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Triple monoamine inhibitor tesofensine decreases food intake, body weight, and striatal dopamine D2/D3 receptor availability in diet-induced obese rats

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Abstract

The novel triple monoamine inhibitor tesofensine blocks dopamine, serotonin and norepinephrine re-uptake and is a promising candidate for the treatment of obesity. Obesity is associated with lower striatal dopamine D2 receptor availability, which may be related to disturbed regulation of food intake. This study assesses the effects of chronic tesofensine treatment on food intake and body weight in association with changes in striatal dopamine D2/D3 receptor (D2/3R) availability of diet-induced obese (DIO) rats. Four groups of 15 DIO rats were randomized to one of the following treatments for 28 days: 1. tesofensine (2.0 mg/kg), 2. vehicle, 3. vehicle + restricted diet isocaloric to caloric intake of group 1, and 4. tesofensine (2.0 mg/kg) + a treatment-free period of 28 days. Caloric intake and weight gain decreased significantly more in the tesofensine-treated rats compared to vehicle-treated rats, which confirms previous findings. After treatment discontinuation, caloric intake and body weight gain gradually increased again. Tesofensine-treated rats showed significantly lower D2/3R availability in nucleus accumbens and dorsal striatum than both vehicle-treated rats and vehicle-treated rats on restricted isocaloric diet. No correlations were observed between food intake or body weight and D2/3R availability. Thus, chronic tesofensine treatment leads to decreased food intake and weight gain. However, this appears not to be directly related to the decreased striatal D2/3R availability, which is mainly a pharmacological effect.

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1. Introduction

The novel drug tesofensine is a triple monoamine inhibitor which blocks dopamine, serotonin and norepinephrine re-uptake from the synaptic cleft. It is a promising candidate drug for the treatment of obesity and has shown to induce significant weight loss in rodents (Hansen et al., 2010) and in humans, with an average weight loss in humans of ~10% in 24 weeks (Astrup et al., 2008). However, the exact mechanism of action of the drug is not yet elucidated. The weight loss is at least partly caused by reduced food intake and appetite suppression by the drug, as was shown in rodents (Axel et al., 2010; Hansen et al., 2010) and humans (Sjodin et al., 2010). The acute appetite suppressing effect of tesofensine may be mediated via dopamine D1 receptor and α1 adrenoreceptor signaling, which was demonstrated by a reversion of the appetite suppression by blocking these receptors with SCH23390 and prazosin, respectively (Axel et al., 2010). However, in chronic treatment, the appetite suppressing effect diminishes over time (Hansen et al., 2010). Therefore, it is important to know more about the pharmacological effects of the drug during sustained use.

Dopaminergic neurotransmission in the mesolimbic system is thought to affect food intake based on its role in reward function. Food is able to induce a release of endogenous dopamine in the nucleus accumbens (Avena et al., 2008; Bassareo and Di Chiara, 1999), which is a part of the ventral striatum, and thus to exert a rewarding effect. It is postulated that deficits in this part of the reward system play a role in the pathophysiology of obesity by inducing overeating (Volkow and Wise, 2005). Changes in the dopaminergic mesolimbic system related to reward deficits might be reflected in a decreased striatal dopamine D2/D3 receptor (D2/3R) availability, which is observed in both genetic obesity models (Hajnal et al., 2008; Hamdi et al., 1992; Thanos et al., 2008), in diet-induced obesity models (Huang et al., 2006; Johnson and Kenny, 2010), and in humans (Wang et al., 2001). Recently, it has been shown that D2R downregulation can be induced by a cafeteria diet and that D2R downregulation increases the susceptibility for reward deficits and compulsive eating behavior in rats (Johnson and Kenny, 2010). Human research has also found that the Taq1A allele of the gene encoding for D2R increases susceptibility for obesity and is associated with lower striatal D2/3R levels in humans (Noble, 2003; Thompson et al., 1997). Moreover, targeting the D2R with D2R agonists results in reduction of hyperphagia and appetite (Cooper and Al-Naser, 2006; Davis et al., 2009). Thus, the dopaminergic reward system and striatal D2/3R availability are related to regulation of food intake and substances that affect this system and changing striatal D2/3R availability might lead to different food intake and body weight.

As a triple monoamine inhibitor, tesofensine exerts its effects on three monoaminergic systems which all modulate food intake (Nelson and Gehlert, 2006). The interactions of the systems are complex and will both directly and indirectly exert an effect on the mesolimbic dopaminergic system and thus can influence the striatal D2/3R availability. Additionally, the weight loss and reduced food intake itself may affect the striatal D2/3R levels during tesofensine treatment. Therefore, this study is designed to investigate the effects of *chronic* treatment with tesofensine on food intake and body weight and on striatal D2/3R availability in diet-induced obese (DIO) rats. In addition, the possible relations between changes in food intake and body weight with changes in D2/3R availability will be assessed. During the study, the rats are offered a high fat *choice* diet, which enables us to study effects of tesofensine on food preference that might be related to different reward processing from food and striatal D2/3R availability. At last, the long-term effects on food intake, weight gain and striatal D2/3R availability after discontinuation of chronic tesofensine treatment are assessed.

2. Experimental procedures

Sixty male Wistar rats (Horst, Harlan, The Netherlands; weight 225 ± 10 g) were individually housed in a temperature- (21–23 °C) and light-controlled (lights on 7:00 am–7:00 pm) room. They were allowed to adapt to their environment for 7 days. All experimental procedures were approved by the Animal Ethics Committee (AMC, Amsterdam, The Netherlands).

2.1. Experimental design

Rats were randomized into four groups of 15 animals: group 1 treated with tesofensine (T), group 2 treated with vehicle (V), group 3 treated with vehicle combined with a restricted diet that is isocaloric to the caloric intake of group T to correct for feeding effects (V-RD), and group 4 treated with tesofensine followed by a period without treatment to observe chronic post-treatment effects (T-C) (Table 1). Before start of the treatment, all rats were offered an *ad libitum* high-fat (HF) choice diet for 28 days to induce obesity. The HF choice diet consisted of a dish of saturated fat (Beef tallow (Ossewit/Blanc de Boeuf), Vandemoortele, Belgium) presented in the cage on a metal receptacle in addition to normal standard chow (special diet service (SDS), England) and a water bottle (La Fleur et al., 2010). The HF choice diet was continued throughout the whole experiment.

Table 1 Experimental design.

Group	N	Pre-treatment (days 1–28)	Treatment (days 29–56)	Post-treatmen (days 57–84)
T	15	*Ad libitum* HF choice diet	Tesofensine treatment + *ad libitum* HF choice diet	–
V	15	*Ad libitum* HF choice diet	Vehicle treatment + *ad libitum* HF choice diet	–
V-RD	15	*Ad libitum* HF choice diet	Vehicle treatment + restricted HF choice diet isocaloric to caloric intake group T	–
T-C	15	*Ad libitum* HF choice diet	Tesofensine treatment + *ad libitum* HF choice diet	*Ad libitum* HF choice diet

HF = high fat.