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Synergistic attenuation of obesity by Y2- and Y4-receptor double knockout in *ob/ob* mice

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Abstract

Objective: Neuropeptide Y regulates numerous processes including food intake, body composition, and reproduction by at least five different Y receptors. We previously demonstrated a synergistic interaction between Y2 and Y4 receptors in reducing adiposity in chow- or fat-fed Y2Y4-receptor double-knockout mice. In the present study, we investigated whether this synergy could reduce the massive obesity of leptin-deficient *ob/ob* mice.

Methods: Mice with germline deletions of Y2 and Y4 receptors were crossed onto the *ob/ob* strain. Body weight was measured weekly until 15–18 wk of age before decapitation for collection of trunk blood and tissues.

Results: Male and female Y24ob triple mutants showed highly significant reductions in body weight and white adipose tissue mass compared with *ob/ob* mice. This reduction in body weight was not evident in Y2ob or Y4ob double mutants, and the effect on adiposity was significantly greater than that seen in Y2ob or Y4ob mice. These changes were associated with significant attenuation of the increased brown adipose tissue mass and small intestinal hypertrophy seen in *ob/ob* mice and with normalization of the low circulating free thyroxine concentrations seen in female *ob/ob* mice and the high circulating corticosterone concentrations seen in male *ob/ob* mice.

Conclusion: These data reveal a synergistic interaction between Y2 and Y4 receptors in attenuating the massive obesity of *ob/ob* mice, possibly mediated by stimulation of thyroid function and inhibition of intestinal nutrient absorption. Dual pharmacologic antagonism of Y2 and Y4 receptors could help people to attain and maintain a healthy weight.

Keywords: Neuropeptide Y; Adiposity; Intestinal weight; Thyroid hormones; Corticosterone; Femoral bone mineral density; Femoral bone mineral content

Introduction

Neuropeptide Y (NPY) regulates numerous processes including food intake, energy expenditure, fuel partitioning, reproduction, and growth [1–5]. These effects are mediated by at least five different Y receptors whose specific functions and interactions are not yet fully understood. The Y2 and Y4 receptors have attracted increasing attention in recent years as potential targets for antiobesity treatments. This is partly due to reports that other members of the NPY family, the gut hormones peptide YY and pancreatic polypeptide, have been shown to suppress appetite, primarily by stimulating the Y2 and Y4 receptors, respectively [6,7].

We previously demonstrated a synergistic interaction between Y2 and Y4 receptors in regulating adiposity and bone mass, where Y2Y4-receptor double-knockout mice had a more pronounced lean phenotype and enhanced osteoblastic activity than that observed in Y2- or Y4-receptor

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single-knockout mice [8]. The reduction in adiposity in Y2Y4-receptor double-knockout mice occurred despite no change in physical activity. Deletion of the Y2 and Y4 receptors also protected against diet-induced obesity and this synergy was strong enough to counteract the obesogenic effect of Y1-receptor deficiency [9]. Y2Y4 knockout mice demonstrated improved glucose tolerance on a high-fat diet compared with wild-type mice [9]. Interestingly, they also showed increased fecal levels of free fatty acids associated with reduced bile acid pool and changes in intestinal morphology, suggesting impairment in the absorption of digested lipids [9]. However, it is likely that changes in the expression of pro-opiomelanocortin (POMC) contribute at least in part to the lack of obesity in these mice. Although high-fat feeding in wild-type mice results in decreased expression of NPY and POMC in the arcuate nucleus, these changes are absent in Y2Y4 double-knockout mice [9]. A protective role for increased POMC expression against diet-induced obesity has also been shown by others [10], and decreases in POMC signaling are seen in genetically obese *ob/ob* and *db/db* mice [11].

Leptin-deficient, genetically obese *ob/ob* mice show an obese phenotype with chronically elevated hypothalamic NPY levels due to the lack of leptin's inhibitory action on NPY expression [12]. Deleting the Y2 [13] but not the Y4 [14] receptor has been shown to partially attenuate this phenotype. Body weight, food intake, low testosterone levels, and infertility of *ob/ob* mice were unaltered by deletion of the Y2 receptor [13]. However, Y2-receptor deletion attenuated the adiposity, hyperinsulinemia, hyperglycemia, low circulating insulin-like growth factor-1 (IGF-1) levels, lean tissue mass, and increased hypothalamo-pituitary-adrenal axis activity of *ob/ob* mice [13]. In addition, although Y2ob mice had elevated NPY expression similar to that of *ob/ob* mice, POMC expression in the arcuate nucleus was significantly increased compared with *ob/ob* mice, consistent with the attenuated adiposity [13]. In contrast, deletion of the Y4 receptor on the *ob/ob* background rescued the infertility of *ob/ob* mice, with no effect on fat mass, insulinemia, or glycemia [14].

Our findings with Y2Y4 double-knockout mice under lean and diet-induced obesity conditions suggest that the dual antagonism of Y2 and Y4 receptors would provide the greatest antiobesity benefits in genetic obesity. Combined with the fact that Y2-receptor deletion attenuated different aspects of the *ob/ob* phenotype from Y4-receptor deletion, we propose that dual Y2- and Y4-receptor deletion would be able to reduce the phenotype of genetically obese *ob/ob* mice to a greater extent that deletion of any one Y receptor. If true, this could have a great effect on the development of antiobesity treatments. To test this hypothesis, we generated *ob/ob* mice that were deficient in the Y2 and Y4 receptors (Y24ob mice) and analyzed the magnitude of the obese phenotype compared with *ob/ob* mice.

In addition, it is now well established that leptin can markedly influence the regulation of bone mass with differing effects on cortical versus cancellous bone [15]. Although leptin deficiency in *ob/ob* mice results in increased cancellous bone volume, it reduces cortical bone mass as evidenced by reduced total body bone mineral density, reduced long bone mineral content, cortical area, and before cortical area. Therefore, combined with the fact that we previously reported a synergistic interaction between the Y2 and Y4 receptors in the regulation of bone volume [8], we investigated the bone phenotype of the Y24ob mice.

Materials and methods

Animals

Generation of Y2-, Y4-, and Y2- and Y4-receptor double-knockout mice has been published previously [8]. These mice were crossed with male and female heterozygous (*OB/ob*) mice on the same mixed C57BL/6-129/SvJ background to obtain $Y2^{-/-}$*ob/ob* and $Y4^{-/-}$*ob/ob* mice as previously described [13,14]. Triple heterozygous ($Y2^{+/-}Y4^{+/-}$*OB/ob*) animals were crossed again to eventually obtain $Y2^{-/-}Y4^{-/-}$*OB/ob* animals, which were then bred to obtain triple knockouts. The *ob* genotype was determined by restriction fragment-length polymorphism analysis as previously described [13].

All research and animal care procedures were approved by the Garvan Institute/St. Vincent's Hospital animal ethics committee. Mice were housed under conditions of controlled temperature (22°C) and illumination (12-h light cycle, lights on at 0700 h). All mice were fed a normal chow diet ad libitum (6% calories from fat, 21% calories from protein, 71% calories from carbohydrates, 2.6 kcal/g; Gordon's Speciality Stock Feeds, Yanderra, NSW, Australia). Body weight was measured weekly from 4–6 wk of age onward.

Tissue collection and analysis

At 15–18 wk of age, animals were sacrificed by cervical dislocation for the collection of trunk blood between 1100 and 1600 h. Brains were immediately removed and frozen on dry ice. White adipose tissue (WAT) deposits (right inguinal, right epididymal or right periovarian, right retroperitoneal and mesenteric) and the interscapular brown adipose tissue (BAT) were dissected out and weighed. The small intestine was excised, its length measured, then flushed with isotonic saline, blotted on paper towels, and then weighed with other internal organs.

Bone densitometry

Whole femoral bone mineral content and bone mineral density were measured in excised left femora using a dedicated mouse dual X-ray absorptiometer (Lunar Piximus II, GE Medical Systems, Madison, WI, USA). Femora were scanned with tibiae attached and the knee joint in flexion to 90 degrees, to ensure consistent placement and scanning of the sagittal profile.

Serum analyses

Serum hormone levels were determined with commercial radioimmunoassay kits from ICN Biomedicals (Costa Mesa, CA, USA; corticosterone, free thyroxine [T_4], testosterone) and Bioclone Australia (Marrickville, Australia; IGF-1).

Statistical analyses

All data are expressed as mean ± SEM. Differences among groups of mice were assessed by analysis of variance or repeated measures analysis of variance, followed by Fisher's post hoc comparisons if appropriate (StatView 4.5, Abacus Concepts Inc., Berkeley, CA, USA). Statistical significance was defined as $P < 0.05$.

Results

Reduced body weight and adiposity in Y24ob mice

The combination of Y2- and Y4-receptor deficiency had a strong impact on the body weight and adiposity of *ob/ob* mice, as shown in Figure 1. Despite a significantly greater body weight at 4 wk of age, Y24ob mice of both sexes demonstrated a slower rate of body weight increase than *ob/ob* mice or the double-mutant Y2ob and Y4ob animals (Fig. 1A). Consistent with their lower body weight, male and female Y24ob mice exhibited significant reductions in the sum of WAT mass compared with *ob/ob* mice (Fig. 1B). This reduction was even greater than that observed when only the Y2 receptor was deleted on the *ob/ob* background and was also evident when WAT mass was expressed as a percentage of body weight (male wild-type 2.00 ± 0.10; male *ob/ob* 8.14 ± 0.31, $P <$ 0.001 versus wild-type mice; male Y24ob 6.61 ± 0.38, $P <$ 0.001 versus wild-type mice, $P < 0.001$ versus *ob/ob* mice; female wild-type 2.30 ± 0.20; female *ob/ob* 9.31 ± 0.21, $P <$ 0.001 versus wild-type mice; female Y24ob 8.07 ± 0.32, $P <$ 0.001 versus wild-type mice $P < 0.01$ versus *ob/ob* mice; data are means ± SEMs of ≥10 male and ≥5 female mice per group). In the individual WAT depots, the decrease in weight was more marked in the epididymal or periovarian and mesenteric regions and the retroperitoneal region in males and the inguinal region in females when expressed as absolute weight (Fig. 1C) and as percentage of body weight (data not shown).

Reduced BAT weight and normal free T_4 levels in Y24ob mice

The lower body weight of the Y24ob triple mutants could be due to higher energy expenditure due to increased thermogenesis as indicated by significantly lower BAT mass compared with *ob/ob* mice (Fig. 2A). As an index of hypothalamo-pituitary-thyroid function, an important determinant of resting metabolic rate [16], serum free T_4 levels were measured. Interestingly, female *ob/ob* mice had significantly lower levels of serum free T_4 than their wild-type counterparts, and this effect of leptin deficiency was normalized with deletion of Y2 and Y4 receptors (Table 1). This corresponds with the differences observed in BAT mass. However, no difference in free T_4 levels was observed among males of any genotype.

Y2 and Y4 receptor deletion reduced intestinal and liver hypertrophy of ob/ob mice

The intestinal hypertrophy observed in *ob/ob* mice was normalized in Y24ob mice as shown by intestinal weight (Fig. 2B) and intestinal length (Fig. 2C). This change in Y24ob mice may also have contributed to their leaner phenotype because intestinal mass has been positively correlated with nutrient absorptive capacity [17]. In addition, *ob/ob* mice have significantly larger livers than wild-type mice. Male and female Y24ob animals had liver weights significantly lower than those in *ob/ob* mice, albeit still higher than wild-type levels (Table 1). This effect was still apparent when liver weights were expressed as a percentage of body weight (data not shown). Kidney weights were also normalized to wild-type levels in Y24ob mice, although their pancreas, heart, and stomach weights were no different from *ob/ob* mice when expressed as absolute weight or relative to body weight (Table 1, data not shown).

Effect of Y2- and Y4-receptor deletion on hypercorticosteronemia of ob/ob mice

Male *ob/ob* mice demonstrate significant hypercorticosteronemia and it has been shown that Y2- or Y4-receptor deficiency separately can normalize serum levels of corticosterone to those of male wild-type mice [13,14]. We observed that deleting Y2 and Y4 receptors also normalizes serum levels of corticosterone in male *ob/ob* mice (Table 1). No differences in serum corticosterone levels were observed among female mice of any genotype (Table 1).

No effect of Y2- and Y4-receptor deletion on serum levels of IGF-1 and testosterone in ob/ob mice

Insulin-like growth factor-1 is the main mediator of the growth effects of growth hormone and often corresponds with changes in the amount of lean body mass [18]. We observed no significant differences in the serum levels of IGF-1 in any of our groups, although *ob/ob* and Y24ob animals of both genders tended to have lower serum IGF-1 levels than lean wild types (Table 1). Because Y4-receptor knockout rescues fertility in *ob/ob* mice with an associated increase in circulating testosterone levels in males [14], we investigated the testosterone levels of our Y24ob triple mutant males. Intriguingly, this effect of Y4-receptor deficiency was abolished because Y24ob mice had very low serum testosterone levels

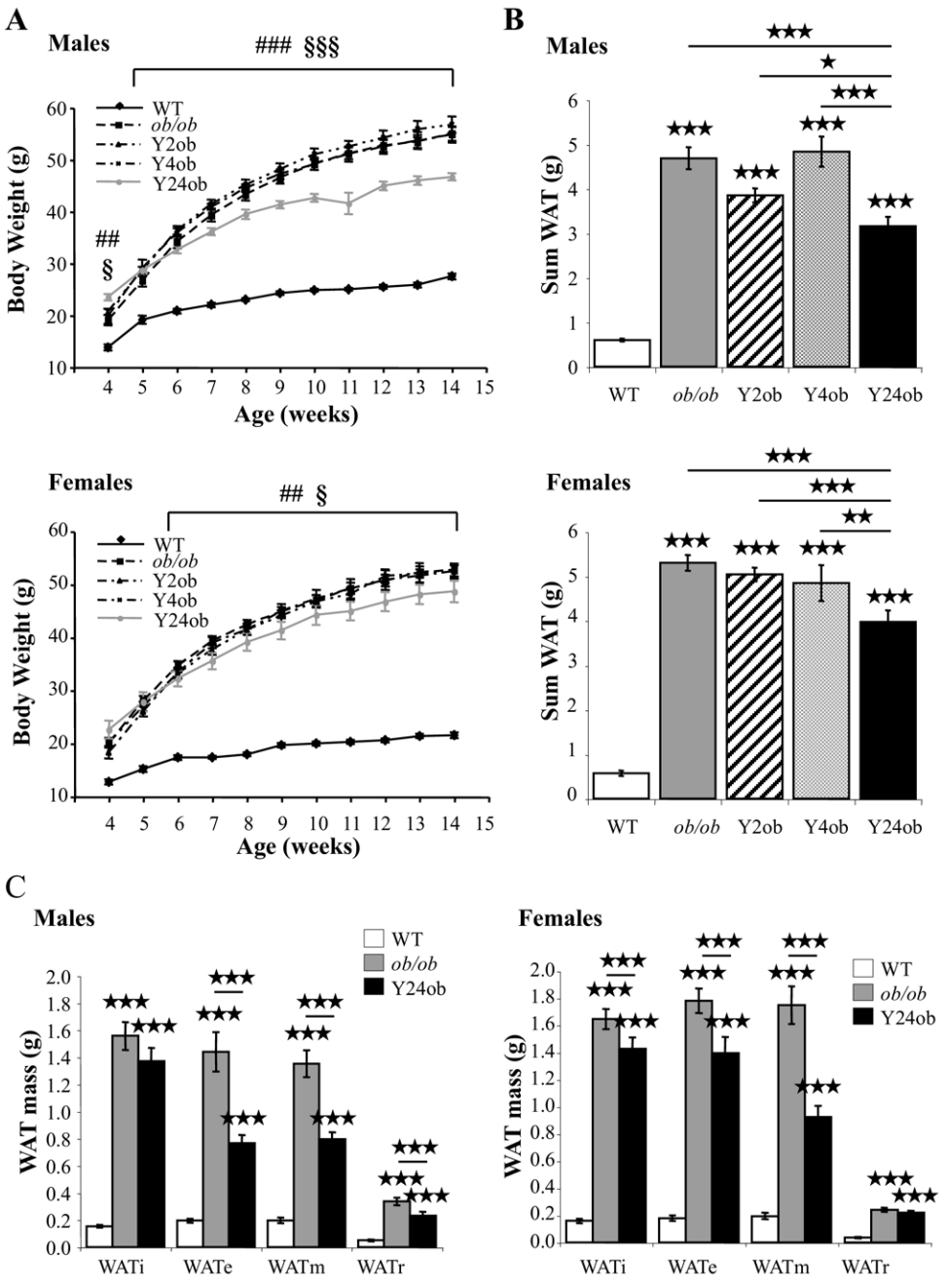

Fig. 1. Reduced body weight and adiposity in Y24ob mice. (A) Body weight curves for male and female mice demonstrate reduced body weight over time in Y24ob mice versus *ob/ob*, Y2ob, and Y4ob mice. (B) These animals also show a reduction in total WAT mass, (C) with the weight contribution of individual WAT depots shown. Data are means ± SEMs of ≥10 male and ≥5 female mice per group. $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ for Y24ob versus *ob/ob*. $^{\S}P < 0.05$, $^{\S\S\S}P < 0.001$ for Y24ob versus Y2ob and Y4ob. $^{\star}P < 0.05$, $^{\star\star}P < 0.01$, $^{\star\star\star}P < 0.001$ versus WT or as indicated by horizontal bars. WAT, white adipose tissue; WATe, epididymal or periovarian white adipose tissue; WATi, inguinal white adipose tissue; WATm, mesenteric white adipose tissue; WATr, retroperitoneal white adipose tissue; WT, wild type.

similar to those of obese *ob/ob* mice (Table 1). Other markers of rescued fertility in Y4ob male mice were normalized testes and seminal vesicle weights [14]. Interestingly, Y24ob mice demonstrated normalized testes weights, although seminal vesicle weights remained low at levels similar to those of *ob/ob* mice, as shown in Table 1.

Combined Y2- and Y4-receptor deletion enhances cortical bone responses to leptin deficiency

The potential for leptin-mediated responses in the $Y2^{-/-}Y4^{-/-}$ mice was examined after crossing of these mice onto the leptin-deficient *ob/ob* background. In cortical

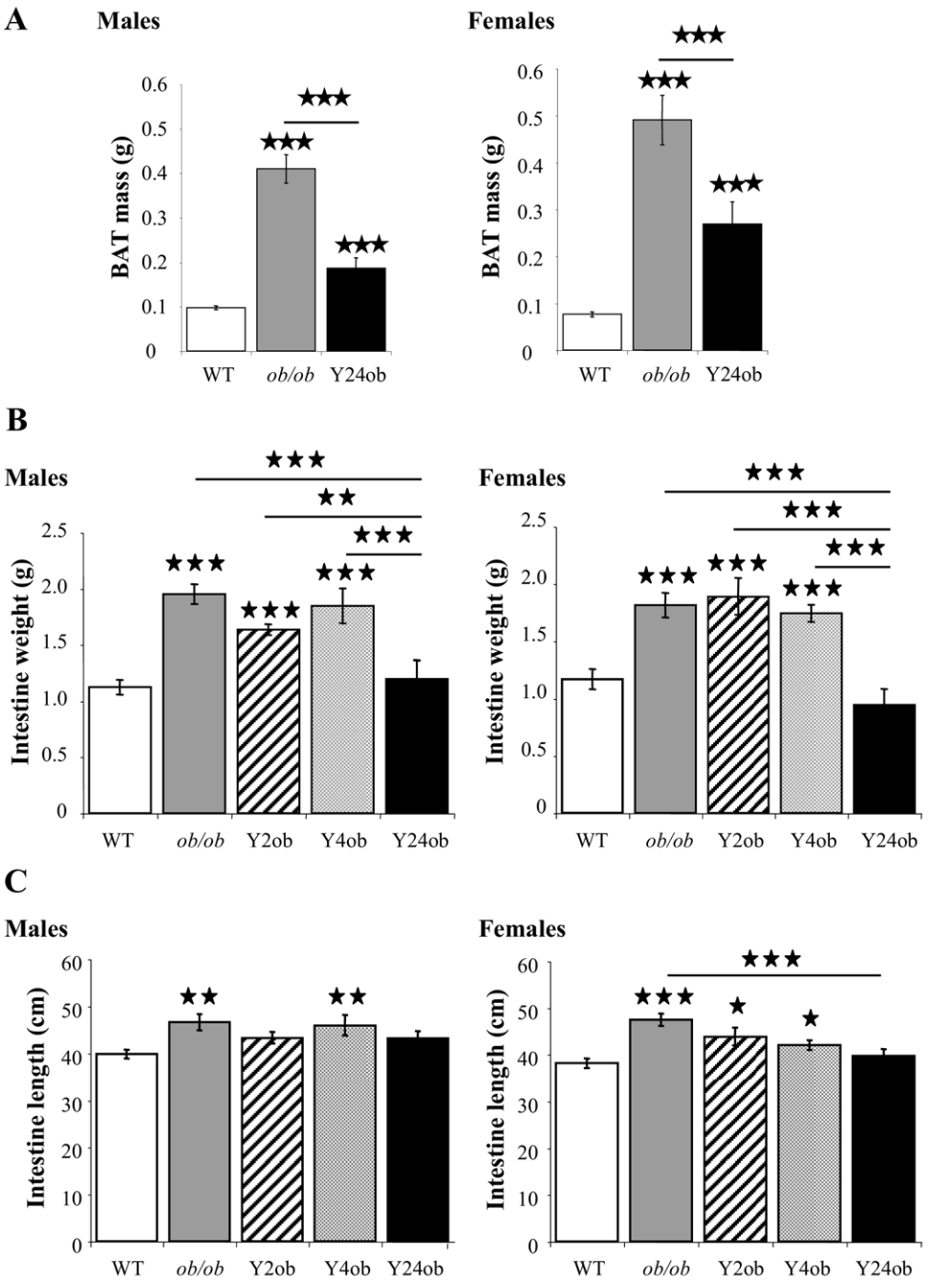

Fig. 2. Effect of combined Y2- and Y4-receptor deficiency on BAT mass and intestinal weight and length in *ob/ob* mice. (A) Male and female Y24ob mice have a marked reduction in BAT mass compared with *ob/ob* mice. Intestinal weight (B) and length (C) are normalized to WT levels in Y24ob animals. Data are means ± SEMs of ≥6 male and ≥4 female mice per group. $^{\star}P < 0.05$, $^{\star\star}P < 0.01$, $^{\star\star\star}P < 0.001$ versus WT or as indicated by horizontal bars. BAT, brown adipose tissue; WT, wild-type.

bone, Y24ob mice displayed a genotype-specific response. Femoral bone mass, known to be reduced in ob/ob mice [15,19], was further reduced after the additional loss of Y2 and Y4 signaling (Fig. 3). Femoral bone mineral density and bone mineral content were significantly reduced in both sexes of Y24ob mice compared with the wild type, even in the absence of correction for body weight. Critically, this reduction was also evident compared with *ob/ob* mice, although this failed to be significant in bone mineral content in Y24ob females ($P = 0.06$). This additional reduction occurred despite no consistent effect of single Y2- or Y4-receptor deletion on the *ob/ob* background, suggesting that even when leptin levels were constant $Y2^{-/-}Y4^{-/-}$ mice responded more markedly than other genotypes.

Table 1
Comparison of serum parameters and organ weights in Y24ob and control wild-type and *ob/ob* mice*

	Wild type	*ob/ob*	Y24ob
Males			
Corticosterone (ng/mL)	78.58 ± 16.18	472.41 ± 119.66[§]	124.47 ± 35.64[¶]
Free T_4 (pmol/L)	15.51 ± 1.55	15.81 ± 2.79	15.34 ± 2.06
IGF-1 (ng/mL)	374.45 ± 55.13	293.39 ± 26.15	274.90 ± 40.27
Testosterone (ng/mL)	11.15 ± 4.39	2.13 ± 0.74[‡]	1.14 ± 0.47[‡]
Liver (g)	1.29 ± 0.03	4.63 ± 0.34[§]	3.35 ± 0.18[§#]
Kidney (g)	0.34 ± 0.03	0.44 ± 0.04[†]	0.26 ± 0.01[#]
Pancreas (g)	0.33 ± 0.02	0.41 ± 0.03[‡]	0.40 ± 0.02[†]
Testes (g)	0.240 ± 0.009	0.202 ± 0.011[†]	0.247 ± 0.004[‖]
Seminal vesicle (g)	0.35 ± 0.03	0.18 ± 0.02[§]	0.20 ± 0.01[§]
Females			
Corticosterone (ng/mL)	155.47 ± 16.60	162.06 ± 30.19	196.25 ± 25.72
Free T_4 (pmol/L)	21.09 ± 2.60	10.65 ± 1.85[‡]	19.41 ± 3.37[‖]
IGF-1 (ng/mL)	335.74 ± 26.17	271.58 ± 46.71	223.93 ± 33.80
Liver (g)	1.06 ± 0.03	4.11 ± 0.43[§]	2.34 ± 0.23[§#]
Kidney (g)	0.22 ± 0.03	0.39 ± 0.04[§]	0.18 ± 0.02[#]
Pancreas (g)	0.26 ± 0.01	0.35 ± 0.02[‡]	0.36 ± 0.04[‡]

IGF-1, insulin-like growth factor-1; T_4, thyroxine
* Data are means ± SEMs of at least six male and at least five female mice per group.
[†] $P < 0.05$ versus wild-type mice.
[‡] $P < 0.01$ versus wild-type mice.
[§] $P < 0.001$ versus wild-type mice.
[‖] $P < 0.05$ versus *ob/ob* mice.
[¶] $P < 0.01$ versus *ob/ob* mice.
[#] $P < 0.001$ versus *ob/ob* mice.

Discussion

This study shows that dual ablation of Y2 and Y4 receptors results in synergistic reductions in body weight and WAT mass in genetically obese leptin-deficient *ob/ob* mice of both genders. Whereas Y2- and Y4-receptor dual ablation has been shown to synergistically reduce the adiposity of mice on a lean background [8] and to protect against obesity due to a high-fat diet or Y1-receptor deficiency [9], this study demonstrates the strength of the antiobesity effect of Y2Y4-receptor double ablation in significantly reducing the massive obesity of *ob/ob* mice. Other studies have shown that deletion of individual Y1, Y2, or Y4 but not Y5 [20] receptors can significantly reduce the body weight or adiposity of *ob/ob* mice [13,14,21,22], but no individual Y-receptor knockout has been shown to reduce body weight or WAT mass to such a great extent and so consistently in males and females as Y2 and Y4 dual knockout.

Attenuation of obesity in *ob/ob* mice by double Y2Y4-receptor knockout may be related to 1) reduced ingestion or absorption of nutrients and/or 2) increased energy expenditure. Evidence suggests that both pathways contribute to the leaner phenotype of Y24ob animals. Y2Y4-receptor ablation resulted in synergistic reductions in intestinal length and/or weight in *ob/ob* animals. This finding extends previous work to show that not only on a lean background [9] but also on a genetically obese background, Y2 and Y4 receptors interact in the regulation of gut function and morphology. The markedly reduced gut size in Y24ob mice may have contributed to their leaner phenotype by reducing nutrient absorption, because increases in intestinal mass in *ob/ob* mice correlate with increased absorption of all nutrient groups [17]. In addition to possibly reduced nutrient absorption, reduced food intake may have contributed to the lean phenotype of Y24ob mice. Indeed, whereas individual deletion of Y2 receptors does not have any significant effect on the hyperphagia of *ob/ob* mice [13,22], and Y4-receptor deletion reduces the food intake of male but not of female *ob/ob* mice [14], double deletion of Y2 and Y4 receptors in lean mice results in marked and significant reductions in chow or high-fat food intake [9].

The synergistic effects of Y2- and Y4-receptor deletion to reduce body weight and adiposity in *ob/ob* mice were associated with marked and significant reductions in BAT mass. Because reduced BAT mass and increased BAT expression of uncoupling protein-1 are frequently associated in conditions of increased energy expenditure, it is possible that increases in energy expenditure may have contributed to the antiobesity effects of Y2- and Y4-receptor dual deletion. In keeping with this, male and female Y24ob mice demonstrated circulating free T_4 levels no different from those of lean wild-type mice, and in female mice this represents a significant increase in the low free T_4 levels of *ob/ob* mice. Because free T_4 levels are an indicator of activity of the hypothalamo-pituitary-thyroid axis, an important regulator of thermogenesis and metabolic rate [16], it is possible that Y2Y4-receptor knockout reduced adiposity in *ob/ob* mice by increased

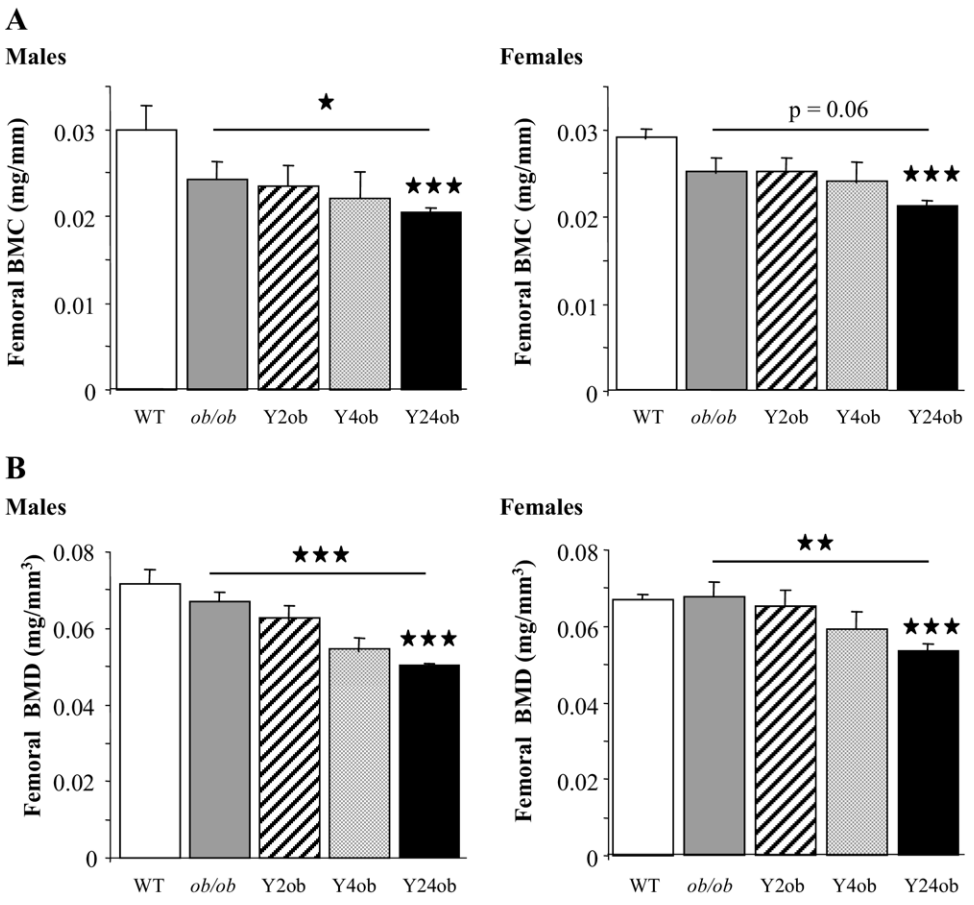

Fig. 3. Synergistic effect of combined Y2- and Y4-receptor deficiency on femoral BMC and BMD in *ob/ob* mice. Femoral BMC (A) and BMD (B) are significantly reduced in male Y24ob mice compared with *ob/ob* and WT mice, with a similar trend observed in female Y24ob mice. Data are means ± SEMs of ≥6 male and ≥4 female mice per group. $^{\star}P < 0.05$, $^{\star\star}P < 0.01$, $^{\star\star\star}P < 0.001$ versus WT or as indicated by horizontal bars. BMC, bone mineral content; BMD, bone mineral density; WT, wild-type.

thyroid function and metabolic rate. This effect is probably mediated within the hypothalamus by Y4 but not Y2 receptors, because male Y4- or Y2Y4-receptor knockout mice on a lean background show significant increases in expression of thyrotropin-releasing hormone in the hypothalamic paraventricular nucleus, whereas male Y2-receptor knockout mice show marked decreases in paraventricular nuclear thyrotropin-releasing hormone mRNA levels [8,13].

We previously reported that the synergy between Y2 and Y4 receptors in reducing adiposity may be related to differential effects on the hypothalamo-pituitary-somatotropic and -gonadotropic axes [23,24], both of which are inhibited by NPY [3]. In two conditions of elevated hypothalamic NPY expression (24-h fasting and leptin-deficient obesity) [12], germline or hypothalamus-specific Y2- but not Y4-receptor deletion prevents the associated decrease in activity of the somatotropic axis, whereas Y4- but not Y2-receptor deletion prevents the associated decrease in activity of the gonadotropic axis [13,14,23]. In our Y24ob mice, measurements of circulating IGF-1, the main mediator of the growth-promoting effects of growth hormone [18] and testosterone, do not suggest any increases in the activity of the somatotropic or gonadotropic axes relative to *ob/ob* mice. However, it cannot be excluded that stimulation in the activity of these axes independently of total IGF-1 or total testosterone levels as measured in this study (for instance, changes in the circulating ratio of free to bound hormone) may have contributed to the lean phenotype of Y24ob mice. Indeed, Y2Y4-receptor double deletion normalized the reduced testicular weight of *ob/ob* mice.

Another means by which Y2 and Y4 receptors may interact in the reduction of massive obesity in *ob/ob* mice is by the additive effects mediated in central and peripheral sites. It was recently shown that sympathetically derived NPY acts directly on adipose tissue to promote fat accumulation under stress conditions in a glucocorticoid-dependent pathway, and that this effect is attenuated by pharmacologic antagonism or genetic ablation of Y2 receptors [25]. Therefore, it is possible that in Y24ob mice a lack of Y2 receptors on WAT attenuated these adipogenic effects of NPY. The normalization of circulating corticosterone levels seen in Y24ob mice per se is unlikely to account for their dramatically reduced adiposity, because Y2ob and Y4ob mice also show normalization of corticosterone concentrations [13,14] but only a slight reduction in adiposity. Therefore, with the lack of Y4 receptors in

the brain-promoting activity of the hypothalamo-pituitary-thyroid and -gonadotropic axes as discussed above, combined with the lack of Y2 receptors on adipose tissue inhibiting fat storage by local tissue effects [25], Y2Y4 double knockout mice show a lean phenotype that is likely the result of several different pathways.

In addition to synergistic reductions in body weight and adiposity in Y24ob mice, these animals display an exaggerated loss of cortical bone mass compared with that evident in *ob/ob* mice. This response was specific to leptin-deficient Y2Y4-receptor–deficient mice, because Y2ob and Y4ob mice were similar to *ob/ob* mice with respect to cortical bone mass, indicating a heightening of the normal skeletal response to leptin deficiency.

Conclusion

Deletion of Y2 and Y4 receptors results in synergistic attenuation of the massive obesity of *ob/ob* mice, likely due to a combination of central and peripheral effects. Novel combination weight-loss medications that antagonize Y2 and Y4 receptors could help more people to attain and maintain a healthy body weight.

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