Effectiveness of medium-chain fatty acids on feed intake and weight gain in animal: Depending on balance

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ABSTRACT

Medium-chain fatty acids (MCFAs) has been used in animal production, not only as an energy substance, but also as a kind of functional material, especially in pig production. At present, however, the action mechanism of MCFAs on ingestion and growth is not fully clear. In addition, there is no consensus for effect of MCFAs on feed intake and weight gain in animals. In this review, we summarized the information from comprehensive and rational arguments for the role of MCFAs on feed intake and weight gain in monogastric animal studies (mainly in rats and pigs). As a result, the supplementation level of MCFAs in diet is a key influence factor on animal ingestion, of which underlying action mechanism may be attributed to influence of MCFAs on appetite hormones (mainly, insulin and Acyl ghrelin) and fluctuation of energy balance. Additionally, the influence of MCFAs on growth performance is related to addition level of MCFAs, the types of MCFAs, characteristics of based diet, as well as the physiological status of animal. The effectiveness of MCFAs on ingestion and weight gain depend on the balance of the various influence factors.

Key words: Feed intake, Medium-chain fatty acid, Mechanism, Weight gain.

Abbreviations: MCFAs: medium-chain fatty acids, LCFAs: long-chain acids, FAO: hepatic fatty acid oxidation, MCTs: medium-chain triglycerides, LCTs: long-chain triglycerides

INTRODUCTION

Medium-chain fatty acids (MCFAs) have several unique physiological and biological characteristics compared with long-chain acids (LCFAs) (Takeuchi et al., 2006). Antimicrobial effects and protective effects on the intestinal microarchitecture of MCFAs have been described by Dierick et al., (2003). In addition, MCFAs have also been suggested to have immune-modulating effects (Wang et al., 2006). Therefore, MCFAs, as specific nutritional and functional materials, are increasingly studied in animals to improve performance and, at the same time, to sustain health of animal. Nevertheless, published literatures for MCFAs have no consensus for effect of MCFAs on feed intake and weight gain in animals. In some studies, MCFAs supplementation increased feed intake or weight gain in pigs (Dierick et al., 2002, 2003). In contrast, other studies indicated that MCFAs supplementation not only had no significantly effect on feed intake and weight gain compared with LCFAs in rats (Shinohara et al., 2005, 2006; Terada et al., 2012) or in pigs (Allee et al., 1972; Frobish et al., 1970), but also led to a reduction for feed intake and weight gain in rats (De Vogel-van den Bosch et al., 2011) or pigs (Price et al., 2013). So far, although some reasons caused inconsistent results have been mentioned in several reports (Ferreira et al., 2014; Zentek et al., 2011), action mechanism of MCFAs on feed intake and weight gain was not thoroughly understood.

Therefore, the objective of this literature review was to determine the reasons of inconsistent results induced by MCFAs supplementation for feed intake and growth performance in monogastric mammal, and especially to explore a possible underlying mechanism of MCFAs influence on ingestion and growth.

MATERIALS AND METHODS

In this review, typical studies for effect of MCFAs on ingestion and growth in monogastric mammal, mainly in rats and piglets, are selected from public reports on the basis of one criterion that they can provide comprehensive and specific information on MCFAs in studies (see items in Table 3). The reasons of inconsistent results induced by MCFAs supplementation for feed intake and growth performance in monogastric mammal were summaried based on these information and an underlying mechanism of MCFAs influence on ingestion and growth was discussed.

RESULTS AND DISCUSSION

MCFAs are saturated 6–12 carbon fatty acids, which occur naturally as MCTs in milk fat and various feed materials, especially coconut, palm oils and cuphea seed oils. The main fatty acids that comprise MCTs are caprylic acid (C8:0, 50–80%), capric acid (C10: 0, 20–50%) and, to
a lesser extent, caproic acid (C6:0, 1–2%) and lauric acid (C12:0, 0.1–2%) (Ferreira et al., 2014). Due to a shorter hydrocarbon chain length compared to LCFAs, MCFAs have a smaller molecule size, less energy dense, lower melting point and pKa value and a comparatively high solubility in water. The chemical properties of common saturated fatty acid with different chain length are summarized in Table 1.

Because of distinct chemical and physical properties, MCFAs differ significantly from LCFAs in digestion, absorption and metabolism. The main difference between MCTs and LCTs is summarized in Table 2. Briefly, intraluminal hydrolysis of MCTs is faster and more efficient than hydrolysis of LCTs. Likewise, absorption of MCFAs is faster and more efficient than LCFAs. Furthermore, oxidation of MCFAs is higher than LCFAs, and energy supply is faster as well.

In order to study effects of MCFAs on ingestion and growth, numerous studies have been carried out by feeding MCTs diet to animals. Nevertheless, published literatures have not shown conclusive evidence that MCFAs or MCTs supplementation are beneficial for animal performance at all times. For further comparison and better demonstration on the varying results, some representative studies on MCTs or MCFAs supplementation in rats and piglets were summarized in Table 3.

It is observed that the level of inclusion of MCTs or MCFAs in diet may be a key influence factor caused inconsistent results of feed intake and weight gain in literatures (Table 2). Generally, a lower level of MCFAs in diets (2-6%) may be beneficial to improve performance of animals. A higher level of MCT in diets (more than 10%) may not be beneficial, and even detrimental, to the growth performance of animals.

A variety of evidence indicated that hepatic fatty acid oxidation (FAO) influenced feed intake of animals. The peripheral administration of inhibitors of fatty acid oxidation stimulated ingestion in rats (Horn et al., 2004). Furthermore, a growing body of evidence showed that a decrease in hepatic FAO could simulate feeding behavior (Horn et al., 2004). In contrast, an increase in hepatic FAO contributed to the inhibitory control of feed intake (Jambor de Sousa et al., 2006). Therefore, the effect of MCFAs on ingestion can be attributed to hepatic FAO.

Although hepatic FAO was involved in ingestion regulation of MCFAs, action mechanism of how hepatic FAO affect ingestion remains unclear. This mechanism may be related to effect of MCFAs on systemic energy balance. Previous “energostatic hypothesis” has proposed that a common metabolic measure of energy, rather than a particular nutrient, controls eating (Booth, 1972). The MCFAs in diet are absorbed through the portal system without resynthesis of triacylglycerol in intestinal cells, and are predominantly subjected to β-oxidation in liver compared to LCFAs (Leyton et al., 1987). The rapid oxidation of MCFAs in the liver leads to an increase ATP content in the liver (Ooyama et al., 2006). Therefore, the effect of MCFAs on ingestion can be attributed to hepatic FAO.

Table 1: Chemical properties of acetic, propionic, caproic, caprylic, capric, lauric, palmitic and stearic acid

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Molecular weight</th>
<th>Melting point (°C)</th>
<th>pKa</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid (C2:0)</td>
<td>60.05</td>
<td>16.6</td>
<td>4.76</td>
<td>Dawson et al., 1989</td>
</tr>
<tr>
<td>Propionic acid (C3:0)</td>
<td>74.08</td>
<td>-21–20</td>
<td>4.88</td>
<td>Frobish et al., 1970;</td>
</tr>
<tr>
<td>Caproic acid (C6:0)</td>
<td>116.2</td>
<td>-3.4</td>
<td>4.88</td>
<td>HSDB, 2011</td>
</tr>
<tr>
<td>Caprylic acid (C8:0)</td>
<td>114.2</td>
<td>16.7</td>
<td>4.89</td>
<td>Hsiao et al., 1999</td>
</tr>
<tr>
<td>Capric acid (C10:0)</td>
<td>172.3</td>
<td>31.9</td>
<td>4.89</td>
<td>Kanicky et al., 2000</td>
</tr>
<tr>
<td>Lauric acid (C12:0)</td>
<td>200.3</td>
<td>44.0</td>
<td>5.13</td>
<td>Kanicky et al., 2002</td>
</tr>
<tr>
<td>Palmitic acid (C 16:0)</td>
<td>256.4</td>
<td>62.9</td>
<td>8.6–8.8</td>
<td></td>
</tr>
<tr>
<td>Stearic acid (C 18:0)</td>
<td>284.4</td>
<td>67.0</td>
<td>10.15</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: The comparison of main properties difference of MCTs and LCTs

<table>
<thead>
<tr>
<th>Properties</th>
<th>LCTs</th>
<th>MCTs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water solubility</td>
<td>relative insolubility</td>
<td>higher water solubility</td>
<td>Valdivieso, 1972; Hill et al., 1990; Guillot et al., 1993; Guillot et al., 1994; Bach et al., 1996</td>
</tr>
<tr>
<td>Digestion</td>
<td>necessity for emulsion with bile and require lipase</td>
<td>without the necessity for emulsion with bile and lipase</td>
<td></td>
</tr>
<tr>
<td>Absorption</td>
<td>reach the bloodstream via the lymphatic system</td>
<td>absorbed predominantly via the portal vein into the liver</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>require binding to fatty acid-binding protein, fatty acid transport proteins or fatty acid translocase (FAT); oxidation mainly occur in muscle tissue and most be stored in adipose tissue</td>
<td>do not require binding to fatty acid-binding protein, fatty acid transport proteins or fatty acid translocase (FAT); oxidation mainly occur in liver and less be stored in adipose tissue</td>
<td></td>
</tr>
<tr>
<td>Enter mitochondria</td>
<td>Depend on carnitine</td>
<td>Independent on carnitine</td>
<td></td>
</tr>
<tr>
<td>Oxidation rate</td>
<td>slow</td>
<td>fast</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Typical studies for effect of MCFAs on ingestion and growth in rats and piglets

<table>
<thead>
<tr>
<th>Animal</th>
<th>Age (weeks)</th>
<th>Control</th>
<th>MCFAs source</th>
<th>Level % (diet weight)</th>
<th>Test period (days)</th>
<th>Feed intake</th>
<th>Weight gain</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In rats (recent ten years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats 3–4</td>
<td>LCTs</td>
<td>MCTs or MLCT</td>
<td>32</td>
<td>7</td>
<td>↓</td>
<td>↓</td>
<td>Birk et al., 2004</td>
<td></td>
</tr>
<tr>
<td>Rats 3–9</td>
<td>LCTs</td>
<td>MCTs or MLCT</td>
<td>15–20</td>
<td>7–56</td>
<td>No</td>
<td>↓</td>
<td>Han et al., 2003; Birk et al., 2004; Matsuo et al., 2004; Takeuchi et al., 2006</td>
<td></td>
</tr>
<tr>
<td>Rats 3–4</td>
<td>LCTs</td>
<td>MCTs</td>
<td>18</td>
<td>7</td>
<td>↓</td>
<td>No</td>
<td>Birk et al., 2004; Birk et al., 2004; Matsuo et al., 2004; Shinohara et al., 2005; Shinohara et al., 2006</td>
<td></td>
</tr>
<tr>
<td>Rats 3–12</td>
<td>LCTs</td>
<td>MCTs or MLCT</td>
<td>5–10</td>
<td>7–31</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>In weaned piglets (recent thirty years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piglets 3</td>
<td>LCTs</td>
<td>MCTs</td>
<td>13</td>
<td>14</td>
<td>↓</td>
<td>↓</td>
<td>Price et al., 2013; Frohlich et al., 1970; Allee et al., 1972; Mahan, 1991; Fakler et al., 1992; Cera et al., 1989; Rodas et al., 1990; Dove, 1993; Jin et al., 1998; Dierick et al., 2002; Dierick et al., 2003</td>
<td></td>
</tr>
<tr>
<td>Piglets 3–4</td>
<td>LCTs</td>
<td>MCTs or MCFAs</td>
<td>8–10</td>
<td>14–28</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piglets 3–4</td>
<td>LCTs</td>
<td>MCTs or MCFAs</td>
<td>2.5–6</td>
<td>7–28</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

of energy balance is very important for mammal, and the mammal usually keep stability of energy balance by changing food intake (Magni et al., 2009).

However, how rapid oxidation of MCFAs in the liver affect systemic energy balance is not clear by now. Langhans (2008) stated that meal-related changes in FAO may occur at critical sensor sites in particular tissues. A recent study from Nagata et al. (2012) have identified hepatic Shp2, a novel regulator of systemic energy balance, could regulate systemic energy balance under conditions of high-fat feeding in mice, which is related to enhanced mitochondrial signal transducer. Additionally, besides the liver, the small intestine appears to be an attractive candidate site for peripheral energy sensing in control of eating (Langhans, 2008), but there is no direct evidence supports this hypothesis.

Therefore, action mechanism of MCFAs on feed intake of animal may be attributed to fluctuation of systemic energy balance energy balance caused by a mass of rapid oxidation of MCFAs in the liver. It could also be an important reason for high level MCFA supplementation led to decreased feed intake of animals.

Several studies indicated that not only some metabolic products level (such as ketone bodies, free fatty acid), but also appetite hormone concentration (such as Acylghrelin, insulin, cholecystokinin) was changed after feeding MCFAs or MCTs diets in mammal. In this respect, the changes of metabolic products and appetite hormones secretion, at least partly, involved in the action mechanism of MCFAs on feed intake.

In fact, although ketone bodies or precursors of ketone bodies affected feeding (Noguchi et al., 2002), this appears to be a purely pharmacological effect (Scharrer, 1999), hence it is unlikely that the plasma levels of ketones or free fatty acid per se influence feeding (Jambor de Sousa et al., 2006). However, there is also a possibility that changes in free fatty acid levels in the liver provide a hepatic feedback signal that affects pre-absorptive gastrointestinal functions such as gut hormone release or gastric emptying (Jambor de Sousa et al., 2006), and further lead to the changes of feeding behavior. Additionally, it is reported that the carnitine increased food intake in rats with anorexia (Laviano et al., 1996). Therefore, the changes of carnitine induced by MCFAs may be an important regulation factor of ingestion. Moreover, it was reported that appetite hormones leptin and PYY played no role in effect of MCFAs on feed intake (Ooyama et al., 2009), and the secretion of CCK played only a minor role in MCFAs-regulate feeding (Symersky et al., 2002).

In addition, there has been accumulating evidence indicated that MCFAs affected insulin secretion (Shinohara et al., 2006; Ooyama et al., 2009), as well improved insulin sensitivity (Terada et al., 2012). These results implied insulin may play an important role in regulating action of MCFAs on feed intake. Former study showed that pancreatic insulin secretion is centrally regulated via the vagal efferent nerve.
(Ionescu et al., 1983), while this regulation is ineffective for obesity rats (Yamatani et al., 1998). Interestingly, for obesity rats, neither high nor low level of MCTs in diet had significantly influence on feed intake and weight gain compared to LCTs (Terada et al., 2012; Lee et al., 2000). It is reported that increased ATP in liver supposedly affects vagal afferent nerve activity (Langhans, 1996; Friedman et al., 1999). Furthermore, a stimulus on vagus afferent nerve can regulate insulin secretion (Ionescu et al., 1983) which has a suppressing effect on feeding behavior (Dietrich and Horvath, 2009). Take together, these results indirectly indicated that the influence of MCFAs on ingestion may occur through “vagal nerve-insulin mechanism”, and further confirmed the role of insulin in regulating action of MCFAs on feed intake.

Additionally, the recent studies found that MCFAs (octanoic acid, C8:0) directly increased level of Acyl ghrelin in stomach of mice, and the total concentration of Ghrelin (Acyl ghrelin and Des-acyl ghrelin) were not influenced (Nishi et al., 2012). Furthermore, it was reported that Des-acyl ghrelin can be transformed into Acyl ghrelin by Ghrelin O-acyltransferase (GOAT) which is mainly expressed in the gastrointestinal tract as well as in the pituitary and hypothalamus (Gahete et al., 2010). These results implied ingestion of MCFAs (octanoic acid, C8:0) can directly increase Acyl ghrelin concentration in gastrointestinal tract. Acyl ghrelin have multiple physiological functions including GH release, appetite stimulation, energy balance regulation, gastrointestinal motility effect and so on (Soares and Leite-Moreira, 2008). Therefore, Acyl ghrelin may be involved in the mechanism for influence of MCFAs on feed intake. To go further, gastrointestinal may be another important organ for regulation of energy balance besides the liver.

In fact, both insulin and Ghrelin are regulation hormones of energy balance. Moreover, Acyl ghrelin can decrease insulin level and vice versa, but, the effect of insulin on Acyl ghrelin happens only under the condition that the level of insulin is higher than physiological level of itself (Cummings et al., 2005). Collectively, the underlying action mechanism of MCFAs on feed intake may be attributed to influence of MCFAs on appetite hormones (mainly, insulin and Acyl ghrelin) and fluctuation of systemic energy balance (Figure 1).

**Table 4:** The influence factors for application effect of MCFAs on weight gain compared with LCFAs

<table>
<thead>
<tr>
<th>Items</th>
<th>Factors</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>pH value of base diet</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Source of MCFAs</td>
<td>MCT</td>
<td>MCFA</td>
<td></td>
</tr>
<tr>
<td>Additional level of MCFAs</td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Types of MCFAs</td>
<td>C 8:0</td>
<td>Uncertain</td>
<td></td>
</tr>
<tr>
<td>Lipase content</td>
<td>Moderate</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Experiment period</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td></td>
<td>Energy status</td>
<td>Negative</td>
<td>Positive/obesity</td>
</tr>
</tbody>
</table>

**The influence of MCFAs on weight gain:** Some studies indicated that dietary addition of MCFAs had a negative influence on weight gain compared with LCFAs in animals. It was worth noting that this phenomenon mainly in animals fed high level supplementation of MCFAs diets (more than 10%) rather than low level supplementation of MCFAs diets. The negative influence of MCFAs on weight gain may be attributed to reduction of fat accumulation, energy efficiency and feed intake.

A few early studies suggested that MCFAs have a direct metabolic impact on adipocytes (Lavau et al., 1978; Turkenkopf et al., 1982) and cause significantly less fat accumulation in rats compared with LCFAs (Noguchi et al., 2002b). MCFAs are largely oxidized in the liver, hence reduce the substrate availability for triglyceride (TG) synthesis in fat tissue (Bach et al., 1996). Moreover, MCFAs diets can lower adipocyte fat storage capacity by affecting the expression of PPARγ, C/EBP, and their downstream targets in adipose tissue, forcing some of the dietary fatty acids to be directed to muscle and other organs (Han et al., 2003). In nonadipocytes, MCFAs are minimally esterified into TG and are likely to be disposed through oxidative pathway (Guo et al., 2000). In addition, some studies indicated that MCTs had a stronger thermic effect than LCTs, hence lower energy efficiency (Han et al., 2003). Furthermore, an increase in hepatic FAO contributes to the inhibitory control of feed intake Jambor de Sousa et al., 2006). In conclusion, diminished fat accumulation, lowered energy efficiency and the lower net caloric intake for animal might explain MCFA-induced lower weight gain compared to LCFAs.

In contrast, other studies have shown that MCFAs could improve growth performance of animals compared to LCFAs when fed low level supplementation MCFAs diets to animals. The positive effects on weight gain are closely related with increased feed intake and improved the intestinal microbial environment and the feed utilization efficiency (Dierick et al., 2002, 2003; Decuyper et al., 2003; Yen et al., 2015). It was reported that MCFAs can be utilized directly by the enterocytes in energy production and thereby
help to support the integrity of the intestinal tissue (Guillot et al., 1993). Meanwhile, MCFAs have a positive effect on epithelial function (villus length, crypt depth) in the upper small intestine (Dierick et al., 2003; Takase et al., 1990). An increased absorptive surface could facilitate uptake and more efficient utilization of nutrients for growth. Furthermore, MCFAs have also been suggested to have immune-modulating effects (Wang et al., 2006). Collectively, the positive effects on weight gain after feeding MCTs diet can be attributed to selective antibacterial effects, enhanced epithelial function, immune-modulating effects and increased feed intake.

The aforementioned data suggest that the addition level of MCFAs in diet is a key influence factor for application effect of MCFAs in animals. Generally, a lower level of MCFAs in diets (2-6%) may be beneficial to improve performance of animals. A higher level of MCT in diets (more than 10%) may not be beneficial, and even detrimental, to the growth performance of animals. In addition, other factors including types of MCFAs, pH of basal diet and physiological status of animals may also be related to effect of MCFAs on application effect of MCFAs in animals.

Some studies have indicated that the acylation of Ghrelin only occur with MCFAs(C8:0) but not MCFAs(C10:0) (Feltrin et al., 2006). Odd chain MCFAs(C:7 and C:9) are utilized more efficiently by hepatocytes than MCFAs (C8:0) and especially MCFAs(C10:0) (Odle et al., 1991). Furthermore, some studies demonstrated that antibacterial effects of MCFAs depended on types of MCFAs (Sprong et al., 2001) and immune reactions were also related to the types of MCFAs (Hara et al., 2003). In addition, in vitro studies showed a negative correlation between increasing pH values and the antibacterial efficacy of the MCFAs (Boyen et al., 2008). Hence, the pH of the surrounding environment is considerable importance for antibacterial effect of the MCFAs. It is found that MCFAs has a stronger effect as pH is between 3 and 6 (Dierick et al., 2002). Consequentially, that secretion level of gastric acid of animals and the pH of basal diet has a closely relation to antibacterial efficacy of the MCFAs.

Collectively, there are some favorable and unfavorable factors when using MCFAs to improve the growth performance of animals (Table 4). Generally, relatively lower level of MCFAs in diet (2-6%), more C8:0 of MCFAs, lower pH of basal diet and negative energy status of animal may be more beneficial to performance.

**CONCLUSION**

In conclusion, the supplementation level of MCFAs in diets is a key influence factor on animal ingestion, of which underlying action mechanism may be attributed to influence of MCFAs on appetite hormones (mainly, insulin and Acyl ghrelin) and fluctuation of energy balance. Additionally, the influence of MCFAs on growth performance is related to addition level of MCFAs, the types of MCFAs, characteristics of basal diet, as well as the physiological status of animal. The effectiveness of MCFAs on ingestion and weight gain depend on the balance of the various influence factors.

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Dierick, N.A., Decuyper, J.A., Molly, K., van Beek, E. and Vanderbeke, E. (2002). The combined use of triacylglycerols (TAGs) containing medium chain fatty acids (MCFAs) and exogenous lipolytic enzymes as an alternative to nutritional antibiotics in piglet nutrition. II. In vivo release of MCFAs in gastric cannulated and slaughtered piglets by endogenous and exogenous lipases; effects on the luminal gut flora and growth performance. Livestock Production Science. 76: 1-16.


