Mosapride improves food intake, while not worsening glycemic control and obesity, in \textit{ob/ob} obese mice with decreased gastric emptying

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Abstract

Many patients with diabetes mellitus complain of early satiety and postprandial gastric fullness and discomfort. Mosapride citrate, a 5-HT\textsubscript{4} receptor agonist, enhances gastric emptying and alleviates gastrointestinal discomfort in patients with diabetic gastroparesis. This study was undertaken to investigate the effects of mosapride citrate on feeding behavior in \textit{ob/ob} obese mice with decreased gastric emptying. Mosapride citrate (1 mg/kg/day) was orally administered for 7 days. Food and water intake and body weight were measured daily. Blood glucose, serum insulin, and fructosamine concentrations were measured after 7 days of treatment. Orally administered mosapride citrate significantly increased food intake in \textit{ob/ob} obese mice, with a tendency to decrease fasting blood glucose and fructosamine concentrations compared with controls. There were no significant changes in body weight after 7 days of treatment with oral mosapride citrate. These observations suggest that mosapride citrate may be useful in the treatment of appetite loss and improve the quality of life in patients with diabetes mellitus.

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Keywords: Mosapride citrate; 5-HT\textsubscript{4} receptor; Diabetes mellitus; Food intake; \textit{Ob/ob} mouse

1. Introduction

Mosapride citrate, a substituted benzamide, is a 5-HT\textsubscript{4} receptor agonist (Sakurai-Yamashita et al., 1999). It has been reported that mosapride increases gastric emptying in rats, stimulates gastric motor activity in conscious dogs, and increases electrically evoked contractions in isolated guinea pig ileum (Yoshida et al., 1989; Yoshida, Ito, Karasawa, & Itoh, 1991). Its prokinetic action derives from facilitating Ach release from neurons of the myenteric plexus via stimulation of 5-HT\textsubscript{4} receptors (Yoshida et al., 1991; Yoshida, Kato, & Ito, 1993). In clinical studies, mosapride alleviates such dysfunctions in GI motility as nonulcer dyspepsia, gastroparesis, gastric stasis, and gastroesophageal reflux disease (Yoshida et al., 1993; Kanaizumi et al., 1991). In addition, mosapride has beneficial effects on glycemic control in patients with Type 2 diabetes mellitus (Sanger & Gaster, 1994). It increases the number of and the tyrosine autophosphorylation of insulin receptors on erythrocytes of diabetic patients. Moreover, the 5-HT\textsubscript{4} receptor has been reported to exist in the brain and muscle, as well as in the intestine (Sakurai-Yamashita et al., 1999; Sanger & Gaster, 1994; Ueno et al., 2002). However, little is known about the pharmacological action of mosapride on energy balance. We investigated the effects of mosapride on feeding behavior in \textit{ob/ob} obese mice.

2. Methods

We used male obese (\textit{ob/ob}) C57BL/6J mice (46–53 g, 14–16 weeks of age; Shionogi, Shiga, Japan). The mice

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were individually housed in a regulated environment (22±2 °C, 55±10% humidity, 12:12-h light/dark cycle with light on at 7:00 a.m.). Food and water were available ad libitum except as otherwise indicated. Mosapride citrate was suspended in 0.5% tragacanth gum at a concentration of 0.5 mg/ml, and 2 ml/kg of the suspension was given by stomach tube. Repeated orally administrations were continued for 7 days. The mice were treated daily at 10 a.m. Food and water intake and body weight were measured daily. On the final day, serum was separated from the blood obtained from the orbital sinus under ether anesthesia at the end of the experiment (6 h after the removal of food and the final oral administration). The entire sampling procedure was done in less than 2 min. Mice were killed by cervical dislocation. Blood glucose was measured by the glucose oxidase method. Serum insulin and fructosamine concentrations were measured by enzyme immunoassay and colorimetric methods, respectively. All experiments were approved by our university animal care committee. Results are expressed as mean value±S.E. Analysis of variance (ANOVA), followed by Bonferroni’s t test, was used to assess differences among groups; P<.05 was considered to be statistically significant.

3. Results

Orally administered mosapride (1 mg/kg/day) significantly increased food intake in ob/ob obese mice (5.414±0.208 vs. 4.822±0.084 g/day [control]; P<.022; Fig. 1). Mosapride showed a tendency to decrease fasting blood glucose and fructosamine concentrations compared with controls (Table 1). There were no significant changes in body weight after 7 days of treatment with oral mosapride.

![Graph showing food and water intake](Image)

**Fig. 1.** Effects of orally administered mosapride (1 mg/kg/day for 7 days) on food and water intake in ob/ob obese mice. Results are expressed as mean±S.E.; n indicates the number of mice used. *P<.05 compared with the control group by Bonferroni’s t test.

<table>
<thead>
<tr>
<th>Vehicle (n=7)</th>
<th>Mosapride 1 mg/kg (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight gain (g/day)</td>
<td>0.094±0.066</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>204.8±28.92</td>
</tr>
<tr>
<td>Insulin (ng/ml)</td>
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<td>Fructosamine (μmol/l)</td>
<td>23.57±0.685</td>
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4. Discussion

Diabetes mellitus is a principal cause of morbidity and mortality in human populations and is rapidly increasing in prevalence in the world (Zimmet, Alberti, & Shaw, 2001; King, Aubert, & Herman, 1998). Now, it is reported that over 5% of the adult population in most developed countries is affected by the disease. The main focus of management is aimed at preventing and treating the various complications. A failure of the body’s blood-glucose control results in multiple systemic complications, including retinopathy, neuropathy, nephropathy, macrovascular disease, and enteropathy (King et al., 1998; Kockar, Kayahan, & Bavbek, 2002). Many patients with diabetes mellitus complain of early satiety and postprandial gastric fullness and discomfort (Kockar et al., 2002; Stacher, 2001; Verne & Sninsky, 1998; Kong, Horowitz, Jones, Wishart, & Harding, 1999). Diabetic gastroparesis is a well-recognized delay of gastric emptying in Types 1 and 2 diabetic patients. The disordered gastric emptying may contribute to not only uncomfortable gastrointestinal symptoms but also unstable glycemic control. Although the pathogenesis of diabetic gastroparesis is complex and remains to be determined, autonomic neuropathy and abnormalities of the gut hormones appear to play a major role (Kockar et al., 2002; Stacher, 2001; Verne & Sninsky, 1998; Kong et al., 1999). It was recently reported that intravenous infusion of D-glucose, which increased blood glucose levels, significantly delayed gastric emptying in normal rats (Ishiguchi, Tada, Nakagawa, Yamamura, & Takahashi, 2002).

Mosapride is now widely used in Japan as a prokinetic agent after extensive preclinical and clinical evaluation (Yoshida, 1999). Mosapride dose-dependently increases the gastric emptying rate of a liquid or solid meal with a potency equal to that of cisapride and more potent than that of metoclopramide. In addition, mosapride has no antagonist activity for dopamine D2 receptor, in contrast to other gastrokinetic agents such as cisapride and metoclopramide (Yoshida et al., 1993). On the other hand, cisapride was recently withdrawn from the market.

Table 1

<table>
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<th>Body weight gain (g/day)</th>
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<td>23.57±0.685</td>
</tr>
<tr>
<td>Mosapride 1 mg/kg (n=7)</td>
<td>0.096±0.030</td>
<td>177.1±18.07</td>
<td>20.67±3.416</td>
<td>23.29±0.565</td>
</tr>
</tbody>
</table>

Notes: *P<.05 compared with the control group by Bonferroni’s t test.

**References**

2. King, Aubert, & Herman (1998).
9. Ishiguchi, Tada, Nakagawa, Yamamura, & Takahashi (2002).
because it prolongs QT interval and has a propensity to induce torsade de pointes arrhythmias (Di Diego, Belardinelli, & Antzelevitch, 2003). It has been reported that mosapride enhances gastric emptying and alleviate gastrointestinal discomfort in patients with diabetic gastroparesis (Asakawa, Hayashi, Fukui, & Tokunaga, 2003). In the present study, we investigated the effects of mosapride on feeding behavior in ob/ob obese mice. Ob/ob obese mice are known as the genetic model of obesity and diabetes with insulin resistance and abnormality of gastric emptying (Inui, 2000; Asakawa, Inui, et al., 2003). Considerable evidence cumulatively indicates that gastric emptying is closely related to feeding behavior (Duggan & Booth, 1986; Inui, 2002). As previously reported, the gastric emptying rate in ob/ob obese mice decreases with age and worsening glycemic control (Asakawa, Inui, et al., 2003). We showed here that orally administered mosapride stimulated food intake, while not worsening glycemic control and obesity in ob/ob obese mice with decreased gastric emptying. These observations suggest that mosapride may be useful in the treatment of appetite loss and improve the quality of life in patients with diabetes mellitus.

References


