Intermittent Fasting and Leptin

Readers Summary

1. How does Intermittent Fasting (IF) work biochemically?
2. Who has great protocol on IFing?
3. What is the AMPk pathway and how does it affect IF?
4. What happens in the brain, liver, and muscles when you IF?
5. Why does IFing not work when someone is leptin resistant?

Today, I decided to blog about Intermittent fasting (IF). Since I wrote the Leptin FAQs, I have been bombarded with requests about IFing and how it relates to leptin signaling. I mentioned in the FAQs that I love IFing, but not when someone is LR. The reason for this is how the AMP-activated protein kinase pathway (AMPk) works. THe AMPk pathway is best described as a fuel sensor for lipid and glucose metabolism. In humans, the control of glucose homeostasis is governed by the balance between intestinal absorption and endogenous hepatic production by the liver and the uptake done in the muscles. Intermittent fasting is a behavioral modification that specifically alters feeding behavior to cause disruptions in glucose and lipid metabolism in humans. It also has specific times when exercising is done as well. When it is practiced well is can lead humans to shred body fat and really control their ability to generate muscle with workouts and re-feeds. I would strongly recommend that you take a look at the leangains protocol sometime on Martin Berkhan's site. The key question many have asked me is how does it work and why can't I do it right off the bat regardless of my leptin status. This is a loaded question with an answer that may make your head hurt but you will understand why IFing won't work if you are

leptin resistant (LR).

The reason why it is counter productive in LR is the AMPk pathways requires really optimal leptin sensitivity and signaling to be occurring between the brain, liver, and muscles. At its core, when one IF's it creates a "temporary" cellular stress due to lack of food at certain times. The reason for this is tied to the microbiome's ability to stimulate molecular hydrogen release from the microbiome. IFing's main benefit is in creating a diverse microbiome in the gut. Molecular hydrogen is another sophisticated way to repair an altered microbiome besides IF. AMPk is specifically upregulated in times of cellular stress. Some examples, are nutrient deprivation, ischemia, hypoxia, exercise, glycogen depletion and oxidative stress. When one fasts, this also counts as a cellular stressor.

Exercise or fasting increase glycogen depletion in the liver, which in turn increases whole body fat oxidation. Fasting always increases autophagy but exercise has the capability to both increase it or turn it off. This is why exercise comes with caveats. It turns out when someone is LR or their circadian signals are exercise is detrimental. Few 'crossfitters' or endurance athletes know this.

AMPk is activated by exercise and muscular contraction because both deplete energy stores from ATP to AMP. The key signal is glucagon for turning autophagy . It turns out glucagon is a hormone that enhances macro-autophagy. When the redox potential is high it has a stimulatory effect of glucagon and on autophagy. Here is the caveat: It has no longer been observed in old animals. Moreover, it is also absent in endurance athletes and it is one of the reasons so many marathoner's die of acute heart disease at races. WHY? A low redox state is present. With aging we lose 9% of our redox potential per decade. Autophagy is evolutionarily conserved stress response that is present in all living cells. Like apoptosis, autophagy is a programmed response and has

several sub-pathways. Unlike apoptosis, autophagy ***promotes life*** rather than death. Apoptosis is a suicide program for cells. Autophagy is the best way to get rid of bad mitochondria without killing the cell.

Exercise also increases AMPk in the liver and at adipocytes simultaneously. The amount determines the back ground redox state.

AMPk is also controlled by leptin and adiponectin. Both hormones are released from adipocytes in response to nutrient excess and both activate AMPk in peripheral tissues. Leptin however, also appears to decrease AMPk levels in the brain while ghrelin (stomach incretin released in fasting causing hunger) increases levels of AMPk in the brain. Ghrelin is also a potent stimulant to growth hormone release and builds leans muscle mass. AMPk activation also inhibits glycogen storage and increases glucose re-uptake, it appears to be very involved in improving insulin sensitivity.

When AMPk is activated in the brain it down regulates protein synthesis in the body. So the brain effect is quite different then the peripheral effects at the liver or the muscles. Therefore we cannot make muscle when AMPk is upregulated in the brain. Protein and glucose nutrients both decrease AMPK pathways and simultaneously increase mTOR activity in the hypothalamus. A higher mTOR signal in the hypothalamus decreases our appetite and food intake and this inhibits our ability to make muscle. It does this by decreasing neuropeptide Y (NPY). This also explains why the leptin Rx calls for a very high protein and low carbohydrate intake at breakfast. A high protein breakfast (think Leptin Rx) leads to decreased food intake and eventually a decreased body weight. This is precisely what humans experience in a leptin reset. It essentially becomes a very natural way to IF without trying to.

Normally in the brain, leptin increases hypothalamic mTOR

activity and decreases appetite and food intake. The inhibition of mTOR signaling diminishes leptin's anorectic effect and we increases food intake. Thus, mTOR also acts a cellular fuel sensor (opposite effect of AMPk) whose hypothalamic activity is directly tied to the regulation of energy intake. Consistent with this cross-regulation between AMPK and mTOR to control food intake, research also now shows that the activation of these pathways occurs in the same specific neuronal subtypes of the hypocretin neurons that leptin controls. In essence, this means that for this system to work well in IFing you must have good leptin functioning in the brain to get the maximum effect.

I can hear you asking yourself now, how does AMPK lean you out if your brain won't allow you to make muscle? AMPk allows us to become very sensitive to insulin peripherally at the muscle and fat cell levels. This is why many researchers are now looking at the AMPk pathway for T2D and for Alzheimers. AMPK switches off all anabolic pathways such as fatty acid synthesis, triglyceride synthesis, and cholesterol synthesis as well as protein synthesis and transcription that consume ATP, and switches on catabolic pathways that generate ATP, such as fatty acid oxidation and glycolysis. If you are dehydrated you can not take maximum advantage of this.

That means that AMPk stops us from making all fat, stops the liver from making fats from protein and carbs that need storage, while simultaneously making us burn fat and sugar to replete our energy stores (ATP). So if a human is LS and uses intermittent fasting you can stimulate muscle building with re-feeds. How, you ask? When a human re-feeds they are dramatically increasing mTOR and decreasing AMPk at this time. The re-feeds also are dramatically increasing leptin too. If you are already leptin resistant your brain will never see this signal. This is why IFing is worthless in LR states. Re-feeding immediately turns on muscle rebuilding.

Martin's Leangains protocol seems to take advantage of this by

favoring muscle growth while trying to limit the creation of fat peripherally. Since re-feeds raise leptin quickly, the person is activating AMPk in skeletal muscle (explaining why people often lean out after a re-feed) and inhibiting it in the brain. This helps explains why people will also lean out after a re-feed as well provided they are leptin sensitive and have a good redox potential.

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Cites

- http://www.ncbi.nlm.nih.gov/pubmed/18057094
- http://www.ncbi.nlm.nih.gov/pubmed/18583936
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