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Effect of Angiotensin I-Converting Enzyme Inhibitor, Captopril on Body Weight, Food and Water Consumption in Oral Contraceptive-Treated Rats

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Abstract: Studies have shown that hormonal changes that occur during menstrual or oestrous cycle influence angiotensin-induced water intake. However, little is known about the effects of Oral Contraceptive (OC) on body weight and eating habit when Renin-Angiotensin System (RAS) is suppressed. This study documents the effect of OC on weight gain and food and water consumption. It also assesses whether suppression of RAS by captopril would affect OC-induced changes. About 40 female rats distributed into 4 groups (10 rats in each) were used for the experiment. Vehicles-treated, OC-treated, captopril-treated and OC + captopril-treated groups. Body weight, food and water intake were recorded daily throughout the experiment period. Food and water consumed per day per 100 g body weight was also calculated. OC-treated and OC + captopril-treated rats had significantly lower body weight when compared with those of vehicle treated and captopril-treated rats. OC-treated rats consumed significantly less food than vehicle-treated and captopril-treated groups. OC + captopril-treated rats consumed significantly less food than other groups but when food consumption was adjusted to body weight, there was significant decrease in food consumption in OC-treated group. OC administration is associated with reduction in weight gain and food and water consumption. Co-administration of captopril significantly augments this effect.

Key words: Oral contraceptive, captopril, body weight, food intake, water intake, rennin-angiotensin system

INTRODUCTION

A number of behaviour has been demonstrated to be influenced by fluctuations in ovarian hormonal levels during menstrual cycle in women. Among the behaviour are sexual receptivity, dressing, choice of colour, appetite, food ingestion and water consumption (Hee and Tokura, 1995; Wallen *et al*., 2001). Studies have also shown that ovarian hormones can modulate body weight, appetite, food and water ingestion (Kisley *et al*., 1999; Wallen *et al*., 2001; Akhigbe *et al*., 2008).

It has been reported in female rats that spontaneous drinking and thirst elicited via the activation of Renin-Angiotensin System (RAS) is attenuated at oestrous (Findlay *et al*., 1979; Krause *et al*., 2003). It has also been shown that administration of oestrogen to ovariectomized female rats results in reduction of food and water consumption (Wallen *et al*., 2001; Krause *et al*., 2003). Oestrogen administration has been demonstrated to cause attenuation of water intake in response to peripheral intracerebroventricular administration of angiotensin II (ang II) (Findlay *et al*., 1979). On the other hand, administration of progesterone-only has been reported to increase body weight, food and water intake in ovariectomized female rats (Gray and Wade, 1981; Kisley *et al*., 1999). Studies have shown that suppression of cyclic fluctuation of ovarian hormones with long-term use of Oral Contraceptive (OC) is not associated with increase in body weight (Brill *et al*., 1994; Oelkers *et al*., 1995; Rosenberg, 1998). Despite these reports, it is a common perception the OC causes weight gain.

Therefore, the purpose of this study is to determine whether the use of combined OC causes fluctuation in body weight, food and water intake and to investigate the possible role of RAS.

MATERIALS AND METHODS

Experiments were conducted in 40 rats aged 10-12 weeks. They were distributed into 4 groups (10 rats

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in each) housed in a wire-bottomed, stainless steel cages in a well-ventilated, temperature controlled room (25°C) on 12:12 h light-dark cycle.

Vehicles-treated received 2 mL olive oil/100 g body weight daily intragastrically, OC-treated group received OC containing 1.0 μg ethinyloestradiol and 10.0 μg norgestrel (Wyeth Ayerst, Inc., Canada) intragastrically, captopril-treated group received captopril (S Q-14225, Bristol-Meyers Squibb Pharmaceutical Research Institute, Princeton, NJ, USA) dissolved in tap water to achieve a dose of 0.1 mg mL^{-1}, OC + captopril-treated group received OC as in OC-treated group as well as captopril as in captopril-treated group. Rats were fed *ad libitum*. All experimental procedure conformed to the guideline of Guiding Principle for Research Involving Animals.

Body weight, food and water intake were recorded daily throughout the 9 weeks of the experiment between 08:00 and 11:00 h. Food and water consumed per day per 100 g body weight was also calculated. Data were analysed using SPSS version 11.0.

Analysis Of Variance (ANOVA) was performed in all the data and the Bon Ferroni's test was used as a post-hoc test with the significant level set at $p<0.05$. Data are presented as mean±Standard Error of Mean (SEM).

RESULTS AND DISCUSSION

OC-treated and OC + captopril-treated rats weighed significantly less than vehicle-treated captopril-treated rats between 8th and 9th week of treatment (Table 1, Fig. 1). OC-treated and OC+captopril-treated rats consumed significantly less food than the other groups throughout the experimental period (Table 2, 3 and Fig. 2) except on the 6th week of treatment (Fig. 2). Food consumed by OC + captopril-treated rats were significantly less than that of the OC-treated rats in the 9th week of treatment (Fig. 2).

Water intake decreased significantly from the 4th to 9th week of treatment in OC-treated and OC+captopril-treated rats while the captopril-treated group consumed significantly more water in the 5th and 7th week (Fig. 3). Water intake increased significantly in captopril-treated rats when compared with other groups while OC + captopril group consumed lowest volume of water. Water consumption adjusted for body weight in OC-treated rats was significantly less than that of the vehicle-treated rats (Table 4 and 5).

Studies have documented variable effect of hormonal contraceptive on absolute body weight in women (Brill *et al*., 1994; Oelkers *et al*., 1995; Berenson and Wiemann, 1995; Rosenberg, 1998; Pelkman *et al*., 2001). and in female Sprague-dawley rats (Fowler *et al*., 1985).

Table 1: Effect of oral contraceptive and captopril on body weight

Values	Vehicle-treated	OC-treated	Captopril-treated	OC+ Captopril-treated
I (g)	111.7±6.0^a	110±5.6^a	113.3±6.7^a	113.3±4.9^a
F (g)	182.5±8.8^a	155.0±9.8^b	185.0±8.8^a	152.5±9.1^b
Δ (%)	70.8 (63)^a	45 (40)^b	71.7 (63)^a	39.2 (37)^c

I = Initial value: F = Final value; Δ = Changes; ^{abc}Values with different letter (s) in the same row are significantly different at $p<0.05$

Table 2: Effect of oral contraceptive and captopril on food ingestion: absolute value

Values	Vehicle-treated	OC-treated	Captopril-treated	OC+ Captopril-treated
I (g)	20.0±0.9^a	19.0±0.5^a	20.0±6.7^a	19.2±11.1^a
F (g)	18.1±1.2^a	13.1±0.9^b	18.5±1.1^a	10.8±0.300^c
-Δ (%)	1.9 (10)^a	6.0 (31)^b	1.9 (10)^a	8.4 (44.0)^c

I = Initial value: F = Final value; Δ = Changes; ^{abc}Values with different letter (s) in the same row are significantly different at $p<0.05$

Table 3: Effect of oral contraceptive and captopril on food Ingestion: body weight-corrected value (100^{-1} g)

Values	Vehicle-treated	OC-treated	Captopril-treated	OC+ Captopril-treated
I (g)	17.9±3.0^a	17.4±3.1^a	17.7±3.7^a	16.9±3.0^a
F (g)	9.4±5.0^a	8.5±5.3^b	10.0±4.0^a	7.1±4.7^b
-Δ (%)	8.5 (47)^a	8.9 (51)^b	7.7 (44)^c	9.8 (58)^d

I = Initial value: F = Final value; Δ = Changes; ^{abc}Values with different letter(s) in the same row are significantly different at $p<0.05$

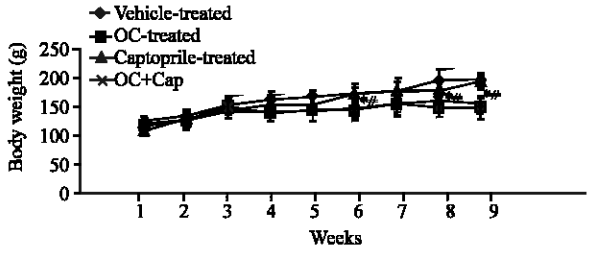

Fig. 1: Effect of oral contraceptive and captopril on body weight, *$p<0.05$ vs. vehicle-treated, #$p<0.05$ vs. captopril-treated

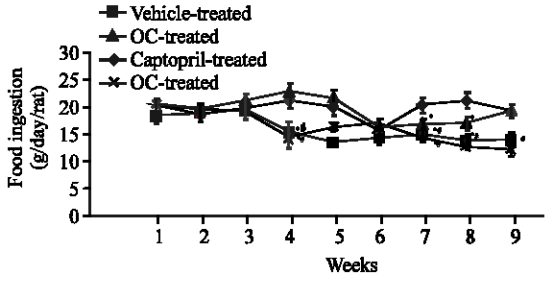

Fig. 2: Effect of oral contraceptive and captopril-treated on food ingestion; *$p<0.05$ vs. vehicle-treated, #$p<0.05$ vs. captopril-treated, ~$p<0.05$ vs. others

However, they have not systematically documented the weekly changes or what effect ang I-converting enzyme inhibitor (ACE-inhibitor), captoril would have on these weekly changes. This study seems to be the first to

Table 4: Effect of oral contraceptive and captopril on water intake: absolute values

Values	Vehicle-treated	OC-treated	Captopril-treated	OC+ Captopril-treated
I (g)	22.9±1.7[a]	23.1±0.9[a]	23.0±0.7[a]	22.9±0.7[a]
F (g)	25.7±1.1[a]	18.0±1.9[b]	27.2±2.9[a]	15.3±2.2[b]
Δ (%)	2.8 (12)[a]	-5.1 (22)[b]	4.2 (18)[c]	-7.6 (33)[d]

I = Initial value: F = Final value; Δ = Changes; [abc]Values with different letter (s) in the same row are significantly different at $p<0.05$

Table 5: Effect of oral contraceptive and captopril on water intake: body weight-corrected value (100^{-1} g)

Values	Vehicle-treated	OC-treated	Captopril-treated	OC+ Captopril-treated
I (g)	20.5±3.8[a]	21.0±3.0[a]	20.3±3.0[a]	20.2±2.8[a]
F (g)	14.1±4.0[a]	11.6±5.8[b]	14.7±6.9[c]	10.1±5.6[d]
-Δ (%)	6.4 (31)[a]	9.4 (45)[b]	5.6 (27)[c]	10.1 (50)[d]

I = Initial value: F = Final value; Δ = Changes; [abc]Values with different letter (s) in the same row are significantly different at $p<0.05$

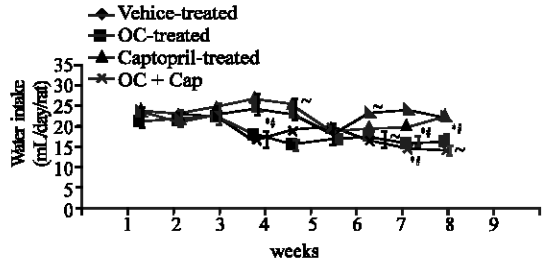

Fig. 3: Effect of oral contraceptive and captopril on water intake; *$p<0.05$ vs. vehicle-treated, #$p<0.05$ vs. captopril-treated, ~$p<0.05$ vs. others

provide information and document the steady changes in body weight with its relation to food and water intake. This study also demonstrates the effects of captopril on OC induced changes.

In the findings, administration of combined OC steroid were consistent with studies in female rats fed on combined OC steroid (Fowler *et al*., 1985; Ciavatti *et al*., 1989; Akhigbe *et al*., 2008) and with a large study in 4746 adolescent users of a low dose combine OC (Brill *et al*., 1994). Evidence from this study shows that the OC steroids used in this study exert a modulating influence on the body weight because the vehicle-treated rats where endogenous ovarian hormones may be suppressed had significant weight gain than OC-treated rats. Previous studies have demonstrated that administration of oestradiol reduced body weight gain while administration of progesterone increased weight gain (Schwartz and Wade, 1981; Gray and Wade, 1981). The fact that administration of a combined OC steroid reduced body weight gain suggests that the oestrogen component of the OC steroid may be responsible for the loss of body weight. Observations in this study show that OC-treated rats had a decrease in food and water consumption. This is consistent with previous studies (Schwartz and Wade, 1981; Wallen *et al*., 2001; Akhigbe *et al*., 2008) but inconsistent with respect to administration of oestrogen only and in combination with progesterone (Fregly *et al*., 1985). The decrease in weight caused by OC administration is likely due to the observed reduction in food and water consumption. Interestingly, OC-treatment produced reduction in food and water intake in the 4th week of treatment earlier than the reduction in body weight which started in the 7th week of treatment. This study provides evidence that reduction in body weight seen in OC-treated rats is likely to be a secondary effect to the hypophagic and hypodipsogenic effect of OC steroids. When food and water consumption were normalized to the body weight, the decrease in OC-treated rats persisted. This suggests that the OC-treated rats were either expending more energy or were more efficient at utilizing food and water consumed. This is in consonance with studies in women using combined OC (McNeil *et al*., 1988). OC use as be shown to stimulate RAS activity and thus found to increase plasma concentration of ang II, the effector substance of the RAS (Gray and Wade, 1981; McNeil *et al*., 1988). Angiotensin II has been documented to act on CNS and regulate the feeding and drinking habit in rats (Fowler *et al*., 1985; Kisley *et al*., 1999). However, the results of this finding suggest that the direct effect of OC to suppress water intake overrides the effect of RAS to induce drinking. We found that drinking habit in captopril-treated rats was improved when compared to the control rats. This is in consonance with previous studies (Rowland *et al*., 1996, 1997; Thunhorst and Johnson, 2003). The decrease in food and water intake found in OC-treated rats and OC+ captopril-treated rats relative to the vehicle-treated and captopril-treated rats may also suggest the anti-dipsogenic effect of OC steroids as previously demonstrated by the administration of oestrogen-only or in combination with progesterone (Kisley *et al*., 1999; Akhigbe *et al*., 2008). The co-administration of captopril significantly augmented anti-dipsogenic effect of OC as observed in OC + captopril-treated rats. This suggests that ang II-induced thirst is blunted by OC therapy and augmented in combination with captopril.

The administration of combined OC steroid has similar effect on food and water intake and appears to provide a means to associate these ingestive behaviour. The results are in agreement with previous results which show that oestrogen therapy reduces body weight (Donohoe and Stevens, 1982, 1983; Thunhorst and Johnson, 2003). This result strongly supports that the antidipsogenic effect of OC steroids seen in these rats is not merely secondary to its hypophagic and anorectic effect but it is an independently modulated mechanism, possibly via the higher centers.

CONCLUSION

Long-term use of synthetic oral oestrogen, ethinyloestradiol in combination with progestogen, norgestrel at a dose high enough to suppress cyclic fluctuation of endogenous ovarian hormones, significantly reduces body weight gain, possibly by decreasing food and water consumption. The effect is augmented by ang-I converting enzyme inhibitor, captopril. The results of this study also suggest an interaction between OC steroid, captopril and the activation of RAS.

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