Cold Shocking the Body

Exploring Cryotherapy, Cold-Water Immersion, and Cold Stress

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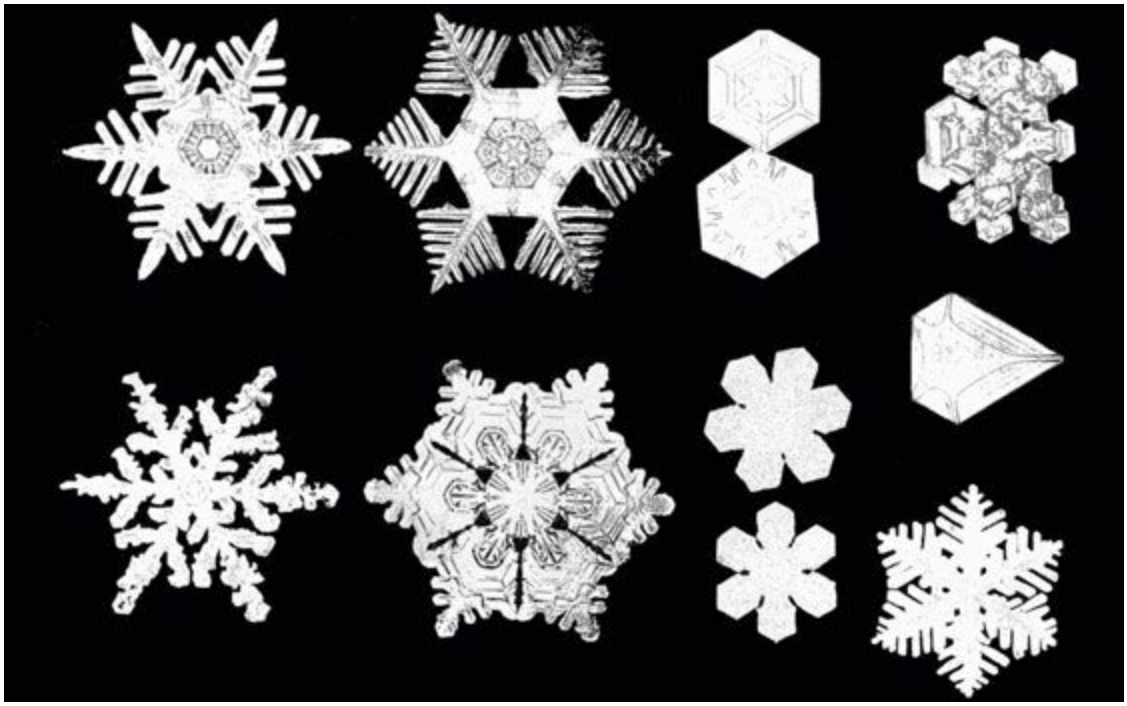

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Are you stressed? Let's hope so!

Most of us probably think of stress primarily as a bad thing... and it is! This negative stress, called distress, can be the result of (or result in) inadequate sleep, emotional stress and rumination, poor gut health and much more. But stress can also be good. Good stress can be referred to as eustress, and can include any number of activities, chiefly among them, exercise, but in some contexts probably also things like fasting, heat stress (sauna), and cold stress (things like cold-water immersion or cryotherapy). In general, things that fall into the category of eustress have the quality of being hormetic, which means that, in the right dose, they serve as a short-term stressor that can trigger cellular responses in the body that exceed what is actually needed to compensate for the otherwise damaging insult. In other words, at the right dose, even things that can be harmful at higher doses, can trigger a net gain in resilience. This occurs by a variety of different mechanisms.

Previously, I have written about the hormetic benefits of heat stress, in particular, through the use of a sauna. Some examples of potential benefits might include:

- improving athletic endurance
- preventing muscle atrophy
- improving insulin sensitivity
- increasing neurogenesis (the growth of new brain cells)
- improved learning/memory
- improved longevity

You can read a little more about heat stress in particular here. (Or watch a video summary here and here.)

In this article, however, I would like to, instead, focus on some of the empirical benefits and mechanisms at play that short bursts of cold exposure (both through cold-water immersion and whole body cryotherapy) may have on the brain, the immune system, body composition, your metabolism, exercise performance and recovery.

The Effects Cold Stress on the Brain

When people think about cryotherapy or cold-water immersion the first thing they think about is, perhaps, the effect on metabolism, muscle soreness, and recovery, athletic performance or just the more immediate effects on the body in general.

What I find the most interesting, and maybe a bit more clear cut in some ways, are the effects on the brain. It's also an area that just generally interests me more, so let's talk about that first. There is anecdotal evidence that cold exposure improves mood and it has been suggested that cold showers may even be used to prevent and treat depression. Let's take a quick dive into one of the mechanisms by which cold exposure may improve mood.

One of the most consistent and profound physiological responses to cold exposure is a robust release of norepinephrine into the bloodstream, as well as in the locus coeruleus region of the brain. What makes norepinephrine so interesting is that it's not only a hormone but also a neurotransmitter and is involved in vigilance, focus, attention and mood. The cold induces this robust increase in norepinephrine in both mice and humans and is a response mediated by the sympathetic nervous system, the primary purpose of which is to stimulate the body's fight-or-flight response. Decreased norepinephrine neurotransmission is associated with inattention, decreased focus and cognitive ability, low energy, and poor mood (generally). When norepinephrine is depleted in people by pharmacological intervention, it causes depression. In fact, both ADHD and depression are sometimes treated with norepinephrine reuptake inhibitors, which of course may come with its own set of drawbacks. Norepinephrine also acts as a hormone and, when released into the bloodstream, acutely increases vasoconstriction (which is the constriction of blood vessels). This last part, of course, helps to explain why norepinephrine plays a really important part in our response to cold: by increasing vasoconstriction, we decrease the total surface area by which the blood is able to lose heat to the environment.

Let's talk about temperatures. Just how cold do you have to get in order to get that hit of norepinephrine? There does appear to be a temperature threshold for activating the sympathetic nervous system. For example, cold-water immersion at 68°F (20°C) for 1 hour does not appear to activate norepinephrine release whereas 1 hour at 57°F (14°C) increased it by 530% and also increased dopamine by 250%. Personally, I think dopamine accompanies norepinephrine quite nicely.

Long durations, however, aren't necessarily required for a potent release of norepinephrine. A long-term study in humans directly compared people that immersed themselves in cold water at 40°F (4.4°C) for 20 seconds to those that did whole body cryotherapy for 2 minutes at -166°F (-110°C) three times a week for 12 weeks and found that in both cases, plasma norepinephrine increased 2 to 3-fold (200 to 300%) and this release of norepinephrine didn't seem to be reduced with habituation to cold. Those levels did, however, drop over the course of an hour after the exposure.
On a side note, guess what else increases norepinephrine release? Heat, as well as lactate, the latter of which is produced by exercise. Learn more about lactate as a brain fuel with this video interview of renown exercise physiologist and pioneer of the lactate shuttle theory Dr. George Brooks… or… learn more about heat-induced norepinephrine release in my video on sauna use.

Finally, one last note about norepinephrine: it also has other profound effects on pain, metabolism, and inflammation. This last point, in particular, may be relevant to the dialogue surrounding mood since inflammation has the quality of being able to also inhibit serotonin release. We will return to the topic of pain, metabolism, and inflammation in a moment, however.

A cold shock protein in the brain. In previous articles and videos, I've talked ad nauseam about the benefits of heat shock proteins, and how they may even be involved in human longevity.

Exposure to the other temperature extreme, cold, also triggers heat shock proteins… but in addition to that, there's a class of proteins that are specific to the cold: cold shock proteins.

Much of what we know about the physiological responses to cold come from research on hibernating mammals. Hibernation involves a profound metabolic shift that is driven by the fundamental biological need to conserve energy in the winter. When the body is cooled many genes are shut down, the exception, however, are genes involved in lipid metabolism (fat burning) and the group of proteins known as *cold shock proteins*. The expression of these two categories of genes are increased upon cold exposure.

One particular cold shock protein known as RNA binding motif 3 (RBM3) especially stands out for the purposes of our discussion. RBM3 is found in the brain, heart, liver, and skeletal muscle and increases in activity greatly upon even mild cold exposure.

Bringing lost synapses back from the brink. Synapses between neurons actually break down during cold exposure. Synapses are how neurons communicate with each other and how memories are formed. This interesting phenomenon was first observed from studies done on hibernating animals.

However, when animals that hibernate warm back up close to 100% of the synapses regenerate. That's a pretty amazing feat! The best part is...this effect may not be limited to just hibernating animals. It's also been shown in laboratory mice, which are not hibernating animals.

Mice that were cooled using a special protocol that included a pharmacological way to dramatically lower body temperature in combination with cold air exposure at a temperature of 41°F (5°C) for 45 minutes experienced ~26% loss of synapses in the hippocampus, which is part of the brain responsible for learning and memory. Once these same mice were allowed to warm back up, they were able to rapidly regenerate around 93% of those synapses that were lost to the cold.

Here's the exciting news: the mechanism by which the lost synapses regenerate was found to be dependent on boosting the activity of RBM3, a cold shock protein that is conserved in humans. We have it too!

The reason RBM3 is necessary for this restoration of synapses is because of the role this cold shock protein plays in binding to RNA to increase protein synthesis at the dendrites, which are a part of the neuron that communicates with synapses. This enables the RBM3 cold shock protein to regenerate those damaged neurons.

A single exposure to this cold shock protocol at 41°F (5°C) for 45 minutes was enough to increase RBM3 in the brain for 3 days (in mice). When this procedure was repeated once a week for two weeks in a row, not only did it robustly increase the expression of RBM3 for those two weeks but also for an additional six weeks after that.

What if synapses could be brought back from insults other than the cold? This is where things get really interesting. Mice that were experimentally induced to have neurodegenerative disease from prion infection, when exposed to two rounds of the cold exposure procedure early in life, were protected against the loss of synapses, allowing them to have more than twice as many synapses (in the brain tissue sampled) as the mice that didn't get the treatment 12 weeks after being infected. The experimental cold stress also prevented cognitive and behavioral deficits that would've normally occurred in these mice as they progressed into later stages of

neurodegeneration. The cold shock they were exposed to increased the expression of the cold shock protein RBM3 for several weeks, and this delayed the neuronal defects that usually occurred in these mice.

It may be pretty obvious that the ability to prevent the loss of synapses is pretty significant and would have huge implications if such a thing could be demonstrated in humans! Losing synapses occur with normal brain aging and is accelerated in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease and also after traumatic brain injury.

Obviously, there are some novel and very interesting mechanisms at play here and the ability to protect synapses effectively might have huge implications for Alzheimer's disease, other neurodegenerative diseases, as well as brain aging in general.

Let's talk about the human relevance of cold shock proteins. This RBM3 stuff is all very new research and we don't *really* know if this effect would occur in the same way in humans. The question is how much does core body temperature need to be lowered to activate RBM3?
It appears that a 2°F reduction in core body temperature is enough to induce cold shock proteins, including RBM3, in human astrocytes (a type of brain cell). As an aside, adding some melatonin to the mix may also have an effect of enhancing RBM3 even more, and supplementing with it also has an effect of lowering core body temperature.

Okay, but, to put that 2ºF in perspective: *this is a very achievable dip in body temperature* that qualifies as only a very mild hypothermia since anything below 96.8ºF is considered hypothermic.
By way of example, in one study, young men that stayed submerged in cold water of 68°F (20°C) for one hour were able to lower their rectal temperature to around 96.9°F (36.1°C) or if they stayed in 57.2ºF (14ºC) water for 1 hour they were able to lower their temperature to 96.1°F (35.6°C). This just goes to illustrate how attainable this level of cold shock is.

The Effects of Cold Exposure on Inflammation and Immune Function

The purpose of inflammation is to eliminate the initial cause of cell injury, clear out dead cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. However, when this process runs awry, in the absence of actual biological threat, we're in trouble. Inflammation has been identified as the key driver of the aging process, and is associated with *most* age-related diseases. A recent study looked at a variety of biomarkers in old people (age 85-99), centenarians (100), semi-supercentenarians (105+) and super-centenarians (110+) and

found that low inflammation was the only biomarker that predicted survival and cognitive capabilities across ALL age groups.

Norepinephrine reduces inflammation. Earlier we focused mostly on the effects of norepinephrine in the context of its role as a neurotransmitter, but when studies show it can be increased by as much as 5-fold from extreme cold stress, it's worth talking a little bit about some of its other roles. One of the roles norepinephrine may also play is in reducing inflammation. Norepinephrine inhibits the inflammatory pathway by decreasing tumor necrosis factor alpha (TNF-alpha), a very potent molecule that increases inflammation. An excess of the inflammatory cytokine TNF-alpha has been implicated in almost every human disease ranging from type 2 diabetes to inflammatory bowel disease to cancer. Believe me, too much of this stuff is bad. In addition to reducing TNF-alpha, norepinephrine has also been shown to decrease other nasty chemicals such as macrophage inflammatory protein-1α (MIP-1α), which is produced by immune cells and may play a role in rheumatoid arthritis.

It's important to note that these anti-inflammatory qualities of norepinephrine qualities of cold-induced norepinephrine, while probably being beneficial in some contexts, may add some level of nuance or complexity to our discussion of the effects of cold modalities, such as winter swimming, cold-water immersion, or cryotherapy in the context of athletic performance. We'll get back to that in a moment, however.

Whole-body cryotherapy and arthritis. Reductions in systemic inflammation are, for the most part, usually unambiguously positive. One such example that stands out and where this might especially be the case is arthritis. In a randomized controlled trial patients with arthritis underwent whole-body cryotherapy -166°F (-110°C) for 2-3 minutes three times a week for 1 week had a significant reduction in pain. There may be many mechanisms at play here including the cold-induced reduction in inflammatory cytokines mentioned a moment ago.

Interestingly, in another study, local cryotherapy, in other words, cooling just the affected tissue, was shown to inhibit harmful collagenase activity on collagen, which is an enzyme that breaks down collagen, and it also decreased the production of inflammatory E2 series prostaglandins.

Some of the pain alleviating effects of cold exposure, particularly in the case of whole-body cryotherapy, may, in fact, be due to increased norepinephrine since inflammation itself causes pain. In fact, spinal injection of compounds that induce a release of norepinephrine has been shown to alleviate pain in human and animal studies.

Let's talk brain inflammation and mood. Pro-inflammatory molecules (such as TNF-alpha and the E2 series prostaglandins) have been shown to cross the blood-brain barrier and activate the brain's immune cells known as microglia. This is bad.

It seems very possible that therapeutic strategies that increase norepinephrine, such as cold-water immersion and whole body cryotherapy, may be a good preventative measure which generally lowers inflammation and thus facilitates this preventative process of attenuating what is otherwise a major contributor to aging in general, but in this case, the brain in particular.

I've also discussed, in a previous publication, the fact that inflammatory molecules probably contribute to depression and anxiety by inhibiting the release of serotonin from neurons. This may be another implication of using cold shock to reduce neural inflammatory processes. Of course, more direct evidence needs to be shown to link cold shock as a strategy for the potential treatment of mood disorders, but it seems like an interesting and promising area of inquiry.

Let's talk general immune function. All this talk of cold exposure, either from cold-water immersion or cryotherapy, lowering inflammation may have you thinking that you might be better off with fewer immune cells since they seem to wreak so much havoc. Actually, having a large number of immune cells is generally a good thing, so long as they're not unnecessarily active. I already mention how inflammation has been identified as a key driver of the aging process but I also want to point out that the immune system plays another important role in the aging process. Aging is associated with immunosenescence (non-functional immune cells) and a general reduction in immune cells. In fact, being very long lived or, making it to the age of a super-centenarian, is associated with having a healthier biological stock of immune cells. You want to have a good number of various types of immune cells, but you also want them to be quiet unless there is a good reason to be loud.

So how does the cold affect our "stock" of immune cells? It appears to increase them, at least certain types of immune cells. Long-term cold-water immersion (3 times a week for 6 weeks) in healthy males was shown to increase lymphocyte numbers. This is in line with the fact that habitual winter swimmers have higher numbers of white blood cells compared to non-habitual winter swimmers. Additionally, another study demonstrated that cold exposure in a climatic chamber at 41°F (5°C) increased white blood cell numbers including cytotoxic T lymphocytes, which are a specialized type of immune cell that kills cancer cells. Males exposed to a cold

(4°C) room for 30 minutes decreases their core body temperature by around 0.45°C and increased natural killer T cell number and activity. Natural T killer cells are another a type of immune cell that kill viruses and tumor cells.

All of this may serve to bolster the anecdote shared often among communities of winter swimmers, which is that they experience fewer everyday cold and flu symptoms. In fact, an association has been demonstrated in epidemiological studies between winter swimming and a 40% decreased incidence of respiratory tract infections. More work needs to be done to better understand what the long-term effects of chronic cold exposure are on immune cell numbers and functions to state definitively what this all means, though.

Cold Exposure, Weight Loss, and Thermogenesis

Taking ice baths has been popularized, in part, due to the effects of the cold on weight loss. One of the body's ways of responding to cold is to increase metabolism, not to produce energy in the form of adenosine triphosphate (known as ATP), but to produce heat to warm the body and, in the process, burn fat. This process is referred to as cold thermogenesis.

There are two types of thermogenesis that occur as a biological response to cold exposure. The first kind of cold-induced thermogenesis occurs in muscle tissue and involves ramping up metabolism in order to produce heat. This works because metabolism is not 100% efficient and produces heat as a byproduct. This is referred to as *shivering thermogenesis,* because the muscle contractions are what actually increases the energy metabolism.

The second type of cold-induced thermogenesis occurs in adipose tissue (fat) and does not involve shivering. It is called *non-shivering thermogenesis*. This type of thermogenesis is what is really responsible for the “fat burning” effect that cold exposure can have and usually happens after the body has adapted to cold exposure.

Let’s talk about non-shivering thermogenesis and brown adipose tissue*.* This process is partly regulated by norepinephrine, which we already know is robustly induced by cold exposure by anywhere from 2 to 5-fold, depending on the intensity of the cold and length of the exposure. Cold-induced norepinephrine increases the expression of protein known as uncoupling protein 1 (UCP1), which has the effect of uncoupling the mitochondria, the energy-producing powerhouses of the cell.

But what does it mean for mitochondria to be uncoupled? When it is said that the mitochondria are coupled, we are referring to the coupling of the generation of a unit of energy (ATP) to the transport of electrons (which have been derived from the food you eat), that create an electrochemical gradient across mitochondria which is negatively charged on the inside and positively charged on the outside. Mitochondria are a little bit like batteries in that sense.

When cold exposure activates the uncoupling protein 1 (UCP1), this uncouples the electrochemical gradient, meaning there is no longer a negative or positive terminal to the mitochondria. In response, the mitochondria try and re-establish the electrochemical gradient by transporting electrons which are derived from stored fat (called fat oxidation) and producing heat as a byproduct of this process.

One of the ways uncoupling protein 1 (UCP1) ramps up metabolism is by producing more mitochondria in adipose tissue, which causes a "browning effect" by converting or "transdifferentiating" the more common white adipose tissue into it's more metabolically active counterpart, brown adipose tissue (BAT). You can think about this is simple terms: the more brown adipose tissue your body has, the more fat your body will burn. The reason it is called brown adipose tissue is because each fat cell has more mitochondria per cell and the mitochondria make the fat appear brown when looking at it under a microscope.

Cold exposure increases non-shivering thermogenesis in humans. It was thought for some time that human adults had negligible amounts of brown adipose tissue (BAT). Increasingly, however, studies are showing that adult humans do have this special type of adipose tissue that is metabolically active. The fact that we have brown adipose tissue at all in adulthood actually overturns old dogma that once stated that BAT was mostly found during infancy in humans. In fact, it's now been shown that brown adipose tissue (BAT) shows an inverse correlation to percent body fat in an individual. Therapeutically enhancing the transdifferentiation or production of brown adipose tissue (BAT) from white adipose tissue (WAT) is a promising and active field of clinically applicable research for the treatment of obesity.

The good news is that repeated intermittent cold exposure has been shown to both increase brown adipose tissue (BAT) in humans and increase our capacity for non-shivering thermogenesis. Healthy young men and women that were exposed to air temperatures of 59-61°F (15-16°C) for 6 hours a day for 10 consecutive days increased their brown adipose tissue by around 37%, and after acclimating also increased non-shivering thermogenesis by

11-18%. It is also interesting to note that if the BAT was sampled during the summer it was only detected in ~25% participants compared to 50% if BAT was sampled during winter.

If having more brown adipose tissue, which becomes more active in cold, helps us stave off obesity then it might reasonably be surmised that being cold would boost our metabolism. In fact, it does! One study done in a small sample of young men showed that cold-water immersion (head out) in 68°F (20°C) for one hour increased metabolic rate by 93% and 1 hour at 57°F (14°C) increased metabolic rate by 350%.

I'd like to discuss one mechanism by which cold exposure may increase the concentration of brown adipose tissue. One study found that the sympathetic nervous system may be playing an intimate role in the production of brown adipose tissue in rats: experimentally blocking beta-adrenergic receptors, which norepinephrine acts on, prevented the production of brown adipose tissue. This relationship is interesting, because it might imply that the greater the release of norepinephrine that we can induce from cold, the more browning of our adipose tissue we might expect to occur.

Our diet may also be a way we can therapeutically brown our adipose tissue. One study recently showed that consumption of fish oil actually increased the metabolism of mice, reduced the fat accumulation between 15 to 25%, and was shown to likely be doing this by a brown adipose tissue-mediated mechanism.

Cold exposure increases activity of antioxidant enzymes. One of the side effects of ramping up fat oxidation to burn stored fat for energy is the production of those damaging reactive oxygen species (ROS) that damage nearly everything inside cells, including DNA. This is actually a normal product of energy metabolism and, in a way, is a natural part of being alive. How we respond to this damage and mitigate it is ultimately what's important.

Reactive oxygen species (ROS), by contributing to things like DNA damage and cellular senescence, are a huge component of the very process of aging. They are also a sign of mitochondrial dysfunction. Being able to prevent that damage from occurring or being able to repair it after it does occur is extremely important to staying healthy, and for one thing, cancer free.

Interestingly enough, it appears as though the exposure to cold, by functioning as a hormetic stressor, actually activates very potent genetic antioxidant systems which are exponentially

more powerful than supplemental antioxidants. For example, young men exposed to cryotherapy for 3 minutes at -202°F (−130°C) everyday for 20 days doubled the activity of one of the most potent antioxidant enzyme systems in the body called glutathione reductase, and increased another potent antioxidant enzyme called superoxide dismutase by ~43%.

Similarly, elite kayakers that engaged in whole body cryotherapy (-248 to -284°F or -120 to -140°C) 3 minutes a day for 10 days increased the activity of superoxide dismutase by 36% and glutathione peroxidase by 68%. That is pretty stout. For those of you not familiar with superoxide dismutase, this enzyme is in your mitochondria cleaning up all that damage that is being produced every second of every day. In other words, it is awesome. It is also important to note that the increase in antioxidant enzyme activity, in this case, took multiple sessions of the whole body cryotherapy...meaning the more frequent cryotherapy was done, the more robust of an increase in activating these powerful antioxidant enzymes.

You can learn more about our endogenous antioxidant systems, some of the nuance surrounding supplemental antioxidants, and the effects of reactive oxygen species in my video "Do Antioxidants Cause Cancer?" by clicking here.

Cold Shock, Muscle Mass, Performance, and Recovery

When it comes to cold exposure in the context of exercise there are two important factors to look at…

- the type of exercise being done ...and…
- the timing of the cold stress in relation to the exercise.

Let's talk about timing. Immediately after exercise activity there is a spike in the production of pro-inflammatory cytokines, which are molecules that activate immune cells and are involved, importantly, in tissue repair. The production of reactive oxygen species and inflammation that occurs immediately after exercise are actually necessary to activate genetic pathways that contribute to creating more mitochondria (mitochondrial biogenesis) and also play a role in muscle hypertrophy. In fact, macrophages, a type of immune cell that can be activated in response to exercise-induced inflammation, produce high levels of the anabolic hormone IGF-1 in response to even slight injury of muscle tissue. There has been some experimental evidence that indicates that these specific immune cells are also likely involved in satellite cell migration. Satellite cells are a type of muscle stem cell that serve as precursors to actual muscle cells and

satellite cell numbers are actually associated very closely with the amount of actual hypertrophy that results from strength training.

Let's get back to the exercise-induced inflammatory response. There is an anti-inflammatory response to this inflammation which begins to peak about 1 hour after exercise. At this point, some of the anabolic hormones such as IGF-1 that are increased with the immune activation seem to also return to pre-exercise levels around 1 hour post-exercise. These anti-inflammatory cytokines help keep our immune system from going overboard. They modulate the activity of the immune cells, preventing them from causing excessive tissue damage.

You might see where I'm going with this already. In the cases where cryotherapy, cold-water immersion, or perhaps even the use of ice packs are used immediately after training, it may undermine certain beneficial effects that actually come from having a small dose of inflammation. In fact, there have been some studies that seem to hint at this fact. We'll dive back into that in a second, but the main thing to remember, for now, is that the peak anti-inflammatory response occurs 1 hour after the activity, and that some inflammation and immune activation before that point is probably a good thing.

Let's talk about the variety of exercise. The other factor that may influence the outcome of studies looking for the effect of cryotherapy or cold-water immersion on athletic performance and recovery is the *type* of activity we're trying to optimize for.

Exercise inflicts stress upon the body, and, in response, the body activates many genes and pathways that build resilience and resistance to that stress. What is important to realize is that the type of exercise actually determines characteristics of the adaptation that occurs: the stress may be predominantly aerobic (such as endurance training), mechanical (such as resistance training) or a mixture of both (plyometric). Activities that are more characteristically aerobic place a greater demand on the cells to be able to utilize oxygen for the purposes of energy production. In other words, aerobic activities have a greater need of supporting mitochondria!

Depending on the nature of the exercise (endurance vs. resistance) and the time of the cold exposure (pre-exercise, immediately after exercise, or later) there may be very different and somewhat opposing outcomes. I believe that these variables can help explain some of the conflicting evidence regarding the benefits of cold exposure in the context of exercise performance that have shown up in the scientific literature and been discussed in the media.

But what does the literature actually say about cold shock and exercise performance?

Strength Training

Whole body cryotherapy at -220 to -319°F (−140 to −195 °C) done 1 hour after plyometric exercise (squat jumps and leg curls) showed improvements in a variety of performance measures up to 72 hours after the treatment. These improvements include: power at the start of the squat jump, and squat jump work up. In addition, pain measures (both at rest and at the next squat jumping session) were also improved.

The next question is what happens if cold exposure occurs immediately after resistance training during that peak pro-inflammatory process? One study has shown that it may actually blunt some of the long-term muscle hypertrophy benefits, at least if you're doing cold-water immersion. Men that performed leg presses and squat jumps twice per week and then immediately engaged in 10 minutes of cold-water immersion (in other words, at the point of peak inflammation) had only ⅓ of the increases in muscle mass in their quadriceps 10 weeks later compared to those that did no cold water immersion post-training. In addition, after the ten weeks of training, muscle strength was significantly lower compared to the control group, they showed smaller increases in type II muscle fibers (required for very short-duration, high-intensity bursts of power), and all of this coincided with a reduction in biomarkers that are usually associated with hypertrophy, including the activation of satellite cells.

Basically, if you were looking to make the argument that cold stress, especially cold-water immersion, should be avoided after strength training… this last study mentioned would be your holy grail. Not just because of the compelling results that the authors demonstrated, but also because they cited other studies that showed similar results with respect to cold exposure and hypertrophy, including some that employed clever investigative methods like having participants do hamstring curls but only immersing one leg in cold water and then going on to measure the difference in hypertrophy between legs afterward.

However, in every single case, both in this study and all of the similar ones cited, there is one singular, unifying theme: the method of cooling whether we're talking about cold-water immersion, icing, or otherwise, was generally applied immediately after training,
So that leaves us with a few open questions, but the most important one is this: *would we still have seen the blunted or reduced hypertrophy training if cold-water immersion was done at literally any point other than immediately after strength training?*

I don't know the answer definitively because no study has investigated this yet, but it's an area I hope future studies will illuminate for us, especially in light of the fact that the occasional cold stress seems to have the possibility of conferring benefits in many other respects. The fact that the first hour after exercise, in particular, stands out as an important anabolic window, at least in terms of the endocrine response, may also be especially meaningful in the context of cold exposure and strength training.

For now, it would seem *extremely prudent* in the context of strength training to exercise caution in how, and especially, when you time any of the various cold modalities whether we're talking cryotherapy, cold-water immersion, or even the use of cold packs.

Endurance

We just talked a lot about strength training in the context of cold-water immersion.

In the case of endurance related activities, the consequences of cold-water immersion, and, in particular, whole-body cryotherapy are slightly more unambiguously positive. This may be characteristic of the type of adaptations that occur that are more specific to endurance activities or it could be that fact that the cold exposure was not done immediately post-exercise. In addition to the effect cold can have on inflammatory processes…

Cold increases mitochondrial biogenesis. Cold stress is able to boost mitochondrial biogenesis. The reason this mechanism exists is pretty straightforward: mitochondria are able to create heat (something you need when cold) as a byproduct of energy production. As the powerhouses of the cell, it can be said that mitochondria are pretty darn useful for *most* of our cells, except red blood cells, which don't have them, however, they're especially important if we want to talk about endurance activity…

That's because mitochondria, and the density or number of them on a per cell basis, affects our *aerobic capacity*. Mitochondria are what gives us the ability to use oxygen in order to produce cellular energy, and if we have more of them, it can be said we may be more adapted to aerobic activity.

Here's how it works…
Cold exposure activates a gene called PGC-1α, which makes more mitochondria in the muscle. This is referred to as mitochondrial biogenesis and PGC-1α is the master regulator of this process. If mitochondrial biogenesis is the orchestra, then PGC-1α is the conductor.

More mitochondria per muscle cell directly translates to aerobic capacity, and a single 15 minute exposure to cold water (50°F or 10°C) following high intensity running, increases PGC-1α in muscle tissue. But even more importantly, cold exposure is actually able to increase mitochondrial biogenesis: men that were immersed in cold water at 50°F (10°C) for 15 minutes 3 times a week for four weeks after running were able to increase mitochondrial biogenesis occurring in their muscle tissue.

Exercise that is highly aerobic, such as jogging or running, has the characteristic of being very metabolically demanding and thus requiring more muscle fibers that are oxidative (oxygen using) and fatigue-resistant. These types of muscle fibers mostly consist of type I (or slow twitch) muscle fibers. In contrast, muscle fibers that are specialized for bursts of short-duration power mostly consist of type II (or fast twitch) muscle fibers which are muscle fibers that are more glycolytic (glycolysis is a process that produces energy that does not require oxygen). There is a category of fast twitch muscle fibers called type IIa that are fast oxidative fibers that are more resistant to fatigue. It turns out that PGC-1α, as part of or in addition to working its magic to trigger mitochondrial biogenesis, also happens to induce a switch to oxidative, fatigue-resistant muscle fibers.

Remember that cold stress induces PGC-1α and this induces mitochondrial biogenesis. It is interesting to note that getting rid of PGC-1α in the muscle tissue of mice has been shown to shift muscle fibers from the slow twitch type I and the fast twitch type IIa muscle fibers that are both oxygen-requiring and more resistant to fatigue, toward fast twitch type IIb muscle fibers, which are glycolytic fibers required for very short-duration, high-intensity bursts of power such as maximal and near-maximal lifts and short sprints. In line with this, genetically engineering mice to express more PGC-1α in muscle tissue than they normally have, causes their muscle cells to show characteristics of type I muscle fibers, such as a greater resistance to fatigue.

In my mind, this suggests that PGC-1α-mediated mitochondrial biogenesis may be slightly more beneficial for endurance athletes than those focused purely on brute strength, if for no reason other than the fact that it seems to shift muscle fibers into a configuration that is more conducive to a higher aerobic capacity and more resistant to fatigue. Of course, I can't say that this is absolutely the case because PGC-1α also increase type IIa muscle fibers and type II fibers do have a higher capacity for hypertrophy.

So now that we've covered a little bit on why endurance activities may be a little bit less likely to experience specific deleterious consequences of mistimed cold stress, let's talk about what the actual literature says about whole-body cryotherapy, and cold-water immersion in the context of performance enhancements.

Elite runners that engaged in whole body cryotherapy 1 hour, 24 hours, or 48 hours post hill sprint running had a 20% increase in speed and power up to two days later. This 20% performance enhancement post-cryotherapy may be attributed to the reduction in inflammation and increase in anti-inflammatory factors. Too high of levels of proinflammatory cytokines post-exercise can result in acute performance deterioration and muscle damage. This can be problematic for training even several days later, since there may be a greater risk of injury due to residual soreness and changes in muscle function. In fact, it has been shown that elite runners who engaged in whole body cryotherapy for 3 min at -166°F (−110°C) performed 1 hour post-exercise and 24 hours post-exercise enhanced muscle recovery by decreasing the inflammatory process (IL-1β and C-reactive protein) and increasing the anti-inflammatory process (IL-1ra) at both time points.

Another study including elite tennis players also showed performance enhancements that were associated with a reduction in inflammation. Elite tennis players that engaged in whole body cryotherapy (-184°F or -120°C) twice a day (in the morning and evening while training in the afternoon) for five days had a 2.5-fold decrease in the potent pro-inflammatory cytokine TNF-alpha and a 23% increase in the cytokine IL-6, which has both pro- and anti-inflammatory properties and plays a role in muscle repair. These professional tennis players also experienced a 4% increase in "stroke effectiveness," meaning they hit more balls in the target zone compared to the players that did not do cryotherapy. Hey, that's what counts, right? Maybe it’s that norepinephrine helping with focus and attention.

These endurance performance enhancements from post-exercise cold exposure may also be sustained over a prolonged time period. Elite cyclists engaged in 15 minutes of cold-water immersion (159.5°F or 15.3°C) 30 minutes post-training 4 times per week. This training lasted 39 days and consisted of a mixture of low–moderate-intensity road rides and high-intensity interval sessions on a exercise bike (ergometer). The cyclists that engaged in cold-water immersion post-training experienced a 4.4% increase in average sprint power, 3% enhancement in repeat cycling performance, and a 2.7% increased power over the 39 day training period. That sounds awesome.

Role in preventing muscle atrophy. So far we've covered effects of various cold exposure modalities on building muscle, but one last area of discussion that I'd like to cover that loosely fits into this area is the topic of muscle atrophy.

Quite a bit earlier when we were still talking about some of the interesting brain effects of cold stress, we talked about the effect cold has on the production of a cold shock protein called RBM3. We also talked a bit about some of the studies done on hibernating animals, which, of course, have to be especially capable at resisting the effects of cold during the winter.

One other interesting aspect of hibernation is the fact that animals that experience this phenomenon, at least in the case of black bears, also experience significantly less muscle atrophy than would be expected for such a long period of fasting and general inactivity.

As you might imagine, this probably is pretty useful for a hibernating animal! There is evidence that black bears actually retain protein balance in their skeletal muscle during hibernation. In other words, they are not, generally degrading more proteins than they are making in their muscle tissue, which would cause muscle atrophy. This phenomenon is not limited to bears. It's been shown that hibernating squirrels also experience an increase in RBM3 in the brain, cardiac, and skeletal muscle. Skeletal muscle cells from mice that have been engineered to have increased levels RBM3 have improved muscle cell survival, and even a larger muscle cell size after being exposed to cold shock. RBM3 is clearly playing an important role in the muscle in multiple organisms and may be serving as a generalized mechanism for decreasing atrophy. This would also explain why RBM3 is the most highly elevated gene in the muscle tissue of black bears that is in concordance with protein synthesis during their hibernation.

RBM3 isn't the only cold-inducible protein that is associated, at least in animal studies, with a reduction in muscle atrophy. PGC-1α, the master regulator of mitochondrial biogenesis that we talked about earlier, like RBM3, has also been shown to be increased in humans under conditions of cold stress. It has been shown to protect against sarcopenia (age-related muscle loss) and metabolic disease in mice that were genetically engineered to express more of the protein.

While it's important to note that all of these studies that I've discussed in the context of muscle atrophy are animal studies, it shows promise when you see a similar effect conserved across multiple different species of animal, because it hints at the fact that this mechanism *might*

extend to us as well, and is probably not a point of specialization… at least not for one specific species.

Finally, one last note on this subject: heat shock proteins, otherwise known as HSPs, can also be induced to some extent by cold, and I've discussed in a previous video on the science of sauna use, how heat stress and the concomitant elevation of heat shock proteins has been demonstrated to greatly increase muscle re-growth by 30% in rats during the two week "reloading phase" that followed a week of forced immobilization (atrophy).

Comparing Whole Body Cryotherapy and Cold-Water Immersion

We've talked a lot about cold-water immersion and whole body cryotherapy, and cold packs, and hibernation, and everything in between in an effort to be comprehensive and see where we can make inferences. However, what we have not done is more directly try to compare whole body cryotherapy and cold-water immersion. In terms of application, this is actually a really important point.

So here's the million dollar question: is whole body cryotherapy the same as cold-water immersion? The answer is probably not.

If we dive into the science we can see that there are three factors that really differentiate whole body cryotherapy from cold-water immersion and all of them have to do with how effectively each technique lowers body temperature. But I also want to point out that in addition to these three factors, which we will discuss in a minute, is the fact that people can remain in cold water for longer durations than cold air cryochambers and this may affect how robust the cold shock response is.

These factors are...
1.) Thermal conductivity. This is essentially how well heat is extracted from the body.
2.) How much of the body is exposed to the cold (surface area).
3.) Temperature gradient

Each of the mediums (ice, water, and air) have different properties that affect how well heat is extracted from the body. Starting with the first factor, thermal conductivity (how well heat is extracted from the body). Ice has the greatest capability to extract heat from the body, followed

by cold water, and finally air. Cryotherapy is slightly less effective at heat transfer since it only uses air. The second factor, surface area, also plays a role in cooling the body. In the case of cold-water immersion the surface area of cold water covering the body really depends on the protocol and can vary from submerging just the legs or can involve submersion all the way up to the shoulders. In any case, your head will usually not be submerged. This is different from a cryotherapy chamber where the entire body including the head is exposed. Although some cryo tanks do not expose the head to cool air. Finally, the third factor is the temperature gradient which is the actual temperature difference between your body temperature (98.6ºF or 37ºC) and the modality being used to suck the heat right out of you. This is really where cryotherapy shines because the air temperature can be as low as -289°F (-178°C). That is cold.

Lastly, another important factor to consider when comparing cold-water immersion differences with exposure to cryogenic temperatures in the air is that fact that people can stay submerged in the cold water for much longer time periods than cryotherapy air temperatures.

So what's the final word? Well, what is clear is that there is a very robust release of norepinephrine in the brain and the body that is consistent with both cold-water immersion and whole body cryotherapy. There have even been studies comparing the norepinephrine response to cold-water immersion (whole body submerged for 20 seconds in 40°F) with whole body cryotherapy (2 min at -166°F) and found they are more or less identical, at least in that respect. Now, if you were to stay submerged in that cold water for an hour as opposed to just 20 seconds we know that norepinephrine would increase 5-fold. Which brings us back to the point that exposing the body to cold for prolonged periods may have a more robust effect. Other than that… I'll leave it as an exercise to the reader (and listener) to make their own value assessment based on the information at hand. It's probably not worth overthinking too much at this point.

The Thousand Mile High Summary

We've covered a lot, so I think now is as good of a time as any to take a step back and ask what's the big picture message here. In other words, what does all of this mean? I think there's many key take homes from all of this. I'll try to summarize just a few.

- ONE. Cold shock shows some interesting promise for helping diseases of neurodegeneration through a special cold shock protein known as RBM3… will we be taking people and putting them through super traumatic freezing temperatures in the future to prevent Alzheimer's? I don't know, but the fact that this neuroprotective,

synapse fixing effect happens in mice is a very good sign and hints at some really profound things we may find out in the future are applicable to humans as well.

- TWO. Norepinephrine, which can go up a huge amount from a variety of different cold stressors, has some pretty interesting properties and is a very versatile neurotransmitter and hormone! We need it for vasoconstriction, as part of our body's dynamic response to cold, but it is also anti-infammatory. For this reason it may have special relevance for diseases of inflammation, like arthritis, as well as mood and even depression.
- THREE. Giving yourself short bouts of intense cold stress may be applicable if you have some degree of chronic pain, because of the analgesic effect, which may also be partly mediated by… you guessed it… norepinephrine.
- FOUR. There may be some truth to winter swimming improving immune function in regular practitioners.
- FIVE. In contrast to old dogma, adult humans have brown fat and exposure to cold increases it. Brown fat generally decreases as we get older, especially if we're obese. Having more of it, however, is associated with trending towards a lower body fat percentage, and, finally, the amount of brown fat is directly affected by our exposure to cold. Cold-water immersion can definitely increase brown fat, but so can cold air, which means whole body cryotherapy is probably also effective for this purpose.
- SIX. Using cryotherapy and cold-water immersion in the context of exercise is sort of complicated! You can definitely undermine your gains in the context of resistance training *if* you're doing cold-water immersion immediately after training. In other contexts, however, there may be improvements as well. We still have some unanswered and very interesting questions surrounding this. I'm hopeful that the more deleterious effects will turn out to be mostly constrained to the hour long window of time immediately after training, but I'm not really sure. We need more studies to say for certain!
- SEVEN. When comparing whole-body cryotherapy and cold-water immersion, they are are probably pretty similar… at least in many of their hormonal responses. One key point of difference is that it is possible to stay in cold water for a longer period of time than it is to stay in a cryotherapy chamber, which could put you in danger of local tissue damage, such as frostbite. Do what strikes your fancy until better evidence emerges.

Cautionary Note

It is prudent to consult a physician before beginning a new workout program, and this is no less true for activities like cold-water immersion, winter swimming, or cryotherapy. This document is for informational purposes only and not medical advice. Use this information at your own risk.

Additionally, if you have coronary risk factors or other heart related risk factors, it is especially important that you consult a medical physician before attempting anything discussed in this article, but, perhaps, especially before doing contrast therapy (going rapidly from very hot to very cold).