Selective estrogen receptor modulator promotes weight loss in ovariectomized female rhesus monkeys (*Macaca mulatta*) by decreasing food intake and increasing activity

**Elinor L. Sullivan,1,2 Jean Shearin,3 Frank H. Koegler,1 and Judy L. Cameron1,2,4,5**

1Division of Reproductive Sciences and Neuroscience, Oregon National Primate Research Center, Beaverton; 2Department of Physiology and Pharmacology, Oregon Health and Science University, Portland, Oregon; 3Department of Metabolic Diseases, GlaxoSmithKline, Research Triangle Park, North Carolina; 4Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania; and 5Departments of Behavioral Neuroscience and Obstetrics and Gynecology, Oregon Health and Science University, Portland, Oregon

Submitted 3 August 2011; accepted in final form 10 January 2012

Sullivan EL, Shearin J, Koegler FH, Cameron JL. Selective estrogen receptor modulator promotes weight loss in ovariectomized female rhesus monkeys (*Macaca mulatta*) by decreasing food intake and increasing activity. *Am J Physiol Endocrinol Metab* 302: E759–E767, 2012. First published January 17, 2012; doi:10.1152/ajpendo.00327.2011.—The effect of hormone replacement therapy (HRT) on body weight in postmenopausal women is controversial, with studies reporting an increase, a decrease, and no change in body weight. To examine estrogen receptor actions on body weight, we investigated the effects of treatment with a selective estrogen receptor modulator (SERM) on body weight, food intake, and activity and metabolic rate in a nonhuman primate model. Eighteen ovariectomized female rhesus monkeys were treated with a nonsteroidal SERM (GSK232802A, 5 mg/kg po) for 3 mo. GSK232802A decreased luteinizing hormone (P < 0.0001) and follicle-stimulating hormone levels (P < 0.0001), which was due at least in part to a suppression of food intake (3.6 ± 3.7%, P < 0.0001). Physical activity increased during the 3rd mo of treatment (P = 0.04). Baseline activity level and the change in activity due to treatment were correlated, with the most sedentary individuals exhibiting increased physical activity during the 1st mo of treatment (P = 0.02). Metabolic rate did not change (P = 0.58). These results indicate that GSK232802A treatment reduces body weight and adiposity in ovariectomized nonprimates by suppressing food intake and increasing activity, particularly in the most sedentary individuals. These findings suggest that SERM treatment may counteract weight gain in postmenopausal women.

WOMEN GAIN WEIGHT IN ADULTHOOD during the menopausal transition (16, 31, 45, 50, 53, 56). However, it is unclear whether weight gain is due to age-related changes in metabolism and lifestyle, such as eating more or exercising less, or due to the decrease in ovarian hormones that occurs with menopause. The effects of hormone replacement therapy (HRT) on the body weights of postmenopausal women are controversial. Many women believe that HRT increases body weight, and 18% of hormone replacement users report weight gain as the main reason for discontinuing HRT (63, 78). However, the idea that HRT increases body weight is supported by only a few studies (5, 36). The majority of studies report either that postmenopausal women on HRT have lower body weight than nonusers (82, 83) or that HRT decreases (28, 29, 47) or does not affect postmenopausal weight gain (10, 84, 86, 91), and a few studies report that HRT causes weight loss (20). The controversy around the effects of HRT on body weight in postmenopausal women may be related in part to differing effects of the various HRT regimens that are in common use, including differences in the time of initiation, the variety and dose of synthetic hormones, and different routes of administration [e.g., oral vs. transdermal (66)]. Moreover, most forms of HRT include progestins such as medroxyprogesterone, which are added to decrease the risk of uterine cancer. The addition of progestins to HRT has been shown to impact the effect of estrogen on body weight, causing an increase in food intake and body weight in response to HRT (11, 34, 54). It is important to note that GSK232802A, the selective estrogen receptor modulator (SERM) used in this study, does not act on the uterus, and thus there is no need to add a progestin to reduce uterine cancer risk.

Additionally, variables that influence body weight, such as caloric intake, dietary composition, and level of physical activity, are often not controlled for or even measured in epidemiological studies examining the effect of HRT on body weight. Because weight gain occurs in both women and men progressively over adulthood (48, 52, 96), it is possible that weight gain noted during periods of HRT use is simply a continuation of adult weight gain associated with a progressive decline in metabolic rate, eating more calories than utilized, or a sedentary lifestyle.

In animals, the effects of estrogen on body weight and food intake are consistent. In rodents (4, 18, 21, 81, 102) and domestic animals (26, 35, 58), ovariectomy consistently leads to a rapid increase in body weight and hyperphagia, and estradiol treatment reduces food intake and body weight (14, 37, 65, 81, 97). Ovariectomy rapidly increases body weight in nonhuman primates (89), and treatment of ovariectomized monkeys with estradiol has been shown to suppress food intake (24, 44). Because data from animal studies indicate that estrogen modulates body weight and food intake, and the evidence in humans is inconsistent, the goal of this study was to examine the effects of GSK232802A on body weight, body composition, and energy balance in a primate species. Ovariectomized female rhesus monkeys were dosed daily for 3 mo with GSK232802A (5 mg/kg po), an orally available nonsteroidal SERM. Body weight, body composition, food intake, activity,
total energy expenditure, and basal metabolic rate were recorded. Results showed that GSK232802A reduced body weight and body fat by inhibiting food intake and increasing physical activity.

MATERIALS AND METHODS

Animals

Eighteen adult female rhesus monkeys (Macaca mulatta) aged 7–11 yr of age originated from the Oregon National Primate Research Center (ONPRC) animal colony. Monkeys lived in individual stainless-steel cages (0.81 × 0.61 × 0.69 or 0.81 × 0.86 × 0.69 m) in a temperature-controlled room (24 ± 2°C), with lights on from 0700 to 1900.

Monkeys were ovarioctomized 18 mo prior to study (89) and placed on a high-fat diet (35% of calories from fat) for 16.5 mo to approximate the conditions experienced by many postmenopausal women in the Western world (104). The high-fat diet was formulated following the recipe developed by Shadoan et al. (79) and Williams et al. (104) to study diet-induced atherosclerosis in monkeys. Monkeys were fed ad libitum with meals provided at 0915 and 1515. All aspects of the study were reviewed and approved by the ONPRC Animal Care and Use Committee.

Compound Information

The SERM used in this study is a novel cycloalkylidene compound that binds to estrogen α- and β-receptors with equal affinity (GSK232802A, GlaxoSmithKline; Shearin J, unpublished data). SERMs are small molecules that bind to and selectively modulate estrogen receptors. They have the ability to stimulate or block estrogen’s activity in different types of tissue, functioning as an agonist at estrogen receptors in some tissues and an antagonist in others. In rodents, GSK232802A prevents bone loss without stimulating the uterus in ovarioctomized rats, indicating that it acts as an agonist in bone tissue and an antagonist in the uterus (GlaxoSmithKline; Shearin J, unpublished data).

Experimental Design

All animals experienced three experimental periods: a 1-mo baseline period during which monkeys received vehicle daily, followed by a 3-mo experimental period during which monkeys received GSK232802A (5 mg/kg po) daily, and last, a 2-mo recovery period during which they again received vehicle daily. The vehicle (a small piece of palatable fruit, usually melon) and vehicle-containing drug (applied as solid powder into the vehicle) were provided ~15 min prior to the morning meal, normally fed at 0900. Body weight, food intake, and activity were measured throughout the experiment. Body composition and metabolic rate were determined at the end of each of the three experimental periods. Blood samples for measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), leptin, triiodothyronine (T₃), alkaline phosphatase (ALP), and GSK232802A were collected during the baseline period, after 1 and 3 mo of GSK232802A treatment, and at the end of the recovery period.

Experimental Measurements

Body weight. Body weight was measured weekly prior to consumption of the morning meal at ~0800.

Body composition. Percent body fat, central fat mass, peripheral fat mass, and bone mineral density were determined using dual energy X-ray absorptiometry. Animals were sedated with Telazol (3 mg/kg im; Fort Dodge Animal Health, Fort Dodge, IA), supplemented with potassium HCl (10–20 mg/kg im, Ketaset; Fort Dodge Animal Health), and positioned supine on the bed of a Lunar DPX scanner (Lunar, Madison, WI). Total body scans were acquired in the “pediatric medium” scan mode with a voltage of 76 kV. Lunar software version 3.4 was used to calculate body composition. Two or three scans were performed on each monkey at the end of each experimental period, and the average was calculated. To delineate central fat mass from peripheral fat mass, fat in the trunk (including both the subcutaneous and visceral compartments) and in the extremities was calculated using standard methodology (22, 94).

Food intake. Each monkey was fed more food than was routinely consumed at each meal to ensure ad libitum food intake. Food consumed at each meal was recorded daily. Food intake was quantified by counting the number of biscuits fed at each meal and the number of biscuits remaining prior to the next meal. Weight for this dry quantity of food was then calculated on the basis of the average weight of 10 biscuits. Biscuit spillage/waste was estimated on the basis of a standard since food that remained in the cage pan was often urine-soaked, making direct weighing inaccurate.

Activity. Activity was measured continuously throughout the experiment using Actical omnidirectional accelerometers (Respironics, Phoenix, AZ) and previously published methods (88, 90). Each monkey was fitted with a loose-fitting metal collar (Prime Products, Immokalee, FL) that housed the accelerometer in a snug, protective, stainless-steel box. All monkeys had been acclimated to wearing collars with activity monitors for several months prior to data collection for this study. Monitors were programmed to store the total number of activity counts per minute. Activity data were downloaded at least every 45 days while animals were under sedation (Ketaset, 10–20 mg/kg im; Fort Dodge Animal Health). Total daily activity level was averaged for the baseline period and for each month of the study. The most and least active quartiles of monkeys were determined on the basis of their activity during the baseline period.

Metabolic rate. Metabolic rate was measured during the baseline period, at the end of the treatment phase, and at the end of the recovery period using a metabolic chamber and a computer-controlled, indirect open-circuit calorimeter (Oxymax System; Columbus Instruments, Columbus, OH) and previously published methods (88, 90). Each monkey was placed in a sealed transparent chamber (Columbus Instruments) that was approximately the same size as the monkey’s home cage (inside dimensions of 30 × 24 × 24 in.) from 0000 to 0900 on the subsequent day. To prevent social isolation during metabolic testing, two familiar monkeys (i.e., 2 monkeys routinely housed across the room from the experimental monkey) were placed in plain view of the subject in separate cages during the duration of data collection. Before placement in the chamber, monkeys were fed a standard meal at 0915 and then fed a banana (114 ± 10 g, 108 calories) at 1515 while they were in the chamber. Water was available ad libitum throughout metabolic testing. Basal metabolic rate was calculated from oxygen consumption and carbon dioxide production and presented as the average number of kilocalories expended per hour from 2300 to 0300. This time period was selected because this is when monkeys typically sleep and is when physical activity (88, 90) and heart rate are lowest (Cameron JL, unpublished observations). The thermic effect of an isocaloric meal (the banana fed at 1515) was calculated by subtracting basal metabolic rate and activity-associated energy expenditure from total energy expenditure for the 4 h after the banana was consumed [when the majority of energy is expended in response to a meal (12, 74, 87)].

Blood sampling. Blood samples (12 ml) were collected by femoral venipuncture under sedation with ketamine HCl (10–20 mg/kg im, Ketaset; Fort Dodge Animal Health) during the baseline period, at the end of the 1st and 3rd mo of GSK232802A treatment, and at the end of the recovery period to measure LH, FSH, leptin, T₃, and ALP.
Assays

The Endocrine Services Core Facility at ONPRC determined plasma leptin and T3 concentrations. Leptin was measured using a commercially available double antibody RIA kit for porcine leptin (PLR-1101) from Linco Research (St. Charles, MO). All samples were measured in a single assay, and the intra-assay variability was 3.5%. Plasma T3 was measured using a Roche Elecsys 2010 clinical instrument and assay reagents for human T3 from Roche Diagnostics (Indianapolis, IN). The assay variability of the machine was 6%. LH and FSH were measured by RIA at the RIA Core Laboratory of the Center for Research in Reproductive Physiology, University of Pittsburgh (105). For FSH, the intra-assay variability was 2% and the interassay variability was 7%. For LH, the intra- and interassay variability were 4 and 11%, respectively. ALP was assayed by the Metabolic Disease Core Assay Facility of GlaxoSmithKline (Research Triangle Park, NC) using an automated chemistry analyzer (Technicon Axon, Tarrytown, NY) and reagents for human ALP (Olympus Life and Material Science, O’Callaghan’s Mills, Ireland). The within-run variability for ALP was 2%, and the between-day variability was 4%.

Statistical Analyses

Body weight, activity, and food intake measurements were averaged during the baseline period to obtain mean baseline values for each monkey. Changes in food intake, body weight, and activity were expressed as percent of baseline values for each monkey. Statistical comparisons were also made between the average body weight, food intake, and activity during each month of the experiment.

For all analyses, normality and homogeneity of variance were tested. If these criteria were met, a repeated-measures ANOVA was utilized to examine differences in variables over time. A Mauchly’s test of sphericity was used to test the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is identity. In case of significant Mauchly’s test of sphericity, the sphericity correction was utilized to adjust the degrees of freedom. Least squares multiple regression was used to examine differences in variables over time. A Mauchly’s test of sphericity was used to test the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is identity. In case of significant Mauchly’s test of sphericity, the sphericity correction was utilized to adjust the degrees of freedom. Least squares multiple regression was used to examine differences in variables over time. A Mauchly’s test of sphericity was used to test the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is identity. In case of significant Mauchly’s test of sphericity, the sphericity correction was utilized to adjust the degrees of freedom. Least squares multiple regression was used to examine differences in variables over time.

RESULTS

Plasma LH concentrations changed during the experiment ($F_{2,34} = 22.5, P < 0.0001$), with mean plasma LH decreasing from 12.9 ± 1.0 ng/ml during the baseline period to 9.86 ± 0.94 ng/ml during GSK232802A treatment (18.1 ± 4.3% decrease, $P < 0.0001$) and returning to baseline levels by the end of the recovery period ($P = 0.23$). Similarly, FSH levels changed during the experiment ($F_{2,34} = 20.83, P < 0.0001$), with plasma FSH concentrations decreasing from 13.18 ± 0.92 ng/ml during the baseline period to 10.89 ± 1.01 ng/ml during GSK232802A treatment (23.7 ± 3.8% decrease, $P = 0.001$) and increasing to levels higher than during the baseline period (14.95 ± 1.24 ng/ml, $P = 0.02$) by the end of the recovery period.

Plasma estradiol levels changed over the course of the experiment ($F_{1,03,17,58} = 46.96, P < 0.0001$). The average estradiol level during the control period was 0.561 ± 0.32 pg/ml and increased to 24.39 ± 2.53 pg/ml during GSK232802A treatment; the average estradiol during the recovery period was 6.61 ± 0.57 pg/ml.

Body weight changed over the experiment ($x^2 = 41.28, df = 5, P < 0.0001$; Fig. 1). Average body weight was 7.9 ± 0.49 kg during the baseline period. Body weight was reduced after the 1st mo of treatment to 7.79 ± 0.47 kg ($P = 0.01$) and continued to progressively decrease throughout the 3 mo of GSK232802A treatment. At the end of the treatment phase, body weight was 4.6% less than initial body weight (7.53 ± 0.45 kg, $P = 0.002$). At the end of the recovery period, body weight returned to baseline levels (8.07 ± 0.49 kg, $P = 0.09$). There was also a change in percent body fat across the three experimental periods ($x^2 = 20.7, df = 2, P < 0.0001$; Fig. 2A). Three months of GSK232802A treatment caused a 4.7% reduction in percent body fat ($P = 0.001$). By the end of the recovery period, the percentage of body fat returned to baseline levels ($P = 0.74$). The decrease in percent body fat correlated with weight loss such that the monkeys that lost the most weight also lost the most fat mass ($r = 0.63, P = 0.005$). Initial percent body fat also correlated with the amount of weight loss [i.e., monkeys with the highest %body weight as fat during the pretreatment period lost the most weight ($r = -0.50, P = 0.04$; Fig. 2B)]. Central fat mass was affected by treatment ($x^2 = 20.9, df = 2, P < 0.0001$) such that central fat mass decreased from 21.0 ± 4.0% during the baseline period to 15.6 ± 3.3% at the end of the GSK232802A treatment period ($P = 0.001$). Central fat mass returned to baseline values at the end of the recovery period ($P = 0.88$). Peripheral fat mass also changed with treatment ($x^2 = 10.78, df = 2, P = 0.005$) such that peripheral fat mass decreased from 12.33 ± 2.03 to 9.97 ± 1.65% during GSK232802A treatment ($P = 0.006$) and returned to baseline values at the end of the recovery period ($P = 0.33$).

Fig. 1. Body weight decreased with estrogen replacement therapy ($x^2 = 41.3, df = 5, P < 0.0001$). Body weight was significantly lower than baseline levels during the 1st ($P = 0.01$), 2nd ($P = 0.005$), and 3rd mo ($P = 0.002$) of treatment and was not different from baseline levels during the 1st ($P = 0.20$) and 2nd mo ($P = 0.09$) of the recovery period. *Significant difference from the baseline period, $P < 0.05$. 

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Leptin levels did not decrease significantly after 3 mo of GSK232802A treatment ($F_{1.3.23} = 0.423, P = 0.58$; Table 1). As expected, initial leptin levels correlated with initial percent body fat ($r = 0.96, P < 0.001$) and central fat mass ($r = 0.95, P < 0.0001$) such that the fattest monkeys had the highest leptin levels. Initial plasma leptin concentration correlated with weight loss such that monkeys with the highest leptin levels lost the most weight ($r = -0.49, P = 0.04$).

Daily treatment with GSK232802A decreased daily food intake ($F_{2.6.45.0} = 8.6, P < 0.0001$). Food intake was lower than baseline levels during the 1st ($P = 0.04$), 2nd ($P = 0.04$), and 3rd mo ($P = 0.045$) of treatment (Fig. 3A). Food intake was higher than baseline levels during the 1st mo of the recovery period ($P = 0.03$) but returned to baseline levels by the end of the 2nd mo of recovery ($P = 0.53$). Not surprisingly, the decrease in food intake correlated with weight loss ($r = 0.52, P = 0.03$; Fig. 3B). There was no difference in the metabolic rate at any time of day between baseline, treatment, or recovery periods ($F_{2.34} = 0.551, P = 0.58$; Fig. 4A). Also, no difference in basal metabolic rate ($F_{2.34} = 1.0, P = 0.38$) or the thermic effect of an isocaloric meal ($F_{2.26} = 1.96, P = 0.16$) occurred. Baseline total metabolic rate ($r = -0.55, P = 0.02$; Fig. 4B) and basal metabolic rate ($r = -0.55, P = 0.02$) correlated with weight loss such that monkeys with the highest metabolic rate lost the most weight.

Physical activity level changed across the three experimental periods ($F_{2.15.36.5} = 16.63, P < 0.0001$). The average level of physical activity did not change from baseline levels during the 1st ($P = 0.40$) and 2nd mo ($P = 0.29$) of treatment in the group as a whole, but by the 3rd mo of treatment, activity was higher than baseline levels ($P = 0.04$). Activity remained elevated during the 1st ($P < 0.0001$) and 2nd mo ($P < 0.0001$) of the recovery period. The change in activity correlated with initial activity level such that the most inactive monkeys increased their activity the most ($r = -0.61, P = 0.009$; Fig. 5A). The most sedentary quartile of monkeys increased their activity during the 1st ($P = 0.02$), 2nd ($P = 0.01$), and 3rd mo ($P = 0.006$) of treatment (Fig. 5B). Change in activity also correlated with initial percent body fat ($r = 0.73, P = 0.001$) and initial plasma leptin levels ($r = 0.79, P < 0.0001$) such that the fattest monkeys increased their activity the most. Percent body fat decreased with GSK232802A treatment ($F_{2.16} = 17.12, P < 0.0001$). However, the most sedentary quartile of monkeys had a significantly higher percent body fat at each experimental period compared with the least active quartile of monkeys (control $P = 0.01$, treatment $P = 0.04$, recovery $P = 0.02$; Fig. 6).

$T_3$ levels changed over the experiment ($F_{1.2.21} = 16.2, P < 0.0001$). $T_3$ levels increased 26.5 $\pm$ 5.7% during GSK232802A treatment ($P < 0.0001$; Table 1) compared with baseline levels, and by the end of the recovery period, $T_3$ levels were lower than baseline levels ($P = 0.04$). $T_3$ levels during treatment correlated with a change in activity ($r = 0.69, P = 0.002$) such that monkeys who increased their activity the most had the highest $T_3$ levels. $T_3$ levels during treatment also correlated with weight loss such that monkeys with the highest levels of $T_3$ lost the most weight ($r = -0.51, P = 0.03$).

ALP levels changed significantly over the course of the study ($F_{2.34} = 59.1, P < 0.0001$), decreasing 44% during treatment ($P < 0.0001$) and increasing during the recovery period to levels higher than baseline ($P = 0.002$).

Although there was a trend for a decreased level of GSK232802A after 12 wk of study, this did not reach statistical significance, and GSK232802A levels remained unchanged across the study ($F_{1.5.25.36} = 3.02, P = 0.08$).

**DISCUSSION**

GSK232802A, a nonsteroidal SERM, decreased body weight (a 4.6% decrease in 3 mo) and percent body fat (a 4.7% decrease in 3 mo) in ovariectomized female monkeys. Of particular interest, the 4.6% weight loss over 3 mo with estrogen replacement therapy was similar in magnitude to the amount of weight gained by these monkeys after ovariectomy (4.8% increase) (89). A decrease in food intake (a 5% decrease over the 3-mo period of weight loss) was partially responsible for the reduction in body weight. Interestingly, GSK232802A was most effective in causing weight loss in the heaviest individuals, those with the greatest adiposity. This is likely because the individuals with the most adipose tissue were the most sedentary individuals in this study, and GSK232802A rapidly increased physical activity of these animals. The results show that, as in nonprimate species, GSK232802A causes weight loss in primates. This finding supports epidemiological studies showing that HRT decreases postmenopausal weight loss in primates. This finding supports epidemiological studies showing that HRT decreases postmenopausal weight loss in primates.

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**Table 1. Summary table**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin, ng/ml</td>
<td>5.48 ± 1.18</td>
<td>4.21 ± 0.61</td>
<td>5.12 ± 1.03</td>
</tr>
<tr>
<td>T₃, ng/ml</td>
<td>2.27 ± 0.15</td>
<td>2.85 ± 0.23*</td>
<td>2.10 ± 0.09#</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>133.5 ± 10.5</td>
<td>77.4 ± 5.0*</td>
<td>162.8 ± 9.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. T₃, triiodothyronine; ALP, alkaline phosphatase. *Difference from baseline levels; #difference from levels during the treatment period.
The finding that GSK232802A suppresses food intake is consistent with other studies in ovariectomized nonhuman primates (7, 24, 43, 44) and rats (6, 75, 81) indicating that estrogen reduces food intake to the level of ovary-intact controls. In this study, GSK232802A decreased food intake during the 1st mo of treatment. Other studies in ovariectomized monkeys report a similar time course (1–4 wk) (7, 24, 43, 44). In rodents, estrogen has been reported to suppress food intake within 1 day to 2 wk after the initiation of treatment (2, 80, 92) and that estrogen treatment increases activity to preovariectomy levels within 1–12 days of treatment initiation (3, 23, 32, 67). The similar time course of estrogen action suggests that the increase

![Fig. 3](http://ajpendo.physiology.org/)

Fig. 3. A: food intake decreased over the course of the study ($F_{3,43} = 8.6, P < 0.0001$). Food intake was lower than baseline levels during the 1st ($P = 0.04$), 2nd ($P = 0.04$), and 3rd mo ($P = 0.045$) of treatment, was higher than baseline levels during the 1st mo of the recovery period ($P = 0.03$), and then was not different from baseline levels during the 2nd mo of recovery ($P = 0.53$). B: the decrease in food intake correlated with %weight loss ($r = 0.52, P = 0.03$).

![Fig. 4](http://ajpendo.physiology.org/)

Fig. 4. A: there was no difference in the metabolic rate at any time of day between the baseline, treatment, and recovery periods ($F_{3,34} = 0.551, P = 0.58$). B: basal metabolic rate correlated with weight loss ($r = -0.55, P = 0.02$).

 gain (1, 28, 29, 47) and clinical studies finding that HRT causes weight loss in obese postmenopausal women (20, 68).

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Individual data points for each monkey in the study in the scatter plots.

GSK232802A increased physical activity level, and this effect was greatest in the most sedentary monkeys. This finding is consistent with results of rodent studies showing that ovariectomy reduces physical activity (2, 80, 92) and that estrogen treatment increases activity to preovariectomy levels (73, 92). Additional evidence that estrogen increases physical activity comes from rodent studies that report that wheel running increases at the time of estrus (high estrogen) (38, 106). Also, female rats are more active than male rats, and transplanting ovaries into male rats raises their activity level to that typical of a female rat (99). Further support comes from studies showing that estrogen knockout mice have lower levels of physical activity than wild-type mice (42, 61). This is the first report that GSK232802A increases activity in a primate species and suggests that HRT treatment in women may decrease body weight in part by increasing activity. This hypothesis deserves further study, which will be facilitated by the availability of small three-way accelerometers for reliable, continuous activity measurement in humans (17, 59, 71). Physical activity level is an important predictor of adult weight gain in primates, with active individuals gaining less weight than sedentary individuals (90). Thus, GSK232802A will not only promote weight loss but will also help to combat future weight gain over adulthood. Also, in primates, weight loss due to a reduction in food intake is normally accompanied by a compensatory decrease in physical activity and energy expenditure (88), and thus GSK232802A counteracted the compensatory decrease in energy expenditure in response to weight loss and elevated physical activity above baseline levels.

In this study, GSK232802A increased the physical activity of the most sedentary individuals within the 1st mo of treatment, and their activity remained elevated during the subsequent 2 mo of treatment and throughout the recovery period. In rodents, activity decreases within 1–9 days of ovariectomy, and estrogen treatment increases activity to postovariectomy levels within 1–12 days of treatment initiation (3, 23, 32, 67). The similar time course of estrogen action suggests that the increase...
in activity in primates and rodents has a similar underlying mechanism. In this study, plasma T₃ levels increased during GSK232802A treatment and may underlie the increase in activity. T₃ treatment has been shown to increase activity in rats (51), and men with high T₃ levels are reported to be more active than men with lower T₃ levels (72). Also, individuals with elevated T₃ are hyperactive (101). However, in both human studies (72, 101) and the current study, it cannot be determined whether the increase in T₃ caused the increase in activity or whether the metabolic demand caused by increased physical activity led to an increase in T₃. Moreover, estrogen treatment has been documented to act on the corticollimbic circuits to increase social behavior in nonhuman primates (8, 77); thus, GSK232802A may increase physical activity by increasing social behaviors, although in the current study monkeys were housed individually, so an increase in social behavior could not be assessed.

It is noteworthy that the fattest monkeys lost the most weight during GSK232802A treatment. This finding is consistent with results of a clinical study that found that HRT caused significant weight loss in the fattest individuals (68) and our recent study that HRT caused weight loss in the fattest premenopausal monkeys (24). Also, Chmoulovskiy et al. (20) found that HRT caused weight loss in obese postmenopausal women. Moreover, the majority of studies of diet-induced weight loss show that obese individuals lose more weight than lean individuals (95). We did not observe a higher level of circulating estrogen in the heaviest monkeys prior to GSK232802A treatment, and plasma estrogen level was not correlated with body weight ($r = -0.19$, $P = 0.46$). Thus, we hypothesize that the leaner monkeys lost less weight in response to GSK232802A treatment since the compensatory mechanisms used to defend body weight were more powerful in these animals. Specifically, they exhibited a larger compensatory decrease in energy expenditure in response to weight loss similar to the decrease in activity we documented previously in female rhesus macaques in response to diet-induced weight loss (88).

The present study is the first to report that GSK232802A preferentially increases activity of the most sedentary individuals. This is likely because studies looking at the effect of HRT on postmenopausal women or nonhuman primates have not measured activity. Our findings suggest that HRT will be most effective in causing weight loss in sedentary, obese postmenopausal women. It will be important to follow up these findings by measuring changes in physical activity by postmenopausal women taking HRT.

The nonsteroidal SERM utilized in this study, GSK232802A, binds with equal affinity to both the α- and β-estrogen receptors (GlaxoSmithKline; Cameron JL, unpublished data). Although binding affinity for GSK232802A in rhesus monkeys was not measured, the nonhuman primate ER has high sequence homology to the human ER; thus, it is likely that GSK232802A has high binding affinity in nonhuman primates. It is well documented that estrogen and other SERMs decrease plasma LH and FSH in women and nonhuman primates (19, 30, 46, 69, 103). Thus, the finding that GSK232802A treatment suppressed plasma LH and FSH is consistent with the estrogenic action of this compound.

ALP is considered a marker of bone remodeling (60, 100) and a high correlation exists between bone-specific and total ALP (93). In this study, ALP decreased with GSK232802A treatment, suggesting that GSK232802A therapy may have decreased bone resorption. Because ALP levels are closely associated with liver function and have been shown to decrease in response to weight loss (64), it is likely that improved liver function also contributed to this change. Similar findings have been reported in monkeys and in postmenopausal women treated with estrogen or various SERMs (15, 27, 49, 55). It is
well documented that treating postmenopausal women or monkeys with HRT increases bone mineral density (27, 29, 40, 41, 49, 62). However, an increase in bone mineral density is not usually detected until after 1 yr of HRT, and studies examining change in bone mineral density after 6 mo of HRT do not detect an effect (29, 62). Thus, it is not surprising that an increase in bone mineral density was not detected after 3 mo of treatment.

In summary, this study showed that GSK232802A, a non-steroidal SERM, decreases body weight and body fat in primates, similar to the effects of estrogen in rodents. Weight loss was associated with both a reduction in food intake and an increase in physical activity level. The latter effect was particularly marked in the fattest, most sedentary monkeys. In this study, ALP, a metabolic marker associated with bone resorption, was decreased during GSK232802A treatment. In conclusion, this study suggests that GSK232802A treatment of postmenopausal women will reduce body weight and adiposity while at the same time have beneficial effects on bone mineral density.

DISCLOSURES

J. Shearin works as a staff scientist for GlaxoSmithKline, which is the company that has made GSK232802A, the compound tested in this study. Dr. Shearin was the company liaison for this study, but all aspects of the study were performed separate from Dr. Shearin’s influence at the ONPRC.

AUTHOR CONTRIBUTIONS

E.L.S., F.H.K., and J.L.C. performed the experiments; E.L.S. and J.L.C. analyzed the data; E.L.S. and J.L.C. interpreted the results of the experiments; E.L.S. and J.L.C. prepared the figures; E.L.S. and J.L.C. drafted the manuscript; E.L.S., J.S., F.H.K., and J.L.C. edited and revised the manuscript; E.L.S., I.S., and J.L.C. approved the final version of the manuscript; J.S. and J.L.C. did the conception and design of the research.

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