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# Body weight gain under long-term progesterone administration.

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**ABSTRACT**

According to experts WHO, there is an epidemic of obesity in the world. Some causes of the obesity development is associated with certain endocrine diseases, central nervous system disorders and other illnesses. It is known that progesterone has fat accumulation effect as the natural hormone during pregnancy. The aim of this study was to investigate the influence of long-term progesterone administration on rats food behavior and their body weight gain. In our study, female rats were used. Our results have demonstrated that progesterone promotes fat accumulation of rats. Nevertheless, we have not found significant differences of food intake between control group and group of rats under long-term progesterone administration.
**Keywords:** progesterone, obesity, food behavior, body weight gain.

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## INTRODUCTION

Progesterone is a steroid hormone that is important for reproductive function, pregnancy, menstrual cycle, embryogenesis, and involved in brain function as a neurosteroid [12]. Besides this progesterone is the precursor to androgens and estrogens. The primary source of endogenous production of progesterone is the corpus luteum and placenta during pregnancy [2, 10, 12]. Endogenous progesterone binds to the progesterone receptor, resulting in dissociation of selected proteins, phosphorylation of the receptor itself, and activation of transcription factors [11].

During the second phase of pregnancy quality of progesterone increased and it fundamentally changed the functioning of the organism. One of those consequences is increase of body fat. This is due to the slowdown movement of food through the intestine because of reduced elasticity of its walls. Progesterone launched in a woman's body artificially has the same fat accumulation effect as the natural hormone during pregnancy. Substantial evidence links progesterone excess in pathophysiology of eating and affective disorders [11].

Regulation of feeding behavior has always attracted the attention of physiologists, biochemists and physicians, but recently this line of research has gained special importance because of the growing problem of obesity.

Obesity is a multifactorial, heterogeneous disease. The factors that determine the development of obesity are: genetic, demographics, socio-economic, psychological and behavioural. The obtained data of multiple factors in the pathogenesis of obesity leaves no doubt that a study of various experimental models of the disease, which would have answered pathogenic levels of the disease in humans is timely and could be the basis for finding promising new drugs, ways of correcting cognitive and motor disorders which occur in conditions of obesity. Some reports suggest the use of progesterone-containing preparations as contraceptive or for the hormone replacement therapy to cause sufficient weight gain by causing hyperphagia and increased fat deposition in the body [1].

Some reports suggest the use of progesterone- and estrogen-containing preparations as contraceptive or for the hormone replacement therapy to cause sufficient weight gain by causing hyperphagia and increased fat deposition in the body [13]. Thus, we investigated general characteristics of feeding behavior and major biochemical serum parameters of rats under progesterone long-term administration.

## MATERIALS AND METHODS

Research was conducted in compliance with the standards of the Convention on Bioethics of the Council of Europe's 'Europe Convention for the Protection of Vertebrate Animals' used for experimental and other scientific purposes' (1997). The general ethical principles of animal experiments, approved by the First National Congress on Bioethics Ukraine (September 2001) and other international agreements and national legislation in this field. Animals were kept in a vivarium that was accredited in accordance with the 'standard rules on ordering, equipment and maintenance of experimental biological clinics (vivarium)'. Instruments to be used for research are subject to metrological control.

### *Animals and housing conditions.*

The present study used white nonlinear female rats weighing 146±9,57g at the begining of experiment. Studies were conducted on 30 rats which were divided into two groups of 15 animals each. The animals of each experimental group were individually housed in polypropylene cages in an environmentally controlled clean air room, with a temperature of 22±3C, a 12 h light/12 h dark cycle and a relative humidity of 60±5%.

### *Induction of progesterone-induced obesity.*

Progesterone (Biopharma, Kyiv, Ukraine) in a dose of 10 mg/kg [9] was administered subcutaneously in the dorsal neck region of rats for 28 days. The control group consisted of rats, which at the same age were administered same volumes of arachis oil, which was used for breeding progesterone.

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***Food consumption and body weight.***

Food consumption (g) and body weights of rats (g) were determined daily at the scheduled time (09:00 to 10:00 h) for 28 days in each group.

***Statistical analysis.***

Statistical analysis was performed by using 'Statistica 7.0' software. All data in this study were expressed as means ± standard deviation (M ± SD). Statistical analyses were performed by using one-way analysis of variance (ANOVA). The difference between groups was defined to be statistically significant when a p-value was less than 0.05.

## RESULTS AND DISCUSSION

***Effect of progesterone long-term administration on body weight***

Body weight of all experimental groups of animals during 28 days is shown in Figure 1. The initial weight of the animals in the control group was 146±9,57g. After 28 days of the experiment a gradual increase of this indicator was shown. The final body weight of the animals in the control group was 179±7,031g. It was found that after 28 days of progesterone administration body weight of rats was significantly higher in comparison with initial weight(initial weight 147±7,75g and final weight 204±7,404). The final weight of this group of animals was increased by 25g compared to the control group.

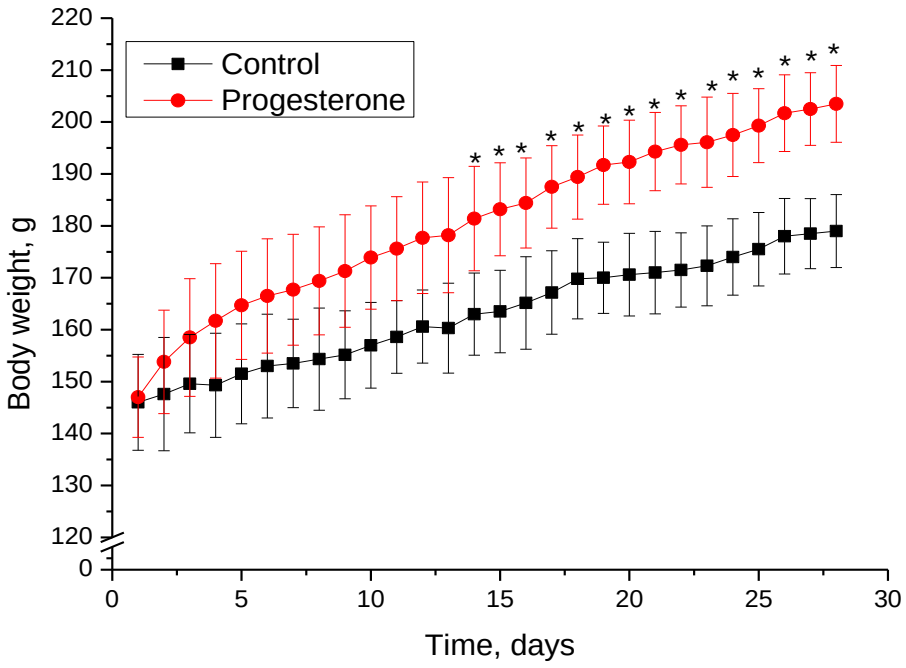


**Figure 1. Body weight of rats in progesterone group compared with a control group of animals**

*$p$<0.05 compared to the control

After 28 days of the experiment body weight of the animals in control group and group under progesterone administration increased by 33±4,522g and 56,5±3,146g respectively, and this parameter changed gradually. Cumulative body weight gain of animal in each group is shown in Figure 2.

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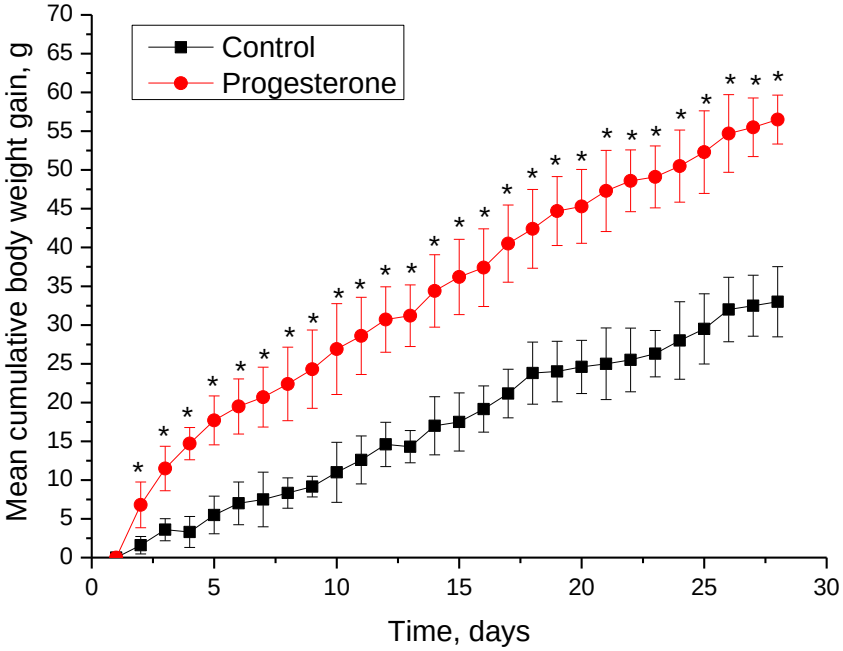


**Figure 2. Cumulative body weight gain (g) in progesterone group compared with a control group of animals**

*$p<0.05$ compared to the control

***Effect of progesterone long-term administration on food intake***

The next stage of our work was to study the food intake by rats of all experimental groups. As is shown in Figure 3 and Figure 4, the control group of rats consumed an average of 15,97±1,637g and the group of rats under progesterone administration consumed 18,72±1,819g of standard food per day.

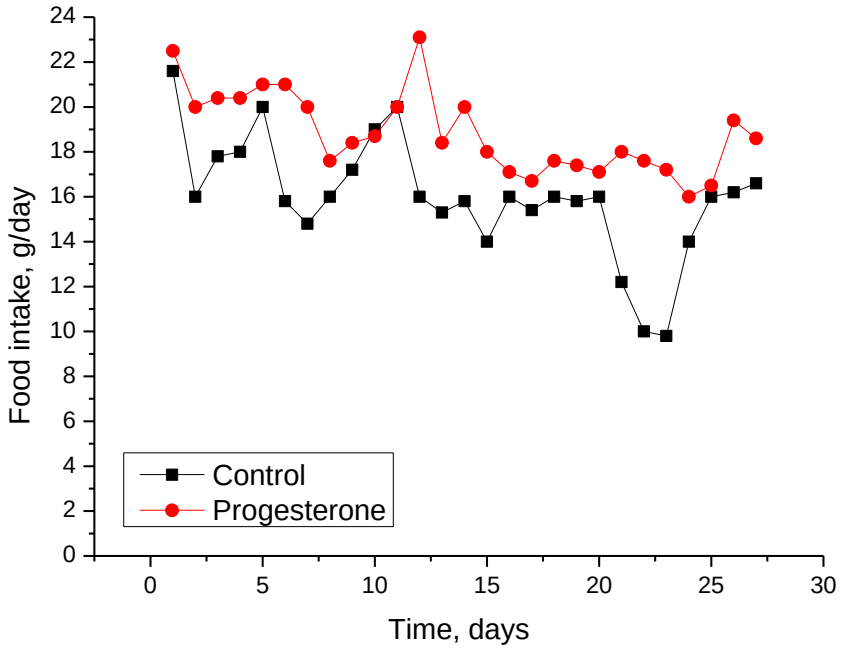


**Figure 3. Food intake (g/day) in progesterone group compared with a control group of animals**

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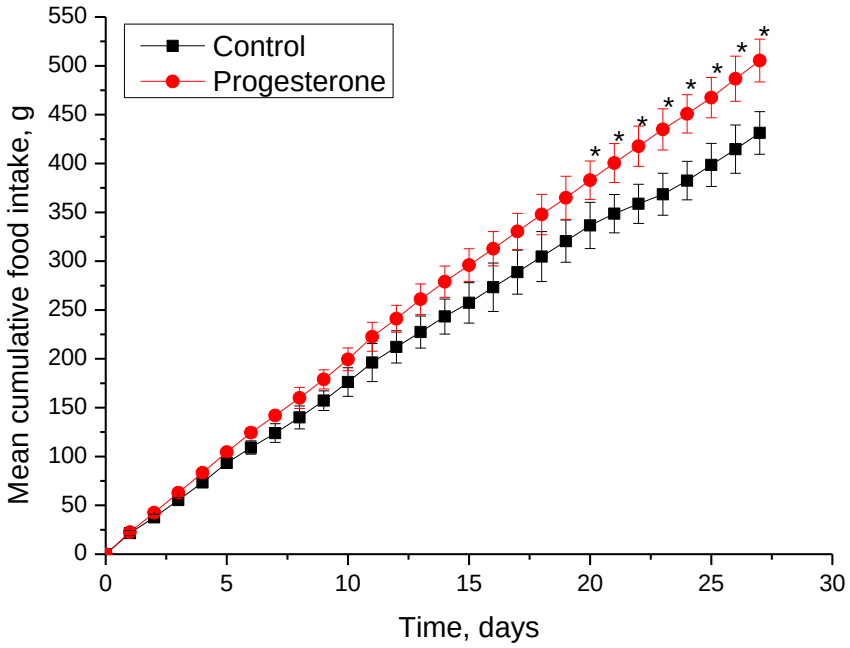


**Figure 4. Cumulative food intake (g) in progesterone group compared with a control group of animals**

*$p<0.05$ compared to the control

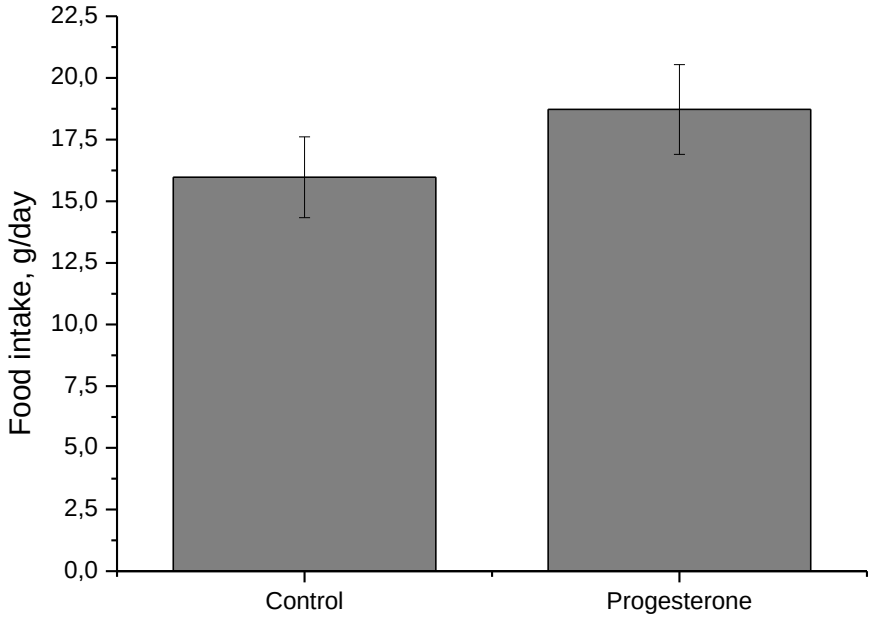


**Figure 5. Mean food intake (g/day) in progesterone group compared with a control group of animals**

Cumulative food intake of all experimental groups during 28 days is shown in Figure 5. At the end of the experiment accumulated food intake in the control group and the group under progesterone administration was 431,3±21,765g and 505,4±21,865g respectively.

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Figure 1, 2, 3, 4, 5 and Tab. 1 summarize the general characteristics and body weight in the control group and in the group of rats under progesterone administration during 28 days. The group of rats under progesterone administration has significantly increased of body weight gain, final body weight and accumulated food intake. Figure 6 shows that progesterone rats had significantly higher cumulative feeding efficiency than control rats.

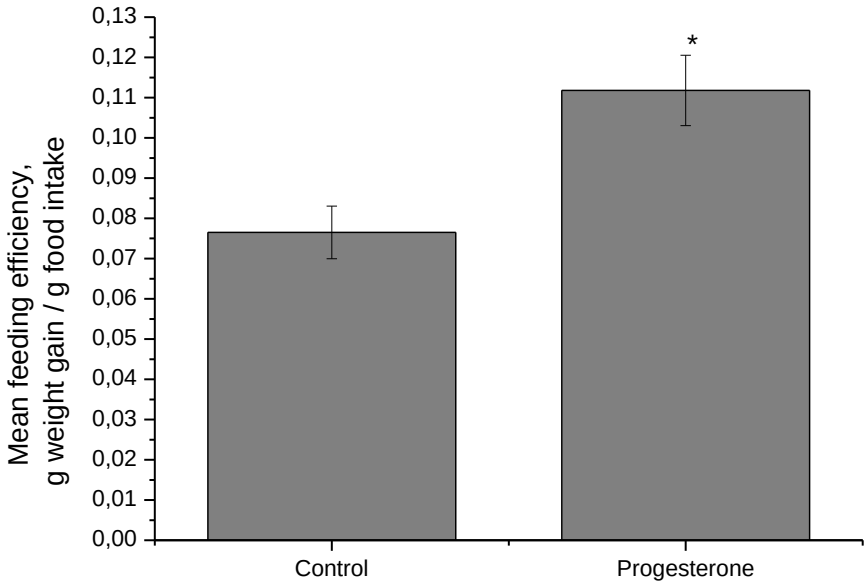


**Figure 6. Cumulative feeding efficiency in progesterone group compared with a control group of animals**

*$p$<0.05 compared to the control

**DISCUSSION**

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally, there has been: an increased intake of energy-dense foods that are high in fat; and an increase in physical inactivity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization.

Our results demonstrated that progesterone (10 mg/kg) induced hyperphagia in female rats. But the exact neurochemical mechanisms by which progesterone regulates appetite remains to be elucidated. Progesterone stimulates food intake, probably via its antiestrogenic action [4].

Previous studies showed for the first time that the sulphated neurosteroid progesterone, at high doses, produced anorectic effects in male mice. The progesterone showed a biphasic response on food intake. Although low and anxiolytic doses of progesterone (< 5 mg/kg) did not influence food intake in food deprived animals, higher doses (≥ 5 mg/kg) induced an anorectic-like response [9].

According to the literature progesterone, a mixed agonist/antagonist neurosteroid at the GABA-A receptor, at high concentration blocks the GABA-A receptor-mediated currents, and at low doses progesterone shows an agonistic profile [6-8]. Previously, was shown that progesterone produces picrotoxin-resistant anxiolytic effects, possibly mediated by the neuronal $Ca^{2+}$ channels. NMDA (N-methyl-D-aspartate) receptor antagonist, dizocilpine, does not block the anorectic actions of progesterone. The GABA-A receptor agonist, muscimol reversed the progesterone-induced hypophagia, which is consistent with its in-vitro GABA-A receptor antagonistic properties [7,9].

These data indicate that the hyphophagic effect of progesterone could, at least partly, be mediated via an antagonistic interaction with the GABA-A receptor.

Thus, our results are confirmed by the literature. Recent studies demonstrated that neurosteroid progesterone produced hyperphagic effects in food deprived mice [9].

The hyperphagic effects of progesterone resembled that of neurosteroid allopregnanolone. Therefore, the effect of progesterone may be imputed to its metabolism to allopregnanolone. The progesterone-induced hypophagia may be mediated by GABA-A or other receptor systems. Thus, these data suggest a pivotal role for GABA-A and mitochondrial DBI (diazepam binding inhibitor) receptors in the hyperphagic effects of neurosteroids and reinforces a role for endogenous neurosteroids in regulating feeding behavior.

According to the adipostatic theory, increases in food intake would promote greater fat depots which, in turn, would produce higher leptin levels that would counterbalance the progesterone enhanced food intake [14]. Since this counterbalance does not take place in pregnant or progesterone-treated rats, it would be interesting to investigate in vivo changes in the WAT-leptin system in rats with experimentally increased levels of progesterone.

In the present study, subchronic treatment with the neuroactive steroid progesterone (10 mg/kg s.c.) for 28 days produced significant increases in body weight and elicited marked hyperphagia as compared to a vehicle-treated control group at all time intervals as observed on days 1, 7, 14, 21 and 28.

## CONCLUSIONS

The final weight in the group of rat under progesterone long-term administration significantly increased compared with the control group. In addition, we found significant differences of accumulated food intake between investigated groups of animals. This reveals that progesterone change eating behavior and promotes fat accumulation. In addition, our results are consistent with previous data in other models of obesity [3, 5].

Taking into account the foregoing the use of progesterone-induced obesity model of rats can be effective for the study of different types of therapy of obesity and its consequences.

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