

Blocking Cortisol Extends Lifespan by Improving Mitochondrial Function

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STORY AT-A-GLANCE

- › Research shows blocking cortisol with mifepristone extended fruit fly lifespan by over 100%, performing better than rapamycin by improving mitochondrial function through enhanced mitophagy processes
- › Chronic elevated cortisol leads to muscle degradation, brain tissue damage and inflammation while weakening immune function, ultimately accelerating aging and compromising overall health
- › Low-carb diets may unintentionally raise cortisol as the hormone triggers muscle and tissue breakdown for glucose production when blood sugar drops, suggesting healthy carbohydrates should be reintroduced for optimal health
- › Cortisol acts as a defense mechanism to prevent dangerously low blood glucose levels, but its persistent elevation creates a cycle of food cravings and metabolic issues
- › Natural progesterone effectively blocks cortisol by reducing blood concentrations and regulating adrenal activity, while also enhancing GABA function for stress reduction and better sleep

Have you ever considered how cortisol, often dubbed the "stress hormone," impacts your aging process? Recent research using fruit flies – *Drosophila melanogaster* – sheds light on this intriguing connection.¹ Scientists explored how blocking cortisol's effects could extend lifespan.

By focusing on mated female flies, which naturally experience reduced longevity due to reproductive stresses, researchers investigated the benefits of mifepristone, a well-known anti-cortisol drug. Their findings revealed that mifepristone significantly increased the median lifespan of these flies by over 100%.

This dramatic extension suggests that cortisol plays a pivotal role in the aging process, and its inhibition could be a key strategy in promoting longevity. Understanding cortisol's impact on lifespan not only offers insights into fundamental biological aging mechanisms but also opens avenues for developing interventions that could enhance healthspan in humans.

Cortisol Accelerates Aging

In the study with fruit flies, mifepristone was utilized for its ability to block cortisol by antagonizing the type II glucocorticoid receptor (GR).² This action is key because cortisol, through the GR, influences various physiological processes that accelerate aging. As noted on Georgi Dinkov's blog, which is inspired by the work of the late Ray Peat:³

"Yet another confirmation that cortisol, while being life-saving in acute stress situations, can shorten lifespan if chronically elevated. In fact, according to the study ... antagonizing the effects of even normal cortisol levels may extend lifespan.

This corroborates Ray's statement that all the symptoms of aging (and thus every chronic disease) can be reliably reproduced in even youthful organisms by the administration of sufficiently high doses of cortisol."

Mifepristone is not easily available but is also known as RU-486 or the abortion pill. It terminates pregnancy by blocking progesterone but it also inhibits cortisol's effects. Mifepristone helps mitigate the negative consequences of stress hormones on the body. Additionally, mifepristone activates PPAR γ , a transcription factor involved in regulating metabolism and immune function, further contributing to its antiaging benefits.

This dual action not only enhances lifespan in fruit flies but also suggests therapeutic applications for humans. By targeting cortisol, mifepristone offers a promising approach to managing age-related decline and improving overall health.

Rapamycin, a prescription immunosuppressant drug with autophagy-stimulating properties, is another drug of considerable interest due to its ability to inhibit the mTOR pathway, a critical regulator of cell growth and metabolism.

In the same fruit fly study, rapamycin was tested alongside mifepristone to assess their combined effects on lifespan. While both drugs individually extended the median lifespan of mated female flies – rapamycin by approximately 81% and mifepristone by 114% – their combination did not yield additive benefits.⁴

Instead, combining these drugs reduced the lifespan extension achieved by either drug alone. This non-additive interaction suggests that mifepristone and rapamycin may operate through the same biological pathway to promote longevity. Dinkov explained:⁵

"The study compared the effects of cortisol blocking to the effects of the well-known life-extension drug rapamycin, which works by blocking the mTOR protein. In fact, blocking cortisol extended lifespan by 40%+ more, compared to rapamycin and without the known (and very dangerous) side effects of rapamycin (immunosuppression)."

Enhancing Mitochondrial Health Through Mitophagy

A cornerstone of the study's findings lies in the improvement of mitochondrial function via mitophagy⁶ – the process by which damaged mitochondria are selectively degraded and recycled. Mitochondria, the powerhouses of the cell, are essential for energy production and overall cellular health.

As we age, mitochondrial dysfunction becomes more prevalent, contributing to various age-related diseases. The researchers employed a mito-QC mitophagy reporter to monitor this process in live flies. Both mifepristone and rapamycin were found to

significantly activate mitophagy in the fat-body and midgut tissues of mated female flies.

This activation leads to the removal of dysfunctional mitochondria, thereby enhancing cellular efficiency and longevity. By promoting mitochondrial quality control, these drugs help maintain cellular health, reduce oxidative stress and delay the onset of age-related decline. This means ensuring optimal mitochondrial function could be a key strategy in promoting a longer, healthier life. Dinkov noted:⁷

"An interesting finding of the study was that the antiaging effects was due to improved mitochondrial function, so this suggests (again) that any benefit or risk from a specific substance is likely ultimately due to its effects on metabolism/mitochondria. And it just so happens that cortisol does suppress mitochondrial function, while simultaneously enhancing both fatty acid synthesis and fatty acid oxidation, as well as lipolysis."

In addition, the study found that both mifepristone and rapamycin effectively reduced midgut hypertrophy in mated female flies. Midgut hypertrophy, or gut enlargement, is a physiological response to increased reproductive demands that comes at the cost of reduced lifespan. This hypertrophy is associated with inflammation and metabolic stress, which are detrimental to longevity.

By mitigating this enlargement, mifepristone and rapamycin help maintain gut health and reduce systemic inflammation. The study demonstrated that treating mated female flies with either drug brought midgut size back to levels comparable to virgin females, who naturally have longer lifespans.

This finding highlights the importance of maintaining gut integrity and reducing metabolic stress as important factors in promoting longevity. Supporting gut health through targeted therapies and lifestyle changes could be an effective way to enhance overall well-being and extend lifespan in humans as well.

The Detrimental Impact of Chronic Cortisol Elevation

Persistently high levels of cortisol exert harmful catabolic effects on your body, gradually leading to muscle degradation over time. This hormone not only compromises muscle integrity but also inflicts damage on brain tissue, contributing to the brain atrophy commonly associated with dementia and depression.⁸

Furthermore, in addition to speeding up the aging process, cortisol promotes the breakdown of stored fat through lipolysis, a process that heightens reductive stress and enhances the body's capacity to produce cellular energy.

At first glance, the increase in lipolysis might appear advantageous, as it mobilizes stored fat for energy. However, this process fails to eliminate the harmful visceral fat that accumulates around internal organs, a fat depot known to trigger inflammation.

As a result, chronic excess cortisol not only fosters inflammation but also weakens your immune system, all while breaking down essential body tissues. This dual impact undermines overall health and accelerates the decline associated with aging.

The persistent presence of elevated cortisol leads to sustained inflammation, which is also harmful to various bodily functions. Inflammation is a key driver of numerous chronic diseases and significantly impairs immune function, making your body more susceptible to infections and illnesses.

The ongoing inflammatory state caused by excessive cortisol disrupts your body's ability to repair and regenerate tissues, further exacerbating health issues and contributing to a decline in physical resilience.

In other words, high cortisol impairs your body's anabolic functions, which are necessary for tissue growth and repair. Without the ability to effectively build and maintain tissues, your body becomes more vulnerable to injuries, degenerative conditions, and a general decline in physical capabilities, all of which are hallmarks of aging. **Cortisol face** and **behavioral problems** in children are also linked to elevated cortisol.

Beyond its physical degradation effects, cortisol also triggers the release of neurotransmitters that lead to food cravings.⁹ This hormonal surge increases the risk of

developing unhealthy eating habits, such as overeating or craving high-sugar and high-fat foods. These poor dietary choices contribute to weight gain, further elevating cortisol levels and creating a vicious cycle that exacerbates both metabolic and psychological health issues.

Rethinking Low-Carb Diets Through Cortisol's Lens

Often labeled merely as a stress hormone, cortisol fulfills many other functions within your body. Its main role is to act as a vital defense mechanism, ensuring that your blood glucose levels do not plummet to hazardous lows. By maintaining these levels, cortisol safeguards you against the severe danger of a hypoglycemic coma.¹⁰

Cortisol's fundamental role has reshaped my perspective on low-carbohydrate diets. Although cortisol's actions are beneficial in the short term, consistently high levels negatively impact your health. The very name "cortisol" hints at its biological significance and origins, emphasizing its connection to metabolic processes.

Cortisol is classified as a glucocorticoid steroid hormone, intricately linked to the regulation of glucose metabolism and synthesized in your adrenal cortex. When your blood sugar starts to drop and your liver's glycogen stores are depleted, cortisol steps in. It triggers the breakdown of lean muscle, bone and even brain tissue into amino acids.

These amino acids are then converted into glucose by your liver through a process known as gluconeogenesis, ensuring your body continues to receive the necessary energy.

This biochemical pathway explains why maintaining a **low-carb diet indefinitely** may not be ideal for everyone. While reducing carbohydrate intake and intermittent fasting are effective short-term strategies for those dealing with weight management and metabolic challenges, it's important to reintroduce carbohydrates once your metabolic flexibility improves.

Neglecting to do so leads to impaired metabolic health and weakened mitochondrial function, undermining your overall well-being.

Understanding cortisol's dual role highlights the importance of balance. Short-term elevation of cortisol is protective and necessary for survival, especially during periods of low carbohydrate intake. However, chronic elevation leads to detrimental health effects, including muscle wasting, bone density loss and impaired cognitive function. Therefore, managing cortisol levels through a balanced diet and lifestyle is essential for long-term health and longevity.

Once your body adapts to improved metabolic flexibility, reintroducing carbohydrates becomes essential. This reintegration supports sustained metabolic health and ensures that your mitochondria function efficiently. By doing so, you prevent the adverse effects associated with prolonged low-carb dieting, such as decreased energy levels and compromised cellular function.

Striking the right balance allows cortisol to perform its protective roles without tipping into harmful territory, promoting a healthier, more resilient body.

Progesterone Is a Safe and Inexpensive Cortisol Blocker

One of the most powerful and accessible strategies to lower cortisol levels is through the use of natural progesterone, as opposed to its [synthetic counterparts](#) known as progestins. This endogenous hormone is celebrated for its robust anti-cortisol and anti-adrenaline effects, and is a hormone that nearly every adult should be on.

Progesterone operates on multiple fronts to mitigate stress impacts. Primarily, it neutralizes cortisol's influence by reducing its concentration in your bloodstream. This direct antagonism not only diminishes the physical manifestations of stress but also fosters a sense of enhanced well-being and resilience.

Moreover, progesterone amplifies the function of GABA (gamma-aminobutyric acid), your brain's chief inhibitory neurotransmitter. By boosting GABA activity, progesterone induces a calming effect, effectively easing anxiety and promoting mental tranquility.

Another critical mechanism by which progesterone combats stress is through the regulation of adrenal gland activity. It meticulously balances the secretion of stress hormones like cortisol and adrenaline, ensuring a more stable and controlled stress response. Additionally, progesterone plays a pivotal role in improving sleep quality, which is essential for maintaining optimal cortisol cycles and effective stress management.

The advantages of incorporating progesterone into your health regimen are extensive. Users often report a noticeable decline in anxiety and irritability, greater mood stability and better sleep patterns. Physical stress symptoms, including muscle tension and headaches, frequently lessen. Furthermore, optimized progesterone levels enhance cognitive performance during stressful periods, contributing to clearer thinking and improved focus.

However, it's important to approach hormone therapy with caution. Progesterone supplementation should always be supervised by a health care professional to ensure appropriate dosing. Individual needs vary greatly, making personalized medical guidance indispensable for achieving the best outcomes.

Additionally, progesterone should be integrated into a holistic health strategy to **reduce cortisol levels** for maximum effectiveness. Combining hormone therapy with regular physical activity, a nutritious diet, and stress-reduction practices like meditation significantly enhance progesterone's ability to regulate cortisol and manage stress comprehensively.

How to Use Progesterone

Before you consider using progesterone, it is important to understand that it is not a magic bullet, and that you get the most benefit by implementing a Bioenergetic diet approach that allows you to effectively burn glucose as your primary fuel without backing up electrons in your mitochondria that reduces your energy production. My new book, "Your Guide to Cellular Health: Unlocking the Science of Longevity and Joy," covers this process in great detail.

Once you have dialed in your diet, an effective strategy that can help counteract estrogen excess is to take transmucosal progesterone (i.e., applied to your gums, not oral or transdermal), which is a natural estrogen antagonist. Progesterone is one of only four hormones I believe many adults can benefit from. (The other three are thyroid hormone T3, DHEA and pregnenolone.)

I do not recommend transdermal progesterone, as your skin expresses high levels of 5-alpha reductase enzyme, which causes a significant portion of the progesterone you're taking to be irreversibly converted primarily into allopregnanolone and cannot be converted back into progesterone.

Ideal Way to Administer Progesterone

Please note that when progesterone is used transmucosally on your gums as I advise, the FDA believes that somehow converts it into a drug and prohibits any company from advising that on its label. This is why companies like Health Natura promotes their progesterone products as "topical."

However, please understand that it is perfectly legal for any physician to recommend an off-label indication for a drug to their patient. In this case, progesterone is a natural hormone and not a drug and is very safe even in high doses. This is unlike synthetic progesterone called progestins that are used by drug companies, but frequently, and incorrectly, referred.

Dr. Ray Peat has done the seminal work in progesterone and probably was the world's greatest expert on progesterone. He wrote his Ph.D. on estrogen in 1982 and spent most of his professional career documenting the need to counteract the dangers of excess estrogen with low-LA diets and transmucosal progesterone supplementation.

He determined that most solvents do not dissolve progesterone well and discovered that vitamin E is the best solvent to optimally provide progesterone in your tissue. Vitamin E also protects you against damage from LA. You just need to be very careful

about which vitamin E you use as most supplemental vitamin E on the market is worse than worthless and will cause you harm not benefit.

It is imperative to avoid using any synthetic vitamin E (alpha tocopherol acetate – the acetate indicates that it's synthetic). Natural vitamin E will be labeled "d alpha tocopherol." This is the pure D isomer, which is what your body can use.

There are also other vitamin E isomers, and you want the complete spectrum of tocopherols and tocotrienols, specifically the beta, gamma, and delta types, in the effective D isomer. As an example of an ideal vitamin E, you can look at the label on our vitamin E in our store. You can use any brand that has a similar label.

You can purchase pharmaceutical grade bioidentical progesterone as Progesterone Powder, Bioidentical Micronized Powder, 10 grams for about \$40 on many online stores like Amazon. That is nearly a year's supply, depending on the dose you choose.

However, you will need to purchase some small stainless steel measuring spoons as you will need a 1/64 tsp, which is 25 mg and a 1/32 tsp, which is 50 mg. A normal dose is typically 25 to 50 mg and is taken 30 minutes before bed, as it has an anti-cortisol function and will increase GABA levels for a good night's sleep.

Unfortunately, this vendor frequently runs out of product, and if that's the case, then you can use [Simply Progesterone by Health Natura](#). It's premixed with vitamin E and MCT oil. Again, while Health Natura states that its product is for "topical use only," I recommend applying it transmucosally, by rubbing it on your gums.

If you are a menstruating woman, you should take the progesterone during the luteal phase or the last half of your cycle, which can be determined by starting 10 days after the first day of your period and stopping the progesterone when your period starts.

If you are a male or non-menstruating woman, you can take the progesterone every day for four to six months and then cycle off for one week. The best time of day to take progesterone is 30 minutes before bed as it has an anti-cortisol function and will increase GABA levels for a good night's sleep.

This is what I have been personally doing for over a year with very good results. I am a physician so do not have any problems doing this. If you aren't a physician, you should consult one before using this therapy, as transmucosal progesterone therapy requires a doctor's prescription.

Sources and References

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