Involvement of type I corticosteroid receptor in the effects of ovariectomy on energy balance

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Dagnault, Anne, Yves Deshaies, and Denis Richard. Involvement of type I corticosteroid receptor in the effects of ovariectomy on energy balance. Am. J. Physiol. 270 (Regulatory Integrative Comp. Physiol. 39): R199–R206, 1996.—The effects of the glucocorticoid receptor antagonist, RU-38486 (RU-486), and the mineralocorticoid receptor (MR) antagonist, RU-28318, on energy balance were investigated in a 2 [surgery: ovariectomy (OVX) and sham operation] × 3 (corticosteroid antagonist: placebo, RU-28318, RU-486) experimental design. Rats were treated for 28 days. Food intake and body weight were monitored throughout the treatment period. At the end of the treatment, rats were killed and their carcasses were analyzed for energy and nitrogen contents. Energy content was determined by adiabatic bomb calorimetry, whereas nitrogen was determined in 250- to 300-mg samples of dehydrated carcasses, with the use of the Kjeldahl procedure. The energy as protein was subtracted from total carcass energy to determine energy as fat. The gains in energy, fat, and protein were calculated by subtracting the values obtained at the end of the treatment period from initial values estimated from the body weights measured at the beginning of the experiment. A significant interaction effect of surgery and corticosteroid antagonist was observed on body energy gain, energetic efficiency, and fat gain. Whereas body energy gain, energetic efficiency, and fat gain were larger in OVX rats than in sham-operated animals, surgery also affected corticosterone levels in OVX rats. Surgery, but not corticosteroid antagonist, had a significant effect on digestible energy intake, energy expenditure, and protein gain. All of these variables were increased in OVX rats than in sham-operated animals. Surgery also affected corticosterone levels and adrenal weight. Both of these variables were lower in OVX rats than in sham-operated animals. By demonstrating the ability of RU-28318 to attenuate the effects of OVX on energy balance, the present study provides evidence that MR occupation by corticosteroids facilitates the OVX-induced changes in energy balance.

RU 38486; RU 28318; mineralocorticoid receptor; glucocorticoid receptor; castration; body fat; body protein; energy intake; corticosterone; adrenocorticotrophic hormone; adrenals

It has been known for many years that castration accelerates the deposition of fat and protein masses in the females of many species (4, 18, 30, 43). Studies conducted in rats have provided evidence that the rapid rate at which castrated animals store energy is primarily brought about by a rise in energy intake (30). This increase in food intake has been attributed to the removal of circulating estradiol (E2) (30). In fact, treatment with E2, whose anorectic attribute has long been recognized (44), prevents or reverses the food intake increase induced by castration (30, 43). The full mechanism underlying the effects of castration on energy balance of the female rats has not been thoroughly investigated. However, the observation that adrenalectomy (ADX) can attenuate the increased rate of energy deposition in ovariectomized (OVX) rats (28) suggests that corticosteroids are part of this mechanism. Corticosteroids are known to promote energy gain by increasing food intake and blunting energy-dissipating processes such as brown adipose tissue thermogenesis (13). The main corticosteroids, corticosterone (19, 41) and aldosterone (10), have been reported to reverse the action of ADX, which, similarly to what it does in castrated female rats, attenuates the increased rate of energy deposition in most models of animal obesity (7, 11, 31, 33, 40, 42, 48, 49).

Corticosteroids exert their physiological effects via two types of receptors (8, 12), whose respective involvement in energy balance regulation has gained support in recent years (9, 10, 20, 26, 39). The corticosteroid receptors are referred to as type I corticosteroid receptors, or mineralocorticoid receptors (MR), and as type II corticosteroid receptors, or glucocorticoid receptors (GR). MR binds corticosterone and aldosterone with an equally high affinity, whereas GR binds corticosterone with an affinity ~10 times lower than that of MR. Although MR has equal affinity for both corticosterone and aldosterone, it generally binds corticosterone because the circulating levels of corticosterone are much higher than those of aldosterone. The reasons for MR specificity for aldosterone in some peripheral mineralocorticoid target tissues such as the kidney have yet to be fully clarified, but recent data tend to indicate that this specificity may be conferred by the enzyme 11β-hydroxysteroid dehydrogenase, which metabolizes corticosterone to its 11 keto metabolites but does not metabolize aldosterone (12). The involvement of MR in the regulation of energy balance has been suggested by a series of experiments demonstrating the ability of either low doses of corticosterone or aldosterone to accelerate body weight gain in ADX obese and nonobese rats (9, 10). The involvement of GR has been supported by studies emphasizing the ability of the GR antagonist, RU-38486 (RU-486) to attenuate the development of obesity in the Zucker rat (20) or in the high-fat-fed Osborne-Mendel rat (27).

In this study, the roles played by MR and GR in the regulation of energy balance were further investigated by examining the respective and interactive effects of OVX and corticosteroid antagonists on energy balance. Both sham-operated and OVX groups of rats were treated for a period of 4 wk with a placebo, the MR antagonist RU-28318, or the GR antagonist RU-486.
MATERIALS AND METHODS

**Animals, diet, and treatments.** Sixty female Sprague-Dawley rats, initially weighing ~200 g, were purchased from the Canadian Breeding Laboratories (St-Constant, PQ, Canada). All rats were cared for and handled in conformity with the Canadian Guide for the Care and Use of Laboratory Animals. The animals were housed singly in wire-bottom cages suspended above absorbent paper. They were subjected to a 12:12-h light-dark cycle (lights on between 0500 and 1700) and kept under an ambient temperature of 23 ± 1°C. Each rat had free access to water and a purified diet, with an energy density of 17.72 kJ/g wet weight. Rats of all groups were provided with water supplemented with NaCl (0.9%). The energy content of the diet was determined by adiabatic bomb calorimetry (Parr Instruments, Moline, IL) calibrated with a dry benzoic acid standard. The diet contained the following components (g/100 g): 23.0 casein, 0.3 methionine, 38.6 dextrose monohydrate, 24.5 corn starch, 2.5 cellulose, 5.0 corn oil, 5.0 mineral mix (AIN76), and 1.0 vitamin mix (Teklad no. 40060).

The rats were assigned to a 2 (surgery: sham and OVX) × 3 (corticosteroid antagonist: placebo, RU-28318, RU-486) experimental design. The six groups formed were labeled as follows: 1) sham-placebo, 2) sham-RU-28318, 3) sham-RU-486, 4) OVX-placebo, 5) OVX-RU-28318, and 6) OVX-RU-486. Each group was composed of 10 animals. The bilateral removal of ovaries was achieved through two small lateral skin incisions made under isoflurane anesthesia. Each ovary was pulled out of the body by grasping the periovary fat and then severing the junction between the fallopian tube and the uterine horn in a single cut. Blood vessels were ligated and incisions were thereafter appropriately sutured. The total procedure was completed within 15 min. Sham-operated animals were handled in the same way as OVX animals except that ovaries were not excised. RU-28318, RU-486, and the placebo were administered in pellet form. The pellets were prepared by Innovative Research of America (Toledo, OH) to deliver the doses used with reference to previous experiments (5) conducted with OVX animals. RU-28318 and RU-486 were kindly provided by Dr. D. Philibert from Roussel-UCLAF (Romainville, France). RU-28318 and RU-486 were selected for their relatively high degree of specificity in antagonizing MR and GR, respectively. RU-486 is also recognized for its antiprogesterone effects (29).

**Procedures.** The rats were assigned to a 2 × 3 × 2 factorial design. The six groups formed were labeled as follows: 1) sham-placebo, 2) sham-RU-28318, 3) sham-RU-486, 4) OVX-placebo, 5) OVX-RU-28318, and 6) OVX-RU-486. Each group was composed of 10 animals. The bilateral removal of ovaries was achieved through two small lateral skin incisions made under isoflurane anesthesia. Each ovary was pulled out of the body by grasping the periovary fat and then severing the junction between the fallopian tube and the uterine horn in a single cut. Blood vessels were ligated and incisions were thereafter appropriately sutured. The total procedure was completed within 15 min. Sham-operated animals were handled in the same way as OVX animals except that ovaries were not excised. RU-28318, RU-486, and the placebo were administered in pellet form. The pellets were prepared by Innovative Research of America (Toledo, OH) to deliver the doses used with reference to previous experiments (5) conducted with OVX animals. RU-28318 and RU-486 were kindly provided by Dr. D. Philibert from Roussel-UCLAF (Romainville, France). RU-28318 and RU-486 were selected for their relatively high degree of specificity in antagonizing MR and GR, respectively. RU-486 is also recognized for its antiprogesterone effects (29).

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Energy, protein, and fat gains were determined as previously described (30). At the end of the treatment period, rats were killed by decapitation between 1200 and 1400. On the day of decapitation, food was removed from the cages at 0800. Immediately after decapitation, adrenals, ovaries, retroperitoneal white adipose tissues (WAT), and the vastus lateralis muscle were dissected out and weighed. All these tissues were added back to the carcass prior to energy and nitrogen determinations. Meanwhile, the gastrointestinal contents were removed from the carcasses. Carcasses were then autolaved at 125 kPa for 20 min. This procedure, which has been reported not to affect energy yield (21), was used to soften hard tissues. Once autolaved, carcasses were homogenized in a volume of water corresponding to 1.5 times their weight. Samples of homogenized carcasses were freeze-dried pending the determination of their energy and nitrogen contents. Carcass energy content was determined by adiabatic bomb calorimetry, whereas carcass nitrogen was determined in 250- to 300-mg samples of dehydrated carcasses, with the use of the Kjeldahl procedure. Carcass protein content was computed by multiplying the carcass nitrogen content by 6.25. The energy as protein was subtracted from total carcass energy to determine energy as nonprotein matter. Because carbohydrate represents a negligible part of carcass total energy, energy from nonprotein matter was assumed to be essentially that of fat. Such an assumption tends to be confirmed by studies in which energy, fat, and protein were directly determined (1). Values of 23.5 and 39.3 kJ/g were used (45) for the calculation of the energy content of protein and fat, respectively. Initial energy, fat, and protein contents of carcasses were estimated from the live body weights of the rats with reference to the baseline group of rats killed at the beginning of the experimental period. Such estimates allow gains in energy, fat, and protein to be determined for the treatment period. The 10 rats in the baseline group were killed at the beginning of the energy balance trial, and the carcass of each rat was analyzed for fat, protein, and energy. The body weight densities in fat (g fat/g body wt), protein (g protein/g body wt), and energy (kJ/g body wt) were then computed and averaged. The average densities were then multiplied by the initial body weight of each rat in the experimental groups. Rats in the initial group were identical in every respect (strain, age, gender) to those of the six experimental groups.

Apparent energy expenditure was calculated by subtracting the energy gain from DE intake. Gross energetic efficiency represents the ratio of energy gain to DE intake multiplied by 100.

**Hormone assays.** At the time of decapitation, blood was collected and centrifuged, and the plasma was frozen at –70°C. Plasma corticosterone was determined by a competitive protein-binding assay (25), using the plasma of a dexamethasone-treated female rhesus monkey as the tracersource. The plasma levels of adrenocorticotropic hormone (ACTH) were measured by immunoassay (Allegro ACTH Immunoassay Kit; Nichols Institute, San Juan Capistrano, CA). This ACTH immunoassay incorporates monoclonal and polyclonal antibodies, both of which have a high affinity and specificity for defined amino acid regions of the ACTH molecule.

Statistical analysis. Analysis of variance (ANOVA) was used to determine the main and interaction effects of surgery and corticosteroid antagonist on the different dependent variables of this study. The significant surgery × corticosteroid antagonist interactions were analyzed by examining the simple main effects. The analysis of the simple main effects...
consists of measuring the effects of one factor at every level of the other factors. In this study, the effects of surgery were assessed in placebo-, RU-28318-, or RU-486-treated rats, and the effects of corticosteroid antagonist were assessed in sham-operated or OVX rats. When a simple main effect of corticosteroid antagonist was detected, comparisons of individual means were carried out. The levels of significance were adjusted to 0.05, 0.03, and 0.005 for ANOVA, the analysis of the simple main effects, and the mean comparisons, respectively.

RESULTS

Body weight. Body weight growth curves and gains are presented in Fig. 1. Only statistics concerning body weight gain are considered here and in Fig. 1 because they reliably reflect growth curves. Body weight growth curves are nonetheless presented in Fig. 1, the illustration of growth providing relevant information. ANOVA revealed significant main and interaction effects of surgery and corticosteroid antagonist on body weight gain. As illustrated by the bar graph and corroborated by the analysis of the simple main effects, the effect of surgery on body weight gain was significant regardless of whether rats were treated with placebo, RU-28318, or RU-486. Body weight gain was larger in OVX groups of rats than in sham-operated ones. As is also indicated by the analysis of the simple main effects, the effect of corticosteroid antagonist on body weight gain was significant in OVX rats but not in sham-operated animals. In OVX rats, body weight gain was lower in RU-28318-treated rats than in placebo-treated ones.

Energy balance. DE intake, energy gain, energy expenditure, and gross energetic efficiency (energy gain/DE intake x 100) are presented in Fig. 2. ANOVA revealed significant main effects of surgery and corticosteroid antagonist on energy gain and gross energetic efficiency. As suggested by the examination of Fig. 2 and confirmed by the analysis of the simple main effects, the effect of surgery on energy gain and gross energetic efficiency was significant in placebo and RU-486-treated rats but not in RU-28318-treated animals. In rats treated with either the placebo or RU-486, energy gain and gross efficiency were higher in OVX rats than in sham-operated ones. As is also revealed by the analysis of the simple main effects, the effect of corticosteroid antagonist on energy gain was significant in OVX rats but not in sham-operated animals. In OVX rats, energy gain was lower in RU-28318-treated animals than in placebo-treated ones. The effect of corticosteroid antagonist on gross energetic efficiency was significant in both sham-operated and OVX rats. In sham-operated rats, gross energetic efficiency was lower in RU-486-treated animals than in placebo administered rats. In OVX rats, gross energetic efficiency was lower in RU-28318-treated rats than in placebo-administered animals.

Fat and protein gains. Fat and protein gains are illustrated in Fig. 3. ANOVA revealed significant main and interaction effects of surgery and corticosteroid antagonist on fat gain. As emphasized by the analysis of the simple main effects, the effect of surgery on fat gain was significant in placebo- and RU-486-treated rats but not in RU-28318-treated rats. In rats treated with the placebo or RU-486, fat gain was higher in OVX rats than in sham-operated animals.

Fig. 1. Body weight growth curves (A) and body weight gains (B) of 6 groups of rats included in a 2 [surgery: sham (sh) and ovariectomy (OVX)] X 3 [corticosteroid antagonist (CA): placebo, RU-28318, RU-486] experimental design. Data shown are means (growth curves) or means ± SE (body wt gain). Only statistics applying to body weight gain were considered. In the case of significant interactions, statistically significant differences are identified by asterisk. Analysis of variance (ANOVA) revealed significant (P < 0.05) main and interaction effects of surgery and CA on body weight gain. Examination of the interaction through analysis of simple main effects unveiled significant (P < 0.03) effects of surgery at placebo, RU-28318, and RU-486 and of CA at OVX. Examination of the CA simple main effect at OVX through individual mean comparisons revealed a significant (P < 0.005) difference between OVX-placebo and OVX-RU-28318. S, surgery.
Rats than in sham-operated ones. The effect of corticosteroid antagonist on fat gain was significant in OVX rats but not in sham-operated animals. In OVX rats, fat gain was lower in RU-28318-treated animals than in placebo-administered ones. ANOVA revealed a significant main effect of surgery but no significant surgery × corticosteroid antagonist interaction effect on protein gain; protein gain was larger in OVX rats regardless of whether they were treated with placebo, RU-28318, or RU-486.

**Retroperitoneal WAT and vastus lateralis muscle weights.** The weights of retroperitoneal WAT and vastus lateralis muscle are presented in Fig. 4. ANOVA revealed significant main effects of surgery and corticosteroid antagonist on retroperitoneal WAT weight and of surgery on vastus lateralis muscle weight. Retroperitoneal fat weight was higher in OVX rats than in sham-operated animals. The nearly significant (P = 0.06) surgery × corticosteroid antagonist interaction effect on retroperitoneal WAT weight nonetheless suggested caution in generalizing the main effect of surgery on retroperitoneal WAT weight to the RU-28318 group. As seen in Fig. 4, the effects of OVX on retroperitoneal WAT weight appeared stronger in groups treated with either the placebo or RU-486 than in the group treated with RU-28318. The analysis of the simple main effects (which was performed despite the lack of significant surgery × corticosteroid antagonist interaction) indicated that the effect of surgery on retroperitoneal WAT weight was highly significant in placebo- and RU-486-treated rats but not (P = 0.54) in RU-28318-treated rats. ANOVA also revealed a significant main effect of surgery and no significant surgery × corticosteroid antagonist interaction effect on vastus lateralis

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**Fig. 2. Digestible energy (DE) intake (A), energy gain (B), apparent energy expenditure (C), and gross energetic efficiency (energy gain/DE intake × 100) (D) of 6 groups of rats included in 2 × 3 experimental design described in Fig. 1. Data shown are means ± SE. In the case of significant interactions, statistically significant differences are identified by asterisk. ANOVA revealed significant (P < 0.05) main effects of surgery on DE intake, energy gain, apparent energy expenditure, and gross energetic efficiency and of CA on energy gain and gross energetic efficiency. ANOVA also revealed significant surgery × CA interaction effects on energy gain and gross energetic efficiency. Examination of surgery × CA interaction on energy gain through analysis of the simple main effects indicated significant (P < 0.03) effects of surgery at placebo and RU-486 and of CA at OVX. Examination of CA effect at OVX through individual mean comparisons indicated a significant (P < 0.005) difference between OVX-placebo and OVX-RU-28318. Examination of surgery × CA interaction on gross energetic efficiency through analysis of the simple main effects indicated significant (P < 0.03) effects of surgery at placebo and RU-486 and of CA at sham and OVX. Examination of CA effect at sham through individual mean comparisons indicated a significant (P < 0.005) difference between sham-placebo and sham-RU-486. Examination of CA effect at OVX through individual mean comparisons indicated a significant (P < 0.005) difference between OVX-placebo and OVX-RU-28318.**

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It is noteworthy that analysis of the simple main effects pointed to a nearly significant ($P = 0.037$) effect of surgery on ACTH levels in RU-28318-treated rats.

**DISCUSSION**

The present results demonstrate that treatment with the selective MR antagonist RU-28318 attenuated the increased rate of energy deposition that ensued from OVX in rats. Interestingly enough, the influence of RU-28318 in preventing OVX-induced changes in energy balance was exerted mainly on fat deposition. In fact, at the dose used in these experiments, RU-28318 attenuated OVX-induced growth of total fat mass and retroperitoneal WAT but not that of total lean mass and vastus lateralis muscle. The present results also indicate that the effect of RU-28318 in preventing OVX-induced changes in energy and fat balances was more related to an increase in energetic efficiency than to a reduction in food intake or an increase in energy expenditure. Indeed, energetic efficiency more closely reflected energy and fat gains than either energy intake or energy expenditure taken separately.

By demonstrating the ability of RU-28318 to attenuate the effects of OVX on energy balance, the present study provides evidence that MR occupation partici-

Fig. 3. Fat (A) and protein (B) gains of 6 groups of rats included in $2 \times 3$ experimental design described in Fig. 1. Data shown are means + SE. In the case of significant interactions, statistically significant differences are identified by asterisk. ANOVA revealed significant ($P < 0.05$) main and interaction effects of surgery and CA on fat gain. Examination of interaction through the simple main effects indicated significant ($P < 0.03$) effects of surgery at placebo and RU-466 and of CA at OVX. Examination of CA effect at OVX through individual mean comparisons indicated a significant ($P < 0.005$) difference between OVX placebo and OVX RU-28318. ANOVA also revealed a significant ($P < 0.05$) effect of surgery on protein gain.

Fig. 4. Retroperitoneal white adipose tissue (WAT) weight (A) and vastus lateralis muscle weight (B) of 6 groups of rats included in $2 \times 3$ experimental design described in Fig. 1. Data shown are means + SE. ANOVA revealed significant ($P < 0.05$) main effects of surgery and CA on retroperitoneal WAT weight. ANOVA revealed a significant ($P < 0.05$) main effect of surgery on vastus lateralis muscle weight.

muscle weight; vastus lateralis muscle weight was larger in OVX rats than in sham-operated animals regardless of whether OVX rats were treated with placebo, RU-28318, or RU-486.

Adrenal weight and corticosterone and ACTH levels. Adrenal weight and plasma ACTH and corticosterone levels are illustrated in Fig. 5. ANOVA indicated a significant main effect of surgery on adrenal weight and corticosterone levels. Both of these variables were lower in OVX rats than in sham-operated animals. ANOVA also indicated a significant surgery X corticosteroid antagonist interaction effect on ACTH levels. Although the analysis of simple main effects did not reveal any significant ($P < 0.03$) effect of either surgery or corticosteroid antagonist, it is reasonable to assume from the examination of ACTH results in Fig. 5 that the significant interaction emerged because the effects of OVX in RU-28318-treated rats were contrary to those seen in either placebo-treated or RU-486-treated rats.
MR are found in brain areas known to be involved in the control of food intake and energy expenditure (15, 32, 34), and the suggestion has recently been made that recruitment of this receptor can favor the expression of the corticosteroid anabolic action. This proposition has emerged from two series of observations. First, it has been shown that the effects of ADX in reducing food intake and body weight gain are abolished by very low doses of corticosterone, suggesting that the action of corticosterone is mediated by MR. Second, it has been demonstrated that the MR agonist aldosterone has the ability to stimulate food intake and body weight gain in ADX lean (9) and obese (10) rats. In addition, studies investigating the effects of the specific MR agonist aldosterone on nutrient preference (37) have led to the conclusion that MR stimulation is associated with an increased preference for fat, a common feature of a positive energy balance (anabolism). The mechanisms underlying the effects of RU-28318 on the energy balance of OVX rats cannot be thoroughly specified on the basis of the present results. It is noteworthy that surgery and corticosteroid antagonist interacted on ACTH levels, which tended to be higher in OVX than in sham-operated rats in the presence of RU-28318. Whether ACTH is part of the mechanisms underlying the effect of RU-28318 in OVX rats is not certain. Given that an increase in ACTH levels is indicative of a rise in corticotropin-releasing factor (CRF) activity, it can be argued that the effects of RU-28318 on energy balance of OVX rats are CRF mediated. CRF is concentrated in the parvocellular division of the paraventricular nucleus, a region known to contain MR receptors (32, 34). Furthermore, CRF has been reported to be involved in the anorectic effect of E2 (6). The possibility that CRF is involved in the MR-related anabolic action of corticosteroid warrants further investigations.

The reasons why the effects of RU-28318 on fat accretion, which is not apparent in gonadally intact rats, become predominant after OVX have yet to be determined. However, the possibility that the removal of ovary-derived factors improves the relative importance of MR in corticosteroid actions in OVX animals cannot be ruled out. E2 and progesterone have been reported to decrease either MR gene expression or MR binding affinity (3).

The present study does not provide evidence for a GR involvement in the effects of OVX on energy balance. In fact, at the dose used in this study, RU-486 did not block any of the effects of OVX on energy balance. Similar to MR, GR has been located in brain areas involved in the control of food intake and energy expenditure (15, 32, 34) and implicated in corticosteroid action in the regulation of energy balance (36, 39, 47). In two recent studies, RU-486 was reported to block the development of obesity in female Zucker (20) and high-fat-fed Osborne-Mendel rats (27), clearly suggesting that GR occupation has a permissive action in the expression of the anabolic function of corticosteroids in these models. Because RU-486 did not exert any effect on ACTH and corticosterone levels in this study, it can be argued that RU-486 treatment was not effective. However, this possibility seems unlikely. The dose (25 mg·kg⁻¹·day⁻¹) that was used in this study exceeded that (10 mg·kg⁻¹·day⁻¹) needed to block access to GR (23). In addition, it must be underlined that RU-486 reduced energetic efficiency in sham-operated rats.
indicating that the dose used was effective at producing effects on energy balance. Nonetheless, it is not certain that the effect of RU-486 on energetic efficiency of sham-operated rats was GR mediated. Given that progesterone may promote energy deposition (16), it is plausible that a GR progesterone receptor (PR) antagonist such as RU-486 can reduce energetic efficiency through blocking PR access to progesterone. It is noteworthy that the evidence for a role of RU-486 in the expression of corticosteroid anabolic function has emerged from two studies (20, 27) conducted in gonadally intact female rats in which it is likely that RU-486 also antagonized progesterone.

By providing evidence that MR occupation is involved in the effects of OVX on energy balance, the present results further support the suggestion that corticosteroids are involved in the regulation of the energy balance of castrated animals (28). This suggestion has previously emerged from studies that demonstrated that the removal of corticosteroids by ADX markedly blunted the effects of castration on body weight (24) and energy balance (28) of female rats. The proposition that corticosteroids could participate in the effects of OVX on energy balance is reasonable, considering that both aldosterone (9) and corticosterone (13) have the ability to promote energy deposition. Corticosteroids have also been reported to be implicated in the regulation of the energy balance of most models of animal obesity (2, 7, 11, 33, 34, 40, 42, 48, 49), in which the removal of corticosteroids by ADX blocks the rapid rate of energy deposition. In contrast to most experimental obesities, OVX-induced energy gain is not associated with an adrenal hyperfunction. Indeed, the results of this and previous studies (22, 46) suggest a decrease rather than an increase in adrenal function in castrated females. In this study, corticosterone levels as well as adrenal weight (per 100 g body wt) were lower in OVX rats than in sham-operated animals. That corticosteroids are involved in OVX-induced alterations in energy balance, despite the fact that OVX tends to reduce adrenal function, is an interesting observation of this study that needs to be further investigated.

Given the expected loss of feedback inhibition in rats treated with corticosteroid antagonists, an increase in corticosterone and ACTH levels was anticipated in rats treated with either RU-28318 or RU-486. It is unclear why this decrease did not occur. Because of the relatively long duration of the corticosteroid antagonist treatment in this study, the possibility that some adaptive mechanisms might have compensated for the known short-term effect of RU-486 and RU-28318 on ACTH and corticosterone levels cannot be excluded.

In conclusion, the present results demonstrate that the treatment with the selective MR antagonist RU-28318 attenuated the increased rate of energy gain brought about by OVX in rats. The influence of RU-28318 in preventing OVX-induced changes in energy balance was exerted mainly on fat deposition.

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