

Rock Beats Scissors; Insulin Beats Fat Loss

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Tuesday, 13 January 2009

In games and contests, there are always elements that are devastating in their dominance. It may be as simple as rock always beating scissors in the hand game "Rock, Paper, Scissors," or it may be as complex as the M1A1/2 Abrams main battle tanks loaded with depleted uranium penetrators in Operation Desert Storm. In the battle against fat, the devastator is insulin.

Body fat generally reflects long-term energy balance. In other words, it is a sign of how your eating habits (calories in) compare to your metabolic demand (calories out). It is not as simple as that though, as many people can attest after diligently carrying calorie tables about in a futile effort to match the numbers to the readout of a treadmill or recumbent bike. For decades, nutritionists and cardiologists extolled the virtues of low-fat dieting to reduce the risk of heart disease and aid in weight loss. On the surface, it made sense to replace the most calorie-dense macronutrient (fat) with carbohydrates, which contain less than half the number of calories, gram for gram. Yet, cardiovascular health was not greatly improved and the prevalence of obesity nearly tripled in the United States.

When dieting pioneers such as Barry Sears (the Zone Diet) and Dr. Robert Atkins (the Atkins Diet) suggested reducing carbohydrates dramatically and thusly adding fat back into the diet, the ideas were scoffed at by experts who staked their reputations on the risks and dangers inherent with such food practices. When the diet programs were newly released to the public's attention, they were called "fads." Over the next several months to years, as it was discovered that low-carbohydrate diets were effective for many people and became increasingly popular, the challenge of "no long-term studies" was pulled out of the critic's handbook. Yet, as studies showed low-carbohydrate diets to be as effective, quicker and resulting in some cardiovascular benefits (not risks) when compared to low-fat diets, fickle America turned its attention-deficit addled focus to other issues. Doughnut sales began to recover from the Atkins-induced drop-off and crowds waited to form about the Alli stands at the local retailers. Even when a reasonable answer exists to a problem as personal and encompassing as obesity, America's "been there, done that, bought the T-shirt" mentality has caused the nation to move on.

Yet, there is a silver lining to the large-scale social experiment that was the Atkins craze. It stimulated research in the field of fat loss and pressured the editors of medical and science journals to publish articles that otherwise would have been passed over, since weight loss is considered to be a trivial subject by many professionals. A great deal has since been learned about fat loss. Given the success of low-carbohydrate dieting and the focus placed on the hormone insulin, which controls blood sugar, many researchers designed and reported on elaborate studies that investigated insulin's role in weight management with unprecedented detail.

Though often thought of in terms of its role in regulating blood sugar and treating diabetes, insulin has other functions. Among these is the regulation of fat stores in adipocytes (fat cells). Fat cells are sensitive to a number of hormones that

control whether fat is taken up from the bloodstream and stored or if stored fat is broken down and released back into the circulation; chief among these hormones is insulin.

Insulin carries a double-whammy of obesity, in that it is able to increase fat storage as well as reduce fat loss. This comment has been repeated time and again. Knowing what insulin does (increase fat storage and decrease fat loss), it then becomes useful to understand how that happens if one is interested in fat loss or weight management. Fortunately, an excellent series of experiments were recently published in the Kobe Journal of Medical Sciences revealing how insulin prevents fat loss. How insulin increases fat storage will not be addressed in this article.

In the fat cell, fat is stored in large globules surrounded by a thin protein-based envelope called perilipin. Think of perilipin as a Ziploc bag. The stored fat is present in a form called a triglyceride, which is three fatty acids, each attached to a common glycerol molecule. It is like a three-legged stool, with glycerol being the seat and each fatty acid being one of the three legs. In order for the fat to be released into the bloodstream, the perilipin envelope has to open so that an enzyme can attach to the triglycerides and break it down to fatty acids and glycerol.

There are a number of hormones and neurotransmitters that stimulate fat loss. People are most familiar with adrenalin, also called epinephrine, and the related neurotransmitter norepinephrine. Adrenalin stimulates fat loss by activating a class of receptors called beta-adrenergic receptors that are present on the surface of a fat cell. In humans, specific types of beta-adrenergic receptors account for the vast majority of the fat loss signal, those being the beta1- and beta2-adrenergic receptors (abbreviated by the Greek symbol $\beta 1$ and $\beta 2$). β receptors can be stimulated by a number of drugs; ephedrine-caffeine supplements worked well for fat loss by increasing β stimulation.

In the experiments reported in the Kobe Journal of Medical Sciences, the investigators looked at the effect of insulin on $\beta 2$ -stimulated fat loss. Those who are really interested in the science of fat loss can read the study online at <http://www.med.kobe-u.ac.jp/journal/contents/53/99.pdf> free of charge. $\beta 2$ -stimulated fat loss occurs in a series of steps, with one reaction causing another until stored fat is broken down and released. Using isoproterenol, a potent stimulator of β -receptors, the scientists measured fatty acid release from fat cells exposed to the drug. They compared these results to fat cells that had been exposed to insulin before being stimulated by isoproterenol and found that insulin blocked fatty acid release to a remarkable degree. The researchers then worked down the biochemical pathway, finding that the negative effect of insulin on fat loss also blocked the fat-loss effect of caffeine (which represents the second step in $\beta 2$ -stimulated fat loss). A third step in fat loss involves an enzyme called PKA, which activates or turns on the actual fat breakdown process. Not surprisingly, insulin also blocked this step from being activated. PKA turns on the enzymes that open the perilipin envelope surrounding the stored triglyceride-fat, as well as the enzyme that attacks triglycerides and breaks them down to individual fatty acids and glycerol.

Clearly, insulin interferes with fat loss in several different ways, making it very difficult for anyone to lose fat when insulin levels are high. Not only that, but under the long-term influence of insulin, fat cells burn less fat, because insulin

interferes with the creation of mitochondria, which are the tiny parts of the cell that burn fatty acids to make energy. The experiment did not look at other cell types, but it is likely that a similar effect would be noted in other insulin-sensitive tissue, like muscle.

Fascinating as such research is to physio geeks and biochem nerds (like me), what practical use are the discoveries revealed in the study? First, it gives greater credence to the power of low-carbohydrate and low glycemic-load diets. If insulin is blocking the release of stored fat, it makes little sense to incorporate a diet that periodically stimulates the release of high concentrations of insulin (traditional low-fat diets). When fat loss is the goal, carbohydrate intake should be reduced and the choice of carbohydrates should be limited to slow-releasing, low glycemic carbohydrates to keep insulin levels from becoming elevated. Secondly, it appears that insulin can severely limit, nearly blocking fat loss, even when the sympathetic system is activated. In other words, it does little good to exercise or take a fat burner sooner than 2 hours after eating if the main intent of training is to break down and burn stored fat. All those bottles of ephedrine-caffeine and other stimulants were wasted if they were taken right before or after a meal, even if they gave a "buzz." Perhaps some of the success noted by people following Atkins-type diets was due to an increased fat-loss effect of fat burners. Third, it also shows the folly of drinking a "sports drink" in the gym. The simple ingestion of a 60-gram carbohydrate-laden drink not only replaces the calories that might be expended exercising, but also prohibits the fat cells from contributing to the energy needs by releasing fatty acids, so the body is forced to use up muscle and liver glycogen stores and rob certain amino acids to maintain blood sugar levels when glycogen levels drop. Fourth, it introduces a suggestion that long-term eating habits that stimulate elevated insulin concentrations may reduce fat burning or the basal metabolic rate (how many calories are burned at rest) by inhibiting the production of mitochondria, which is the part of a cell that burns fat for calories.

America has been growing in a bad way, getting fatter and fatter over the last 30-plus years. Perhaps it is no coincidence that this occurred during the time when doctors and dietitians were telling everyone to eat low-fat diets that replace fat with carbohydrates. Research, such as the study reviewed herein, suggests that limiting the exposure of fat cells to insulin is a vital first step to controlling and managing weight. It may not be a popular message with grain producers, bakeries and confectionaries. For the health of America, it is important to realize the dangers and long-term consequences of succumbing to the temptation of tasty treats. Sadly, the audience most receptive to this message will be athletes and fitness enthusiasts who are already exercising and following a sensible diet in order to maintain a level of performance or physical appearance.

For those of you interested in how many different steps in the breakdown and release of stored fat that are inhibited by insulin:

- High concentrations of insulin disrupt the close apposition of β -receptors with protein kinase A (PKA).
- Insulin increase phosphodiesterase 3B concentration, inactivating cAMP.
- Insulin inhibits the activation of PKA by cAMP or its phosphodiesterase-resistant analog, 8-bromo-cAMP.
- The insulin-based inhibition of PKA signaling results in markedly reduced phosphorylation of perilipin, which reduces the exposure of triglycerides to hormone sensitive lipase (HSL).
- The insulin-based inhibition of PKA signaling results in markedly reduced phosphorylation of HSL, reducing the lysis of triglycerides to free fatty acids and glycerol.
- The insulin-based inhibition of PKA signaling results in markedly reduced phosphorylation of CREB, which results in a marked reduction of mitochondrial biogenesis in the adipocyte.

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