Биомика, 2016, Том 8, № 3, 239-245

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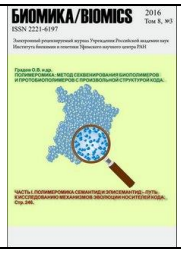

HOUSE FLY AS A MODEL SYSTEM FOR AGING STUDIES

Benkovskaya G.V., Kitaev K.A., Akhmetkireeva T.T., Nikonorov Y.M.

Institute of Biochemistry and Genetics, Ufa Scientific Center of Russian Academy of Sciences, Russia,
bengal2@yandex.ru

Resume

The review aimed to complete the picture of usage the model species of insects in aging studies. The central object of review is *Musca domestica* L., house fly. All data will be engaged to application of house fly in the numerous investigations in accordance some problems, important for gerontology:

1) Investigation of the determinants of intrapopulation polymorphism by complex of fitness indices, first of all the life span.

2) Search for effective biomarkers of senescence.

3) Reveal of physiological and genetic mechanisms of action for pharmacological preparations delaying senescence.

4) Investigations of environmental impact on life span, mostly effects of food quality and availability, light and photoperiodic regime, different stressors.

5) Development of models for analysis of certain genetic systems role in manifestation of age-related human diseases.

KEY WORDS: *Musca domestica* L., house fly, aging, gerontology, fitness, life span

Introduction

Insects belong to the category of model objects recognized in the most complicated and progressive branches of biology: developmental biology, genetics of life span, evolutionary and theoretical biology. Publication of reviews concerning these models expecting always very enthusiastically. So, we are very glad to see the review created by scientific collective from South Korea [Lee et al., 2015]. That article is very actually. Nevertheless, we'd like to complete the picture of usage the model species of insects in aging studies. We assumed that gerontology apart from search and comparison the "genes of longevity" in humans and animals genomes posed the following problems:

1) Investigation of the determinants of intrapopulation polymorphism by complex of fitness indices, first of all the life span.

2) Search for effective biomarkers of senescence.

3) Retrieval of physiological and genetic mechanisms of action for pharmacological preparations delaying senescence.

4) Investigations of environmental impact on life span, mostly effects of food quality and availability, light and photoperiodic regime, different stressors.

5) Development of models for analysis of certain genetic systems role in manifestation of age-related human diseases.

We will try to show the use of insects as model objects for each of listed branch of science, and we advise to avoid references listed in Lee and co-authors review.

Whereas the house fly *Musca domestica* L is our constant object in research of genetic base and realization of the program defines the life span we want to supply the review with our obtained data.

It is the historical fact that house fly took part in the space flight as a model for investigation of space effects toward the fecundity and life span [Lee et al., 1985]. Since the middle of last century house fly became one of the most using objects in the study of insecticide susceptibility [Sohal et al., 1984], resistance development mechanisms and genetic base [Brown, 1958; Tate et al, 1974; Wang et al., 1991; Thompson et al., 1993; Acevedo et al., 2009; Zhang et al., 2010; Li et al., 2013; Kavi et al., 2014]. Rearing facilities, easy

synchronization of developmental stages and opportunity of mass production of insects combine nowadays with results of genome and transcriptome sequence [Liu et al., 2012; Scott et al., 2014]. Small body size and fast generations replacement allow the opportunity to investigate the population aspects of resistance [Gerry, Zhang, 2009; Bell et al., 2010; Kaufman et al., 2010]. The species also became the model of examination of separate fitness components contribution to the integral index named lifespan [Reed, Bryant, 2000, 2004; Benkovskaya, Sokolyanskaya, 2010].

Investigations of intrapopulation polymorphism using fitness evaluation

Life span of *M. domestica* under the laboratory conditions reported in the number of articles [Hucko,1984; Meffert, Regan, 2006]. Results of determination the population indices of fitness for house flies has been published since 2004 [Reed, Bryant, 2004; Meffert, Regan, 2006; Butler et al., 2013; Pastor et al., 2014]. Until this publication [McIntyre, Gooding, 2000] the estimation arrived of maternal age effect toward the survival and development rate of progeny and its competitiveness.

To proof one of central hypothesis of senescence evolution witch is the antagonistic pleiotropy hypothesis [Williams, 1957], house fly populations differed by number of individuals fortunate were chosen [Reed, Bryant, 2000]. In this article the interplay shown between the terms of reproduction and the life span with negative correlation longevity – ability to early reproduction. Authors revealed the drastic reduction of long-livers part in the population during the 5 generations of selection under artificial shortening of reproduction terms. The phenomenon has been explained as the result of natural selection and adaptation to the laboratory conditions.

During the analysis of fecundity and mortality dynamics since the 2007 in the heterogenic house fly strain *Cooper* considered as the standard of susceptibility to the insecticides we detected the intrapopulation groups with essential distinctions in life span as well as in reproduction terms. On the base of this knowledge we selected heterogenic and inbred strains from these groups [Benkovskaya, 2011; Benkovskaya, Mustafina, 2012]. Our successful selection allowing us to suppose that these sort of polymorphic reproductive strategies are the universal occurrence in the animal populations especially distinguish by high population density.

From the point of view of intrapopulation polymorphism the results obtained earlier [Sohal et al., 1986; Reed, Bryant, 2000] seem to be significant evidence of coexistence of the individuals differ by life strategies and life span.

Search of the effective biomarkers of senescence

Lipofuscin accumulation with aging showed in house fly [Sohal, Donato, 1979] as the accelerated senescence associated with higher metabolic rates [Sohal et al., 1981]. Analysis of fatty acids in house fly homogenates indicated an age-associated increase in the ratio of polyunsaturated to saturated fatty acids [Sohal et al., 1985]. The role of genomic transposable elements and genetic instability in life span determination is under investigations for a long time, but for some reason the authors of review (Lee et al., 2015) released of attention the interesting articles with other Diptera species – the house fly [Atkinson et al., 1993; Yoshiyama et al., 2000; Claudianos et al., 2002]. Basing on our previous works we investigated the relation between the changes of transposone *Hermes* DNA copy number during development and shortened or extended life span in *Musca domestica* strains [Nikonorov, Benkovskaya, 2014]. We succeeded more active reproduction of transposone in genome of short-living house flies than in long-living ones. However, the house flies as the object allowing investigating not only such a particular aims in biology of aging.

Reveal of physiological and genetic mechanisms of action of drugs moderating the aging

The inhibitors of enzymes examined for capability of life span extension [Allen et al., 1983; Allen et al., 1984] as well as some mimetics of superoxide dismutase and catalase [Bayne, Sohal, 2002]. A great interest is the antioxidant usage for life span extension in many different species including house fly [Sohal, 1988; Sohal et al., 1989; de Quiroga et al., 1990; Agarwal, Sohal, 1994] and the results support the free radical theory of aging [Cui et al., 1999].

The method of house fly model strains with different life span usage in the assays of physiological activity of the putative geroprotectors as well as stress-protectors warranted itself. During the estimation of ecdysone (20-hydroxyecdysone, 20-HE) effects toward the house flies larvae subjected to heat stress we detected the significant distinction in the response to preliminary applying by 20-HE and following heat stress between the short-living and long-living strains [Benkovskaya et al., 2014].

Investigations of environmental impact on life span, mostly effects of food quality and availability, light and photoperiodic regime, different stressors. The life span and fecundity values of house fly as the environment temperature functions presented in the articles [Buchan, Sohal, 1981; Sohal, Buchan, 1981; Farmer, Sohal., 1987; Fletcher et al., 1990]. House flies have been used as model organisms under investigation of CR (caloric restriction) impact to the life span of adults [Cooper et al., 2004], and this model had interesting feature like use

of males and analysis of their fertility and life span. The next results evidenced that caloric restriction is species-specific [Mockett et al., 2006]. Radiation effect for several generations of house flies was the reduced viability of larvae and decreased life span of adults [Allen, 1985; Khan, Islam, 2006], however radiation-induced life-lengthening in the house fly showed is a consequence of reduced metabolic activity [Allen, Sohal, 1982].

The branch of hormesis effects reveal, i.e. study of mild stress stimulating influence is one of the most important trends in gerontology. The phenomenon of hormesis is one of the fundamental problems requesting their solving to understand the development of resistance to diseases under the environmental factors action, changing of aging rate and life span variability. Experimental evidences obtained in animal models and human populations allowing to assume that hormesis is the effective protecting tool against a lot of diseases including cardiovascular and neurodegenerative ones [Mattson, 2008].

As consistent with modern conception of hormesis origin whatever factor of physical, chemical or biological nature can appear as stimulating agent if it will be applied in very low dose. A number of experiments described in witch minimal doses of ionizing radiation, different toxic components of food, antibiotics or insecticides caused the growth stimulation, increasing of survival rates, reduction of tumor genesis cases, decreasing of affecting by infections, and positive changing of other parameters of viability in different species and in house flies [Allen, Sohal, 1982; Sohal, 1988].

Hormetic effects obtained in laboratory experiments with invertebrate animals showed the stimulation of development rate, extending of adult's life span, enhancement of fecundity and larvae viability [Desneux et al., 2004; Trimble et al., 2004; Cutler et al., 2005; Hackenberger et al., 2008; Benkovskaya, 2011]. Interpretation of those effects is limiting nowadays as phenomenology. The importance and urgency of this branch of investigations are closely related to the perspective of human life quality improving by the way of physical activity modification, rational using of adaptogens and strict regulation of drugs application [Calabrese et al., 2008; Hulse et al., 2008; Cox, 2009; Li, He, 2009]. Some of similar results have been investigated in house fly [Sohal, Donato, 1979; Sohal, Runnels, 1986]. Reveal of molecular mechanisms of hormesis developing now. The complexity of this research related to multilevel system of compensatory reactions obstructing the choice of genes associated with hormesis effects manifestation. It is clear only that the realization of those effects depending on the functions of signal ways [Hulse et al., 2008]. Phosphorylation of tyrosine hydroxyl groups of proteins which is inherent to signal transduction realizing with cytokines might be induced by neurotransmitters such the acetylcholine or gamma-aminobutyric acid (GABA) [Swope et al., 1999]. We assume that this moment could be the main point of understanding the molecular base of toxic hormesis whereas the action of xenobiotics including insecticides targeted toward the synapses and their components (neurotransmitter degradation enzymes, neurotransmitter receptors and membrane channels). The most effective insecticides are the inhibitors of acetylcholine esterase (organophosphate compounds) and detoxifying oxydases, antagonists or agonists of acetylcholine receptors (neonicotinoids, nereistoxins), inhibitors of ionotropic channels of GABA receptors (phenylpyrazoles) and electron-depending membrane channels (pyrethroids) [Thaker, 2002; Buckingham et al., 2005; Khan et al., 2013]. It is very probably that commonality of phosphorylation activation involved cytokines is the key parameter of mechanism of insecticide resistance and cross-resistance (unexpected high resistance to not applied early insecticide) development. An example of cross-resistance to phenylpyrazoles (fipronil) with 430-fold level has been detected in the *M. domestica* strain resistant to γ-hexachlorocyclohexane [Kristensen et al., 2004].

One of the hottest points of prevention and moderation of aging is the role of genotypic peculiarities of individual and group reactions. Our model house fly's strains selected for early and late reproductive efforts conjugated with reduced or extended life span allowed us to obtain some interesting results. We found that short-living individuals is more responsive toward the toxic stress and manifested more extended life span than long-living ones under the hormetic low doses of insecticides [Benkovskaya, 2011; Benkovskaya et al., 2011].

The models for the analysis of genetic base of age-related human diseases

To complete praise fly as an object of research, we must notice that for this species we showed the mutation occurrence manifesting only in "advanced age" in males from *Cooper* strain. The mutation is lethal for females in homozygous state, i.e. it seems to be linked with X-chromosome [Benkovskaya, Mustafina, 2012]. It manifests as the increased fragility of wing and at the glance could be the model of age osteoporosis in humans, but we don' risk making such a conclusion due the different ways of development for human's bones and fly's wing. We believe that the possibility of using the house fly as a model has not yet been exhausted, and it deserves the honor of being included in the list of insect species which could be the objects in aging and longevity investigations.

Acknowledgements

The investigations funded by RFBR 15-04-04801-a.

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КОМНАТНАЯ МУХА КАК МОДЕЛЬНАЯ СИСТЕМА ДЛЯ ГЕРОНТОЛОГИЧЕСКИХ ИССЛЕДОВАНИЙ

Беньковская Г.В., Китаев К.А., Ахметкиреева Т.Т., Никоноров Ю.М.

Федеральное государственное бюджетное учреждение науки
Институт биохимии и генетики Уфимского научного центра Российской академии наук
Россия, Республика Башкортостан, 450054, Уфа, пр. Октября, 71
bengal2@yandex.ru

Резюме

Обзор написан как дополнение к опубликованному коллективом южнокорейских исследователей в 2015 г. обзору: “Insects as a model system for aging studies” [Lee et al., 2015]. Однако в этом обзоре отсутствуют данные, полученные в многочисленных экспериментах с комнатной мухой (*Musca domestica* L.). Мы представляем дополнения к этому обзору, учитывающие, что перед наукой, изучающей проблемы старения и долголетия, стоят следующие задачи:

1) исследования популяционных механизмов, определяющих внутрипопуляционный полиморфизм по комплексу показателей приспособленности, в первую очередь – продолжительности жизни;
2) поиск эффективных биомаркеров старения;
3) выявление физиологических и генетических механизмов действия фармакологических препаратов, замедляющих старение;
4) исследование механизмов внешнесредового влияния на продолжительность жизни, в первую очередь – влияния качества и доступности пищи, воздействия света, фотопериодического режима, стрессов различного характера;
5) создание моделей для анализа роли отдельных генетических систем в проявлении и развитии возрастзависимых заболеваний человека.

Ключевые слова: *Musca domestica* L., комнатная муха, старение, геронтология, приспособленность, продолжительность жизни