Hyperthermic Conditioning's Role In Increasing Endurance, Muscle Mass, and Neurogenesis

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For the most part, people don't like to get hot.

The massive indoor climate control systems and pleasantly chilled water fountains found in most gyms speak to this fact. There are some exceptions — Bikram yoga, for example — but they're few and far between.

But here's the surprise: increasing your core temperature for short bursts is not only healthful, it can also dramatically improve performance.

This is true whether it's done in conjunction with your existing workout or as an entirely separate activity. I'm going to explain how heat acclimation through sauna use (and likely any other non-aerobic activity that increases core body temperature) can promote physiological adaptations that result in increased endurance, easier acquisition of muscle mass, and a general increased capacity for stress tolerance. I

will refer to this concept of deliberately acclimating yourself to heat, independent of working out, as “hyperthermic conditioning.”

I'm also going to explain the positive effects of heat acclimation on the brain, including the growth of new brain cells, improvement in focus, learning, and memory, and ameliorating depression and anxiety. In addition, you’ll learn how modulation of core temperature is even responsible for or plays a major role in what has been termed the "runner's high" via an interaction between the dynorphin/beta-endorphin opioid systems.

The Effects of Heat Acclimation on Endurance

If you’ve ever run long distances or exercised for endurance, it’s intuitive that increased body temperature will ultimately induce strain, attenuate your endurance performance, and accelerating exhaustion. What might not be as intuitive is this: acclimating yourself to heat independent of aerobic physical activity through sauna use induces adaptations that reduce the later strain of your primary aerobic activity.

Hyperthermic conditioning improves your performance during endurance training activities by causing adaptations, such as improved cardiovascular and thermoregulatory mechanisms (I will explain what these mean) that reduce the negative effects associated with elevations in core body temperature. This helps optimize your body for subsequent exposures to heat (from metabolic activities) during your next big race or even your next workout.

Just a few of the physiological adaptations that occur subsequent to acclimation to heat include:

- Improved cardiovascular mechanisms and lower heart rate.[1]
- Lower core body temperature during workload (surprise!)
- Higher sweat rate and sweat sensitivity as a function of increased thermoregulatory control.[2]
- Increased blood flow to skeletal muscle (known as muscle perfusion) and other tissues.[2]
- Reduced rate of glycogen depletion due to improved muscle perfusion.[3]
- Increased red blood cell count (likely via erythropoietin).[4]
- Increased efficiency of oxygen transport to muscles.[4]

[Watch Youtube Video Here.]

Hyperthermic conditioning optimizes blood flow to the heart, skeletal muscles, skin, and other tissues because it **increases the plasma volume**. This causes endurance enhancements during your next workout or race when your core body temperature is elevated *again*, and here is why:

Being heat acclimated ***enhances endurance*** by the following mechanisms:

1. t increases plasma volume and blood flow to the heart (stroke volume).[2,5] This results in reduced cardiovascular strain and lowers the heart rate for the same given workload.[2] These cardiovascular improvements have been shown to enhance endurance in highly trained as well as untrained athletes.[2,5,6]

2. It increases blood flow to the skeletal muscles, keeping them fueled with glucose, esterified fatty acids, and oxygen. The increased delivery of nutrients to muscles reduces their dependence on glycogen stores. Endurance athletes often hit a "wall" when they have depleted their muscle glycogen stores. Hyperthermic conditioning has been shown to reduce muscle glycogen use by 40%-50% compared to before heat acclimation.[3,7] This is presumably due to the increased blood flow to the muscles.[3] In addition, lactate accumulation in blood and muscle during exercise is reduced after heat acclimation.[5]

3. It improves thermoregulatory control, which operates by activating the sympathetic nervous system and increasing the blood flow to the skin and, thus the sweat rate. This dissipates some of the core body heat. After acclimation, sweating occurs at a lower core temperature and the sweat rate is maintained for a longer period.[2]

Okay, up until this point we've talked about general mechanisms by which performance gains occur as a consequence of heat acclimation. Equally important, however, is the sort of real world difference that might be expected. So what sort of gains can you anticipate?

One study demonstrated that a **30-minute sauna session two times a week for three weeks post-workout increased the time that it took for study participants to *run until exhaustion by 32%* compared to baseline.**[4]

The 32% increase in running endurance in the aforementioned study was accompanied by a 7.1% increase in plasma volume and 3.5% increase in red blood cell (RBC) count.[4] This increased red blood cell count accompanying these performance gains feed right back into those more general mechanisms we talked about earlier, the most obvious of which being: more red blood cells increase oxygen delivery to muscles. It is thought that heat acclimation boosts the RBC count through erythropoietin (EPO) because the body is trying to compensate for the corresponding rise in plasma volume.[4]

In other words, hyperthermic conditioning through sauna use doesn't just make you better at dealing with heat; it makes you better, period. I do want to mention that while these gains were made with a small sample size (N=6) some of the later studies that I will point out reinforce this conclusion.

The Effects of Hyperthermic Conditioning on Muscle Growth (Hypertrophy)
Exercise induces muscle hypertrophy. Heat induces muscle hypertrophy. Both of these together synergize to induce hyper-hypertrophy.

Okay, but seriously… Here are a few of the basics of how muscle hypertrophy works: muscle hypertrophy involves both the increase in the ***size of muscle cells*** and, perhaps unsurprisingly, an accompanying increase in strength. Skeletal muscle cells do contain stem cells that are able to increase the number of muscle cells but hypertrophy instead *generally* involves an increase in size rather than number.

So what determines whether your muscle cells are growing or shrinking (atrophying)?
A shift in the protein synthesis to degradation ratio…and an applied workload on the muscle tissue (of course). That's it.

At any given time your muscles are performing a balancing act between NEW protein synthesis and degradation of existing proteins. The important thing is your *net* protein synthesis, and not strictly the amount of new protein synthesis occurring. Protein degradation occurs both during muscle use and disuse. This is where hyperthermic conditioning shines: **heat acclimation reduces the amount of protein degradation** occurring and as a result it increases *net* protein synthesis

and, thus muscle hypertrophy (as is the case during muscle use). Hyperthermic conditioning is known to increase muscle hypertrophy by increasing *net* protein synthesis through three important mechanisms:

- Induction of heat shock proteins.[8,9]
- Robust induction of growth hormone.[1]
- Improved insulin sensitivity.[10]

Exercise induces both protein synthesis and degradation in skeletal muscles but, again, it is the ***net protein synthesis*** that causes the actual hypertrophy. When you exercise, you are increasing the workload on the skeletal muscle and, thus, the energetic needs of your muscle cells. The mitochondria found in each of these cells kick into gear in order to help meet this demand and start sucking in the oxygen found in your blood in order to produce new energy in the form of ATP. This process is called oxidative phosphorylation. A by-product of this process, however, is the generation of oxygen free radicals like superoxide and hydrogen peroxide, which is more generally referred to simply as "oxidative stress".

Heat Stress Triggers Heat Shock Proteins That Prevent Protein Degradation
Oxidative stress is a major source of protein degradation. For this reason, any means of preventing exercise-induced oxidative protein damage and/or repairing damaged proteins, while keeping the exercise induced protein synthesis, will ultimately cause a net increase of protein synthesis and therefore will be anabolic.

Heat shock proteins (or HSPs), as the name implies, are induced by heat and are a prime example of hormesis. Intermittent exposure to heat induces a hormetic response (a protective stress response), which promotes the expression of a gene called heat shock factor 1 and subsequently HSPs involved in stress resistance.

- HSPs can prevent damage by directly scavenging free radicals and also by supporting cellular antioxidant capacity through its effects on maintaining glutathione.[8,9]
- HSPs can repair misfolded, damaged proteins thereby ensuring proteins have their proper structure and function.[8,9]

Okay, let's take a step back from the underlying mechanisms and look at the big picture of heat acclimation in the context of *increasing muscle hypertrophy*:

It has been shown that a 30-minute intermittent hyperthermic treatment at 41°C (105.8°F) in rats induced a robust expression of heat shock proteins (including HSP32, HSP25, and HSP72) in muscle and, importantly, this correlated with **30% more muscle regrowth than a control group during the seven days subsequent to a week of immobilization.**[8] This HSP induction from a 30-minute whole body hyperthermic exposure can persist for up to 48 hours after heat shock.[8,9] Heat acclimation actually causes a higher basal (such as when not exercising) expression

of HSPs and a more robust induction upon elevation in core body temperature (such as during exercise).[11-13] This is a great example of how a person can theoretically use hyperthermic conditioning to increase their own heat shock proteins and thereby reap the rewards.

Heat Stress Triggers A Massive Release of Growth Hormone

Another way in which hyperthermic conditioning can be used to increase anabolism is through a massive induction of growth hormone.[1,14,15] Many of the anabolic effects of growth hormone are thought to be mediated by IGF-1, which is synthesized (mainly in liver but also in skeletal muscle) in response to growth hormone. There are two important mechanisms by which IGF-1 promotes the growth of skeletal muscle:

1. Activation of the mTOR pathway, which is responsible for protein synthesis.[16]
2. Inhibition of FOXO activation, which inhibits protein degradation. [16]

Mice that have been engineered to express high levels of IGF-1 in their muscle develop skeletal muscle hypertrophy, can combat age-related muscle atrophy, and retained the same regenerative capacity as young muscle. [17,18] In humans, it has been shown that the major anabolic effects of growth hormone in skeletal muscle may be due to inhibition of muscle protein degradation (anti-catabolic) and thereby increasing net protein synthesis.[16] In fact, growth hormone administration to endurance athletes for four weeks has been shown to decrease muscle protein oxidation (a biomarker for protein degradation) and degradation by 50%.[19]

My point is good news. You don't need to take exogenous growth hormone. Sauna use can cause a robust release in growth hormone, which varies according to time, temperature, and frequency.[1,15]

For example, two 20-minute sauna sessions at 80°C (176°F) separated by a 30-minute cooling period elevated growth hormone levels two-fold over baseline.[1,15] Whereas, two 15-minute sauna sessions at 100°C (212°F) dry heat separated by a 30-minute cooling period resulted in a five-fold increase in growth hormone.[1,15] However, what's perhaps more amazing is that repeated exposure to whole-body hyperthermia through sauna use has an even more profound effect on boosting growth hormone immediately afterward: **two one-hour sauna sessions a day at 80°C (176°F) dry heat (okay, this is a bit extreme) for 7 days was shown to increase growth hormone by 16-fold on the third day**.[14] The growth hormone effects generally persist for a couple of hours post-sauna.[1] It is also noteworthy, however, is that sauna use and exercise can synergize to significantly elevate growth hormone when used in conjunction with each other.[20]

Increased Insulin Sensitivity

Insulin is an endocrine hormone that primarily regulates glucose homeostasis, particularly by promoting the uptake of glucose into muscle and adipose tissue. In

addition, insulin also plays a role in protein metabolism, albeit to a lesser degree than IGF-1. Insulin regulates protein metabolism in skeletal muscle by the two following mechanisms:

1. It increases protein synthesis by stimulating the uptake of amino acids (particularly BCAAs) into skeletal muscle.[21]
2. It decreases protein degradation through inhibition of the proteasome, which is a protein complex inside cells that is largely responsible for the degradation of most cellular proteins.[22]

In humans, there is more evidence indicating that the major anabolic effects of insulin on skeletal muscle are due to its inhibitory action on protein degradation.

For example, insulin infusion in healthy humans, which increased insulin to normal physiological postprandial (after a meal) levels, suppressed muscle protein breakdown without significant affecting muscle protein synthesis. [21,23] In contrast, insulin deficiency (such as in type 1 diabetes mellitus) and insulin resistance (to a lesser extent) are both associated with increased skeletal muscle breakdown. [22,24]

For this reason, hyperthermic conditioning may also lend itself to promoting muscle growth by improving insulin sensitivity and decreasing muscle protein catabolism. Intermittent hyperthermia has been demonstrated to reduce insulin resistance in an obese diabetic mouse model. Insulin resistant diabetic mice were subjected to 30 minutes of hyperthermic treatment, three times a week for twelve weeks. **This resulted in a 31% decrease in insulin levels and a significant reduction in blood glucose levels, suggesting re-sensitization to insulin**.[10] The hyperthermic treatment specifically targeted the skeletal muscle by increasing the expression of a type of transporter known as GLUT 4, which is responsible for the transporting of glucose into skeletal muscle from the bloodstream. Decreased glucose uptake by skeletal muscle is one of the mechanisms that leads to insulin resistance.

Relevance for Muscle Injury

Muscle atrophy primarily occurs as a consequence of tipping the balance towards protein degradation and away from protein synthesis in the muscles. This is particularly important after muscle injury, which causes immobilization and disuse of muscles for some time. Of course, this does result in some muscle atrophy. Animal studies using rats have shown that whole body hyperthermia at 41°C (105.8°F) for 30 minutes and 60 minutes attenuates hindlimb muscle atrophy during disuse by 20% and 32%, respectively.[9,25] In order to return to a hypertrophic state after injury, muscle regrowth ("reloading") must occur. Muscle reloading, while important for hypertrophy, induces oxidative stress particularly after periods of disuse, which slows the rate of muscle regrowth. A 30-minute hyperthermic treatment at 41°C (105.8°F) increased soleus muscle regrowth by 30% after reloading as compared to non-hyperthermic treatment in rats.[8] The effects of whole body hyperthermia on preventing muscle atrophy and increasing muscle regrowth

after immobilization were shown to occur as a consequence of elevated HSP levels.[8,9,25]

During injury you may be immobilized but you don't have to be very mobile to sit in the sauna a few times a week to boost your HSPs! This is a clear win in the injury and recovery department. Remember, hyperthermic conditioning (from sauna use) results in an elevation in HSP levels under normal conditions and an even greater boost during exercise (or when core body temperature is elevated).[11-13]

Relevance for Rhabdomyolysis

Hyperthermic conditioning may also be able to protect against rhabdomyolysis (muscle breakdown due to severe muscle overuse) through the induction of HSP32 also known as heme oxygenase 1.[26,27] Rhabdomyolysis releases myoglobin, a byproduct from broken down muscle tissue, into the bloodstream causing kidney failure. Since myoglobin is a heme-containing protein, HSP32 (heme oxygenase 1) can rapidly degrade myoglobin before it has toxic effects on the kidney.[26,27] In fact, induction of HSP32 in rats has been shown to protect against rhabdomyolysis in rats.[26] Again, heat acclimation causes a higher basal expression of HSPs and a more robust expression upon heat stress. [11-13] The more heat acclimated your body is (the pre-conditioning is key here), the higher your HSP32 expression will be during physical activity and this will protect your kidneys from the toxic myoglobin breakdown product.

That's a sweet deal.

Longevity

In flies and worms, a brief exposure to heat treatment has been shown to increase their lifespan by up to 15% and it's been shown that this effect is specifically mediated by HSPs.[28-30] One possible explanation for the increased lifespan is heat stress is known to induce hormesis. This boosts the expression of heat shock proteins, which are known to improve longevity.

While studying the effects of something like hyperthermic conditioning on longevity is inherently hard in humans (obviously), there have been some preliminary positive associations with variations in the HSP70 gene associated with increased expression and longevity.[31]

Effects of Heat Stress and Acclimation on The Brain

One of the ways that the brain actually responds to injury on the cellular level is increased HSP production. This includes ischemic injury (stroke), traumatic injury, and excitotoxicity (epileptic).[32] What complicates things, however, in the context of "hyperthermic conditioning" (or deliberate heat acclimation) is that while on the one hand hyperthermia has been shown to reduce the frequency of seizures and the damage they cause post-conditioning, hyperthermia can actually increase the

damage caused by seizures if they occur during a period of heat stress. In other words, the stress and its damaging effects are additive.[33,34]

That (and it's implicit warning) being said, sauna-induced hyperthermia has been shown to induce a robust activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. One study demonstrated that men that stayed in the sauna that was heated to 80°C (176°F) until subjective exhaustion increased norepinephrine by 310%, had a 10-fold increase in prolactin, and actually modestly decreased cortisol.[1,15] Similarly, in another study, women that spent 20-minute sessions in a dry sauna twice a week had a 86% increase in norepinephrine and a 510% increase in prolactin after the session.[35]

Norepinephrine helps with focus and attention while prolactin promotes myelin growth, which makes your brain function faster, which is key in repairing nerve cell damage.[36,37] In addition to increasing norepinephrine, heat acclimation has actually been shown to increase biological capacity to store norepinephrine for later release.[38] In light of the fact that the norepinephrine response to exercise has been demonstrated to be blunted in children with ADHD and that norepinephrine reuptake inhibitors (NRI) are frequently prescribed to treat ADHD (among other things), use of heat stress and subsequent acclimation should be tested for it's effectiveness as an interesting alternative therapeutic approach.[39]

Neurogenesis

Heat stress has been shown to increase the expression of brain-derived neurotrophic factor (BDNF) more than exercise alone when used in conjunction with exercise.

This is important because BDNF increases the growth of new brain cells as well as the survival of existing neurons. An increase in neurogenesis is thought to be responsible for enhancing learning. [40] BDNF's role in the brain is also to modulate neuronal plasticity and long-term memory, while also having been shown to ameliorate anxiety and depression from early-life stressful events.[41] In addition to the function BDNF plays in the brain when it's released as a consequence of exercise, BDNF is also secreted by muscle where it plays a role in muscle repair and the growth of new muscle cells.[42]

While BDNF has specifically been shown to play some role in ameliorating depression from early-life stressful events, whole-body hyperthermia has also been demonstrated to improve depression in cancer patients.[43] In this particular study, however, it was speculated that beta-endorphin (which is also induced by hyperthermia), not BDNF, may have been the agent responsible for this effect. As an aside, one of the reasons whole-body hyperthermia is sometimes used with cancer patients is because it can enhance the effects of chemotherapeutic agents.[44]

The Runner's High and The Role of Dynorphin

Ever wonder what is responsible for the "runner's high" or the post-exercise high, in general? You may think it is due to endorphins but that's not the whole story. Beta-endorphins are endogenous (natural) opioids that are a part of the body's natural painkiller system, known as the mu opioid system, which block pain messages from spreading from the body to the brain in a process called antinociception. You are probably familiar with this concept, but what is less well known is that the body also produces a peptide known as dynorphin (a "kappa opioid"), which is generally responsible for the sensation of dysphoria. The discomfort experienced during intense exercise, exposure to extreme heat (such as in a sauna), or eating spicy food (capsaicin) is due to the release of dynorphin. The release of dynorphin causes an upregulation and sensitization of mu opioid receptors, which interact with beta-endorphin.[45] This process is what underlies the "runner's high" and is directly precipitated by the discomfort of physical exercise. Translation: the greater the discomfort experienced during your workout or sauna, the better the endorphin high will be afterward. Now you understand the underlying biological mechanism that explains this.

Why is this relevant to hyperthermic conditioning and sauna use?
Heat stress from heat exposure in a dry sauna has been demonstrated to cause a potent increase in beta-endorphin levels, even more than exercise alone.[1,15]

A study in rats explains this somewhat: dynorphin delivered directly into a part of the hypothalamus in the brains of rats triggers a drop in their body temperature, while blocking dynorphin with an antagonist was shown to prevent this same response. Similarly, mu receptor agonists have been shown to induce increases in body temperature in rats.[46] What this seems to imply is that perhaps, by deliberately manipulating your body temperature you are actually ***directly*** engaging the mu (endorphin) and kappa opioid (dynorphin) systems since they clearly play a role in temperature regulation in general.

In Conclusion
To recap and drive the point home: acclimating your body to heat stress by intermittent whole-body hyperthermia through sauna use ("hyperthermic conditioning") has been shown to:

Enhance endurance by:

- Increasing nutrient delivery to muscles thereby reducing the depletion of glycogen stores.
- Reducing heart rate and reducing core temperature during workload.

Increase muscle hypertrophy by preventing protein degradation through the following three means:

- Induction of heat shock proteins and a hormetic response (which has also been shown to increase longevity in lower organisms).
- Cause a massive release of growth hormone.
- Improving insulin sensitivity.

NOTE It also accomplishes this arguably without the same risk that might otherwise be associated with exogenous or supraphysiological levels of other hormones, like growth hormone.

Hyperthermic conditioning also has robust positive effects on the brain:

- Increases the storage and release of norepinephrine, which improves attention and focus.
- Increases prolactin, which causes your brain to function faster by enhancing myelination and helps to repair damaged neurons.
- Increases BDNF, which causes the growth of new brain cells, improves the ability for you to learn new information and retain it, and ameliorates certain types of depression and anxiety.
- Causes a robust increase in dynorphin, which results in your body becoming more sensitive to the ensuing endorphins.

Life is stressful. When you exercise you are essentially forcing your body to become more resilient to stress (somewhat paradoxically) through stress itself.

Hyperthermic conditioning is a novel and possibly effective tool that can improve your resistance to the sort of stress associated with fitness pursuits as well as some that are not traditionally associated with fitness such as the protective effects of HSPs on various types of stress. **That being said, deliberately applied physical stress, whether heat stress or ordinary exercise, is something that requires caution.**

You shouldn't avoid it altogether, but you should use good common sense, not overwhelm yourself, and make sure to know your limits. (NOTE: you should not drink alcohol before or during sauna use as it increases the risk of death).[47] Personal variation probably comes into play when finding your own sweet spot for building thermal tolerance while avoiding over-extending yourself.

I believe that hyperthermic conditioning in general may be worth a closer look as a tool in the toolbox of athletes. Perhaps it can be used for much more than just relaxation?

But no matter how enthusiastic you might be, remember:

Heat responsibly and with someone else, never alone.
Never heat yourself while drunk, and friends don't let friends sauna drunk.
If you are pregnant or have any medical condition, saunas are not for you. Speak with your doctor before starting this or any regimen involving physical stressors.

Be careful, ladies and gents.

References

1 Hannuksela, M. L. & Ellahham, S. Benefits and risks of sauna bathing. *The American journal of medicine* **110**, 118-126 (2001).
2 Ricardo J. S. Costa, M. J. C., Jonathan P. Moore & Neil P. Walsh. Heat acclimation responses of an ultra-endurance running group preparing for hot desert-based competition. *European Journal of Sport Science*, 1-11 (2011).
3 King, D. S., Costill, D. L., Fink, W. J., Hargreaves, M. & Fielding, R. A. Muscle metabolism during exercise in the heat in unacclimatized and acclimatized humans. *J Appl Physiol* **59**, 1350-1354 (1985).
4 Scoon, G. S., Hopkins, W. G., Mayhew, S. & Cotter, J. D. Effect of post-exercise sauna bathing on the endurance performance of competitive male runners. *Journal of science and medicine in sport / Sports Medicine Australia* **10**, 259-262, doi:10.1016/j.jsams.2006.06.009 (2007).
5 Michael N. Sawka, C. B. W., Kent B. Pandolf. Thermoregulatory Responses to Acute Exercise-Heat Stress and Heat Acclimation. *Handbook of Physiology, Environmental Physiology* (2011).
6 Garrett, A. T., Creasy, R., Rehrer, N. J., Patterson, M. J. & Cotter, J. D. Effectiveness of short-term heat acclimation for highly trained athletes. *European journal of applied physiology* **112**, 1827-1837, doi:10.1007/s00421-011-2153-3 (2012).
7 Kirwan, J. P. *et al.* Substrate utilization in leg muscle of men after heat acclimation. *J Appl Physiol (1985)* **63**, 31-35 (1987).
8 Selsby, J. T. *et al.* Intermittent hyperthermia enhances skeletal muscle regrowth and attenuates oxidative damage following reloading. *J Appl Physiol (1985)* **102**, 1702-1707, doi:10.1152/japplphysiol.00722.2006 (2007).
9 Naito, H. *et al.* Heat stress attenuates skeletal muscle atrophy in hindlimb-unweighted rats. *J Appl Physiol* **88**, 359-363 (2000).
10 Kokura, S. *et al.* Whole body hyperthermia improves obesity-induced insulin resistance in diabetic mice. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group* **23**, 259-265, doi:10.1080/02656730601176824 (2007).
11 Yamada, P. M., Amorim, F. T., Moseley, P., Robergs, R. & Schneider, S. M. Effect of heat acclimation on heat shock protein 72 and interleukin-10 in humans. *J Appl Physiol (1985)* **103**, 1196-1204, doi:10.1152/japplphysiol.00242.2007 (2007).
12 Moseley, P. L. Heat shock proteins and heat adaptation of the whole organism. *J Appl Physiol (1985)* **83**, 1413-1417 (1997).
13 Kuennen, M. *et al.* Thermotolerance and heat acclimation may share a common mechanism in humans. *American journal of physiology. Regulatory, integrative and comparative physiology* **301**, R524-533, doi:10.1152/ajpregu.00039.2011 (2011).
14 Leppaluoto, J. *et al.* Endocrine effects of repeated sauna bathing. *Acta physiologica Scandinavica* **128**, 467-470, doi:10.1111/j.1748-1716.1986.tb08000.x (1986).

15 Kukkonen-Harjula, K. *et al.* Haemodynamic and hormonal responses to heat exposure in a Finnish sauna bath. *European journal of applied physiology and occupational physiology* **58**, 543-550 (1989).
16 Velloso, C. P. Regulation of muscle mass by growth hormone and IGF-I. *British journal of pharmacology* **154**, 557-568, doi:10.1038/bjp.2008.153 (2008).
17 Coleman, M. E. *et al.* Myogenic vector expression of insulin-like growth factor I stimulates muscle cell differentiation and myofiber hypertrophy in transgenic mice. *The Journal of biological chemistry* **270**, 12109-12116 (1995).
18 Barton, E. R., Morris, L., Musaro, A., Rosenthal, N. & Sweeney, H. L. Muscle-specific expression of insulin-like growth factor I counters muscle decline in mdx mice. *The Journal of cell biology* **157**, 137-148, doi:10.1083/jcb.200108071 (2002).
19 Healy, M. L. *et al.* High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes. *The Journal of clinical endocrinology and metabolism* **88**, 5221-5226 (2003).
20 Ftaiti, F. *et al.* Effect of hyperthermia and physical activity on circulating growth hormone. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* **33**, 880-887, doi:10.1139/H08-073 (2008).
21 Louard, R. J., Fryburg, D. A., Gelfand, R. A. & Barrett, E. J. Insulin sensitivity of protein and glucose metabolism in human forearm skeletal muscle. *The Journal of clinical investigation* **90**, 2348-2354, doi:10.1172/JCI116124 (1992).
22 Lecker, S. H., Goldberg, A. L. & Mitch, W. E. Protein degradation by the ubiquitin-proteasome pathway in normal and disease states. *Journal of the American Society of Nephrology : JASN* **17**, 1807-1819, doi:10.1681/ASN.2006010083 (2006).
23 Chow, L. S. *et al.* Mechanism of insulin's anabolic effect on muscle: measurements of muscle protein synthesis and breakdown using aminoacyl-tRNA and other surrogate measures. *American journal of physiology. Endocrinology and metabolism* **291**, E729-736, doi:10.1152/ajpendo.00003.2006 (2006).
24 Guillet, C., Masgrau, A., Walrand, S. & Boirie, Y. Impaired protein metabolism: interlinks between obesity, insulin resistance and inflammation. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **13 Suppl 2**, 51-57, doi:10.1111/j.1467-789X.2012.01037.x (2012).
25 Selsby, J. T. & Dodd, S. L. Heat treatment reduces oxidative stress and protects muscle mass during immobilization. *American journal of physiology. Regulatory, integrative and comparative physiology* **289**, R134-139, doi:10.1152/ajpregu.00497.2004 (2005).
26 Nath, K. A. *et al.* Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. *The Journal of clinical investigation* **90**, 267-270, doi:10.1172/JCI115847 (1992).

27 Wei, Q., Hill, W. D., Su, Y., Huang, S. & Dong, Z. Heme oxygenase-1 induction contributes to renoprotection by G-CSF during rhabdomyolysis-associated acute kidney injury. *American journal of physiology. Renal physiology* **301**, F162-170, doi:10.1152/ajprenal.00438.2010 (2011).
28 Khazaeli, A. A., Tatar, M., Pletcher, S. D. & Curtsinger, J. W. Heat-induced longevity extension in Drosophila. I. Heat treatment, mortality, and thermotolerance. *The journals of gerontology. Series A, Biological sciences and medical sciences* **52**, B48-52 (1997).
29 Lithgow, G. J., White, T. M., Melov, S. & Johnson, T. E. Thermotolerance and extended life-span conferred by single-gene mutations and induced by thermal stress. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 7540-7544 (1995).
30 Tatar, M., Khazaeli, A. A. & Curtsinger, J. W. Chaperoning extended life. *Nature* **390**, 30, doi:10.1038/36237 (1997).
31 Singh, R. *et al.* Anti-inflammatory heat shock protein 70 genes are positively associated with human survival. *Current pharmaceutical design* **16**, 796-801 (2010).
32 Yenari, M. A., Giffard, R. G., Sapolsky, R. M. & Steinberg, G. K. The neuroprotective potential of heat shock protein 70 (HSP70). *Molecular medicine today* **5**, 525-531 (1999).
33 Duveau, V., Arthaud, S., Serre, H., Rougier, A. & Le Gal La Salle, G. Transient hyperthermia protects against subsequent seizures and epilepsy-induced cell damage in the rat. *Neurobiology of disease* **19**, 142-149, doi:10.1016/j.nbd.2004.11.011 (2005).
34 Lundgren, J., Smith, M. L., Blennow, G. & Siesjo, B. K. Hyperthermia aggravates and hypothermia ameliorates epileptic brain damage. *Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale* **99**, 43-55 (1994).
35 Laatikainen, T., Salminen, K., Kohvakka, A. & Pettersson, J. Response of plasma endorphins, prolactin and catecholamines in women to intense heat in a sauna. *European journal of applied physiology and occupational physiology* **57**, 98-102 (1988).
36 Salbaum, J. M. *et al.* Chlorotoxin-mediated disinhibition of noradrenergic locus coeruleus neurons using a conditional transgenic approach. *Brain research* **1016**, 20-32, doi:10.1016/j.brainres.2004.03.078 (2004).
37 Gregg, C. *et al.* White matter plasticity and enhanced remyelination in the maternal CNS. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **27**, 1812-1823, doi:10.1523/JNEUROSCI.4441-06.2007 (2007).
38 Christman, J. V. & Gisolfi, C. V. Heat acclimation: role of norepinephrine in the anterior hypothalamus. *J Appl Physiol (1985)* **58**, 1923-1928 (1985).
39 Wigal, S. B. *et al.* Catecholamine response to exercise in children with attention deficit hyperactivity disorder. *Pediatric research* **53**, 756-761, doi:10.1203/01.PDR.0000061750.71168.23 (2003).

40 van Praag, H., Christie, B. R., Sejnowski, T. J. & Gage, F. H. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences of the United States of America* **96**, 13427-13431 (1999).
41 Maniam, J. & Morris, M. J. Voluntary exercise and palatable high-fat diet both improve behavioural profile and stress responses in male rats exposed to early life stress: role of hippocampus. *Psychoneuroendocrinology* **35**, 1553-1564, doi:10.1016/j.psyneuen.2010.05.012 (2010).
42 Pedersen, B. K. Muscle as a Secretory Organ. *Comprhensive Physiology* (2013).
43 Koltyn, K. F., Robins, H. I., Schmitt, C. L., Cohen, J. D. & Morgan, W. P. Changes in mood state following whole-body hyperthermia. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group* **8**, 305-307 (1992).
44 Liu, X. L. *et al.* [Therapeutic effect of whole body hyperthermia combined with chemotherapy in patients with advanced cancer]. *Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical sciences* **31**, 350-352 (2006).
45 Narita, M. *et al.* Heterologous mu-opioid receptor adaptation by repeated stimulation of kappa-opioid receptor: up-regulation of G-protein activation and antinociception. *Journal of neurochemistry* **85**, 1171-1179 (2003).
46 Xin, L., Geller, E. B. & Adler, M. W. Body temperature and analgesic effects of selective mu and kappa opioid receptor agonists microdialyzed into rat brain. *The Journal of pharmacology and experimental therapeutics* **281**, 499-507 (1997).
47 Heckmann, J. G., Rauch, C., Seidler, S., Dutsch, M. & Kasper, B. Sauna stroke syndrome. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* **14**, 138-139, doi:10.1016/j.jstrokecerebrovasdis.2005.01.006 (2005).