes these losses [35]. Indication for certain controllability of age-dependent alterations of the brain is the fact that age-dependent changes in the grey substance differ in obese people from the norm and not always for the worst at that [36]. Aged macaques also differ from more younger monkeys in the increased reduction of grey substance in the frontal and temporal regions of the brain [37]. However, cognitive abilities of an aged macaque are disturbed more badly due to the alterations of white rather than grey substance: there occurs demyelinization of nerves and a global drop in the volume of white substance of the anterior brain. In the cells of white substance, translation of many proteins is lowered and the content of the antistress protein Klotho is increased [38]. Too advanced aging of a human being is associated with the increase in the volume of ventricles of the brain and cerebrovascular diseases [39].

Practically all the above-mentioned age-dependent changes, diminution of the volume of the brain including, are usually automatically considered as a consequence of the process of aging caused by different reasons, among which accumulation of random breaches under the action of free radicals and other factors is usually named. However, the same pictures of alterations of the brain could be interpreted completely differently, as fulfillment by an organism of a task which is vitally important for it, in other words, its own development, which is impossible without the control over internal time of the organism. In this case, all these changes of the brain prove to be a product of activity of the genetic program, rather than a result of errors.

A causal link between aging and such neurodegenerative diseases as Alzheimer's disease, frontal-temporal dementia and Parkinson's disease still remains unclear [40]. Syntheses of corresponding factors: amyloid beta-protein, proteins tau and alpha-sinuclein are characteristic of these pathologies. It is essential to check whether these syntheses also result from dedifferentiations, now abnormal, developing against the background of a normal process of age-dependent dedifferentiation. However, to begin with, one should make sure in the correctness of the main postulate – the idea of using differentiation by an organism as a normal, programmed process without which either the work of the brain clock or the development in itself are not feasible. Aging is the charge for development.

REFERENCES

1. Anisimov, V.N., *Molecular and Physiological Mechanisms of Aging*, St. Petersburg: Nauka, 2008, 2nd ed., vols. 1, 2.
2. Dilman, V.M., *Development, Aging and Disease. A New Rationale for an Intervention Strategy*, Chur: Harwood Academic Publ., 1994.
3. Olovnikov, A.M., *Ontohen.*, 2007, vol. 38, no. 2, pp. 104–123.
4. Finch, C.E., *Gerontology*, 2009; vol. 55, no. 3, pp. 307–313.
5. Cutler, R.G., *Arch. Gerontol. Geriatr.*, 1991, vol. 12, nos. 2–3, pp. 75–98.
6. Cutler, R.G., *Ann. New York Acad. Sci.,* 1991, vol. 621, pp. 1–28.
7. Zs-Nagy, I., Cutler, R.G., and Semsei, I., *Ann. New York Acad. Sci.,* 1988, vol. 521, pp. 215–225.
8. Whitfield, J., *PLoS Biol*, 2004, vol. 2, no. 12, p. e440.
9. Zhang, G.Q. and Zhang, W., *Ageing. Res. Rev.*, 2009, vol. 8, no. 1, pp. 52–60.
10. Carter, J.B., Banister, E.W., and Blaber, A.P., *Sports Med.,* 2003, vol. 33, pp. 33–46.
11. Hambrecht, R., Walther, C., Mobius-Winkler, S., Gielen, S., Linke, A., Conradi, K., Erbs, S., Kluge, R., Kendziorra, K., Sabri, O., Sick, P., and Schuler, G., *Circulation* , 2004, vol. 109, pp. 1371–1378.
12. Cornelissen, V.A. and Fagard, R.H., *Hypertension*, 2005, vol. 46, pp. 667–675.
13. Hemmati-Brivanlou, A. and Melton, D., *Annu. Rev. Neurosci.,* 1997, vol. 20, pp. 43–60.
14. Kuroda, H., Fuentealba, L., Ikeda, A., Reversade B., and De Robertis, E.M., *Genes Dev.,* 2005, vol. 19, pp. 1022–1027.
15. Zaraĭskiĭ, A.G., *Mol. Biol.*, 2007, vol. 41, no. 2, pp. 200–215.
16. Levine, A.J. and Brivanlou, A.H., *Dev Biol.*, 2007, vol. 308, no. 2, pp. 247–256.
17. Gaulden, J. and Reiter, J.F., *Hum. Mol. Genet.*, 2008, vol. 17, pp. R60–R66.
18. Vujovic, N., Davidson, A.J., and Menaker, M., *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 2008, vol. 295, no. 1, pp. R355–R360.
19. Cailotto, C., Lei, J., van der Vliet, J., van Heijningen, C., van Eden, C.G., Kalsbeek, A., Pévet, P., and Buijs, R.M., *PLoS ONE,* 2009, vol. 4, no. 5, p. e5650.
20. Olovnikov, A., *Ann. New York Acad. Sci.,* 2005, vol. 1057, pp. 112–132.

21. Arendt, T., *Neurobiol. Aging*, 2000, vol. 21, no. 6, pp. 783–796.
22. Zarahn, E., Rakitin, B., Abela, D., Flynn, J., and Stern, Y., *Neurobiol. Aging,* 2007, vol. 28, pp. 784–798.
23. Sullivan, E.V. and Pfefferbaum, A., *Br. J. Radiol.,* 2007, vol. 80, no. 2, pp. S99–S108.
24. Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., and Smith, M.R., *Proc Natl. Acad. Sci. USA*, 2004, vol. 101, no. 35, pp. 13091–13095.
25. Voss, M.W., Erickson, K.I., Chaddock, .L, Prakash, R.S., Colcombe, S.J., Morris, K.S., Doerksen, S., Hu, L., McAuley, E., Kramer, A.F., *Brain Res*., 2008, vol. 1244, pp. 121–131.
26. Rajah, M.N. and D'Esposito, M., *Brain*., 2005, vol. 128, no. 9, pp. 1964–1983.
27. Dreher, J.C., Meyer-Lindenberg, A., Kohn, P., Berman, K.F., *Proc. Natl. Acad. Sci. USA*, 2008, vol. 105, no. 39, pp. 15106–15111.
28. Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., and Acker, J.D., *Cereb. Cortex,* 2005, vol. 15, pp. 1676–1689.
29. Desgranges, B., Kalpouzos, G., and Eustache, F., *Rev. Neurol. (Paris)*, 2008, vol. 164, no. 3, pp. S102–S107.
30. Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., Buckner, R.L., *Neuron*, 2007, vol. 56, no. 5, pp. 924–935.
31. Tumeh, P.C., Alavi, A., Houseni, M., Greenfield, A., Chryssikos, T., Newberg, A., Torigian, D.A., Moonis, G., *Semin. Nucl. Med*., 2007, vol. 37, no. 2, pp. 69–87.
32. Fotenos, A.F., Snyder, A.Z., Girton, L.E., Morris, J.C., and and Buckner, R.L., *Neurology*, 2005, vol. 64, pp. 1032–1039.
33. Fotenos, A.F., Mintun, M.A., Snyder, A.Z., Morris, J.C., and Buckner, R.L., *Arch. Neurol*., 2008, vol. 65, no. 1, pp. 113–120.
34. Pieperhoff, P., Hömke, L., Schneider, F., Habel, U., Shah, N.J., Zilles, K., and Amunts, K., *J. Neurosci*., 2008, vol. 28, no. 4, pp. 828–842.
35. Gordon, B.A., Rykhlevskaia, E.I., Brumback, C.R., Lee, Y., Elavsky, S., Konopack, J.F., McAuley, E., Kramer, A.F., Colcombe, S., Gratton, G., and Fabiani, M., *Psychophysiology*, 2008, vol. 45, no. 5, pp. 825–838.
36. Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., Uchida, S., Kawashima, R., and Fukuda, H., *Obesity (Silver Spring)*, 2008, vol. 16, no. 1, pp. 119–124.
37. Alexander, G.E., Chen, K., Aschenbrenner, M., Merkley, T.L., Santerre-Lemmon, L.E., Shamy, J.L., Skaggs, W.E., Buonocore, M.H., Rapp, P.R., and Barnes, C.A., *J. Neurosci*., 2008, vol. 28, no. 11, pp. 2710–1718.
38. Duce, J.A., Podvin, S., Hollander, W., Kipling, D., Rosene, D.L., and Abraham, C.R., *Glia*, 2008, vol. 56, no. 1, pp. 106–117.
39. Brickman, A.M., Schupf, N., Manly, J.J., Luchsinger, J.A., Andrews, H., Tang, M.X., Reitz, C., Small, S.A., Mayeux, R., DeCarli, C., and Brown, T.R., *Arch. Neurol*., 2008, vol. 65, no. 8, pp. 1053–1061.
40. Yankner, B.A., Lu, T., and Loerch, P., *Annu. Rev. Pathol*., 2008, vol. 3, pp. 41–66.