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Article

Transgenerational epigenetic compensation and natural selection

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The term "epigenetics" defines all meiotically and mitotically heritable changes in gene expression that are not coded in the DNA sequence itself. Transgenerational epigenetic compensation was discovered in the untreated progeny of drug-treated males (rats and mice) as the opposite quantitative phenotypic changes. In natural populations, the hereditary basis of transgenerational epigenetic compensation develops mainly in homozygous mutant males, but it does not affect their phenotype. In their descendants, being in an independent locus, this heritable epigenetic compensation increases fitness and lifespan of homozygous mutant females and decreases lifespan of wild-type females, starting from F_2. Here we show that this transgenerational epigenetic compensation is a guiding agent of natural selection. Natural selection is not a directing or driving force of evolution anymore. Natural selection needs some guidance. Transgenerational epigenetic compensation can initiate speciation through segregation of mutants and wild-types and/or it can change the selection coefficient of a given mutation.

Transgenerational epigenetic compensation was discovered in the experiments with paternal drug treatment[1-4]. Prenatal, neonatal and adolescent treatment of males leads to observation of inversed phenotype in their F_1, F_2 and F_3 untreated descendants, at least in some traits[1-10].

In this article we will use these experiments with parental drug treatment in order to achieve better understanding of the results of natural selection, observed in the population of laboratory mice, consisted of wild-type, heterozygous and mutant *Per2*^{Brdm1} animals, lived under semi-natural conditions in outdoor pens (**Fig. 1**) during two years[1,11].

Four pens contained four independent populations of mice, at the beginning with 250 animals (in total), Mendelian distribution of genotypes 1:2:1 and equal numbers of females and males. Food and water were supplied by humans and both were constantly placed in two locations inside each pen. Each animal was injected with transponder (Trovan ID100). A square antenna was placed in a horizontal plane around a combination of a food pod with a water bottle, in order to register animals' visits to estimate their drinking and feeding behaviour. All mice were live trapped twice a year and all new mice (born inside pens) were genotyped and received transponders. The lifespan of each mouse was estimated using its visits of food-water places. Food and water consumption could not be analyzed separately, because each of two places contained both food and water.

Pens were protected from terrestrial predators by an electric fence on the top of slate walls. However all local aerial predators had free access to mouse populations. Aerial predators were represented by a tawny owl (*Strix aluco*) [it has been seen many times], a short-eared owl (*Asio flammeus*) [it was possible to hear it sometimes], and other aerial predators could not be excluded. Trovan transponders, injected into mice previously, were found several times in mouse residues in owl pellets, left by birds outside the pens, and this is a direct confirmation of owls' feeding behaviour. All attempts to find transponders from the missing mice inside the pens have brought negative results (practically impossible to find), but the explanation can be different, for example, a transponder can not be read, if it has gone into the wet soil.

Figure 1 | Semi-natural environment for investigation of natural selection. Wild-type, heterozygous and mutant *Per2*^{Brdm1} mice were breeding at will during two years in four pens 20 × 20 m each, each with two shelters[11]. At the beginning of experiment there were 250 mice in total with Mendelian distribution of genotypes 1:2:1 and equal presence of females and males. Tawny owls (*Strix aluco*) were hunting for mice all the year round.

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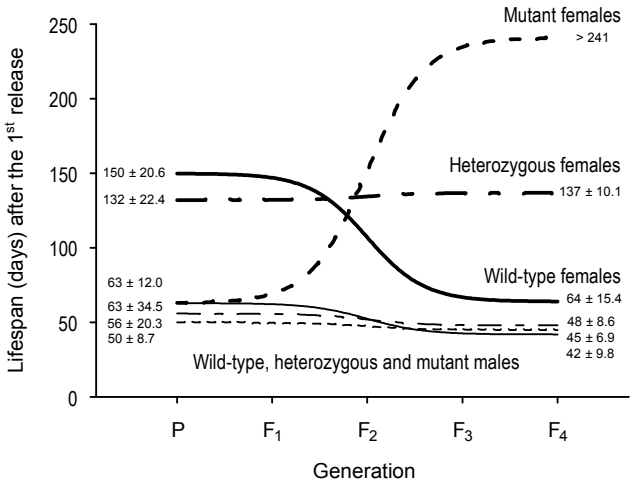

Figure 2 | Lifespan of *Per2*^{Brdm1} mice in pens after the first release[1,11]. All mice were taken out of pens (**Fig. 1**) and released back twice a year. New ones (born during previous half-year) were genotyped. Transponders, bearing individual numbers, were injected into all mice. Antennae, placed around feeding places, were used for registration of behaviour and estimation of lifespan. Lifespan, calculated from the day of 1st release, is shown here. Note an unexpected increase of lifespan in mutant females and simultaneous decrease of lifespan in wild-type females. Median ± SE.

We assume that the presence of Per2 mutant gene in a homozygous state and under harsh semi-natural conditions (*e.g.* temperature conditions) produces the same kind of transgenerational epigenetic compensation as paternal drug treatment (prenatal, neonatal or adolescent).

We know that so different parental treatments as prenatal (E8-E14) vinclozolin treatment and adolescent (P30-P50) maternal morphine treatment tend to produce common gender-specific phenotype in the F_1 and F_2 descendants, observed in the elevated plus-maze. Namely, females, but not males, of generations F_1 and F_2, show decreased time spent on open arms of elevated plus-maze (**Supplementary Fig. 2**). This is an indicator of their increased caution. Pharmacologists usually say that this is an increased "anxiety". However all observations of wild-caught voles, like bank vole (*Clethrionomys glareolus*) and root vole (*Microtus oeconomus*), in laboratory conditions, demonstrate that it is not a correct interpretation of animal behaviour. Wild-caught voles, those do not move at all in many laboratory tasks (due to so-called "freezing" behaviour), demonstrate in fact an increased "caution", but not "anxiety". It is so because the same wild-caught voles outperform any laboratory mouse strain and any laboratory F_1 hybrid, like B6D2F1, in the Morris water maze task[12]. Wild-caught voles are not more "anxious", but they are more "normal" creatures than any laboratory mouse stock.

It is possible that transgenerational epigenetic compensation, being genotype-specific, nevertheless activates some universal mechanisms, those were useful in wild nature, but useless in laboratory conditions during previous more than 100 years. The observed induction of increased caution in females (F_1 and F_2) may have the same level of generalization as general adaptation syndrome, described by Hans Selye[13].

In the **Fig. 2** we can see increased lifespan in the homozygous mutant females (starting from F_2) and decreased lifespan in the wild-type females. Thus, given semi-natural external conditions induced stress in homozygous mutants that resulted in formation of transgenerational epigenetic compensation, expressed in their descendants as increased caution in homozygous mutant females and as disrupted caution in wild-type females. Then, tawny owls have selected the least cautious mice as a source of food.

There is a belief that the main source of mouse losses in these pens is a male-male competition, during which male mice fight with each other up to death. This belief is only partially correct, because, indeed, a fighting mouse is an easy prey for an owl. Note, however, that both strong and weak fighters can be equally good food for an avian predator (an owl has very good hearing abilities and very good vision). The only way to escape from the owl is to avoid male-male fighting in general, and it seems that our laboratory male mice in these pens could not do this. That is why we have very interesting genotype-specific profile of lifespan in females and only low and genotype-non-specific lifespan in males (**Fig. 2**). Note also, that the most intense genotype-specific selection among females took place during summer, when snow was absent and owls could hunt with high efficacy (Supplementary Fig. 3[2]).

Why we are so sure that we are dealing with epigenetic inheritance[14-17] and transgenerational epigenetic compensation, but not with some other factor? Let's look now at the experiments with parental drug treatment and at very-very interesting observations on guinea pigs. We shall move through our data in the following order: 1) mice, 2) rats, 3) guinea pigs.

Neonatal (P0-P11) thyroxine treatment of inbred DBA/2J mice has led to improved two-way avoidance performance in drug-treated animals and to impaired two-way avoidance performance in the F_1 male and female descendants of thyroxine-treated males. In the F_2 animals the impaired two-way avoidance was observed only in females. In the F_3 generation the impaired two-way avoidance was observed only in males of outcross subline (**Fig. 3**).

Other significantly modified traits in all these F_1-F_3 animals, namely decreased birthweight and decreased intra- and infrapyramidal hippocampal mossy fiber projections (shortly: brain morphology), were not correlated with each other and with two-way avoidance performance (no individual correlations)! It was easy to suppose that several independent loci can be involved, but in this case it remains a mystery how all these 3 traits occurred to be recollected together in the F_3-outcross males (Table 1[1] and Supplementary Fig. 2[1]). Only guinea pigs were able to provide insight (several years later). Note that the presence of impaired phenotype in the F_1 and F_3-F_4 males, but not in the F_2 males, was described with respect to humans more than 3000 years ago (see **Supplementary Table 2**).

Adolescent (P42-P79) chronic morphine treatment of male outbred Wistar rats has led to decreased analgesic effect of standard dose of morphine (10 mg/kg) in these treated animals and to increased analgesic effect of standard dose of morphine in their F_1 male descendants. All descendants were tested twice with time interval 24 hours, in tail-withdrawal test (**Fig. 4**). In the F_1 generation, during the first day, F_1 males have shown enhanced analgesic effect, but F_1 females have shown normal phenotype. During the second day all F_1 males and F_1 females have shown normal phenotype. Very high speed, at which abnormal phenotype of F_1 males was converted into normal one, is amazing.

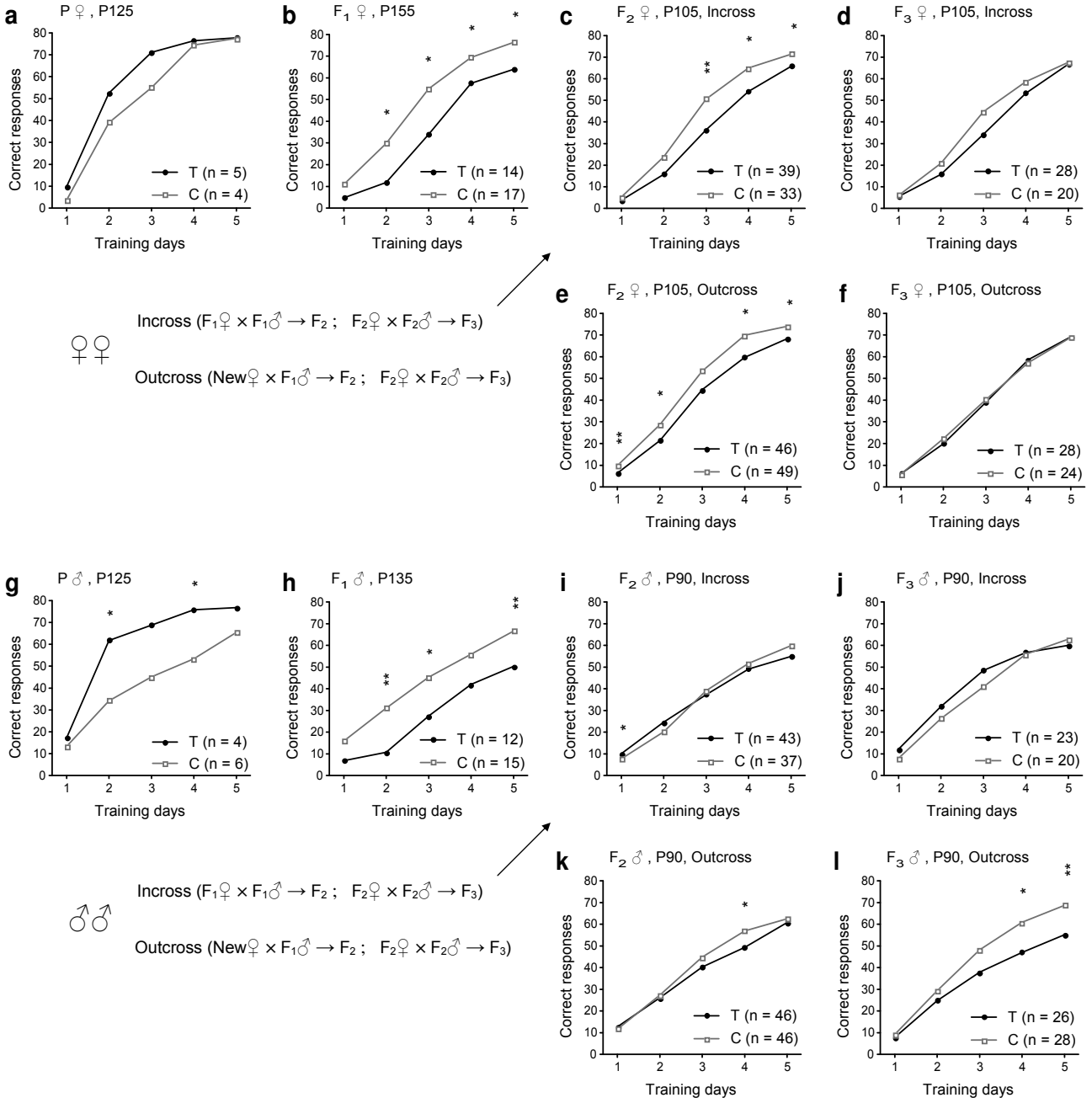

Figure 3 | Two-way avoidance in the thyroxine-treated DBA/2J mice and in the F_1-F_3 progeny of thyroxine-treated males. Note improved performance in the neonatally (P0-P11) thyroxine-treated males (**g**), but decreased performance in their descendants (**b**-**c**,**e**,**h**,**l**). Both Incross and Outcross F_2 females have decreased performance (**c**,**e**). In males the decreased performance was observed in the F_1 (**h**) and in the F_3-outcross (**l**), but not in the F_2 (**i**,**k**). Torah, the Second Commandment (Shemot 20:3-6; Devarim 5:7-10), teaches us that the misbehaviour of fathers (P) leads to problems in their sons (F_1) and problems in the third (F_3) and the fourth (F_4) generations. The second generation (F_2) is not in the original text (**Supplementary Table 2**). T – descendants of treated males, C – control. P125 – postnatal day 125. Asterisk, $P < 0.05$; double asterisk, $P < 0.01$. Mann-Whitney U test. Mean.

In the F_2 generation the vast majority of females have shown enhanced analgesic effect during the first day, but all of them have shown normal phenotype during the second day. In the F_2 generation males the situation is very complex (**Fig. 4**). First, 1/4 (20 males from 80) have shown enhanced analgesic effect during the first day. Second, 1/16 (5 males from 80) have shown enhanced analgesic effect during the second day only – it means that they had normal phenotype during day 1 and abnormal one during day 2. Third, another 1/16 (5 males from 80) have shown enhanced analgesic effect during both day 1 and day 2. Note that one or two such males were present in the F_1 generation, but the total number of experimental males in the F_1 (29 males) was not sufficient to assess whether this is a random mistake or real phenomenon. Note the absence of such strange animals in the control groups. Anyway, the change from "abnormal" to "normal" in the majority of animals and simultaneous change

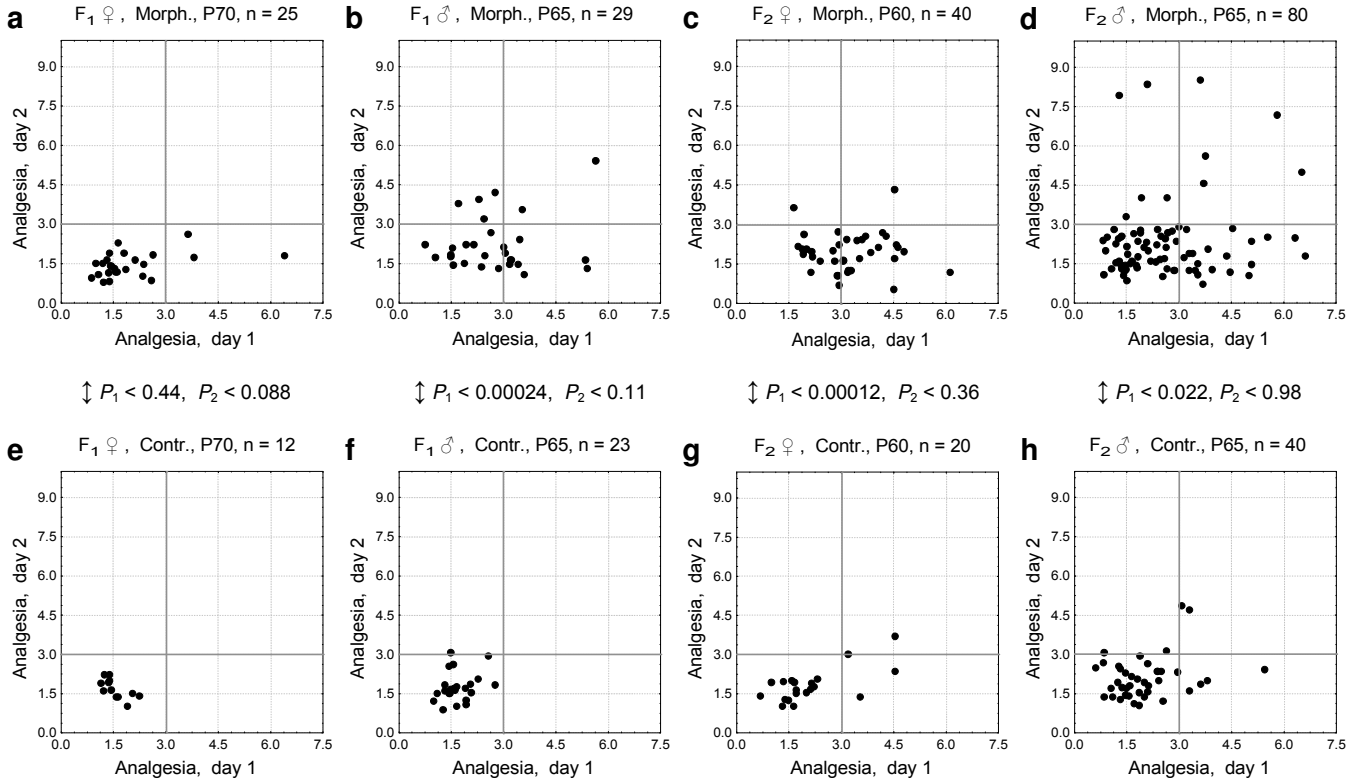

Figure 4 | Tail-withdrawal test in the F_1 & F_2 descendants of morphine-treated male Wistar rats. Each animal was tested twice (days 1 & 2) with the same dose of morphine 10 mg/kg. Morphine was administered i.p. each day after the first measurement of tail-withdrawal latency (baseline latency). Abscissa (day 1) and ordinate (day 2) of each dot (animal) show the ratio of tail-withdrawal latency, measured 30 min after 10 mg/kg morphine injection, to baseline latency. The effect is dominant in F_1 males (**b**,**f**) and F_2 females (**c**,**g**) (day 1), but recessive in F_1 females (**a**,**e**) and F_2 males (**d**,**h**; 1st day – ¼ has effect; 2nd day – 1/8, including 1/16 during both days and 1/16 during exclusively day 2). Heritable changes in two independent loci are sufficient to explain this pattern. P_1 & P_2 – statistical significance between experimental and control groups during day 1 & day 2, respectively. Mann-Whitney U test.

from "normal" to "abnormal" in few ones, during the same 24 hours and treatment procedure, does not have self-evident physiological explanation. At least, it is very unusual, when the second standard dose of morphine produces greater analgesic effect than the first one. Observations on guinea pigs have provided some clue later, more than 10 years after the end of this experiment with rats and morphine.

Once a female animal with unusual phenotype was born among our short-haired multicoloured guinea pigs (*Cavia porcellus*). This female was born in a litter of four (2 females and 2 males; all others with standard phenotype), obtained from multi-coloured female from Elm Hill Labs (Chelmsford, MA; www.elmhilllabs.com) and short-haired multicoloured male with contrasting whorl on its head (so-called "American crested"), obtained from an independent source (hybrid dysgenesis is possible). Video record, taken at postnatal day 1, is available: www.evolocus.com/Video/GuineaPigs2011-09-17.MOV . This video is not absolutely necessary for further understanding of our article, but an experienced observer can extract a lot of non-trivial information from it (all animals, including both parents, are shown). Day of birth is counted as P0 and it is 2011-09-16. At birth, at P1 and during the first several weeks this animal was not recognized as "unusual", despite post-hoc analysis of above-mentioned video record has revealed that this animal was able to demonstrate slightly increased activity already at P1, because it was called "the hard one to get". During her adolescence this female had increased locomotor activity, *e.g.* it was able to move up and down in a 3-level chinchilla's "Super Pet®" cage, using its plastic ramps and being self-motivated. This behaviour was never observed in any other laboratory guinea pig and it is more typical for animals like rats. This female was behaviourally active, but the most interesting its feature was the following: being behaviourally active, it had very low water consumption. Its water consumption, as soon as it was detected, was 3-4-fold lower than daily water consumption of any other guinea pig.

This female with low water consumption and high behavioural activity was crossed with normal male and two pups were obtained in a litter: one was found dead at P0, but another one was considered "normal" until its daily water consumption was measured. This F_1 pup was a female. Water consumption of her mother remained lower than norm during pregnancy and lactation. However water consumption of this F_1 female occurred to be 3-4-fold higher than water consumption of any control animal (**Fig. 5** and **Supplementary Fig. 3**). Increased water consumption was associated with increased urination, occurring in a different location inside the cage. This increased water consumption was stable, it was observed during several months, and it produced an impression that it will be so forever.

On the other hand, it would be interesting to see how this increased water consumption will be normalized and we were

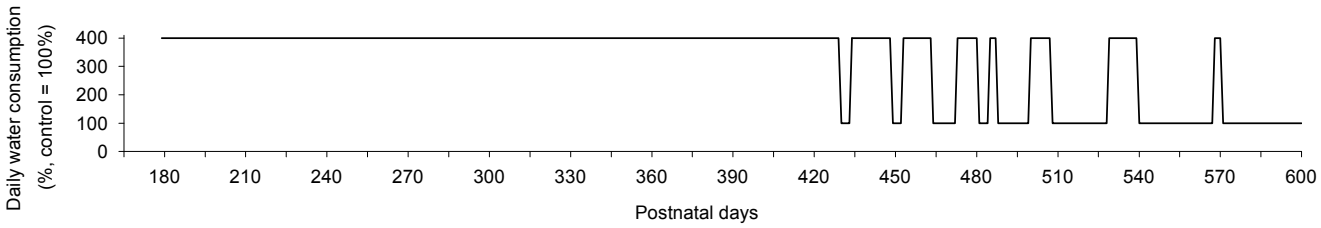

Figure 5 | Water consumption of one female guinea pig, obtained from female with unusually low water consumption (schema). In our heterogeneous outbred stock of guinea pigs (*Cavia porcellus*), one female was obtained that had unusually low (20-25%) water consumption during her adulthood. Contrary to this female, her F_1 female descendant (shown) had enormously increased (300-400%) water consumption (P180-P430). Later (P430+), some periods of normal water consumption appeared, without any intermediate state between "high" and "low" states. There is no physiological reason for the absence of gradual regulation here and, thus, "all-or-none" switch is an intrinsic feature of transgenerational epigenetic compensation.

expecting some smooth curve. We never obtained such smooth curve. At some time point water consumption was normalized abruptly – it has jumped down to the normal level in 24 hours! Water consumption was normal during few days and then it has jumped up as fast as it was jumping down previously **(Fig. 5**). There were only two stable states of this process: normal and high. Any intermediate possibility was absent.

Water consumption had a tendency to switch from "high" to "normal" each time when fresh high quality grass was becoming available on a regular basis (a guinea pig prefers the same species of grass as a white-tailed deer (*Odocoileus virginianus*) in the New York area). And water consumption had a tendency to switch from "normal" to "high" each time when grass quality was going down and, in addition, each time when bedding material in the cage was changed from old and "dirty" to new and "fresh" (we use pine bedding "PetsPick™"). May be, behavioural stress from this change together with temporal unavailability of feces, those are an important source of nutrients for a guinea pig, are the main factors for switching from normal to very high water consumption. It seems that stress of any kind can switch water consumption in this animal from normal level to very high one (**Supplementary Fig. 3**). Note that in normal animals, in both males and females, slight stress leads to slight decrease in water consumption, whereas in this female the same slight stress leads to disproportional increase.

High and abruptly switching water consumption, observed in this female, obtained from female with low water consumption and normal male, indicates that the phenotypic expression of transgenerational epigenetic compensation is not only gender-dependent (see our previous article "Transgeneraional epigenetic compensation and sexual dimorphism"[3]), but it is also stress-dependent, and it is stress-dependent in a very sharp manner in temporal dimension. For such cases Trofim D. Lysenko has introduced the term "unstable, destabilized, heredity" (p. 298[18]).

We have seen very sharp temporal response, very fast switching of transgenerational epigenetic compensation from "off" to "on" state and *vice versa*, and possibility to be "on" during different periods of ontogenesis. It means that, most likely, we do not have here something distributed among many-many independent loci, but we probably have only one change in one locus. Namely, one previously absolutely dormant gene has become transcriptionally active (that is why it is dominant), but the switching of its transcription between "off" and "on" states is heavily gender-dependent (probably, through the effects of sex hormones) and, in addition, the above-mentioned switching is heavily stress-dependent (probably, through the effects of stress hormones). Dormant genetic locus, being brought out of dormancy, becomes open for further regulation of its expression, but not for unconditional presence of its product in the organism.

The idea about dormant genes belongs to Wilhelm Jürgen Heinrich Harms, known as J.W. Harms, and it was proposed by him in 1929[19,20]. At that time it was absolutely unexpected that a re-opened dormant gene can demonstrate so sharp temporal regulation of its expression immediately, during lifespan of a single animal. Similar switching of gene activity, but between generations, was shown for genes *fused* and *star* by Dmitry K. Belyaev and co-authors in 1981[21,22]. It seems that even using 1-bit regulation of the level of expression ("on" or "off"), but having non-trivial temporal structure of this expression during ontogenesis, an organism can achieve a variety of phenotypic results, including a variety of morphological ones, uncorrelated with each other (**Supplementary Fig. 6**).

Dormant genes, being brought out of dormancy by transgenerational epigenetic compensation, are changing the evolutionary landscape faster than natural selection does.

Methods

***Per2*^{Brdm1} mouse experiment.** Mutant *Per2*^{Brdm1} allele is known to compromise circadian organization and entrainment and to cause multiple physiological disturbances[23]. Male and female animals (1/4 homozygous mutants, 2/4 heterozygous and 1/4 wild-types; 250 mice in total; mixed background of C57BL/6 and 129SvEvBrd) were individually numbered by means of injected transponders, which can be read by an external antenna, and were placed in 4 independent (20 × 20 m each) open outdoor pens, isolated from each other and terrestrial predators by slate walls (1 m high and sunk 50 cm into the soil, covered by zinc-plated iron on the top)[11]. Each pen had 2 wooden roofed shelters (3 × 2 m each, 70 cm depth, filled with hay, straw and branches). Inside each pen, but outside of both shelters, there were two feeding places (food + water), each equipped with antenna, which allowed monitoring of animal visits during 2 years in a non-stop manner. The end of feeder visits provided precise information about lifespan of each animal. All animals were live trapped and new (born in field) animals were genotyped and injected with transponders twice a year.

Animals were released into the shelters at the field station Chisti Les (Clear Forest), Bubonizi (Pozhnia, Tvier Region, Western Russia, 56°44'7.99"N; 31°31'34.44"E) on May 21, 2005, at the age of 76 ± 5.4 days (mean ± SD).

Thyroxine experiment. DBA/2J mice (P) were treated as neonates during the first 12 days (P0-P11) by subcutaneous injection of a daily dose of 2 μg L-thyroxine dissolved in 0.05 ml 0.9% NaCl made alkaline (pH 9.0) by adding a few drops of NaOH. Solution was prepared once 24 hr before the first administration (kept at +4°C). All pups in a given litter received the same treatment (between 17:00 and 18:00) and were kept in an original litter under their native DBA/2J mother (110-day-old at breeding). Control animals were left undisturbed. Reversed day-light cycle was used (8:00-20:00 – dark, 20:00-8:00 – light). Adult mice were housed individually.

To have F_1, each DBA/2J male (P) at the age of 60 days was housed with 2 or 3 nulliparous 90-day-old naive DBA/2J females during 7 days. At birth pups were numbered and placed under primiparous NMRI foster-mothers to have 4 experimental and 4 control pups in each foster litter. To have F_2-incross, F_1 males at the age of 200 days were housed with F_1 females (2 females × 1 male, incross, but without inbreeding). To have F_2-outcross, F_1 males at the age of 230 days were housed with naive DBA/2J nulliparous 110-day-old females (2 females × 1 male). To have F_3, F_2-incross males at the age of 180 days were housed with F_2-incross females and F_2-outcross males at the age of 150 days were housed with F_2-outcross females (1 female × 1 male), simultaneously. NMRI foster-mothers were used in F_1, F_2 and F_3.

P, F_1, F_2 and F_3 mice were tested in two-way avoidance task ("Mouse Shuttle Box", Campden Instruments Ltd., UK)[24] at the age 90-155 days. Training: 5 days, 80 trials daily. The condition stimulus was light (5 sec), the negative reinforcement was foot-shock 0.15 mA (10 sec), which was supplied together with additional 10 sec of light, but both could be terminated by escaping to another compartment. This termination had a 0.8 sec delay – in order to have optimal DBA/2J training. Inter-trial interval: 5-15 sec.

Morphine experiment. Male Wistar rats, 42-day-old initially (P42; body weight 197 ± 20 g, mean ± SD), housed in groups 5-10 under normal day-light cycle, were injected intraperitoneally (i.p.) with morphine during 38 days. The first 7 days – twice daily (morning-evening, 8 hr between, mg/kg): 5-10, 15-15, 20-20, 25-30, 35-40, 45-50, 55-60 (10 mg/ml in 0.9% NaCl). Next day – 60 mg/kg in the morning and 6 hr later – injected i.p. with 2 mg/kg of naloxone (2 mg/ml) to induce early in life naloxone-precipitated morphine withdrawal. Next day – injected with morphine 60 mg/kg. The rest 29 days – injected with morphine 60 mg/kg twice daily Monday-Friday, and 60 mg/kg daily Saturday-Sunday. Control males were left undisturbed.

During the last 5 days of morphine treatment P males were housed individually with drug-naive 75-day-old nulliparous Wistar females. To have F_1-2 (F_1, second brood), P males at the age of 175 days (*i.e.* 95 days of withdrawal) were housed individually with familiar females. To have F_2, F_1-2 males at the age of 85 days were bred individually with F_1-2 females (incross, but without inbreeding).

P, F_1, F_2 animals were tested in tail-withdrawal test at the age of 60-95 days. The distal part of the tail of a lightly restrained animal was dipped into circulating water thermostatically controlled at 56 ± 0.2°C. Latency to respond to the heat stimulus, by a vigorous flexion of the tail, was measured to the nearest 0.1 sec, cutoff latency – 15 sec. The test was done once before i.p. 10 mg/kg morphine injection (baseline latency) and 15, 30, 45, 60 and 90 min after. This testing was repeated 24 hours later to assess acute tolerance.

Guinea pig experiment. Outbred short-haired multicoloured guinea pigs (*Cavia porcellus*) were used. Multicoloured female was obtained from Elm Hill Labs (7 Kidder Rd., Chelmsford, MA 01824; www.elmhilllabs.com) and it was bred with short-haired multicoloured male with contrasting whorl on its head (so-called "American crested"), obtained from Petland Discounts #17 (439 Tarrytown Rd., White Plains, NY 10607). Two females and two males were born 2011-09-16. One female from this litter demonstrated low water consumption being an adult.

We had cages "RB100" (100 × 54 × 44.5 cm) and Super Pet "My First Home Chinchilla Cage Kit" (76 × 45.5 × 76.5 cm; a 2-shelf cage, each shelf 44 × 25 cm, placed at 26 cm and 44 cm from the floor in the opposite parts and connected consequently by two ramps 42.5 × 12 cm each). Bottles 500 ml from LM Animal Farms were refilled daily and their weight was measured at 11:00 PM using electronic scale KS/B-2000 (Max: 2000 g, d = 0.1 g). Pine bedding "PetsPick" and bowls with standard guinea pig food were always in cages. Fresh grass was supplied daily, when available. During snow periods animals received "Kaytee Timothy Hay Ultra" and apples. We kept 1-2 adult animals per cage under normal day-light cycle. Each adult animal had its own plastic house "Super Pet Big Igloo" (D = 24.5 cm (lower), d = 19 cm (upper), H = 16 cm (ext.), h = 13.5 cm (int.); entrance tunnel: L = 6 cm, H = 11.5 cm, W = 10 cm).

Above-mentioned female with low adult water consumption was crossed with normal male (her littermate), and from this cross a female with high adult water consumption was obtained, born 2012-03-09.

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