Hormesis does not make sense except in the light of TOR-driven aging.

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Source
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Abstract
Weak stresses (including weak oxidative stress, cytostatic agents, heat shock, hypoxia, calorie restriction) may extend lifespan. Known as hormesis, this is the most controversial notion in gerontology. For one, it is believed that aging is caused by accumulation of molecular damage. If so, hormetic stresses (by causing damage) must shorten lifespan. To solve the paradox, it was suggested that, by activating repair, hormetic stresses eventually decrease damage. Similarly, Baron Munchausen escaped from a swamp by pulling himself up by his own hair. Instead, I discuss that aging is not caused by accumulation of molecular damage. Although molecular damage accumulates, organisms do not live long enough to age from this accumulation. Instead, aging is driven by overactivated signal-transduction pathways including the TOR (Target of Rapamycin) pathway. A diverse group of hormetic conditions can be divided into two groups. “Hormesis A” inhibits the TOR pathway. “Hormesis B” increases aging-tolerance, defined as the ability to survive catastrophic complications of aging. Hormesis A includes calorie restriction, resveratrol, rapamycin, p53-inducing agents and, in part, physical exercise, heat shock and hypoxia. Hormesis B includes ischemic preconditioning and, in part, physical exercise, heat shock, hypoxia and medical interventions.

Mitochondria and Aging

Mitochondrial turnover and aging of long-lived postmitotic cells: the mitochondrial-lysosomal axis theory of aging.

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Source
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Abstract
It is now generally accepted that aging and eventual death of multicellular organisms is to a large extent related to macromolecular damage by mitochondrially produced reactive oxygen species, mostly affecting long-lived postmitotic cells, such as neurons and cardiac myocytes. These cells are rarely or not at all replaced during life and can be as old as the whole organism. The inherent inability of autophagy and other cellular-degradation mechanisms to remove damaged structures completely results in the progressive accumulation of garbage, including cytosolic protein aggregates, defective mitochondria, and lipofuscin, an intralysosomal indigestible material. In this review, we stress the importance of crosstalk between mitochondria and lysosomes in aging. The slow accumulation of lipofuscin within lysosomes seems to depress autophagy, resulting in reduced turnover of effective mitochondria. The latter not only are functionally deficient but also produce increased amounts of reactive oxygen species, prompting lipofuscinogenesis. Moreover, defective and enlarged mitochondria are poorly autophagocytosed and constitute a growing population of badly functioning organelles that do not fuse and exchange their contents with normal mitochondria. The progress of these changes seems to result in enhanced oxidative stress, decreased ATP production, and collapse of the cellular catabolic machinery, which eventually is incompatible with survival.

Men smarter than women

Sex differences in brain volume are related to specific skills, not to general intelligence (via Charles Murray via the Chateau):

Abstract
It has been proposed that males would show higher mean scores than females in general intelligence (g) because (1) men have, on average, larger brains than women, and (2) brain volume correlates with g. Here we report a failure to support the conclusion derived from these premises. High resolution MRIs were acquired in a sample of one hundred healthy young participants for estimating total, gray, and white matter volumes. Participants also completed an
intelligence battery – comprising tests measuring abstract, verbal, and spatial abilities – that allowed the extraction of $g$ scores. Results showed consistent relations between sex differences in brain volumes and non-$g$ spatial and verbal skills but not for $g$.

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Fast Food Addictive?

Is Fast Food Addictive?

Garber AK, Lustig RH.

Source

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Abstract

Studies of food addiction have focused on highly palatable foods. While fast food falls squarely into that category, it has several other attributes that may increase its salience. This review examines whether the nutrients present in fast food, the characteristics of fast food consumers or the presentation and packaging of fast food may encourage substance dependence, as defined by the American Psychiatric Association. The majority of fast food meals are accompanied by a soda, which increases the sugar content 10-fold. Sugar addiction, including tolerance and withdrawal, has been demonstrated in rodents but not humans. Caffeine is a “model” substance of dependence; coffee drinks are driving the recent increase in fast food sales. Limited evidence suggests that the high fat and salt content of fast food may increase addictive potential. Fast food restaurants cluster in poorer neighborhoods and obese adults eat more fast food than those who are normal weight. Obesity is characterized by resistance to insulin, leptin and other hormonal signals that would normally control appetite and limit reward. Neuroimaging studies in obese subjects provide evidence of altered reward and tolerance. Once obese, many individuals meet criteria for psychological dependence. Stress and dieting may sensitize an individual to reward. Finally, fast food advertisements, restaurants and menus all provide environmental cues that may trigger addictive overeating. While the concept of fast food addiction remains to be proven, these findings support the role of fast food as a potentially addictive substance that is most likely to create dependence in vulnerable populations.

“Vulnerable populations” = those with low future time orientation? I tend to
think so. Conscientious people defer gratification and therefore don’t patronize fast food outlets, or do so with great moderation. there’s no mystery that fast food can make one fat, but some people care, others don’t.

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**Keep that testosterone flag flying: don’t gain body fat**

*Body fatness and sex steroid hormone concentrations in US men: results from NHANES III*

**Abstract**

**Objective**

Obesity is associated with a variety of chronic diseases, including cancer, which may partly be explained by its influence on sex steroid hormone concentrations. Whether different measures of obesity, i.e., body mass index (BMI), waist circumference, and percent body fat were differentially associated with circulating levels of sex steroid hormones was examined in 1,265 men, aged 20–90+ years old, attending the morning examination session of the Third National Health and Nutrition Examination Survey (NHANES III).

**Materials and methods**

Serum hormones were measured by immunoassay. Weight, height, and waist circumference were measured by trained staff. Percent body fat was estimated from bioelectrical impedance. Multivariate linear regression was used to estimate associations between body fatness measures and hormone levels.

**Results**

Total and free testosterone and sex hormone binding globulin concentrations decreased, whereas total and free estradiol increased with increasing BMI, waist circumference, and percent body fat (all p trend < 0.05). The magnitude of change in these hormones was similar for a one-quartile increase in each body fatness measure.

**Conclusion**

Measured BMI, waist circumference, and percent body fat led to similar inferences about their association with hormone levels in men.
Training in the fasted state improves glucose tolerance

Training in the fasted state improves glucose tolerance during fat-rich diet

Abstract

A fat-rich energy-dense diet is an important cause of insulin resistance. Stimulation of fat turnover in muscle cells during dietary fat challenge may contribute to maintenance of insulin sensitivity. Exercise in the fasted state markedly stimulates energy provision via fat oxidation. Therefore, we investigated whether exercise training in the fasted state is more potent than exercise in the fed state to rescue whole-body glucose tolerance and insulin sensitivity during a period of hyper-caloric fat-rich diet. [...] This study for the first time shows that fasted training is more potent than fed training to facilitate adaptations in muscle and to improve whole-body glucose tolerance and insulin sensitivity during hyper-caloric fat-rich diet.

Inflammation in depression: is adiposity a cause?

Inflammation in depression: is adiposity a cause?

Abstract

Mounting evidence indicates that inflammation may play a significant role in the development of depression. Patients with depression exhibit increased inflammatory markers, and administration of cytokines and other inflammatory stimuli can induce depressive symptoms. Mechanisms by which cytokines access the brain and influence neurotransmitter systems relevant to depression have also been described, as have preliminary findings indicating that antagonizing inflammatory pathways may improve depressive symptoms. One primary source of inflammation in depression appears to be adiposity. Adipose tissue is a rich source of inflammatory factors including adipokines, chemokines, and
cytokines, and a bidirectional relationship between adiposity and depression has been revealed. Adiposity is associated with the development of depression, and depression is associated with adiposity, reflecting a potential vicious cycle between these two conditions which appears to center around inflammation. Treatments targeting this vicious cycle may be especially relevant for the treatment and prevention of depression as well as its multiple comorbid disorders such as cardiovascular disease, diabetes, and cancer, all of which have also been associated with both depression and inflammation.

In other words, one way to avoid depression is to stay slender.

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**Epigenetic oxidative redox shift (EORS) theory of aging unifies the free radical and insulin signaling theories.**

Brewer GJ.  
Source  
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Abstract  
Harman’s free radical theory of aging posits that oxidized macromolecules accumulate with age to decrease function and shorten life-span. However, nutritional and genetic interventions to boost anti-oxidants have generally failed to increase life-span. Furthermore, the free radical theory fails to explain why exercise causes higher levels of oxyradical damage, but generally promotes healthy aging. The separate anti-aging paradigms of genetic or caloric reductions in the insulin signaling pathway is thought to slow the rate of living to reduce metabolism, but recent evidence from Westbrook and Bartke suggests metabolism actually increases in long-lived mice. To unify these disparate theories and data, here, we propose the epigenetic oxidative redox shift (EORS) theory of aging. According to EORS, sedentary behavior associated with age
triggers an oxidized redox shift and impaired mitochondrial function. In order to maintain resting energy levels, aerobic glycolysis is upregulated by redox-sensitive transcription factors. As emphasized by DeGrey, the need to supply NAD(+) for glucose oxidation and maintain redox balance with impaired mitochondrial NADH oxidoreductase requires the upregulation of other oxidoreductases. In contrast to the 2% inefficiency of mitochondrial reduction of oxygen to the oxyradical, these other oxidoreductases enable glycolytic energy production with a deleterious 100% efficiency in generating oxyradicals. To avoid this catastrophic cycle, lactate dehydrogenase is upregulated at the expense of lactic acid acidosis. This metabolic shift is epigenetically enforced, as is insulin resistance to reduce mitochondrial turnover. The low mitochondrial capacity for efficient production of energy reinforces a downward spiral of more sedentary behavior leading to accelerated aging, increased organ failure with stress, impaired immune and vascular functions and brain aging. Several steps in the pathway are amenable to reversal for exit from the vicious cycle of EORS. Examples from our work in the aging rodent brain as well as other aging models are provided.
One reason may be in human evolutionary history of mild polygyny. Under polygyny, girls who reach puberty earlier gain a reproductive advantage over their age mates by being able to marry polygynous men. The reason for this is that females are in competition with other females for reproductive success. Females who mature earlier than other females can start reproducing earlier and have access to polygynous men, while their age mates who have not yet reached puberty cannot. At the same time, there is no reproductive incentive for men in a polygynous breeding system to mature earlier. Another possible reason for the earlier maturation of girls than boys is that decline in gamete quality with age is a more serious constraint for women than for men. Decline in sperm quality is buffered by the large number of sperm produced. In contrast, ova production is much more limited. Women are therefore under stronger selection pressure to begin mating as soon as possible.

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**Melatonin in Red Wine Is Cardioprotective**

Is red wine a SAFE sip away from cardioprotection? Mechanisms involved in resveratrol- and melatonin-induced cardioprotection

Abstract: Epidemiological studies suggest that regular moderate consumption of red wine confers cardioprotection but the mechanisms involved in this effect remain unclear. Recent studies demonstrate the presence of melatonin in wine. We propose that melatonin, at a concentration found in red wine, confers cardioprotection against ischemia–reperfusion injury. Furthermore, we investigated whether both melatonin and resveratrol protect via the activation of the newly discovered survivor activating factor enhancement (SAFE) prosurvival signaling pathway that involves the activation of tumor necrosis factor alpha (TNFα) and the signal transducer and activator of transcription 3 (STAT3). [...] Both resveratrol and melatonin, at concentrations found in red wine, significantly reduced infarct size compared with control hearts in wild-type mouse hearts (25 ± 3% and 25 ± 3% respectively versus control 69 ± 3%, P < 0.001) but failed to protect in TNF receptor 2 knockout or STAT3-deficient mice. Furthermore, perfusion with either melatonin or resveratrol increased STAT3 phosphorylation prior to ischemia by 79% and 50%, respectively (P < 0.001 versus control). Our data
demonstrate that both melatonin and resveratrol, as found in red wine, protect the heart in an experimental model of myocardial infarction via the SAFE pathway. [...] Conclusion In conclusion, our data strongly support the fact that the presence of melatonin in red wine, together with resveratrol, may contribute to the red wine hypothesis it also suggests that melatonin is a superior antioxidant present in red wine and contributes to the red wine hypothesis. Furthermore, we have delineated a novel mechanism by which low amounts of melatonin and resveratrol protect the heart via the activation of the powerful prosurvival SAFE pathway, which involves the activation of both TNFα and STAT3. Our data provide exciting novel insight into the use of natural compounds in the treatment of cardiac disease.

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**Protein Leverage in Humans**

**Testing Protein Leverage in Lean Humans: A Randomised Controlled Experimental Study**

Key point: “In our study population a change in the nutritional environment that dilutes dietary protein with carbohydrate and fat promotes overconsumption, enhancing the risk for potential weight gain.”

A 15% protein diet prevented weight gain.

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**Exercise training increases mitochondrial biogenesis in the brain**

[http://jap.physiology.org/content/111/4/1066.abstract](http://jap.physiology.org/content/111/4/1066.abstract)

Increased muscle mitochondria are largely responsible for the increased resistance to fatigue and health benefits ascribed to exercise training. However, very little attention has been given to the likely benefits of increased brain mitochondria in this regard. We examined the effects of exercise training on markers of both brain and muscle mitochondrial biogenesis in relation to endurance capacity assessed by a treadmill run to fatigue (RTF) in mice. Male ICR mice were assigned to exercise (EX) or sedentary (SED) conditions (n = 16–19/group). EX mice performed 8 wk of treadmill
running for 1 h/day, 6 days/wk at 25 m/min and a 5% incline. Twenty-four hours after the last training bout a subgroup of mice (n = 9–11/group) were euthanized, and brain (brain stem, cerebellum, cortex, frontal lobe, hippocampus, hypothalamus, and midbrain) and muscle (soleus) tissues were isolated for analysis of mRNA expression of peroxisome proliferator-activated receptor-gamma coactivator-1-alpha (PGC-1α), Silent Information Regulator T1 (SIRT1), citrate synthase (CS), and mitochondrial DNA (mtDNA) using RT-PCR. A different subgroup of EX and SED mice (n = 7–8/group) performed a treadmill RTF test. Exercise training increased PGC-1α, SIRT1, and CS mRNA and mtDNA in most brain regions in addition to the soleus (P < 0.05). Mean treadmill RTF increased from 74.0 ± 9.6 min to 126.5 ± 16.1 min following training (P < 0.05). These findings suggest that exercise training increases brain mitochondrial biogenesis, which may have important implications, not only with regard to fatigue, but also with respect to various central nervous system diseases and age-related dementia that are often characterized by mitochondrial dysfunction.

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**Physical Inactivity: Get Off Your Ass**

*Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies*

Although it is no longer debatable that sedentary behaviors are an actual cause of many metabolic diseases, the physiology of physical inactivity has been poorly investigated for this purpose. Along with microgravity, the physiological adaptations to spaceflights require metabolic adaptations to physical inactivity, and that is exceedingly well-simulated during the ground-based microgravity bed-rest analogs. Bed rest thus represents a unique model to investigate the mechanisms by which physical inactivity leads to the development of current societal chronic diseases. For decades, however, clinicians and physiologists working in space research have worked separately without taking full awareness of potential strong mutual questioning. This review summarizes the data collected over the last 60 years on metabolic adaptations to bed rest in healthy subjects. Our aim is to provide evidence that supports the hypothesis that physical inactivity per se is one of the primary causes in the development of metabolic inflexibility. This evidence will focus on four main tenants of metabolic inflexibility: 1) insulin resistance, 2) impaired lipid trafficking and hyperlipidemia, 3) a shift in substrate use toward glucose, and 4) a shift in muscle fiber type and ectopic fat storage.
Altogether, this hypothesis places sedentary behaviors upstream on the list of factors involved in metabolic inflexibility, which is considered to be a primary impairment in several metabolic disorders such as obesity, insulin resistance, and type 2 diabetes mellitus.

**Phosphatidylserine Increases IQ?**

Phosphatidylserine (PS) is a phospholipid found in cell membranes of most animals and plants. PS has been shown to reduce stress and increase performance in runners, cyclists and golfers. The purpose of this study was to investigate the effects of a PS containing formulation on cognitive function, mood and endocrine response before and after intense resistance exercise. Methods: 18 lower body, resistance trained, college aged males ingested 14 days of supplement (IQPLUS Focus, providing 400 mg of soy-derived PS) and a Placebo (PL), in a randomized, double-blind, placebo controlled, cross-over manner. Following 14 days of supplementation, participants performed an acute bout of lower body resistance training. Mood (Profile of Mood States, POMS) and cognitive function (Serial Subtraction Test, SST) were measured prior to, 5 minutes after, and 60 minutes after exercise. Venous blood samples were collected prior to, and 5, 15, 25, 40 and 60 minutes after exercise. Blood samples were analyzed for plasma cortisol and testosterone. Data were analyzed using repeated measures ANOVA. Results: **PS supplementation significantly reduced the time needed for a correct calculation on the SST by 20% (1.27 s per calculation; PL: 6.4 s, PS 5.13 s; p = 0.001), and reduced the total amount of errors by 39% (PL: 1.28 + .69, PS: .78 + .27, p = 0.53), and increased the amount of correct calculations by 13% (PL: 22.1 + 2.24, PS: 24.9 + 1.52, p = 0.07) prior to or in response to exercise compared to PL.** Following exercise, there was no difference in SST scores between PS and PL. There were no significant changes in regards to mood or endocrine response to exercise as a result of PS supplementation. Conclusion: PS supplementation significantly increased cognitive function prior to exercise. Improved cognitive function could benefit athletes and non-athletes alike. PS did not appear to affect mood or endocrine response prior to or following resistance exercise. **Skepticism is in order here, but the differences in times were pretty large.**
Although, that there wasn’t any difference between placebo and PS after exercise seems strange.

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**Caffeine Prevents Cancer**

*Inhibition of lung carcinogenesis by black tea in Fischer rats treated with a tobacco-specific carcinogen: caffeine as an important constituent.*

Abstract

Here, we examined the effect of black tea and caffeine on lung tumorigenesis in F344 rats induced by the nicotine-derived carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in a 2-year bioassay. NNK was administered s.c. at a dose of 1.5 mg/kg body weight three times weekly for 20 weeks. Animals were given either black tea as drinking water at concentrations of 2%, 1%, or 0.5%, or caffeine in drinking water at concentrations identical to those in 2% and 0.5% tea infusions for 22 weeks. The treatment period began 1 week before and ended 1 week after the NNK administration. The animals were sacrificed on week 101 for the examination of tumors in target organs, including lung, liver, nasal cavity, and other major organs. The NNK-treated group, given 2% black tea, showed a significant reduction of the total lung tumor (adenomas, adenocarcinomas, and adenosquamous carcinomas) incidence from 47% to 19%, whereas the group given 1% and 0.5% black tea showed no change. The 2% tea also reduced liver tumor incidence induced by NNK from 34% in the group given only deionized water to 12%. The tumor incidence in the nasal cavity, however, was not affected by either black tea or caffeine at any of the concentrations tested. The most unexpected finding was the remarkable reduction of the lung tumor incidence, from 47% to 10%, in the group treated with 680 ppm caffeine, a concentration equivalent to that found in the 2% tea. This incidence is comparable to background levels seen in the control group. This study demonstrated for the first time in a 2-year lifetime bioassay that black tea protects against lung tumorigenesis in F344 rats, and this effect appears to be attributed, to a significant extent, to caffeine as an active ingredient of tea.
Addicted to Exercise

https://www.nytimes.com/2011/10/30/opinion/sunday/kristof-addicted-to-exercise.html?_r=1&ref=nicholasdkristof

“Exercise addicts display all of the hallmarks of substance addicts: tolerance, craving, withdrawal and the need to exercise ‘just to feel normal,’” Linden writes.

O.K., I confess. I might be an addict.

Exercise seems to trigger the release of chemicals called endorphins and enkephalins (the brain’s version of opium) and endocannabinoids (the brain’s version of marijuana). In the lab, rats can develop an addiction to exercise on a wheel.

As a former distance runner, I can agree. Furthermore, extensive endurance exercise isn’t a healthy habit, so exercise addiction shares this trait with drug and other addictions.

Someone (me?) should do a post on how the running craze has been just as much misguided propaganda and as harmful as the recommendation to eat a low-fat diet.

Antibodies to Gluten in Bipolar Disorder

Markers of gluten sensitivity and celiac disease in bipolar disorder.

OBJECTIVES:

Increased immune sensitivity to dietary gluten proteins has been reported in schizophrenia but has not been studied in bipolar disorder. In this study, we examine the levels of antibody reactivity to gliadin, deamidated gliadin, and tissue transglutaminase (tTG) in individuals with bipolar disorder and compare these levels to those in individuals who do not have any history of psychiatric disorder.

METHODS:

The sample of 275 individuals included 102 with bipolar disorder and 173 controls without a psychiatric disorder. Immunoglobulin G
(IgG) and immunoglobulin A (IgA) antibodies to gliadin and tTG and IgG antibodies to deamidated gliadin were measured by enzyme immunoassay. Participants’ levels of antibodies to deamidated gliadin and tTG were classified based on the cutoffs for positivity that are predictive of celiac disease. Quantitative levels of antibodies were compared between groups employing regression models which were controlled for demographic variables.

RESULTS:

Individuals with bipolar disorder had increased levels of IgG antibodies to gliadin compared with controls in multivariate analyses. We also found evidence of increased levels of antibodies to deamidated gliadin in the bipolar disorder population. The levels of IgA class antigliadin antibodies and antibodies to tTG did not differ significantly between groups. There was also not a significant difference between groups in the number of persons who were classified as having levels of antibodies to deamidated gliadin or tTG that are predictive of celiac disease.

CONCLUSIONS:

Individuals with bipolar disorder have increased levels of IgG antibodies to gliadin. However, such antibody increase is not accompanied by an elevation in IgA antibodies to gliadin or the celiac disease-associated antibodies against deamidated gliadin and tTG. These results warrant further detailed examination of the molecular specificity and pattern of reactivity of the antibody response to gluten antigens in bipolar disorder.

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**Junk food can make young men infertile**

*Don’t say you haven’t been warned:*

JUNK food, particularly products containing trans fats, can make healthy young men infertile by damaging their sperm, a joint American and Spanish study out today showed.

Fertility doctors from Harvard University and the University of Murcia, southeastern Spain, analysed sperm from hundreds of men aged between 18 and 22 and found those who ate a high proportion of junk food had poorer quality sperm than those with a nutritious diet.

All the men were assessed to ensure they were in optimum shape and had no other problems that may affect their reproductive system, The Sun reported.
The sperm of men with poor diets was found to be less likely to survive the journey to fertilise an egg, even if the men were a healthy weight and exercised.

Meanwhile, a separate Japanese study, also out today, found that taking moderate regular exercise can be good for a man’s sperm.

A study of 215 men attending a fertility clinic in Japan found that those who took part in moderate exercise, such as brisk walking, had sperm with better swimming ability than those who took part in only light exercise.

HT: In Bona Fide.