Metabolically active functional food ingredients for weight control

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Summary
The scale of the obesity epidemic creates a pressing consumer need as well as an enormous business opportunity for successful development and marketing of food products with added benefits for weight control. A number of proposed functional food ingredients have been shown to act post-absorptively to influence substrate utilization or thermogenesis. Characteristics and supporting data on conjugated linoleic acid, diglycerides, medium-chain triglycerides, green tea, ephedrine, caffeine, capsaicin and calcium, are reviewed here, giving examples of how these could act to alter energy expenditure or appetite control. Consideration is also given to other factors, in addition to efficacy, which must be satisfied to get such ingredients into foods. We conclude that, for each of the safe, putatively metabolically active agents, there remain gaps in clinical evidence or knowledge of mechanisms, which need to be addressed in order to specify the dietary conditions and food product compositions where these ingredients could be of most benefit for weight control.

Keywords: energy expenditure, fat oxidation, metabolism, thermogenesis.

Introduction
During the past several decades, the prevalence of obesity has increased worldwide to epidemic proportions. Obesity develops when energy intake is greater than energy expenditure, the excess energy being stored mainly as fat in adipose tissue. Body weight loss and prevention of body weight (re)gain can thus be achieved by reducing energy intake or bioavailability, increasing energy expenditure and/or otherwise reducing storage as fat.

Obligate energy expenditure in humans is relatively fixed, and primarily reflects body weight and composition. Although there may be a modest decrease in metabolic rate in response to a hypocaloric diet, there is little evidence of energy wastage in periods of overnutrition (1–3). On the other hand, energy intake can vary considerably on a moment-to-moment basis, in response to a range of internal and external stimuli. Thus, adjustment of energy intake to energy expenditure is seen as the critical factor for the maintenance of energy balance under conditions of ad libitum food intake (4). However, small increases in energy expenditure, if not accompanied by an equivalent increase in energy intake, would induce a slight negative energy balance and thereby influence body weight regulation on the long term. It is also possible that ingredients could be added to weight loss products specifically to offset the reductions in resting energy expenditure induced by reduced-energy diets (5,6). Thus, direct stimulation of energy expenditure may used as a strategy to improve body weight loss and prevent (re)gain.

Metabolically active agents may also act to inhibit energy (fat) storage through decreased lipid uptake or formation, stimulate fat mobilization through increased lipolysis, or enhance rates of fat oxidation. However, to benefit weight control, these must ultimately alter energy balance through increased expenditure or feedback into appetite control, or perhaps influence the balance of protein and lipid metabolism in a way that affects body composition.
The aim of this review is to provide a more detailed scientific background and evaluation of a selection of potential functional food ingredients that are proposed or claimed to benefit weight control through their effects on energy metabolism. We selected those ingredients that in our opinion are more promising for weight control or have recently emerged in the weight management area, or may be particularly good candidates for use in foods. Other proposed ingredients, such as (-)-hydroxycitric acid, pyruvate, chromium, yohimbine and L-carnitine, were found to merit less consideration as weight control agents, mainly because of a lack of evidence supporting their efficacy or because they have been associated with side effects or health risks.

**Product feasibility aspects of functional food ingredients**

Evidence of efficacy is necessary, but by no means sufficient to make an agent a good candidate for use in a commercial functional food. There are large number of putative weight control agents sold in the form of over-the-counter pills and food supplements, often with dubious claims. Some of these agents can be demonstrated to have (usually very limited) efficacy under certain conditions, but few are currently used in mass market foods. This is largely attributable or due to the different criteria, particularly technical demands and regulatory standards, applied to food products. In order for a functional food ingredient to be considered and accepted for food use, and a new food product to come to market, a number of criteria need to be satisfactorily addressed. These aspects are listed and described in Table 1, and commercial research and development programmes need to consider these in addition to the mechanistic and clinical data, which are the focus of this review.

**Specific examples of food ingredients for weight control**

**Conjugated linoleic acid**

*Background*

Conjugated linoleic acid (CLA) is a term for a group of geometric and positional isomers of octadecadienoic acid (linoleic acid) that occur naturally in food. The primary dietary sources of CLA are animal-based products (e.g. dairy products, beef). Commercial CLA preparations are produced by isomerization of linoleic acid to a mixture of different isomers, particularly *trans*-10, *cis*-12 and *cis*-9,*trans*-11 octadecadienoic acid. These isomers are the most relevant to health and weight control effects. CLA intake from dietary sources is generally <600 mg day^-1 (7,8). The *cis*-9,*trans*-11 isomer is the most abundant in natural food products.

**Mechanisms**

Conjugated linoleic acid has been suggested to reduce body fat. The mechanisms behind a possible effect of CLA are not clear, although several mechanisms have been proposed (Table 2). Lack of clarity on the mechanism of action may partly underlie the inconsistencies in results from different clinical trials designs, as noted below.

**Scientific evidence**

*Animal studies.* Consistent and convincing effects of CLA on body composition have been documented in some but not all animal species. Mice are particularly sensitive to CLA. Studies in growing mice have shown that CLA reduces body fat while increasing lean body mass (9,10,17–20). This effect has been linked to increased lipolysis and fatty acid oxidation and reduced deposition of fatty acids in the adipose tissue (9). Furthermore, CLA was shown to increase energy expenditure (17,18) and to reduce food intake (9,17).

*Human studies.* Research on the effects of CLA in humans has produced inconsistent results. Some human studies suggest that CLA reduces body fat and increases lean body mass, but it appears to be considerably less potent than in mice (Table 3). The CLA mixtures utilized in most experiments were synthetically prepared and were comprised almost entirely of the *trans*-10,*cis*-12 and the *cis*-9,*trans*-11 isomers in equal proportions. However, there is evidence that the *trans*-10,*cis*-12 isomer is the more active isomer affecting lipid metabolism and body composition (12,15,21); thus, the apparently more biologically active form of CLA is not the most abundant naturally occurring isomer. This plus low concentrations raises the question of whether naturally occurring food sources or CLA mixtures are of significant value for weight control. On the other hand, two studies also found no effect of the *trans*-10,*cis*-12 isomer alone on body composition (22,23). In order to maximize effectiveness at lowest dose, it will be important to determine the most effective amount of the different isomers for commercial CLA as a food ingredient.

Only two human studies have looked at the effects of CLA on energy expenditure and fatty acid oxidation. Zambell *et al.* (26) observed no effect of supplementation with 3 g day^-1 CLA during 64 days on energy expenditure or fat oxidation in normal weight women. However, only about 40% of the total CLA mixture was comprised of the *trans*-10,*cis*-12 and the *cis*-9,*trans*-11 isomers. In contrast, Kamphuis *et al.* (32) observed that CLA supplementation (1.8 and 3.6 g day^-1) led to increased energy expenditure after a 13-week weight regain period following weight loss. However, this effect was attributed to improvement of body composition and disappeared when energy expenditure was corrected for lean body mass.
Table 1  Range of factors influencing selection and application of functional food ingredients and technologies for added health benefits

| Quality and quantity of scientific support for efficacy | Regulatory agencies, including those involved in advertising standards and consumer protection, require that scientific evidence supports the product claims in the product as used by the intended target group. In addition, a record of clinical research published in mainstream scientific journals is needed to gain desired endorsement from recognized independent experts and organizations. |
| Safety and toxicology | A thorough safety dossier is required as part of due diligence as well as regulatory approval, and to reassure consumers and external experts. Unlike medications and supplements, where access can be controlled or warnings and contraindications stated on the label, foods must be safe for consumption by all healthy people, including children and pregnant or lactating women. |
| Regulatory approval for specific food compositions | Regulations often specify what levels, purpose and product formats are allowable for a specific ingredient. These may limit amounts to a level below what is required for health benefits, or restrict use to less favourable product formats. |
| Sensory quality | Functional ingredients may impart unwanted tastes, flavours, colours or textures to products, either immediately or after processing or during shelf life. A range of secondary technologies (e.g. encapsulation, antioxidants, flavour masking agents) may be required to overcome this. |
| Stability (including processing and shelf life) | Active ingredients must be shown to remain active and bioavailable after relevant processing steps (e.g. high shear or temperature) and through the product shelf life. The added ingredients also must not diminish stability of the product itself, for example lead to more rapid loss of quality or microbial safety. |
| Sourcing (defined specification, source reliability, quality control) | The active ingredient needs to be reliably available to the product supply chain, in necessary quantities, in a form that has known and stable activity, bioavailability and composition. These can be a particular problem for using plant extracts and highly specialized ingredients or technologies for which the number of suppliers or production capacity may be limited. In the latter case, significant long-term capital investments in new facilities may be required. Although this raises business risk, limited ingredient supply or high specifications can also offer a form of protection against competition. |
| Proprietary opportunities | There is a major competitive advantage if new ingredients or technologies are protected by patents or exclusive licensing arrangements. Products concepts that can be readily copied are less likely to attract the investments needed to get them to market. This can be particularly problematic for ‘natural’ compounds and extracts, though there can still be proprietary opportunities, for example related to specific compositions with added benefits (such as improved stability or bioavailability), or more efficient production routes (implying greater profit margins for a particular producer). |
| Dosing level and schedule | In order to be effective in a food format, a functional ingredient must be effective at a dose level and pattern of intake that is feasible though foods. For example, if an ingredient must be ingested several times a day at regularly spaced intervals, then delivery through food is problematic. If it must be taken before meals, then this also limits the range of suitable food formats. Ingredients that must be used at high levels (several grams) create problems for product formulation and quality. |
| Cost (of development and ingredient) | Cost margins for foods are considerably lower than for medications and supplements. A proven ingredient in a popular, trusted brand may command a significant price premium, but this is the exception in a generally price-competitive market. This means that sustained high sales volumes are usually required to recoup the investments in research and development. Those costs, plus costs of safety testing and regulatory approval processes, will also be much higher for novel ingredients and technologies. |
| Appropriate food vehicle (technical and ethical) | The use of certain ingredients may not be feasible in certain product formats, or require significant process or recipe modifications. Examples are lipid-based ingredients for very-low-fat foods, aqueous ingredients for dry foods, or insoluble ingredients in beverages. Ethical issues may also determine the appropriate food carriers for functional ingredients or added nutrients, particularly whether it is appropriate to add these to foods that otherwise would have a poor nutritional value. Sometimes these can bring conflicting nutritional goals into focus, for example the addition of iron to chocolate confectionery popular with children and young adult women (groups at risk of iron deficiency), or a weight control ingredient in a popular but energy-dense snack food format. |
| Marketing strategy and claims | Functional ingredients need to be aligned with the desired image of the brand or product. For example, an agent with an apparently drug-like activity may not be suitable for a brand characterized by ‘natural’ values. Similarly, ingredients are preferred if they can directly support a claim that is legally allowed, readily understood, and credible, meaningful and motivational to consumers. |

**Feasibility**

Conjugated linoleic acid has low oxidative stability. The cis,cis-CLA isomers are most susceptible to oxidative degradation and the trans,trans-CLA isomers are the most stable (34). CLA must therefore be protected from oxidation when is used as supplement or additive. For example, microencapsulation in cyclodextrins has been shown to improve the oxidative stability of CLA (35). CLA is widely
available in capsules. Self-affirmed GRAS determination (‘Generally Regarded As Safe’ notification with the US Food and Drug Administration) of CLA will provide companies with the opportunity to also use it more widely in food.

Conjugated linoleic acid in the form of triglycerides (TG) is a more palatable preparation, although its preparation is more time-consuming and expensive. Thus, CLA in the form of TG is more suitable to be added to various food products whereas CLA in the form of free fatty acids (FFA) can only be used as capsules because of the unpleasant taste (36). Terpstra et al. (36) showed that administration of CLA in the form of FFA or TG to mice had similar effects on body composition and energy balance. Similar effects of CLA in the form of FFA and TG on body fat have also been confirmed in humans (33).

With respect to safety, CLA supplementation in mice has been shown to lead to significant liver enlargement (20), particularly because of the trans-10, cis-12 isomer (37). In humans, no effects of CLA have been shown on liver parameters during 12-week supplementation with 3.4 g day\(^{-1}\) in overweight and obese humans (24) or during

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**Table 2** Possible mechanisms of conjugated linoleic acid

<table>
<thead>
<tr>
<th>Proposed action/mechanism</th>
<th>Model</th>
<th>Tissue</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ CPT activity</td>
<td>Mice</td>
<td>Adipose tissue</td>
<td>9,10</td>
</tr>
<tr>
<td>↑ CPT activity</td>
<td>Mice</td>
<td>Skeletal muscle</td>
<td>9,10</td>
</tr>
<tr>
<td>↑ HSL activity</td>
<td>Mice</td>
<td>Adipocytes</td>
<td>11</td>
</tr>
<tr>
<td>↓ LPL activity</td>
<td>in vitro</td>
<td>3T3-L1 adipocytes</td>
<td>9,12</td>
</tr>
<tr>
<td>↓ Proliferation/differentiation of preadipocytes</td>
<td>in vitro</td>
<td>3T3-L1 adipocytes</td>
<td>13,14</td>
</tr>
<tr>
<td>↑ UCP2 mRNA expression</td>
<td>ob/ob mice</td>
<td>Brown adipose tissue</td>
<td>15</td>
</tr>
<tr>
<td>↑ UCP2 mRNA expression</td>
<td>ob/ob mice</td>
<td>White adipose tissue</td>
<td>15</td>
</tr>
<tr>
<td>↑ UCP3 mRNA expression</td>
<td>ob/ob mice</td>
<td>Skeletal muscle</td>
<td>15</td>
</tr>
<tr>
<td>Ligand/activator of PPAR-alpha</td>
<td>Rat</td>
<td>Hepatoma cell line</td>
<td>16</td>
</tr>
</tbody>
</table>

CPT, carnitine palmitoyltransferase; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; UCP, uncoupling protein; PPAR, peroxime proliferator activated receptor.

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**Table 3** Effects of conjugated linoleic acid on body weight, body fat and lean body mass

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration</th>
<th>Dose (g day(^{-1}))</th>
<th>c9, t11 (g day(^{-1}))</th>
<th>t10, c12 (g day(^{-1}))</th>
<th>BW</th>
<th>BF</th>
<th>LBM</th>
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</thead>
<tbody>
<tr>
<td>24</td>
<td>12 weeks</td>
<td>3.4</td>
<td>1.7</td>
<td>1.7</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>25</td>
<td>12 weeks</td>
<td>1.7</td>
<td>0.85</td>
<td>0.85</td>
<td>NS</td>
<td>↓</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>1.7</td>
<td>1.7</td>
<td>NS</td>
<td>↓</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1</td>
<td>2.55</td>
<td>2.55</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>3.4</td>
<td>3.4</td>
<td>NS</td>
<td>↓</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>64 days</td>
<td>3.9</td>
<td>0.69</td>
<td>0.88</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>27</td>
<td>2 × 4 weeks</td>
<td>0.7 + 1.4</td>
<td>0.35 + 0.7</td>
<td>0.35 + 0.7</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4 weeks</td>
<td>4.2</td>
<td>1.55</td>
<td>1.55</td>
<td>NS</td>
<td>↓</td>
<td>(SAD)</td>
</tr>
<tr>
<td>28</td>
<td>12 weeks</td>
<td>4.2</td>
<td>2.1</td>
<td>2.1</td>
<td>NS</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>12 weeks</td>
<td>1.8</td>
<td>0.9</td>
<td>0.9</td>
<td>NS</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>4 weeks</td>
<td>6.0</td>
<td>1.6</td>
<td>0.46</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>31</td>
<td>8 weeks</td>
<td>3.0</td>
<td>1.5</td>
<td>1.5</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>2.4</td>
<td>0.6</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>12 weeks</td>
<td>3.4</td>
<td>1.2</td>
<td>1.22</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>32</td>
<td>13 weeks</td>
<td>3.4</td>
<td>1.2</td>
<td>2.37</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>23</td>
<td>18 weeks</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>NS</td>
<td>NS</td>
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<tr>
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<td>3.0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>12 months</td>
<td>3.4 (TG)</td>
<td>1.29</td>
<td>1.29</td>
<td>NS</td>
<td>↓</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3.6 (FFA)</td>
<td>1.40</td>
<td>1.48</td>
<td>NS</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** c9,t11, cis-9,trans-11 isomer; t10,c12, trans-10,cis-12 isomer; BW, body weight; BF, body fat; LBM, lean body mass; SAD, sagittal abdominal diameter; TG, triglycerides; FFA, free fatty acids; NS, not significantly different from control; ↓, significantly lower than control; ↑, significantly higher than control.
6-week supplementation with 7.2 g day\(^{-1}\) in novice body builders (38). There were also no indications of hepatic lipodystrophy or that liver ultrastructure or morphology had changed after 18-week supplementation with 1.5 and 3.0 g day\(^{-1}\) of both the cis-9,trans-11 isomer and the trans-10,cis-12 isomer in overweight humans (23). CLA supplementation with 3.4 g day\(^{-1}\) for 12 weeks resulted however in increased insulin resistance and oxidative stress in obese men with the metabolic syndrome (22,39). This was shown with the trans-10,cis-12 isomer but not with a CLA mixture, and would naturally be of concern because of the association between overweight and type 2 diabetes.

**Conclusion**

Although research on CLA in humans is not in complete agreement, there is some evidence that CLA supplementation might be beneficial in weight management. Importantly, CLA appears to affect body composition rather than body weight, and therefore might be particularly effective during weight (re)gain, rather than during weight loss periods, or perhaps used to offset lean body mass loss occurring with ageing. The trans-10,cis-12 isomer has been suggested to be responsible for the effects, although this has not been proven in humans. However, the trans-10,cis-12 isomer is possibly related to certain adverse effects, such as increased insulin resistance and oxidative stress, indicating that the use of purified trans-10,cis-12 CLA may not be suitable among certain obese individuals. Therefore a mixture of isomers, although probably less potent, may be more suitable for safety reasons. Nevertheless, long-term health aspects and efficacy of CLA in humans warrants further research and monitoring as CLA-supplemented food products enter the market.

**Diglycerides**

**Background**

Diglycerides (DG) occur naturally as a minor component, present at <1% and up to about 10% of weight of various oils (40), and typically present in mixed diets at about 1–5 g day\(^{-1}\). In contrast, commercially available DG-rich oil contains approximately 80% DG. The fatty acid composition will reflect the source oil, and for commercial foods this would preferably be a relatively unsaturated stock such as soybean. DG is not a reduced-energy or poorly digested form of fat; DG have a physiological fuel value (kJ g\(^{-1}\)) and bioavailability similar to the TG which predominate in food fats and oils (41).

Diglycerides molecules may have fatty acids esterified in the 1,2- or 1,3-positions. Under normal conditions, DG mixtures interesterify and relatively quickly reach a thermostable equilibrium balance of about 70% 1,3-DG and 30% 1,2-DG. The 1,2-DG form is also an normal intermediate formed in the process of TG digestion.

**Mechanisms**

In order to understand why DG-rich oil may behave differently from traditional TG, it is necessary to consider the processes occurring during digestion and uptake into the body, especially with regard to the 1,3-DG component. Dietary TG is hydrolysed by 1,3-specific lipase to form 1,2-DG, which is further hydrolysed to 2-monoglyceride (MG). The 2-MG and their hydrolysed fatty acids are absorbed and rapidly re-esterified to TG in the small intestine epithelial cell, and appear as chylomicrons in postprandial plasma. During circulation, the diet-derived TG is largely taken up by the adipose tissue, with small amounts taken up by the liver for metabolism or recirculation in other lipoprotein particles (Fig. 1). In contrast, dietary 1,3-DG is hydrolysed to form 1-MG in the intestinal lumen. In comparison to 2-MG, re-esterification of 1-MG to TG proceeds through a relatively less efficient route, apparently leaving a surplus of FFA in the intestinal lumen cell. A proportion of these fatty acids will bypass the re-esterification step, instead entering the portal vein, where they are transported to the liver and may be directly oxidized (42,43) (Fig. 1). However, the relative amounts of fatty acids derived from 1,3-DG that are re-esterified within the enterocyte vs. delivered directly to the liver are not clear.

**Scientific evidence**

**Animal studies.** In rats, intragastric infusion of 1,3-DG was shown to decrease the rate of lymphatic transport of TG and cholesterol as chylomicrons (44). This was assumed to be attributed to the reduction of re-esterification and chylomicron assembly in the small intestine or to reduction of subsequent secretion of chylomicrons into the circulation. With respect to this, Watanabe et al. (43) showed that DG resulted in less resynthesis of TG. This is in line with the reduction of the magnitude of postprandial triglyceridemia observed with DG compared to TG (44). Moreover, DG was also shown to reduce fasting serum TG concentration (45,46). Over the longer term, DG was shown to reduce total and visceral fat accumulation in rats (43,47,48). Several studies suggest an effect of DG on energy/lipid metabolism. DG has been shown to promote
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formation of ketones in rats (43). Moreover, it has been reported that DG enhances the activity of enzymes involved in β-oxidation and suppresses the activity of enzymes involved in fatty acid synthesis (46,48). It has also been shown that DG stimulates expression of genes involved in lipid metabolism (fatty acid transport, β-oxidation) and thermogenesis in the small intestine in C57BL/6J mice (49,50). In rats, increased oxygen consumption with DG compared to TG was observed up to 80 min after administration, indicating increased (hepatic) fat oxidation (43).

Human studies. In humans the magnitude of postprandial triglyceridemia was shown to be significantly lower with DG (10–44 g) vs. TG, by up to 23% (51,52). Nagao et al. (53) reported that consumption of DG-rich oil (10 g day⁻¹) during 16 weeks in healthy, non-obese men resulted in greater reduction in body weight and abdominal fat compared to TG. Similarly, Maki et al. (54) observed that consumption of DG-rich oil (16–40 g day⁻¹) for 24 weeks during an energy-reduced diet resulted in modestly greater body weight and fat mass loss compared to TG (3.6% vs. 2.5% and 8.3% vs. 5.6%, respectively) in overweight and obese men and women.

The effect of DG on body weight and fat mass has been mainly attributed to putative effects of the 1,3-DG isomer on energy/lipid metabolism, food intake regulation, or both. Given the proposed handling of 1,3-DG, consumption of DG in place of TG could be predicted to result in a higher postprandial fat oxidation, as some fatty acids are delivered directly to the liver rather than entering circulation. With respect to this, DG has been shown to promote formation of ketones both in animals and humans (43,51). Moreover, partial replacement of TG oil by DG-rich oil (55 g) in humans resulted in enhanced fat oxidation (by 4.9 g day⁻¹ on day 1 and 4.0 g day⁻¹ on day 2) and reduced appetite scores during 36 h (55).

Replacement of TG oil by DG-rich oil therefore offers plausible but modest beneficial effects for weight control. The exact mechanism of action is still not clear, but as the energy content and bioavailability of both oils are the same (41), any effects must presumably result from the different post-absorptive handling of DG components (44). Both theory and empirical evidence point to relative enhancement of postprandial fat oxidation. The limited human evidence do no support a thermogenic effect, but is consistent with the notion that rises in fat oxidation may act to give suppressed appetite (55). However, energy intake was not found to be different between high-DG-fed and high-TG-fed mice (41), and there are no data from tightly controlled studies of human appetite and intake behaviour.

Feasibility

Little is known about the minimal dose of DG in place of TG that is required to elicit a meaningful effect, but it appears that relatively high doses (>10 g day⁻¹) are necessary. In humans, modest reduction of postprandial triglyceridemia was seen 4–6 h after administration of 10 g DG compared to TG (52). On the long term, modestly improved body weight loss was shown with 10 g day⁻¹ DG-rich oil (53), indicating that repeated ingestion of smaller doses of DG may be effective to provoke an effect. Dose–response data are required to indicate the optimal dose that should be used. In addition, although DG may deliver modest weight control or other benefits relative to TG, it is still a highly energy-dense ingredient. It is therefore not clear if DG adds benefits when added to or substituted for other macronutrients in foods. However, if it is assumed that DG consumption would replace consumption of other dietary fats and used in the same manner, then DG consumption may offer some modest benefits for weight control and perhaps reduction of other health risks.

Conclusion

Diglycerides shows some potentially promising effects for weight control when used in place of TG. However, more data are needed to define the optimal dose required, the mechanism of action and the actual magnitude of effects that can be expected during use in practice.

Medium-chain triglycerides

Background

Medium-chain triglycerides (MCT) are triglycerides with fatty acids having a chain length of 6–12 carbons. MCT occur naturally, and are especially abundant in coconut and palm oil. Commercially produced MCT-oil is obtained through lipid fractionation, the process in which MCT are separated from other components of the oil. Commercial MCT are predominantly (>90%) comprised of C8 and C10 fatty acids (56).

Mechanisms

Medium-chain triglycerides are readily hydrolysed by lingual and gastric lipases. They differ from long-chain triglycerides (LCT, having fatty acids of >12 carbons) in that the fatty acids of MCT are absorbed directly into the portal circulation and transported to the liver for rapid oxidation (57). Unlike long-chain fatty acids, the intramitochondrial transport of medium-chain fatty acids does not require the enzyme carnitine palmitoyltransferase (58). This fact probably accelerates their oxidation, and limits storage of MCT within tissues. The exact mechanism by which MCT may affect energy balance, through appetite and/or energy expenditure, is not clear, although it has been suggested that increased production of ketone bodies with MCT may be involved (59).
Scientific evidence

Animal studies. Animal studies have shown that MCT consumption results in increased satiety and decreased food intake (60), increased energy expenditure (61,62), reduced body weight (63), smaller fat deposits (64–67) and smaller adipocytes (64,65) compared to isocaloric LCT consumption.

Human studies. In humans, postprandial energy expenditure during 6 h was greater after consumption of a meal containing MCT (30 g) compared to a meal containing LCT in both lean and obese subjects (68). Similar results were observed by Seaton et al. (69). Dulloo et al. (70) investigated four different MCT : LCT (g : g) ratios: 0 : 30, 5 : 25, 15 : 15 and 30 : 0, and showed that 24-h energy expenditure was increased by 5% with the diets providing 15–30 g day⁻¹ of MCT. Hill et al. (71) showed that the thermic effect of liquid formula diets was higher with 40% of energy as MCT vs. LCT (8% vs. 5.8%) and increased significantly during 7-day overfeeding with MCT but not with LCT (12% vs. 6.6%). White et al. (72) observed that postprandial energy expenditure was greater with a MCT diet compared to a LCT diet (40% of energy as fat) after 7 but not after 14 days, suggesting that the effect of MCT on energy expenditure could be transient. Other studies, on the contrary, showed that increased energy expenditure and fat oxidation were still observed after 4-week MCT consumption relative to LCT (73–75). However, the MCT diet in the study by White et al. (72) contained very little amounts of octanoic and decanoic acids (7.9% of total fatty acids), in contrast to most other studies, which might explain the lack of an effect on the longer term.

With respect to appetite and energy intake, Stubbs and Harbron (76) showed that 14-day isonenergetic substitution of MCT for LCT in different ratios (1 : 2, 1 : 1, 2 : 1) during a high-fat diet (61.5% of energy) resulted in decreased energy intake in the diet with the most MCT (40% of energy). Supplementation of a meal with MCT (18–54 g) was shown to decrease energy intake of a subsequent meal compared to LCT, but did not delay meal request or affect appetite (77–79). Although MCT have been shown to induce satiety and reduce food intake, no single satiety hormone (cholecystokinin, peptide YY, gastric inhibitory peptide, pancreatic polypeptide) has been found to be related to the observed MCT effect (80–82).

Despite the effects observed for MCT in relation to energy expenditure and appetite, long-term data for effects of MCT on body weight and body composition have been inconsistent. Tsuji et al. (83) observed that 12-week ingestion of low amounts of MCT (10 g day⁻¹) vs. LCT led to reduced body weight and fat in overweight Asian subjects. During a 4-week very-low-calorie diet, MCT (9.9 g day⁻¹) resulted in a small but significant increase in body fat loss and decrease in fat-free mass loss compared to LCT, but this effect was only evident during the first 2 weeks (3.6 kg vs. 2.3 kg and 1.9 kg vs. 2.5 kg respectively) (59).

In contrast, Yost and Eckel (84) found that MCT (24% of energy as fat) for either 4 or 12 weeks failed to improve rates of weight loss in obese women compared to a LCT diet. This was explained by the low fat content of the diet or by gender differences in the response to MCT. Although no study has examined gender differences in the response to MCT, indirect comparison of the effectiveness of MCT relative to control between studies suggests that women respond less readily to MCT treatment (84) than men (68–71). A number of other studies have also found no effects of MCT on body weight and/or body composition (73,76,85).

Feasibility

It appears that relatively high doses of MCT (> 10 g day⁻¹) are needed to elicit a meaningful effect on energy expenditure and/or energy intake. MCT are likely to be ineffective in small amounts and therefore not suitable for supplementation in a normal diet. Nevertheless, Hill et al. (83) observed beneficial effects of 12 weeks low-dose MCT (10 g day⁻¹) substituted for LCT on body weight and subcutaneous fat in subjects with a BMI ≥ 23 kg m⁻², but not in those with a lower BMI. Also, during a ketogenic diet the amount of MCT used to obtain an effect on body weight and body composition was relatively small (9.9 g day⁻¹) (59). However, to obtain similar effects during normal intake, several times higher amounts of MCT would probably be required, which may not be feasible from a practical point of view. The maximal amount of oral MCT that can be tolerated in the gastrointestinal tract is apparently low relative to LCT, and there are several reports noting minor but unpleasant gastrointestinal side effects with fairly modest doses of MCT (69,86–89). The possibility of side effects would have to be minimized, perhaps through other ingredients or processing, in order for MCT oil to become widely used in everyday foods. MCT oil also does not give the desired textural and mouth-feel qualities of LCT, and large amounts of MCT would probably reduce palatability, especially when used together with a very-low-energy diet (59).

Conclusion

In conclusion, replacement of LCT by MCT shows promising results on energy expenditure and energy intake, but the long-term slimming potential of MCT is less evident. Use of MCT in foods is further likely to be limited by the high doses that are probably required for meaningful efficacy, which creates adverse effects on product quality and palatability, and potential occurrence of gastrointestinal problems.
Green and oolong tea

Background

Green and oolong tea are made from the leaves of Camellia sinensis L. species of the Theaceae family. Green and oolong tea are the non- and partially fermented/oxidized products, respectively, in contrast to black tea that is fully fermented/oxidized. Both oolong and green tea contain high quantities of catechin polyphenols such as epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate, the latter being the most abundant and probably the most pharmacologically active, and caffeine. Green and oolong tea are consumed primarily in Asia, but are growing in popularity in western countries.

Mechanisms

Caffeine is understood to act primarily through inhibition of phosphodiesterase, an enzyme that degrades intracellular cyclic AMP, and by antagonizing the negative modulatory effect of adenosine on increased noradrenalin release (90). Tea catechins have been shown to inhibit catechol O-methyl-transferase (91), the enzyme that degrades noradrenalin. Taken together, both caffeine and tea catechins would be expected to increase and/or prolong the stimulatory effects of noradrenalin on energy and lipid metabolism.

Scientific evidence

In vitro studies. Dulloo et al. (92) reported that green tea extract stimulated thermogenesis in brown adipose tissue in a dose-dependent way compared to caffeine, by 77% and by more than fivefold at 100 μM and 250 μM of caffeine equivalents respectively.

Animal studies. Kao et al. (93) showed that intraperitoneal administration of epigallocatechin gallate (but not of other catechins) dose-dependently decreased body weight and fat mass of rats. Ingestion of 0.5% tea catechins for 4 and 16 weeks reduced body weight and fat gain of rats fed high-fat diets (94,95). Osaki et al. (96) reported that tea catechins increased energy expenditure and fat oxidation in rats after 18 h food depletion. Han et al. (97) observed that oolong tea prevented an increase in body weight, adipose tissue and fatty liver in mice on a high-fat diet.

Human studies. Dulloo et al. (98) showed that green tea (caffeine: 150 mg day\(^{-1}\); catechins: 375 mg day\(^{-1}\)) stimulated 24-h thermogenesis in humans by 3.5% and fat oxidation by 27 g compared to placebo. The effect of green tea was greater than could be attributed to its caffeine content alone (which raised thermogenesis and fat oxidation by 2.5% and 21 g, respectively). Rumpler et al. (99) showed that full-strength oolong tea (caffeine: 270 mg day\(^{-1}\); catechins: 668 mg day\(^{-1}\)) and caffeinated water (caffeine: 270 mg day\(^{-1}\)) produced similar increases in 24-h energy expenditure (2.9% and 3.4% respectively) and fat oxidation (8 g and 5 g respectively). However, no effects were seen with half-strength oolong tea (caffeine: 135 mg day\(^{-1}\); catechins: 334 mg day\(^{-1}\)). More recently, Blom et al. (unpublished data) have found no effect of single administration of green tea (caffeine: 114 mg; catechins: 561 mg) on 3-h postprandial substrate utilization or thermogenesis following a 0.92-MJ liquid meal.

A number of studies have indicated that longer-term consumption of green tea components can have benefits for body weight or fat mass/distribution (100–103). In a nonplacebo controlled trial, Chantre and Lairon (100) observed that 12-week ingestion of green tea (caffeine: 150 mg day\(^{-1}\); catechins: 375 mg day\(^{-1}\)) led to decreases in body weight and waist circumference (4.6% and 4.5% respectively) in moderately obese subjects. A number of Japanese studies have investigated the effects of tea catechins on fatness-related parameters. In a nonplacebo controlled trial, 12-week ingestion of high doses of tea catechins (caffeine: 75 mg day\(^{-1}\); catechins: 483 mg day\(^{-1}\)) during a high-fat diet resulted in decreased body weight, waist circumference and body fat in healthy normal weight to obese men, while low doses of tea catechins (caffeine: 75 mg day\(^{-1}\); catechins: 119 mg day\(^{-1}\)) only resulted in decreased body weight (101).

Nagao et al. (102) reported that 12-week ingestion of oolong tea (catechins: 555 mg day\(^{-1}\) and 902 mg day\(^{-1}\)) decreased visceral fat in a dose-dependent manner compared to control (catechins: 126 mg day\(^{-1}\)) in healthy normal weight to obese men. The higher dose also reduced body weight and total fat. Moreover, they showed that 12-week ingestion of both green and oolong tea (catechins: 541 mg day\(^{-1}\)) decreased visceral fat compared to control (catechins: 130 mg day\(^{-1}\)) (102). Similarly, Tschida et al. (103) observed that 12-week ingestion of green tea (caffeine: 83 mg day\(^{-1}\); catechins: 588 mg day\(^{-1}\)) decreased body weight, visceral and total fat compared to control (caffeine: 81 mg day\(^{-1}\); catechins: 126 mg day\(^{-1}\)) in overweight men and women.

It is perhaps important to note that most of these studies showing significant benefits from green tea limited caffeine intake from other sources. In contrast, Kovacs et al. (104) found no evidence of long-term weight control benefits of green tea components. Green tea supplementation (caffeine: 104 mg day\(^{-1}\); catechins: 573 mg day\(^{-1}\)) for 13 weeks following body weight loss did not improve body weight maintenance compared to placebo. In that study, among subjects given green tea, a higher habitual caffeine intake was associated with a higher weight regain, suggesting that background caffeine intake affects the effectiveness of green tea for weight maintenance.
Background caffeine intakes may contribute towards explaining the discrepancies in outcomes of weight control trials using green tea. It is possible that green tea and oolong tea may only be effective in low-to-moderate caffeine users, a factor that would pose a limitation in the efficacy of green or oolong tea for weight control in many individuals. However, if the effect of green and oolong tea is not solely attributed to their caffeine content, they still may have potential for weight control within a normal diet including caffeine.

Feasibility

Tea catechins have been shown to be bioavailable in humans (105,106), with the gallated catechins (epigallocatechin gallate, epicatechin gallate) showing lower bioavailability than the nongallated catechins (epigallocatechin, epicatechin) (105,106). Because green tea has been shown to exert biological effects, it is possible that the relatively low concentration of circulating catechins in relation to ingested catechins is attributable or due to rapid degradation or uptake by other tissues rather than to low bioavailability. However, significant variation in bioavailability could contribute to variation in the dose-efficacy of different tea preparations. A limitation for the use of green and oolong tea as food ingredients is their bitterness and astringency, also mainly attributable or due to the tea catechins. Although there are ways to decrease the bitterness and astringency of green and oolong tea extracts or to mask the bitterness and astringency of products containing green and oolong tea extracts, production of functional food products containing green or oolong tea remains a challenge because of the relative high doses needed to elicit a physiological effect.

Green tea in the doses used for energy metabolism and weight control trials has been shown to be free of side effects. The most common adverse effects from consuming large amounts (many cups per day) of green tea would be insomnia, anxiety and other symptoms caused primarily by caffeine. On the other hand, green tea may also have beneficial health effects, which are largely believed to be mediated by tea catechins. For example, there is evidence that green tea lowers total cholesterol levels and improves the cholesterol profile (107), reduces platelet aggregation (108) and lowers blood pressure (109). Several other health benefits have been suggested such as antioxidant activity (110,111), anticancer effect (112) and antibacterial properties (113).

Conclusion

Although green and oolong tea have shown promising short-term effects on energy expenditure and fat oxidation, more data are needed to draw a conclusion on the long-term weight control effects. Furthermore, from the studies conducted, it is not clear whether the varying results are attributed to caffeine, to tea catechins or to interference or synergism between these compounds.

Ephedrine and caffeine

Background

Ephedrine is the primary active ingredient of herbal ephe- dra (Ephedra Sinica, also known as Ma Huang). Caffeine, a methylxanthine, is found in a large number of plants such as coffee, tea, cola nuts, cacao beans, mate and guarana. Caffeine is widely used and its daily intake varies largely (0–1000 mg day\(^{-1}\)).

Mechanisms

The thermogenic, lipolytic and anorectic effects of ephedrine are mainly attributed to sympathetic activation of the central nervous system (114). Moreover, ephedrine has been shown to delay gastric emptying (115). Caffeine acts through inhibition of phosphodiesterase and through adenosine antagonism (90), which would result in increased cyclic AMP concentration in the cell and prolonged noradrenalin release.

Scientific evidence

Animal studies. Administration of ephedrine has been shown to reduce body weight and body fat in rodents, mainly through increased energy expenditure (116,117). These effects were accentuated when ephedrine was administered with methylxanthines such as caffeine and/or theophylline (117), while methylxanthines alone were shown to be effective for energy expenditure or weight control in some studies (118), but not in others (117). Also other studies showed that administration of ephedrine and caffeine combined can be effective for weight control, mainly through increased energy expenditure and in some cases through reduced food intake, in rodents (119,120) and monkeys (121).

Human studies on ephedrine. Thermogenic effects of ephedrine have been observed on the short-term, that is, <24 h (122,123), and are maintained on the long-term, that is, >2 weeks (124,125). However, long-term supplementation (24 weeks) with ephedrine (60 mg day\(^{-1}\)) alone in an energy-restricted diet did not result in significant greater weight-reducing effect compared to placebo (114). Other studies showed that a rather large dose of ephedrine (150 mg day\(^{-1}\)) alone had either no effect (125,126) or only a slight effect on body weight (127).

Human studies on caffeine. Short-term thermogenic effects of caffeine in a range of 100–600 mg have been reported in a large number of studies in lean, obese and post-obese individuals (127–136). The effects have been
shown to be dose-dependent (129) and may be different in caffeine users and non-users. With respect to this, improved exercise performance in response to caffeine was shown to be more pronounced in caffeine non-users compared to users (137). There is also some evidence that caffeine stimulates lipolysis (138,139) and fat oxidation (128,136), but these results have been less consistent. Few studies have investigated the effects of chronic caffeine administration. Astrup et al. (114) showed that caffeine administration (3 x 200 mg day\(^{-1}\)) during 24 weeks together with an energy-restricted diet did not result in greater body weight loss compared to placebo. The lack of long-term effect of caffeine alone on body weight may be attributed to development of tolerance to its thermogenic effect, as has been shown for cardiovascular effects (114,140). Although caffeine was found to increase thermogenesis in moderate caffeine users, it is possible that the effect of caffeine disappears with concomitant consumption of other caffeine-containing products (e.g. coffee, tea, cola), as is the case in free-living conditions when daily caffeine intake may be large. In this respect, it has to be noted that in most studies thermogenic effects of caffeine were investigated after 12–48 h of caffeine withdrawal. Another explanation for the lack of a long-term effect of caffeine may be that a compensatory effect on appetite and energy intake would counteract the effect on energy expenditure. Caffeine has been shown to exert an inhibitory effect on energy intake in men, but not in women (141), indicating that this may not be the most plausible explanation.

*Human studies on ephedrine–caffeine combination.* A supra-additive effect (Fig. 2) on thermogenesis, body weight and body composition has been observed with a combination of ephedrine and caffeine (and aspirin) in both lean and obese individuals (114,142–147). The ephedrine–caffeine combination was also shown to be effective for body weight loss when used together with an energy-restricted diet (114,147), while ephedrine or caffeine alone were ineffective. This body weight reducing effect lasted up to 48 weeks (147). A Ma Huang–guarana mixture, an herbal combination of ephedrine and caffeine, was also shown to promote body weight and fat loss up to 6 months (148–150).

**Feasibility**

While the ephedrine–caffeine combination appears to be efficacious for weight loss, ephedrine has been associated with serious adverse events, including elevated blood pressure, rapid heart beat, nervousness, irritability, headache, urination disturbances, vomiting, muscle disturbances, insomnia, dry mouth, heart palpitations and even death attributed to heart failure (151). A review of 140 case reports of adverse effects related to the use of dietary supplements containing ephedrine and related alkaloids was submitted to the US Food and Drug Administration (152). For safety reasons, the US Food and Drug Administration has therefore decided to ban the use of ingredients that contain ephedrine alkaloids (153).

In general, however, individual clinical trials investigating ephedrine alone or in combination with caffeine (and aspirin) show little or no adverse effects (114,144,147). Reasons for this might be that the individuals participating in the clinical trials are healthier (selection is based upon screening), the quality of the supplements used is controlled, the dose and composition of the product is known and the statistical power for adverse events is less. While ephedrine alone or in combination with caffeine (and aspirin) in the amounts recommended for weight control (60 mg day\(^{-1}\) ephedrine, 200 mg day\(^{-1}\) caffeine, 300 mg day\(^{-1}\) aspirin) seems likely to be safe for most healthy individuals, this may pose a higher risk for unhealthy individuals under uncontrolled conditions. For the Ma Huang–guarana mixture, contradictory findings were reported on the occurrence of adverse effects (148,149), indicating again that such mixtures may increase health risks.

Caffeine use is relatively safe. The ingestion of 250 mg caffeine resulted in increased blood pressure, heart rate, plasma renin activity, plasma catecholamines and urinary catecholamines in subjects who were not coffee or tea drinkers (154). These caffeine-related effects disappeared after 3 days when caffeine administration was continued (154). However, large doses (>1000 mg) of caffeine may cause adverse effects such as insomnia, irritability, tremor, palpitations and anxiety, especially in caffeine non-users. As a diuretic, caffeine may increase urine production. When used in moderate amounts, there is little evidence that caffeine has significant long-term health effects. There is some evidence suggesting that caffeine may contribute to

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**Figure 2** Synergism between ephedrine, caffeine and aspirin (adapted from reference 150).
the development of osteoporosis, but the negative effects of calcium on bone metabolism may be small (155).

Conclusion

Although both ephedrine and caffeine have been found to have thermogenic and anorectic properties, long-term administration of ephedrine (up to 150 mg day$^{-1}$) or caffeine (up to 600 mg day$^{-1}$) alone have failed to show benefits of reducing body weight. However, the combination of ephedrine and caffeine (and aspirin), acting through different mechanisms on the sympathetic nervous system, has been shown to be effective for body weight loss and improved body composition, and safe under controlled conditions when taken in a specific ratio (60 : 200 : 300 mg day$^{-1}$ ephedrine : caffeine : aspirin). Nevertheless, because of the possible health risks mainly associated with ephedrine, the combination of ephedrine and caffeine (and aspirin) is not recommended to be used in unmonitored weight control programmes. Ingredients that contain ephedrine are currently banned in the United States and even if this situation changes, lingering safety issues make them unlikely to be used in foods.

Capsaicin and other pungent principles

Background

The pungent spices in foods have attracted interest because of their potential effects on thermogenesis and fat oxidation. The principle ingredients that confer pungency to spicy ingredients such as red pepper, tabasco sauce, mustard and ginger are the capsaiacinoids (capsaicin and dihydrocapsaicin) and capsaiacinoid-homologues (gingerols and shogoals).

Mechanisms

Capsaicin has been reported to act by stimulating catecholamines secretion from the adrenal medulla, mainly through sympathetic activation of the central nervous system (156–161).

Scientific evidence

Animal studies. Capsaicin has been shown to reduce adiposity in rats by increasing energy and lipid metabolism (156,162). However, intraperitoneal injection of capsaicin was found to increase respiratory quotient in another study, indicating reduced fat oxidation (157). Capsaicin also has the potential to decrease food intake (163). This effect is likely to be related to increased sympathetic nervous system activity rather than to taste aversion, as decreased food intake in rats was also observed in infusion studies (158,159). Gingerols and shogoals were shown to be thermogenic in the perfused rat hindlimb (164).

Human studies. There are a number of studies assessing the effects of pungent spices on energy metabolism in humans, though the differing designs, test materials and results do not provide a totally cohesive picture. The actual dose or profile of capsaicinoids is not always clear, especially in studies using peppers.

Henry and Emery (165) showed that capsaicin (chilli) and allyl isothiocyanate (mustard) have thermogenic effects. A 25% greater increase in metabolic rate over 150 min was observed with a meal containing 3 g of chilli sauce and 3 g of mustard sauce compared to a nonspiced control meal. Yoshioka et al. (166) showed that addition of red pepper (10 g; capsaicin: 30 mg) to a meal increased energy expenditure by 23% immediately after the meal. Carbohydrate oxidation was increased and fat oxidation was decreased for 150 min after the meal. β-Adrenergic blockade eliminated the increase in energy expenditure immediately after the meal, but did not affect substrate oxidation. Similarly, Lim et al. (167) showed that addition of red pepper (10 g; capsaicin: 30 mg) to a meal increased carbohydrate oxidation at rest for 150 min and during subsequent exercise. Yoshioka et al. (168) observed that addition of red pepper (10 g; capsaicin: 30 mg) to high-fat and high-carbohydrate meals increased diet-induced thermogenesis and fat oxidation over 210 min in Japanese women. The effect of red pepper on thermogenesis and fat oxidation was greater with the high-fat meal (ca. 60 kJ and 2 g respectively) compared to the high-carbohydrate meal (ca. 20 kJ and 1 g respectively). Addition of red pepper (10 g; capsaicin: 30 mg) to high-fat and high-carbohydrate meals resulted in decreased appetite and subsequent protein and fat intake in Japanese women (163). Again, the effect of red pepper on protein and fat intake was more pronounced with the high-fat meal (5.7 g and 4.9 g respectively) compared to the high-carbohydrate meal (1.7 g and 3.1 g respectively). Similarly, addition of red pepper (6 g; capsaicin: 18 mg) to an appetizer resulted in reduced subsequent carbohydrate (36 g) and energy intake (791 kJ) at lunch and snack time in Caucasian men (163). A combination of red pepper added to two appetizers (27.76 g day$^{-1}$; capsaicin: 83.28 mg day$^{-1}$) and caffeine as coffee (800 mg day$^{-1}$) was shown to reduce 24-h energy intake (3690 kJ equivalent to 17%) and to increase 24-h energy expenditure (320 kJ equivalent to 3.2%) in Caucasian men, resulting in lower positive energy balance (169). The effects on energy intake and energy expenditure were associated with an increase in the sympathetic : parasympathetic nervous system activity ratio (163,169). However, Blom et al. (unpublished data) found no consistent effects of capsaicin (1.1 mg) given as capsule on postprandial substrate utilization or thermogenesis during 3 h following a 0.92-MJ liquid meal. Although this amount of capsaicin appears low relative to other studies, it still led to significantly increased gastrointestinal complaints.
A number of studies have investigated whether the mode of administration may influence the apparent effect of capsaicin on satiety, or energy or macronutrient intake. Westerterp-Plantenga et al. (170) observed that both oral (in tomato juice) and gastrointestinal (in capsules) administration of red pepper (2.7 g day\(^{-1}\); capsaicin: 6.75 mg day\(^{-1}\)) increased satiety, and reduced energy and fat intake over 24 h. The effect of red pepper on energy intake was greater with oral administration (\(-1.6\) MJ day\(^{-1}\) in men and \(-1.5\) MJ day\(^{-1}\) in women) compared to gastrointestinal administration (\(-1.1\) MJ day\(^{-1}\) in both men and women), while fat intake reduction (6% of energy) was independent of administration route. Yoshioka et al. (171) observed that maximum tolerable dose of red pepper (0.923 g; capsaicin: 2.769 mg) suppressed fat intake by 16% when it was added to soup and showed a trend towards suppressed fat intake (\(-13\%)\) when it was given as capsules together with soup. Moreover, there was a similar trend towards reduced energy intake (\(-8\%)\) both when red pepper was added to soup or given as capsules, suggesting that the effect of red pepper may be independent from feelings of spiciness in the mouth. Toubro et al. (172) showed that simple release of capsaicin in combination with green tea, tyrosine and calcium decreased energy intake and increased energy expenditure and that this was not observed with controlled release (enterocoating) of capsaicin.

Data on the long-term effects of capsaicin are scarce. One study showed that red pepper supplementation (2.7 g day\(^{-1}\); capsaicin: 135 mg day\(^{-1}\)) during 3 months after modest body weight loss resulted in increased post-absorptive fat oxidation and resting energy expenditure (173). In that study, red pepper supplementation was not found to improve weight maintenance or suppress fat gain in humans, although capsaicin has been reported to suppress body fat accumulation in animals (156,162).

**Feasibility**

In most human studies, the amount of red pepper used was relatively high, for example 10 g per meal or about 28 g per day. Taken in these amounts, the extreme pungency of capsaicin and the possible burning feeling in the stomach may limit its intake on the long term. In this respect, capsaicin analogues with no pungency may be an alternative. Nonpungent capsaicin analogues have been shown to enhance adrenalin secretion in rats (174,175). Ohnuki et al. (176) observed that CH-19 Sweet, a nonpungent cultivar of red pepper, increased oxygen consumption and suppressed fat accumulation in rats similarly to capsaicin. In humans, Ohnuki et al. (177) observed increased body temperature and oxygen consumption with CH-19 Sweet, suggesting increased thermogenesis. Kobayashi (178) showed that evodiamine, a nonpungent principle of Evodia fruits, prevented body weight and fat accumulation in rats through increased lipolysis, brown adipose tissue activation and heat dissipation.

In addition to the pungency, there are potential health issues, which may need to be resolved before capsaicinoids could be used as functional food ingredients. Reports of a relationship between capsaicin consumption and increased risk of stomach cancer are contradictory (179). According to one study, capsaicin may increase the risk of stomach cancer (180), while another study found the opposite (181).

**Conclusion**

Overall, short-term effects of capsaicin and other pungent principles on energy expenditure and energy intake are promising, while the effects on substrate oxidation are less consistent. However, evidence of long-term benefits is scarce. Moreover, long-term supplementation of capsaicin in foods may be limited by its pungency and burning effect in the stomach. Promising results on energy metabolism have been seen with nonpungent capsaicin analogues, but research in humans, especially on the long term, is lacking.

**Calcium**

**Background**

Several studies have suggested that high dietary calcium intake is negatively associated with obesity. One of the first indications suggesting a relationship between dietary calcium and obesity came from a group of obese African-Americans who lost 4.9 kg body weight in 1 year with a diet that raised dietary calcium intake from 400 to 1000 mg day\(^{-1}\) (182,183). In addition, data from several different sources have found an inverse relationship between self-reported dietary calcium intake and body weight or fat mass (184–187). However, these studies do not clearly isolate effects of calcium from other associated dietary or lifestyle factors, most notably use of dairy products, which may be high in protein and low in energy density.

**Mechanisms**

Two plausible mechanisms have been proposed by which dietary calcium may reduce adiposity. According to in vitro studies, dietary calcium may reduce the stimulus for Ca\(^{2+}\) influx into the adipocyte by suppressing 1,25-dihydroxyvitamin D production (182,183). This would inhibit lipogenesis and stimulate lipolysis, resulting in reduced adipocyte

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*In the period since this manuscript was accepted, there have been a number of reports of randomized, placebo-controlled human clinical trials evaluating the influence of calcium within the normal range of intakes on energy metabolism and weight control. These trials generally found minimal or no added benefit of calcium, in either a dairy or non-dairy context (206–212).*
triglyceride stores. However, a recent study observing a negative association between 1,25-dihydroxyvitamin D and adiposity has suggested that this mechanism may not play a role in promoting/maintaining triglyceride stores in the obese (188). Furthermore, the hypothesis does not provide a clear link to any accompanying change in energy balance (energy expenditure or intake), which would be needed to achieve a long-term change in weight status.

Another potential mechanism by which calcium may reduce adiposity involves stimulation of increased faecal fat and energy losses attributable or due to formation of non-absorbed complexes of calcium and fat. There is evidence for this from both rats (189) and humans (190–192), although this was not seen in a further human study (193).

**Scientific evidence**

**Animal studies.** Several but not all studies in animal models support the hypothesis that higher dietary calcium intake can reduce body weight and body fat (194,195). Zemel et al. (186) observed that mice that overexpress the agouti gene, and thus are genetically obese, have less of an increase in body weight and body fat with a higher calcium intake. However, Zhang and Tordoff (196) have reported that diets differing in calcium content did not affect body weight in rats and mice on a normal or high-energy diet.

**Human studies.** In humans, dietary calcium was found to be related to changes in body weight and body composition (197–199). Lin et al. (198) showed that young women with a high calcium intake gained less weight and body fat (194,195). Lin et al. (198) showed that young women with a high calcium intake gained less weight and body fat (194,195). Zemel et al. (186) observed that mice that overexpress the agouti gene, and thus are genetically obese, have less of an increase in body weight and body fat with a higher calcium intake. However, Zhang and Tordoff (196) have reported that diets differing in calcium content did not affect body weight in rats and mice on a normal or high-energy diet.

**Feasibility**

Although the mechanisms by which calcium may affect adiposity are plausible according to in vitro and in vivo studies, it is not clear whether the negative relationship between dietary calcium intake and adiposity is attributed to the calcium itself. Whilst total calcium may be negatively associated with adiposity, Lin et al. (198) found that the effect of calcium was specific to dairy calcium. A number of hypotheses have been put forward to explain why dairy calcium but not nondairy calcium might be negatively associated to body weight and body fat. Bioavailability is similar for both dairy and nondairy calcium, so this should not explain the difference. It is possible that other components present in dairy products (e.g. protein, conjugated linoleic acid) could influence body weight and body fat. Moreover, the use of a diet high in dairy products may not only result in enhanced calcium intake, but may also increase the use of low-energy dairy products possibly leading to reduced energy intake. In some human intervention trials, dietary guidance given to the volunteers may intentionally or unintentionally lead to substitution of low-energy (dairy) products for higher-energy alternatives (201). Despite the interpretation of the authors, this type of design makes it impossible to unequivocally attribute results to calcium or even dairy products. It is also not clear whether the effects
of increased dietary calcium intake on body weight loss are attributed to a positive ‘functional’ effect, or rather to correction of suboptimal calcium intake (adequate daily dietary intake for calcium is 800–1000 mg day−1). With respect to this, observational studies report higher body weight and body fat in those individuals with calcium intake below the adequate daily level (186,187). Also, studies comparing diets differing in calcium content often use a diet providing an inadequate daily calcium intake in the low-calcium condition (192,193,201,202).

Conclusion
Overall, although a negative relationship between dietary calcium and obesity has been shown, it is not clear whether this is really attributed to calcium itself or to other components or characteristics of calcium-rich products/diets. Clear demonstration of a mechanism through which calcium affects human energy balance would help enormously in improving design of trials (i.e. by understanding the dietary conditions under which the putative calcium effect is most likely to be observed). Additional information on the direct effects of dietary calcium on body weight and body fat should be gained from human intervention studies using calcium supplementation rather than by comparing diets or commercial products differing in calcium content. Lastly, it is not clear how background diet (e.g. daily calcium, fat, or energy content) may influence the effectiveness of calcium for weight loss or maintenance.

Overall conclusions
For each of the agents described here, with the exception of the ephedrine–caffeine combination, there are tantalizing but still inconsistent or incomplete data relating to the mechanism of action and benefits for weight control. In some cases (e.g. calcium, DG, CLA), it is not yet even established what aspect of energy balance (intake, uptake, or expenditure) is actually being affected. In the case of CLA, the agent probably does not directly affect body weight or weight loss, but could benefit body composition during weight maintenance or (re)gain periods. For calcium, reliance upon epidemiological and retrospective data analyses, along with clinical trial designs that confute calcium with other differences in food type and composition, leave doubt about whether and when it influences energy balance. Other ingredients present significant obstacles to use in foods, because of issues such as safety (ephedrine/caffeine) or sensory effects (capsaicin). On the other hand, some proposed ingredients (e.g. calcium, green tea) could be particularly attractive because they have a long history of safe consumption, and also may bring other added health benefits beyond weight control. For bulk fats such as DG and MCT, the levels that would be need to be used may be quite high as a replacement for traditional food oils. This may limit the food formats where they would be of most value, and the putative ‘functional’ benefit for weight control needs to be balanced against the significant amounts of energy delivered by such ingredients at effective doses.

Improved understanding and evidence on each of the reviewed and other proposed weight control ingredients will guide further research, as well as the selection of ingredients and product formats that can deliver the most attractive and effective benefits to consumers.

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