

Melatonin 101: What You Need to Know - Dr Russel Reiter

By Dr. Frank Yap, MD - August 12, 2024

In this interview, Russel Reiter, Ph.D. — a world-class expert on melatonin — discusses some of the biological activities and health benefits of this important molecule. With some 1,600 papers to his credit, as well as three honorary doctor of medicine(1) degrees, he's published more studies on melatonin than anyone else alive.



Melatonin 101

Melatonin is one of the most important antioxidant molecules and certainly the most ancient, as it has been part of biological life for over 3 billion years. It's present in prokaryotes, which are bacteria, and even in plants. In the human body — aside from having direct antioxidant effects — it also stimulates the synthesis of glutathione and other important antioxidants like superoxide dismutase and catalase. Reiter continues:

"Melatonin has been here forever ... and its functions have evolved. It has learned to work successfully with other molecules during this three-billion-year evolution. One of the molecules with which it collaborates is glutathione ... But the antioxidant activity of melatonin is extremely diverse.

It in fact is a very good radical scavenger. There are other radical scavengers — vitamin C, vitamin E and so forth — but melatonin is superior to those. But beyond that, it stimulates antioxidative enzymes, especially in mitochondria. Mitochondria are small organelles in the cell that generate the bulk of the free radicals.

So, it's very important to have a good antioxidant at the level of the mitochondria and melatonin happens to

be located and is, in fact, synthesized in the mitochondria. Melatonin scavenges radicals that are generated, but it also stimulates something called sirtuin-3, which activates or deacetylates super oxide dismutase (SOD), which is a very important antioxidative enzyme.

It also removes free radicals and prevents the degeneration of the mitochondria, and why this is so important is because mitochondria are really the center of the action within a cell. In other words, there's strong evidence that aging, frailty of aging, senescence of cells as we age, relate to molecular damage at the level of the mitochondria, and melatonin seems to be very efficient at protecting mitochondria from that damage."

Melatonin increases glutathione through a genomic effect on the enzyme that regulates the synthesis of gamma glutamylcysteine synthase, the rate limiting enzyme in glutathione synthesis. Melatonin activates that enzyme.

Glutathione tends to be found in high concentrations in cells, although some is also found, to a lesser degree, in the extracellular space and the mitochondria. Meanwhile, 95% of the melatonin in your body is concentrated within the mitochondria inside the cells.

Its antioxidant effects are quite diverse, but include preventing free radical generation by enhancing the efficiency of the electron transport chain so fewer electrons leach onto oxygen molecules to generate super oxide antiradical.

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How Mitochondrial Melatonin is Generated

Mitochondrial melatonin production is one of the reasons why regular sun exposure is so crucial. Most people understand that sun exposure on bare skin generates vitamin D, courtesy of UVB (ultraviolet B radiation). Few, however, understand that the near-infrared spectrum, when hitting your skin, triggers the generation of melatonin in your mitochondria. Reiter explains:

"Near-infrared radiation penetrates relatively easily the skin and subcutaneous tissues. Every one of those cells contains mitochondria and it appears that near-infrared radiation that is detected in fact induces melatonin production. That is important, because we now think that melatonin within mitochondria is inducible under a lot of stressful conditions.

That is not definitively proven, but it appears that under stress, all cells may upregulate their ability to produce melatonin because it's so highly productive. And typically, under stress, free radicals are generated. That is emphasized by the [fact] that in plants ... that happens.

In other words, if you expose plants to drought, heat, cold, to metal toxicity, the first thing they do is upregulate

their melatonin, because all of those situations generate free radicals. And we suspect, although that has not yet been definitely proven, in animal cells as well, including human [cells].”

Identifying the specific wavelengths that trigger melatonin production can be tricky, but generally speaking, it's likely to be the range between 800 to 1,000 nanometers (nm). This range of near-infrared is invisible, and has the ability to penetrate tissue. Visible wavelengths generally do not penetrate the skin, and therefore cannot stimulate your mitochondria.

Anytime your skin is exposed to natural sunlight, however, you can be sure you're receiving the necessary wavelengths of near-infrared to generate melatonin in your mitochondria. Conversely, when indoors under artificial lighting, you can be certain you're not getting any. This is because most window glass is low-e and filters out a good portion of the near-infrared, so even sitting near a window is not going to provide you with this benefit.

To compensate for time spent indoors, I use a 250-watt Photo Beam near-infrared bulb from SaunaSpace in my office. I keep it lit when I'm in my office and have my shirt off. Considering most people spend most of their days indoors, mitochondrial melatonin deficiency is likely rampant. And, since many also do not get enough sleep, they also have a deficiency in the melatonin synthesized in the pineal gland in response to darkness.

The Two Types of Melatonin

As hinted at above, there are two types of melatonin in your body: The melatonin produced in your pineal gland, which traverses into your blood, and subcellular melatonin produced inside your mitochondria.

Importantly, the melatonin that your mitochondria produces does not escape your mitochondria. It doesn't go into your blood. So, you're not going to directly increase your blood or serum level of melatonin by sun exposure. But, bright sun exposure around solar noon will indirectly help your pineal gland to produce melatonin during the night.

It is important to understand that your blood level of melatonin is indicative of the melatonin produced in your pineal gland, and/or oral supplementation. Conversely, the melatonin produced by your pineal gland cannot enter into the mitochondria, which is why it is so important to get regular sun exposure. Reiter explains:

“In other words, if you surgically remove the pineal gland from an animal or human, blood levels of melatonin are essentially zero. Not totally zero – I think what happens is that the mitochondria in other cells continue to produce melatonin and some of that leaks out into the blood and gives you a residual – but you have no circadian rhythm.

Melatonin production in the pineal gland is highly rhythmic, depending on the light-dark cycle. This is not true

for melatonin in mitochondria. It's not cyclic. It's not impacted by the light dark environment. It may be affected by certain wavelengths of energy, but it's not affected by the light dark environment.

So, blood levels are derived from the pineal gland, and this rhythm is very important for setting circadian rhythms. In other words, the function of that melatonin is quite different from the function of the mitochondrial produced melatonin. It sets the rhythm. Of course, there's always some scavenging by that melatonin as well, but the real scavenging is involved with mitochondrial-produced melatonin."

Oral Supplementation Neutralizes Free Radicals

Oral supplementation, however, can enter your cells and mitochondria. This is a detail I was wrong about before, and which Reiter clarifies in this interview:

"If you supplement with melatonin, it can also enter cells and get into the mitochondria as well. And that is also very important ... As you age, mitochondrial melatonin diminishes. If you supplement with melatonin, it will get into your mitochondria and, in fact, do what melatonin does – neutralize free radicals and protect the mitochondria's function."

Melatonin Is Vital to Heart Attack and Stroke Recovery

Considering melatonin's function within your mitochondria, and the fact that mitochondrial dysfunction is a hallmark of most chronic disease, it makes sense that melatonin would be helpful against a number of different diseases, including the two most common – heart disease and cancer.

As explained by Reiter, one of the situations that is most devastating for the heart and brain is temporary interruption of the blood supply as a result of a cardiac arrest or stroke. This deprives the tissues of oxygen, and without oxygen, they rapidly deteriorate.

When the blood vessel reopens, which is called reperfusion, and oxygen flows back into those oxygen-deprived cells, this tends to be the time of maximum damage, as loads of free radicals are generated once the blood starts flowing again.

"There's a large host of studies, including some in humans, where if you give melatonin to induced heart attack in animals or an accidental heart attack in humans, you can preserve or reduce the amount of cardiac infarct, the amount of damage that occurs in the heart," Reiter says.

"There's a very famous cardiologist in the Canary Islands, professor Dominguez-Rodriguez, whom I worked with. And we, about three years ago, published a paper where we infused melatonin directly into the heart after the vessel was opened. That reduced cardiac damage by roughly 40%.

The other thing that happens in a heart attack is that cardiac cells do not regenerate. Once you lose a cardiac cell, they're done ... and are replaced by fibrous tissue. Of course, fibrous tissue is not contractile, so you get heart failure.

We just published a paper, again with this same cardiologist, showing that if people who are potentially suffering with heart failure because of a damaged heart, they survive better and longer if they are given melatonin on a regular basis. It's a small study ... but I think that would be a worthwhile field to exploit."

Dosage Suggestions for Acute Heart Attack

In terms of dosage, it's difficult to translate doses used in animal studies onto human subjects. In animals, doses between 5 to 10 milligrams per kilogram of bodyweight are used. In humans, however, the dose is calculated on the basis of surface area rather than on body size, and that significantly reduces the amount of melatonin that you have to give.

That said, Reiter stresses that melatonin has no known toxic threshold, so even though we don't know what the ideal dose is, we do know it's safe even at high doses. Additionally, the timing of the dose will be important. The first dose should be taken immediately, but subsequent melatonin dosing should follow circadian biology, so around 10 a.m., 4 p.m., and before bed.

"If I had a heart attack and I had melatonin on my person, I would take melatonin," Reiter says. "The question is how much? ... This is not a recommendation to any of your patients, but I would not be hesitant about taking 50 milligrams at the time, and some subsequently for the next 24 hours, even during the day. Because you don't want to lose any more heart cells than is absolutely necessary ...

I have suggested this a number of times. In other words, an emergency medical technician goes out, picks up a patient who has clearly a heart attack. I think on site, immediately, melatonin should be given intravenously rather than orally. It'd be difficult to give it orally. That would be my recommendation."

Emergency Medical Kit for Acute Heart Attack or Stroke

In cases of an acute heart attack or stroke (which have virtually identical tissue damage mechanisms, just one affects the heart and the other your brain), I would also add methylene blue. Methylene blue is well-documented to be highly beneficial for reperfusion injuries, (2) especially if you do it right at the beginning of the event, because it augments cytochromes to allow the continued production of ATP even without the use of oxygen.

Melatonin and methylene blue belong in every emergency medical kit. In cases of an acute heart attack or stroke, melatonin can help limit the damage, while methylene blue augments cytochromes to allow the

continued production of ATP even without the use of oxygen, which also helps minimize cell death and tissue damage.

So, together, methylene blue and melatonin could act as a one-two punch if you've got a stroke or heart attack. They really should be part of every emergency kit.

As an interesting side note, melatonin can also be useful in people with Type 2 diabetes. Reiter notes he has diabetic colleagues who take 1 gram of melatonin daily to counteract the free radical damage caused by hyperglycemia. Keep in mind that melatonin does not treat the cause of the diabetes. It only helps to counteract the damage being caused.

Half Life and Bioavailability of Melatonin

The half life of melatonin in the blood is only about 40 minutes. Within cells, the half life varies according to the level of oxidative stress present. If oxidative stress is high, the melatonin is destroyed much faster, and oxidative stress is low, it remains within the cell much longer.

Reiter also notes that in addition to being a free radical scavenger, all of melatonin's metabolic kin – its active metabolites, such as N-acetyl-5-methoxytryptamine – are also excellent scavengers. While quickly used up in the presence of high oxidative stress, melatonin is also rapidly taken up when used orally, hence the suggestion to take multiple doses spread out.

Ideally, you'd want to use sublingual or intravenous melatonin, because it'll enter your bloodstream much faster. Another option is to make your own rectal suppositories. If you swallow it, it needs to pass through and be metabolized by your liver.

Melatonin Is Also a Potent Antiviral

In addition to its antioxidant potency, melatonin also has antiviral capacity. These two features combined is thought to be why it's been so useful against COVID-19.

"I'm going to give you a very specific example," Reiter says. "Here's a local physician, Dr. Richard Neil, whom I have known for a number of years. When COVID-19 became common, he called me, we discussed it, he started giving 1 mg per kilogram of body weight (once a day) for about five days, at the time of diagnosis. He has now treated more than 2,000 patients, very successfully, with melatonin.

The importance of melatonin in reference to COVID is that it is not specifically for [the original Wuhan strain]. The variants, Delta, Omicron, they're viruses we think will respond. We currently have a paper in press where we showed that in animals, Zika virus toxicity is also prevented by melatonin, and we've checked four different coronaviruses in pigs.

That paper also shows that melatonin prevents the damage – the consequence – of those viruses. I think [melatonin] is generally a quite good antiviral agent and should be considered as useful. When President Trump was hospitalized with COVID, one of the molecules he was given was melatonin. Obviously, the physicians treating him knew this literature.”

So, to summarize, if you have symptoms of COVID, you could consider taking oral or sublingual melatonin 30 to 45 minutes before bedtime, first thing in the morning, at 10 a.m. and again at 4 p.m. You clearly want to avoid it a few hours before and after solar noon, as taking supplementation during that time will likely impair pineal nighttime melatonin secretion.

Reiter points out that slow-release melatonin has not been widely studied, and he generally doesn't recommend it for that reason.

Melatonin for Cancer

Melatonin can also be useful in the prevention and treatment of cancer. Reiter explains:

“Cancer cells are clever. They do everything they can to permit their continued survival. It seems counterintuitive, but what they do is they prevent pyruvate from entering the mitochondria, and that reduces ATP production. But as a consequence of doing that, they accelerate something called glycolysis and that's very inefficient in producing ATP, but it does it very rapidly. So, then they have sufficient energy.

The importance of preventing pyruvate from entering the mitochondria, we now think is the fact that pyruvate is a precursor to something called acetyl coenzyme A. Acetyl coenzyme A is a cofactor for the enzyme that regulates melatonin production in the mitochondria.

So, by eliminating or preventing pyruvate from getting into the mitochondria, [the cancer cells] prevent or reduce melatonin production, because they don't allow the necessary cofactor to be produced. In other words, we predicted about four years ago that, in fact, the mitochondria of cancer cells would produce less melatonin.

We have subsequently shown that in two studies, both uterine cancers. Clearly, melatonin levels and the activity of the enzymes in the mitochondria of these types of cancer cells are at least about half what they would normally be. The prevention of pyruvate into the mitochondria, that's Warburg type metabolism.

The other thing is the pyruvate is metabolized into lactic acid. It escapes the cell and produces an acidic environment for the cancer cell, and cancer cells like that acidic environment. So, if you can reduce the Warburg type metabolism, you may be able to limit the growth of cancer cells and perhaps also the metastasis ...

Some cancer cells may only be part-time cancerous because [during nighttime] when they have high melatonin, then they avoid Warburg type metabolism. The interesting thing about Warburg type metabolism [is that] ... many pathological cells, inflammatory cells, cells that are affected by amyloid beta in the brain, exhibit this specific type metabolism ...

And we know that inflammatory cells – M2 and M1 inflammatory cells – can be converted back and forth by melatonin. The inflammatory cells can be prevented by giving them melatonin [because of] its effect on Warburg type metabolism. So, Warburg type metabolism is common in many, many pathological cells.”

The Link Between Metabolic Flexibility, Melatonin and Cancer

One of the reasons for why cancer is so prevalent likely has to do with the fact that **93% of Americans are metabolically inflexible** (JACC 2022) and cannot seamlessly transition between burning carbs and fats for fuel. Glucose (sugar) is one of the primary fuels that most people have. Glucose has six carbons and is metabolized into pyruvate, which is a three-carbon molecule. Pyruvate, in turn, is metabolized in the mitochondria to acetyl-CoA.

The reason the Warburg Effect works is because pyruvate dehydrogenase kinase (PDK) inhibits the inflow of pyruvate into the mitochondria so it cannot be converted into acetyl-CoA, and acetyl-CoA is not only needed in the production of melatonin, but is also used to efficiently produce ATP in the mitochondria and is how glucose is used in the mitochondria.

Another source of acetyl-CoA is beta oxidation of fats, which breaks down the fat to the two carbon molecule acetyl-CoA, which enters the mitochondria an active transport molecule, courtesy of MCT (mono carboxylase transporter). My point here is that when you are metabolically inflexible, the Warburg Effect becomes massive. But if you're cardiometabolically healthy and can burn fat, you can effectively bypass that defect.

Prior to my interview with Reiter, I certainly knew that limiting carbs and preventing the Warburg effect was important in cancer treatment, but I hadn't realized that one of the metabolic byproducts of acetyl-CoA was needed to produce melatonin. So, being metabolically flexible not only impairs the Warburg effect, but also supplies melatonin to combat the excessive oxidative stress in cancer.

This is why I would strongly encourage each and every one of you to regularly engage in two activities the rest of your life. First, expose as much of your skin as you can to an hour of sunshine a day around solar noon.

Second, you have to eliminate all seed oils from your diet, as excess seed oils are the primary reason why most people are metabolically inflexible. While the average person's consumption of these oils is around 25% to 30% of total daily calories, it should only be about 1% to 2% (mine is 1.5%).

Word of Caution

Just be careful, though, as using high-dose melatonin long term could be a prescription for disaster. This is because doses of over 5 to 10 mg are likely to draw out heavy metals like mercury and unless you are on a good detoxification program and using sauna regularly these heavy metals could cause biological damage.

Sources and References

¹ UT Health. Russel Reiter, Ph.D.

² NIH. Methylene blue reperfusion

³ Journal of the American College of Cardiology Volume 80, Issue 2, 12 July 2022, Pages 138-151

Original Article: <https://articles.mercola.com/sites/articles/archive/2022/08/14/what-you-need-to-know-about-melatonin.aspx>

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