New research over the last five years is clarifying the mechanisms by which capsinoids—thermogenic compounds in certain strains of chili peppers—can regulate fat metabolism and help overweight individuals reduce abdominal fat and improve their health.

Application of the new findings to the formulation of capsinoid-based products holds great potential to improve results obtained with this emerging adjunctive modality.

Capsinoids (Fig. 1) are non-stimulant compounds that increase basal metabolism and fat oxidation, helping people overcome one of the biggest physiological barriers to weight control: the metabolic suppression that follows prolonged calorie restriction.

Unlike capsaicin, the more widely known biochemical constituent of chili peppers, capsinoids are not absorbed systemically; they have much less pungency, do not cause any burning sensation, and have no effects on cardiovascular function, giving them significant advantages for clinical use.

Recent work indicates that at a dose of 9 mg/day, capsinoids also increase the amount and the activity of brown adipose tissue (BAT), an important regulator of overall body fat content. Age-associated loss of BAT and diminution of BAT activity correlate strongly with accumulation of total body fat and with weight gain (Yoneshiro T, et al. *Obesity*. 2011; 19(9): 1755–1760).

Recruitment and reactivation of BAT represents a new and largely untapped mechanism for weight management.
The Physiology of Weight Gain

To improve weight management outcomes, it is important to understand that for many people physiology itself can become a major stumbling block to weight control.

Basal metabolic rate (BMR) is the main determinant of daily energy expenditure, representing 60–70% of total energy output in sedentary adults. BMR declines with age, beginning in the third and fourth decades. It drops by as much as 2% per decade after the age of 20. The changes are due in part to declining thyroid function, loss of lean muscle mass, and reduced metabolic activity in lean tissue.

Though there is considerable variation, the general rule is that older people burn fewer calories at rest than younger ones (Henry CJ. Eur J Clin Nutr. 2000; 54(Suppl 3): S77–S91). In one landmark study, researchers found that BMR was lower—by an average 644 kJ/day—in healthy older adults between 50 and 77 years old compared with young adults aged 18–35. This was true after adjusting for differences in fat and lean tissue mass (Piers LS, et al. J Appl Physiol. 1998; 85(6): 2196–2204).

If caloric input remains constant or increases as someone ages, the stage is set for weight gain, even in people who were lean in youth. Once begun, the process snowballs, because as body mass index (BMI) increases, there is a further attenuation of BMR and resting energy expenditure (DeLuis D, et al. Ann Nutr Metabol. 2005; 49: 381–385. Zhang K, et al. Int J Obes Relat Metab Disord. 2002; 26: 376–383).

Weight gain may reflect a genetic predisposition to low resting metabolic rate (RMR), a measurement that is well-correlated with BMR. According to a Danish metanalysis, formerly overweight people who successfully lost weight showed a 2.9% lower average RMR compared with age-matched control subjects. In the formerly overweight group, 15% had low relative RMRs (greater than 1 standard deviation below the mean of the control group) versus only 3.3% in the control group (Astrup A, et al. Am J Clin Nutr. 1999; 69(6): 1117–1122).

Calorie Restriction & Metabolic Down-Regulation

The heavier a person is, the heavier he or she tends to become. The problem is compounded by the fact that caloric restriction suppresses BMR.

In a study of 48 overweight people (BMI greater than 27), those on caloric-restricted diets (25% fewer total calories than habitual intake), or low-calorie diets (max of 890 kcal/d) for six months had marked reductions in total daily energy expenditure compared with similar non-dieting individuals. The differences remained after adjusting for body composition (Redman LM, et al. PLoS One. 2009; 4(2): e4377).


Simply put, the data indicate that very low caloric diets may end up giving the opposite of their intended effect, because in many people, caloric restriction induces a down-regulation of metabolic rate.

This mechanism, a primitive survival adaptation, is a major obstacle to weight control, and a key reason why calorie restriction diets usually fail.

“The body wants to conserve energy when it senses a major decrease in incoming calories,” explained Robert Tafuri, MD, Founder and Medical Director of Bariatric Associates of New England. “It’s a great reflex in conditions of famine. But in modern conditions, it can make it very difficult for people to lose weight,” said Dr. Tafuri, who has more than 20 years’ experience treating high-risk overweight and overweight individuals.

Over the last decade, researchers have shed considerable light on the role of Brown Adipose Tissue (BAT) in fat metabolism and energy balance (Fig. 2).

Initially discovered in rodents, BAT is a key site of non-shivering thermogenesis. It burns fat to produce heat when the body is exposed to cold, and it plays an important part in regulating total energy expenditure. Its role in human physiology is much the same.

Recent studies using fluorodeoxyglucose-PET (FDG-PET) in combination with computerized tomography (CT) revealed that healthy humans have considerable amounts of BAT (Saito M, et al. Diabetes. 2009; 58(7): 1526–1531). Moreover, the prevalence and metabolic activity of BAT are inversely related to body fat content. Both the amount of BAT and its activity tend to decrease with age. As people grow older, they lose BAT and the tissue that does remain becomes less metabolically active (Yoneshiro T, et al. Obesity. 2011; 19(9): 1755–1760).

Dr. Takeshi Yoneshiro and Dr. Masayuki Saito at the Hokkaido University Graduate School of Medicine and Tenshi College, respectively, have shown that in people with undetectable BAT activity, total body fat content increases with age. In those of subjects with detectable BAT activity, total fat content is unchanged from the 20s to the 40s. This suggests that the age-related decrease in BAT activity accelerates the accumulation of body fat (Fig. 3).
Dr. Saito and Dr. Yoneshiro are among a number of researchers who hypothesize that reactivation and/or recruitment of BAT might be a novel approach to weight management.

They have published studies to suggest that capsinoids can do just that: increase the amount and the activity of BAT tissue. This is the newest chapter of the capsinoids story, and it should be welcome news to clinicians seeking therapeutic agents that could reliably up-regulate thermogenesis and increase BMR without CNS stimulation.

Amphetamines and other psychostimulants used as weight control aids carry a tremendous side-effect burden, are easily abused, and are poorly suited to long-term therapy. While many non-pharma botanical and nutraceutical options are now available, scientific support for these products is highly variable.

**Capsaicin vs Capsinoids as Metabolic Modulators**

The most well-researched and safest botanically derived metabolic up-regulators are compounds found in chili peppers (*Capsicum* genus). The thermogenic effect of capsaicin—the best-known constituent of chili peppers and the one that gives them their pungent flavor—is well documented.


Kyoto University researchers studied the effects of 150 mg capsaicin prior to low intensity exercise in 10 healthy young men. They found significant increases in fat oxidation, which means lipolysis, but no adverse effects on cardiovascular function (Shin KO, Moritani T. *J Nutr Sci Vitaminol (Tokyo).* 2007; 53(2): 124–132).

Practically speaking, capsaicin has limited clinical utility owing to its pungency. Most people simply cannot tolerate capsaicin at levels required to trigger thermogenic changes.

Japanese investigators have been at the forefront of research on bioactive compounds in chili peppers, particularly the capsinoids. These substances, produced by certain strains of chili, are structurally similar to capsaicin but they have distinct properties that make them a much better clinical option.

Capsinoids exert similar thermogenic and lipolytic effects as capsaicin but without noxious sensations of pungency or “hotness.” To put this in perspective, capsinoids are approximately 1,000 times less hot than capsaicin. Further, capsinoids are hydrolyzed into fatty acids and vanillyl alcohol as they pass through the GI tract. These end products are then converted into inactive conjugates, obviating the possibility of systemic side effects.

The difference between capsinoids and capsaicin was well illustrated in a study of 12 healthy Japanese volunteers, each of whom was instructed to eat samples of three different types of peppers: CH-19 Sweet, which produces high levels of capsinoids but no capsaicin; Cayenne Long Slim, which produces much capsaicin but little of the capsinoids; and California-Wandar, a strain producing neither capsaicin nor capsiate.

In contrast to the study published by Shin and colleagues, this trial by Hachiya and colleagues showed that capsaicin-rich Cayenne Long Slims raised systolic blood pressure (on the order of 10–20 mmHg) and heart rate (4–16 bpm). The capsinoid-rich, capsaicin-free CH-19 Sweet pepper had no such effect (Fig. 4).

Given that most overweight people are already at risk for hypertension, it is best to avoid anything that further increases blood pressure or heart rate.

In short, capsinoids deliver the thermogenic punch of capsaicin without the pungency, or the potential adverse effects.

The thermogenic and lipolytic effects of capsinoids, like capsaicin itself, are mediated by the Transient Receptor Potential Vanilloid 1 (TRPV1) receptors in the mouth and throughout the GI tract. When capsinoids bind to the TRPV1 receptors, they activate the vagal afferent nerve, which then stimulates sympathetic nervous system (SNS) activity.

When capsaicin binds to oral TRPV1 sites, one feels the sensation of heat and pungency. Capsinoids also stimulate TRPV1 receptors, but their effect is primarily on receptors in the gut, not the mouth, since capsinoids have high lipophilicity and are easily broken down in normal aqueous conditions, leading to less accessibility to receptors (Iida T, et al. *Neuropharmacology*. 2003; 44: 958–967).

As a result, capsinoids do not produce the oral sensation of heat or the pungent taste, but they do produce the capsaicin-like SNS response. This is important in weight management because SNS activity is suppressed in overweight compared with normal weight individuals (Fig. 5).

"Our human studies have suggested that unlike capsaicin, capsinoids do not induce catecholamine secretion from the adrenal medulla. We believe that capsaicin is an endocrine and neural stimulant, but the capsinoids are only neural stimulants that trigger norepinephrine secretion from the peripheral effe-

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**Figure 4** Effect of Capsaicin and Capsinoids on Blood Pressure and Heart Rate

Capsaicin-rich California Long Slim peppers (labeled “Hot” on graph) trigger marked increases in blood pressure and heart rate following ingestion; in contrast, the CH-19 Sweet pepper, which is rich in capsinoids but produces no capsaicin, has no such vascular effects. (From Hachiya S, et al. 2007)

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**Figure 5** Capsinoid Effects on TRPV1-Mediated Thermogenic Pathways

**Capsinoids Accelerate Energy Expenditure**

1. **Stimulation of TRPV1**
   - Capsinoids activate TRPV1 channel (capsaicin receptor) on the digestive tract surface, without being absorbed into the circulation.

2. **SNS Activation**
   - The signal of capsinoids is transmitted and activates sympathetic nervous system (SNS).

3. **Energy Expenditure Acceleration**
   - The activation of SNS enhances the thermogenesis and the O2 consumption.

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ent sympathetic nerve endings innervating adipose and muscle tissue,” explained Michio Takahashi, PhD, Corporate Advisor on Nutritional Strategic Research at the Ajinomoto Research Institute for Health Fundamentals, Kawasaki, Japan.

Ajinomoto has been at the leading edge of capsinoid research, with a particular focus on dihydrocapsiate, a component of capsinoids. The company introduced the world’s first capsinoid dietary supplement into the US in 2007.

**Impact on Energy Expenditure**

Clinically, supplementation with capsinoids and dihydrocapsiate can have significant impact on human energy expenditure in overweight people.

In 2010, investigators at the Pennington Biomedical Research Center, Baton Rouge, LA, published data from a 4-week study involving 78 overweight men randomized to supplementation with 3 or 9 mg/day dihydrocapsiate—one of the key capsinoid compounds—or placebo. Subjects were permitted to continue on their usual ad libitum diets.

Compared with the men on placebo, those taking the supplements showed an average metabolic rate increase of 54 kcal/day—a small but significant thermogenic increase (Fig. 6). The investigators did not observe a dose-dependent relationship (Galgoni JE, Ravussin E. *Am J Clin Nutr.* 2011; 92(5): 1089–1095).

Also in 2010, investigators at UCLA’s Center for Human Nutrition published a study of capsinoid supplementation in combination with a very low-calorie, high-protein diet in 33 overweight men and post-menopausal women (BMI 26.9–38 kg/m²).

Compared with subjects on placebo, those taking dihydrocapsiate for 4 weeks showed a dose-dependent increase in postprandial energy expenditure. The change was on the order of 1 kcal/kg/day for those taking 3 mg/day, and approximately 2 kcal/kg/day for those on the 9 mg/day capsinoid dose (Lee TA, et al. *Nutrition & Metabolism.* 2010; 7: 78).

Dr. Mary-Jon Ludy and colleagues at the Department of Nutrition Science, Purdue University, undertook a metanalysis of all published human studies of the effects of capsaicin and capsiate on energy expenditure. The Purdue team reports that, “capsaicin and capsiate both augment energy expenditure and enhance fat oxidation, especially at high doses.”

With regard to capsiate specifically, they note that capsiate increased energy expenditure at intermediate (2–3 mg/day) and high doses (6–9 mg/day) but had no effect at low doses (less than 1.5 mg/day). Capsiate also enhanced fat oxidation at high doses but had no effect at low or intermediate doses (Ludy MJ, et al. *Chem Senses.* 2012; 37(2): 103–121).

**Multiple Biological Effects**

Capsinoids have many beneficial biological effects. Dr. Koichiro Ohnuki and colleagues at Kyoto University, who were among the first to document the thermogenic effects, also found that continuous capsinoid intake suppresses body fat accumulation in mice, in much the same way as capsaicin does (Ohnuki K, et al. *Biosci Biotechnol Biochem.* 2001; 65: 2735–2740. Ohnuki K. *Biosci Biotechnol Biochem.* 2001; 65: 638–643).

This fat suppression is not thyroid-mediated, as was shown in a rodent experiment by Masuda and colleagues (Masuda Y, et al. *J Appl Physiol.* 2003; 95: 2408–2415).

Masuda’s group has also been looking at the impact of capsinoids on BAT, especially its role in up-regulating the uncoupling proteins (UCPs), key mediators of fat metabolism found in adipose tissue and skeletal muscle.

UCP1 is exclusively expressed in BAT. UCP2 is expressed in both brown and white adipose tissue (WAT). UCP3, which plays a role in transport of free fatty acids, is expressed in skeletal muscle of all mammals.

The researchers found increased expression of all three UCPs, particularly UCP1 in BAT among the animals fed capsinoids. Of particular importance is the increased expression of mRNA for UCP2 in WAT, likely a primary mechanism in the observed increase in energy expenditure. UCP3 mRNA expression in skeletal muscle, mediated by SNS stimulation, occurred within minutes of capsinoid ingestion, and persisted for 2 hours.

The authors hypothesize that UCP3 activation increases short-term fatty acid transport, and helps suppress fat accumulation.

More recently, Yoneshiro’s team in Hokkaido looked at the effect of supplementation with capsinoids, 9 mg/d, on BAT activity in 10 healthy males.

**Activation of BAT**

To understand the significance of this study, it is important to keep in mind that cold exposure is the most powerful natural physiological stimulus for BAT activation in mammals.

The stimulatory effects of cold on BAT are mediated through the activation of the sympathetic nervous system, initiated by...


Yoneshiro’s group sought to determine if stimulation of TRP channels by capsinoids is effective for enhancement of BAT thermogenesis in humans, as was observed in Masuda’s mouse experiments. After fasting for 12 hours, the 51 subjects in Dr. Yoneshiro’s study underwent FDG-PET/CT scanning following 2 hours of cold exposure at 19°C to assess BAT activity.

The subjects were then divided into two groups based on their levels of BAT activity: 53% showed cold-induced increases in BAT activity and were deemed “BAT-positive.” The remaining subjects showed no significant increases in BAT activity following cold exposure, and were considered “BAT-negative.”

The investigators also measured whole body energy expenditure and respiratory quotient. The level of BAT activity had implications for overall metabolism. They note that cold-induced thermogenesis (CIT), calculated as the difference between energy expenditure values at 27°C and 19°C, was significantly higher in the BAT-positive than BAT-negative subjects.

The investigators then took a subset of 10 BAT-negative subjects, and had them take a capsinoid supplement, 9 mg per day, for six weeks. They found that CIT was markedly increased after capsinoid treatment (200.0 ± 33.9 kcal/d) compared with before capsinoid treatment (20.6 ± 43.0 kcal/d) (Fig. 7). It was also significantly higher than what was observed after placebo treatment (81.0 ± 32.5 kcal/d, \( P < 0.01 \)).

“As CIT was proportional to BAT activity, as assessed by FDG-PET/CT, the capsinoid-induced increase in CIT appears to reflect enhanced thermogenic capacity and BAT activity,” the authors report (Yoneshiro T, et al. J Clin Investig. 2013; 123(8): 3404–3408).

The capsinoid-induced increase in energy expenditure (EE) was associated with a measurable, though not statistically significant 2% reduction of body fat. Keep in mind, however, that the subjects in this study were young, healthy, non-overweight individuals.

Based on what his team observed, Dr. Yoneshiro concludes that “repeated ingestion of capsinoids can mimic the chronic effects of cold exposure on BAT and body fat in humans.” He added that “Human BAT can be recruited by chronic cold exposure and capsinoid ingestion even in individuals who have lost active BAT. Our findings could contribute to developing practical, easy, and effective anti-obesity regimens.”

Capsinoids in Human Clinical Studies

The new findings on BAT recruitment add to an already robust series of human studies of capsinoids on human metabolism.

Dr. Naohiko Inoue and colleagues at the Ajinomoto Research Institute tested a 4-week course of daily treatment with cap-
Capsinoids in 48 Japanese subjects with BMI greater than 23. The cohort consisted of 39 men and 9 women between the ages of 30 and 65, randomized to receive capsinoids at a dose of 3 mg or 10 mg in softgel form, or placebo softgels.

A total of 44 patients completed the study; after 4 weeks, both capsinoid subgroups (3 mg and 10 mg per day) showed increases in oxygen consumption (VO$_2$), resting energy expenditure (REE), and fat oxidation (Fig. 8). Interestingly, the investigators found that subjects with the highest BMI at baseline showed the greatest increases in fat oxidation. People with baseline BMI of 25 or greater (the standard criterion for overweight in Japan) showed the highest increases in VO$_2$ and REE during the first two weeks of capsinoid treatment. This was true at both dose levels, though the effect was more pronounced at 10 mg.

The increase in VO$_2$ and the tendency for increasing REE and fat oxidation by the capsinoid intake for 4 weeks strongly suggest that a long-term treatment with capsinoids would enhance BMR,” the authors conclude. Body weight and BMI tended to decrease slightly in both capsinoid groups compared with the controls (Inoue N, et al. Biosci Biotechnol Biochem. 2007; 71(2): 380–389). Importantly, there were no significant changes in blood pressure or pulse rate, as would be seen with amphetamines or other direct CNS stimulants.

More recently, University of Maryland researchers showed that 12 weeks of daily oral capsinoid consumption, 6 mg per day, produced measurable and significant reductions in abdominal fat in a cohort of 80 overweight men and women. All had baseline BMIs in the range of 25–35 (mean 30.4), and there were no other nutritional or lifestyle interventions.

After 12 weeks, the capsinoid-treated patients showed a mean weight loss of 0.9 kg (± 3.1) versus 0.5 kg (± 2.4) in the placebo group. The capsinoid group also showed higher levels of fat oxidation. These differences were statistically significant and indicate that capsinoids do exert a measurable energy burning effect (Fig. 9).

While there was no significant difference in total adiposity, the capsinoid group showed greater loss of abdominal adiposity compared with the placebo group (~1.11% ± 1.83 vs ~0.18% ± 1.94). The change in abdominal fat (Fig. 10) correlated well with the change in weight (Snitker S, et al. Am J Clin Nutr. 2009; 89(1): 45–50).

These findings echo earlier work showing that capsinoids in CH-19 Sweet peppers could markedly raise body temperature and increase oxygen consumption in healthy human volunteers.

In both the Snitker and Inoue clinical studies, capsinoids showed an excellent safety profile, with no significant changes in blood pressure or pulse rate.

Over the past several years there have been five studies of capsinoid pharmacokinetics and toxicology in humans and animals, all showing the compounds to be safe even at very high doses. In the most recent study, 16 healthy men took softgels containing 15 or 30 mg of the capsinoids. Both doses were well tolerated, and there were no clinically significant changes in blood pressure, heart rate, ECG patterns, hematology, blood chemistry or urinalysis.

The authors noted that, consistent with previous trials, body temperature did increase shortly after ingestion of capsinoids, but remained within normal range. Plasma levels of capsinoids were below the lower limit of measurability, again indicating no systemic absorption (Bernard BK, et al. Int J Toxicol. 2008; 27(Suppl 3): 137–147).

IMPROVING AN EFFECTIVE NON-PHARMACEUTICAL ADJUNCT

In light of the recent studies demonstrating the efficacy of the dihydrocapsiate, a component of capsinoids, at 9 mg, Ajinomoto has recently reformulated its patented Capsiate Natura formulation to provide 9 mg of dihydrocapsiate per capsule, rather than the 3 mg per capsule in the original capsiate formula.

The physiological activity of dihydrocapsiate was nearly equivalent to that of capsinoids. Dihydrocapsiate, which is enzymatically produced, has been granted Generally Recognized As Safe (GRAS) status in the US, and authorized to be a Novel Food Ingredient in the EU. The new formulation will be introduced in December 2014.

Clinicians specializing in weight loss who have utilized capsiate supplements with patients, have observed a consistent increase in metabolic speed and thermogenesis. Patients tend to
lose weight more rapidly, reaching the first 10% milestone (loss of 10% of baseline body weight) in shorter amounts of time.

This 10% threshold is very important because, statistically, when an overweight person loses 10% of baseline weight, risk profiles begin to normalize: blood pressure decreases, blood sugar drops, and cholesterol declines, reducing the risk of myocardial infarction, stroke and other end-stage complications. Consistent with the published studies, there have been no reports of significant adverse effects with capsinoids at the recommended doses.

Though they are not a stand-alone solution for weight reduction, capsinoids and dihydrocapsiate represent a welcome, non-pharmaceutical adjunct that enhances lipolysis and thermogenesis in conjunction with diet, exercise and lifestyle modification. They have the potential to be helpful for anyone concerned about excessive central adiposity.

Ajinomoto’s Dr. Takahashi noted that capsinoids would likely benefit many people in the 40–50 year age bracket, a life-stage during which many people feel a decline in their daily energy levels. “Ingestion of capsinoids sometimes arouses feeling of refreshment and reactivation.”

It is important to keep in mind that capsinoids and dihydrocapsiate do activate the SNS via the TRPV receptors in the GI tract and, at least theoretically, this could interfere with relaxation and sleep. “Practically, based on my experience, capsinoid and dihydrocapsiate ingestion does not disturb sleep. But still, we would recommend that the time of ingestion be kept away from bed time,” Dr. Takahashi said.

In all studies so far, there have been no incidents of allergy or sensitivity to capsinoids or dihydrocapsiate. Because capsinoids are broken down as they pass through the GI tract and not absorbed into the blood, there is little chance of systemic reactions. That said, people with known sensitivities to chili peppers should be monitored closely especially during the first weeks of ingestion.

Capsinoids and dihydrocapsiate have a unique mechanism of action, an excellent safety profile and multiple beneficial physiological effects. A large portfolio of encouraging research clearly indicates that they hold great promise as a botanical adjunct for clinical weight management.