Mechanisms of leptin secretion from white adipocytes

PHILIPPE G. CAMMISOTTO AND LUDWIK J. BUKOWIECKI
Department of Physiology, Faculty of Medicine, Laval University, Quebec, Canada G1K 7P4
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Cammisotto, Philippe G., and Ludwik J. Bukowiecki. Mechanisms of leptin secretion from white adipocytes. Am J Physiol Cell Physiol 283: C244–C250, 2002.—The mechanisms regulating leptin secretion were investigated in isolated rat white adipocytes. Insulin (1–100 nM) linearly stimulated leptin secretion from incubated adipocytes for at least 2 h. The adrenergic agonists norepinephrine, isoproterenol (two nonselective β-agonists), or CL-316243 (potent β3) all inhibited insulin (10 nM)-stimulated leptin release. The inhibitory effects of norepinephrine and isoproterenol could be reversed not only by the nonselective antagonist propranolol but also by the selective antagonists ICI-89406 (β1) or ICI-118551 (β2), the β2-antagonist being less effective than the β1. Insulin-stimulated leptin secretion could also be inhibited by a series of agents increasing intracellular cAMP levels, such as lipolytic hormones (ACTH and thyrotropin-stimulating hormone), various nonhydrolyzable cAMP analogs, pertussis toxin, forskolin, methylxanthines (caffeine, theophylline, IBMX), and specific inhibitors of phosphodiesterase III (imazodan, milrinone, and amrinone). Significantly, antilipolytic agents other than insulin (adenosine, nicotinic acid, acipimox, and orthovanadate) did not mimic the acute stimulatory effects of insulin on leptin secretion under these conditions. We conclude that norepinephrine specifically inhibits insulin-stimulated leptin secretion not only via the low-affinity β3-adrenoceptors but also via the high-affinity β1/β2-adrenoceptors. Moreover, it is suggested that 1) activation of phosphodiesterase III by insulin represents an important metabolic step in stimulation of leptin secretion, and 2) lipolytic hormones competitively counterregulate the stimulatory effects of insulin by activating the adenylate cyclase system.

Lipolytic hormones; phosphodiesterases; β1-, β2-, and β3-adrenoceptors

LEPTIN IS A HORMONE encoded by the ob gene and primarily secreted by white adipocytes (for reviews, see Refs. 1, 13, 14, and 38). It stimulates energy expenditure and inhibits food intake by acting via hypothalamic leptin receptors. The expression of leptin in adipocytes and its plasma concentration are both positively correlated with total adiposity. Therefore, it is generally believed that leptin represents a lipostatic factor contributing to the regulation of body weight via a negative feedback loop (10). In addition to total adiposity, plasma leptin concentrations can be acutely modulated by a variety of physiological conditions (starvation-refeeding and cold exposure) and hormonal factors (insulin, catecholamines, glucocorticoids, thyroid hormones, gonadal steroids, etc.) (26). The observations that starvation decreases both plasma insulin and leptin levels and that obesity is strongly associated with hyperinsulinemia and hyperleptinemia have led many researchers to investigate the effects of insulin on leptin secretion. Although several studies found that insulin stimulates leptin expression and secretion in adipocytes in vitro (3, 6, 11, 15, 30), others found little or no effect of insulin (20, 24, 32). The in vivo effects of insulin on leptinemia are also contradictory; some groups reported that insulin increases plasma leptin levels in rodents or humans (16, 21), whereas others found that insulin does not appear to acutely regulate leptin expression or secretion (8, 36).

In addition to starvation, cold exposure represents another physiological condition known to significantly affect plasma leptin levels, at least in laboratory animals (26). Cold exposure activates the sympathetic nervous system, increases the levels of circulating norepinephrine, and decreases plasma insulin and leptin concentrations (4, 12, 28, 35) as well as leptin gene expression in adipose tissue (34). The effects of cold exposure have been mimicked in vivo by administration of the physiological neurohormone norepinephrine or by treatment with β-agonists in mice (23, 34) and humans (9, 25, 27, 33). However, the nature of the β-adrenoceptor subtypes (β1, β2, and/or β3) mediating the effects of norepinephrine on leptin secretion is still not well understood. Although it has been reported that β3-adrenergic agonists inhibit leptin secretion in vivo and in vitro, at least in rodents (11), few studies have been performed with selective β-antagonists. One study has claimed that the high affinity β1/β2-adrenoceptors play essentially no role in mediating norepinephrine effects on leptin secretion, because it was unaffected by β1/β2-antagonists (11). However, isoproterenol (a nonselective β-adrenergic agonist) acutely decreases the levels of circulating leptin in humans and reduces leptin expression or secretion in cultured adipocytes (9, 27, 30, 33). Because the β3-adrenergic receptor is a low-affinity receptor for β-agonists such as norepinephrine or isoproterenol, these observations suggest that norepinephrine might act, at least
cells were frequency of 150 cycles/min. At the end of incubation, the wise speci
incubated under the same conditions for 2 h (unless other-
bovine serum albumin (KRB 4%). Finally, the cells were
twice with warm (37 °C) KRB containing 4% fatty acid-free
Four times with KRB 1% and preincubated at 37
C for 15
mg/ml collagenase at 37
°
Warner-Lambert. Amrinone and milrinone were obtained
from American Cyanamid. Imazodan was purchased from
Lilly (Toronto, Canada). Insulin (Humulin R) was purchased from Eli
River and were housed in individual cages at 24
°
was partially, via the high-affinity β1/β2-adrenergceptors
Another observation that prompted the present study is that insulin and catecholamines, the principal
hormones acutely regulating energy metabolism, exert antagonistic effects on lipolysis, leptin expression, and
leptin secretion from adipose tissues, suggesting the presence of metabolic interactions between insulin ac-
tivation of phosphodiesterases and the stimulation of the adenylate cyclase system by catecholamines (17,
Thus the sympathetic nervous system (cate-
cholamines) and insulin might play a major role in
controlling leptin metabolism in vivo.
On the basis of these observations, we decided to
investigate the nature of β-adrenergic pathways regu-
lating insulin stimulation of leptin secretion in adipocytes isolated from rat epididymal adipose tissue using
selective β-adrenergic agonists/antagonists, lipolytic
hormones, phosphodiesterase inhibitors, hydrolyzable
and nonhydrolyzable cAMP analogs, and other drugs
known to affect lipolysis or the adenylate cyclase com-
plex.

MATERIALS AND METHODS

Chemicals. Fatty acid-free bovine serum albumin, norepi-
nephrine, isoproterenol, dobutamine, procaterol, propranolol,
cAMP analogs 8-bromo-cAMP (8-Br-cAMP), N6-monobutryl
cAMP (Me-cAMP), and N6-dibutryl cAMP (Db-cAMP),
IBMX, forskolin, pertussis toxin, adrenocorticotropic hor-
mine, thyrotropin-stimulating hormone (TSH), collagenase
(type II, lot 107H8649), caffeine, theophylline, adenosine,
N6-(2-phenylisopropyl)adenosine (PLA), and adenosine
deaminase were all obtained from Sigma Chemical (St.
Louis, MO). Insulin (Humulin R) was purchased from Eli
Lilly (Toronto, Canada). ICI-89406 was a generous gift from
ICI pharmaceuticals. ICI-118551 was purchased from RBI
(Louis, MO). Insulin (Humulin R) was purchased from Eli

Animals. Male Wistar rats were obtained from Charles
River and were housed in individual cages at 24°C with a
12:12-h light-dark cycle. The rats received standard Purina
chow and water ad libitum. The mean body mass of the rats
used in the present experiments was 290 ± 15 g.

Adipocyte isolation. Adipocytes were isolated from epidid-
ymal fat pads by a slight modification of Rodbell's method
(29). Briefly, rats were killed by decapitation, and their
epididymal fat pads were removed and placed in Krebs-
Ringer bicarbonate (KRB) buffer of the following composition
(in mM): 120 NaCl, 4.75 KCl, 2.5 CaCl2, 1.2 KH2PO4, 1.2
MgSO4, 25 NaHCO3, 5.5 glucose, 20 HEPES, and 1% fatty
acid-free bovine serum albumin. 7.4 (KRB 1%). The
minced tissue was incubated in KRB 1% containing 0.5
mg/ml collagenase at 37°C for 15–20 min with a shaking
frequency of 150 cycles/min. At the end of incubation, the
cells were filtered through a 500-µm nylon filter (Nitex) and
diluted with 5 ml of KRB 1%. The floating cells were washed
four times with KRB 1% and preincubated at 37°C for 15 min
in KRB 1% (shaking frequency of 40 cycles/min) and washed
twice with warm (37°C) KRB containing 4% fatty acid-free
bovine serum albumin (KRB 4%). Finally, the cells were
incubated under the same conditions for 2 h (unless other-
wise specified) in the presence of hormones or drugs at a
concentration of 3–5 × 106 cells/ml KRB 4%. The adipocytes
were then allowed to float, and the infranatants were frozen
at −20°C for leptin and glycerol measurements.

Leptin and glycerol assays. Leptin concentrations were
determined by radioimmunoassay using a kit available from
Linco Research (St Charles, MO). Glycerol was measured
using an enzymatic method (37).

Statistics. The data were analyzed using analysis of vari-
ance. Values represent the means ± SE of a number of
individual experiments performed on separate occasions (n),
as indicated in the text. The responsiveness and sensitivity of
adipocytes for the stimulation of leptin secretion or lipolysis
(Ymax and EC50) and the half-effective concentration for inhi-
bition of these parameters (IC50) were determined by com-
puter analysis (SigmaPlot program) of concentration-re-
sponse curves.

RESULTS

Insulin stimulation of leptin secretion. Concentra-
tion-response experiments revealed that insulin ap-
proximately doubled (from 4.1 ± 0.2 to 7.9 ± 0.3 ng
leptin·10−6 cells·2 h−1, P < 0.01) the basal rates of
leptin release from white adipocytes isolated and incu-
bated as described in MATERIALS AND METHODS (Fig. 1).
Insulin acted with an EC50 value of 0.7 nM, which is in the
physiological range of plasma insulin concentra-
tions in the rat. Inulin stimulated leptin secretion in a
linear manner for at least 4 h (Fig. 1, inset). Therefore,
all subsequent incubations were carried out for a 2-h
period.

Inhibition of the stimulatory effects of insulin by
β-adrenergic agonists. Because insulin is a potent an-
tilipolytic hormone, we tested whether lipolytic agents
such as β-adrenergic agonists would reverse the stimu-
latory effects of insulin on leptin release. Adipocytes
Downloaded from http://ajpcell.physiology.org/ by 10.220.33.4 on March 31, 2017
were incubated in the presence of insulin (added at a concentration of 10 nM that induces a near-maximal stimulation of leptin release) (see Fig. 1) and increasing concentrations of \( \beta \)-adrenergic agonists. Extracellular glycerol (an index of lipolysis) and leptin concentrations were measured in parallel in the same cellular preparations (Fig. 2, A and B). Norepinephrine, isoproterenol (two nonselective \( \beta \)-agonists), dobutamine, pro¬
caterol, and CL-316243 (selective \( \beta_1 \)-, \( \beta_2 \)-, and \( \beta_3 \)-agonists, respectively) all inhibited insulin-stimulated leptin secretion with an order of potency (IC\(_{50}\) values: CL-316243 = 10 nM > isoproterenol = 56 nM > norepinephrine = 219 nM > dobutamine = 3 \( \mu \)M > pro¬
caterol = 14 \( \mu \)M) (Fig. 2) that was similar to that by which these agents stimulated lipolysis (EC\(_{50}\) values: CL-316243 = 33 nM > isoproterenol = 47 nM > norepinephrine = 350 nM > dobutamine = 3 \( \mu \)M, pro¬
caterol = 19 \( \mu \)M) (Fig. 2). This provided a first indication that leptin secretion might be metabolically associated with the stimulation of lipolysis via cAMP-depen¬
dendent protein kinases.

Reversal of the inhibitory effects of \( \beta \)-adrenergic agonists on insulin-stimulated leptin secretion by propranolol. To determine whether the inhibitory effects of norepinephrine, isoproterenol, and CL-316243 were reversible, we first tested the effects of propranolol, a potent \( \beta_1 \)/\( \beta_2 \)- and weak \( \beta_3 \)-antagonist. Adipocytes were incubated in the presence of insulin (10 nM), norepinephrine (1 \( \mu \)M), isoproterenol (0.1 \( \mu \)M) or CL-316243 (0.1 \( \mu \)M), and various concentrations of propranolol. The \( \beta \)-agonists were added at concentrations that nearly maximally inhibited insulin-stimulated leptin secretion (see Fig. 2). It can be seen in Fig. 3 that propranolol reversed the effects of norepinephrine and isoproterenol when added at concentrations that were 1–100 times greater than the agonist concentrations. However, propranolol only partially reversed the action of CL-316243, as expected for a weak \( \beta_3 \)-antagonist.

Reversal of the inhibitory effects of norepinephrine on insulin-stimulated leptin secretion by selective \( \beta_1 \)- and \( \beta_2 \)-antagonists. To further assess the contribution of \( \beta_1 \)-, \( \beta_2 \)-, and/or \( \beta_3 \)-adrenoceptors to the inhibitory effects of norepinephrine, adipocytes were incubated in the presence of insulin (10 nM), norepinephrine, and various concentrations of the selective \( \beta_1 \)-antagonist ICI-89406 or \( \beta_2 \)-antagonist ICI-118551 (Fig. 4). Norepinephrine was added at a concentration that nearly...
totally inhibits insulin (10 nM)-stimulated leptin secretion (Fig. 2), whereas ICI-89406 and ICI-118551 were studied at concentrations that were 1–100 times greater than (1–100 μM) than that of norepinephrine (1 μM). Both β-antagonists partially reversed the inhibitory effects of norepinephrine on insulin-stimulated leptin release. However, the β1-antagonist ICI-89406 was more effective than the β2-antagonist ICI-118551. These results indicate that β1- and β2-adrenoceptors mediate norepinephrine action, at least in part. Selective β2-antagonists were not tested because they are not yet available, at least to our knowledge. However, two observations strongly indicate that β2-adrenoceptors also mediate norepinephrine effects: 1) the reversal by β1- and β2-antagonists was only partial (Fig. 4), and 2) the selective β2-agonist CL-316243 effectively inhibited insulin-stimulated leptin secretion (Fig. 2).

Reversal of the inhibitory effects of isoproterenol on insulin-stimulated leptin secretion by selective β1/β2-antagonists. Experiments similar to those described in Fig. 4 were carried out with isoproterenol (Fig. 5). This agent is a potent inhibitor of leptin secretion in humans and acts at much lower concentrations than norepinephrine (Fig. 2). Comparable results to those obtained with norepinephrine (1 μM) (Fig. 4) were obtained with isoproterenol (0.1 μM) but at lower antagonist concentrations (0.1, 1, or 10 μM). The β1/β2-antagonists completely reversed the effects of isoproterenol, as expected from a potent β1/β2-agonist.

Inhibition of the stimulatory effects of insulin by lipolytic hormones, adenylate cyclase activators, methylxanthines, cAMP analogs, and phosphodiesterase inhibitors. The goal of the next experiments was to test whether there is a cause-effect relationship between the stimulation of lipolysis via the adenylate cyclase-phosphodiesterase system and inhibition of extracellular leptin release. If such a relationship exists, then one should expect that all agents stimulating lipolysis (increasing intracellular cAMP levels) would inhibit insulin stimulation of leptin secretion. To test this hypothesis, adipocytes were incubated in the presence of insulin (10 nM) and a variety of agents that increase cAMP levels via different mechanisms (Figs. 6 and 7). In addition to catecholamines and adrenergic agents (Figs. 2), we tested a dozen other agents: 1) lipolytic hormones such as ACTH and TSH, which activate the adenylate cyclase-G protein complex by acting via their specific membrane receptors, 2) the adenylate cyclase activator forskolin, 3) pertussis toxin, which is known to inactivate G protein and promote cAMP increment in fat cells, 4) the phosphodiesterase-hydrolyzable analog 8-Br-cAMP as well as the nonhydrolyzable cAMP analogs MBcAMP and DBcAMP, 5) the methylxanthines caffeine, theophyllin, and IBMX, which inhibit nonspecifically phosphodiesterases, and 6) specific inhibitors of phosphodiesterase III (imazodan, milrinone, and amrinone). Each of these agents was tested at a concentration that maximally stimulates lipolysis and that was determined in preliminary concentration-response experiments. Comparison of Figs. 6A and 7A (lipolysis) with Figs. 6B and 7B (leptin secretion) reveals that all agents that maximally stimulated lipol-
ysis totally inhibited insulin-stimulated leptin secretion. Significantly, the hydrolyzable cAMP analog 8-BrcAMP did not stimulate lipolysis (in the presence of insulin) and did not inhibit leptin secretion. However, the two cAMP analogs that are resistant to phosphodiesterase-dependent hydrolysis, MBcAMP and DBcAMP, both stimulated lipolysis and inhibited leptin secretion. On the whole, these data show that insulin-stimulated leptin secretion can be totally inhibited by lipolytic agents known to increase intracellular cAMP concentration, independently of the mechanisms by which they act.

Effects of adenosine and other antilipolytic agents on insulin-stimulated leptin secretion. We also investigated whether antilipolytic agents other than insulin would mimic its effects on leptin secretion. We tested several insulin mimetics and/or antilipolytic agents acting via different mechanisms on adenylate cyclase: orthovanadate, adenosine, PIA (a nonmetabolizable analog of adenosine), nicotinic acid, and acipimox, a stable analog of nicotinic acid. Sodium orthovanadate is an insulin mimic that stimulates glucose uptake in isolated adipocytes and inhibits lipolysis, presumably by the inhibiting protein phosphotyrosine phosphatases (18). Adenosine, PIA, nicotinic acid, and acipimox are all antilipolytic G_{i}-coupled adenylate cyclase inhibitory agonists (5, 7, 19). Although all these agents completely inhibited norepinephrine-stimulated lipolysis under the present experimental conditions, none of them mimicked the stimulatory effects of insulin on leptin secretion (not shown), at least at short term (within 2 h of incubation). This suggests that an inhibition of lipolysis consequent to an intracellular decrease in cAMP levels does not represent a metabolic event that may, per se, trigger leptin secretion. However, it has been shown that the antilipolytic agent neuropeptide Y is able to stimulate leptin secretion after longer periods of incubation (≥22 h) (31).

Finally, we tested the effects of insulin and lipolytic (norepinephrine, isoproterenol, and CL-316243) and antilipolytic (orthovanadate, nicotinic acid, and acipimox) agents on leptin secretion in the presence of a mixture of adenosine deaminase (0.5 U/ml) and PIA (100 nM), i.e., under the conditions suggested by Londos et al. (19) to stabilize basal cAMP production. These incubation conditions did not significantly alter the concentration-response curves of insulin and other agents cited above on leptin secretion (not shown).

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Fig. 6. Comparison of the effects of lipolytic hormones, adenylate cyclase activators, and cAMP analogs on lipolysis (A) and leptin release (B) in the presence of insulin. Adipocytes were incubated in the presence of insulin (10 nM) and fixed concentrations of ACTH (10 nM), thyrotropin-stimulating hormone (TSH; 0.2 μM), forskolin (For; 10 μM), pertussis toxin (PTX) (1 μg/ml), N^{6}-monobutyryl cAMP (MBcAMP; 1 mM), and N^{6}-dibutyryl cAMP (DBcAMP; 1 mM) or 8-bromo cAMP (8-BrcAMP; 1 mM). Incubation conditions were the same as in Fig. 1. (n = 5–6). Bars and vertical lines indicate means ± SE. Effects of the above agents were compared with basal lipolysis (A) or to insulin-stimulated values (B). *P < 0.05, **P < 0.01.

Fig. 7. Comparison of the effects of specific and nonspecific phosphodiesterase inhibitors on lipolysis (A) and leptin release (B) in the presence of insulin. Adipocytes were incubated in the presence of insulin (10 nM) and fixed concentrations of caffeine (Caf; 1 mM), theophylline (Theo; 1 mM), 3-isobutyl-1-methyl-xanthine (IBMX; 0.1 mM), imazodan (IMA; 0.1 mM), milrinone (MIL; 0.1 mM), or acipimox (AMR; 1 mM). Incubation conditions were the same as in Fig. 1 (n = 5). Bars and vertical lines indicate means ± SE. Effects of the above agents were compared with basal lipolysis (A) or insulin-stimulated values (B). *P < 0.05, **P < 0.01.
Such observations were expected because we observed a very good interexperimental reproducibility.

DISCUSSION

The role of β₁- and β₂-adrenoceptors in mediating norepinephrine action. The present study revealed that insulin-stimulated leptin secretion is mediated not only by the low-affinity β₃-adrenoceptors but also via the high-affinity β₁/β₂-adrenoceptors with β₂-adrenoceptors playing a lesser role than β₁-adrenoceptors. This conclusion is based on the following observations: 1) selective β₁- and β₃-agonists (dobutamine and CL-316143, respectively) and nonselective agonists (norepinephrine and isoproterenol) all completely inhibited insulin-stimulated leptin secretion (Fig. 2); 2) the selective β₂-antagonist propranolol, in contrast, partly inhibited insulin-stimulated leptin secretion and only at high concentrations (0.1 mM); and 3) the selective β₁-antagonist ICI-89406, likewise, reversed more effectively than the β₂-antagonist ICI-118551 the inhibitory effects of norepinephrine or isoproterenol on insulin-stimulated leptin secretion (Figs. 4 and 5). Contrary to the present observations, it has been claimed that the norepinephrine effects were essentially mediated by β₂-adrenoceptors because they were unaffected by selective β₁/β₂-antagonists (11). However, these results are difficult to interpret because the concentrations of the antagonists were either too low or not specified, as in the case of the β₁/β₂-blocker CGP-12177. Furthermore, CGP-12177 may also act as a β₁-agonist, depending on its concentration (22). Another observation that supports a role for β₁-adrenoceptors in regulating leptin secretion is the fact that propranolol inhibited the effects of norepinephrine and isoproterenol when added at slightly higher concentrations than the two agonists (Fig. 3). Direct binding studies have demonstrated that the affinity of propranolol, norepinephrine, and isoproterenol for the β₁-adrenoceptors is about 10⁻⁸ to 10⁻⁹ greater (pKᵦ or pKᵦ values varying between 8 and 9) than the one for β₂-adrenoceptors (pKᵦ or pKᵦ values varying between 4 and 5). Thus it is likely that low concentrations of propranolol reverse the effects of norepinephrine and isoproterenol by competing for the high-affinity β₁/β₂ binding sites. However, at higher concentrations, propranolol may also affect β₂-adrenoceptors. These observations suggest that circulating catecholamines, levels of which rarely exceed 25 nM, would regulate leptin secretion mainly via the high-affinity β₁-adrenoceptors, whereas the low-affinity β₁/β₂-adrenoceptors would mainly be activated when norepinephrine concentrations in the synaptic cleft reached higher concentrations, such as after cold exposure or other intensive stress (2).

The role of the adenylate cyclase-phosphodiesterase system. In addition to β-adrenergic agonists, insulin-stimulated leptin secretion could also be inhibited by a wide variety of agents known to increase intracellular cAMP levels by stimulating its production at the cyclase level (ACTH, TSH, pertussis toxin, or forskolin), inhibiting its degradation by phosphodiesterases (caffeine, theophylline, IBMX, imazodan, milrinone, or amrinone), or mimicking its action (MbcAMP or DBCAMP). Without exception, all these agents stimulated lipolysis in the range of concentrations at which they inhibited insulin-stimulated leptin secretion. Although cAMP levels were not directly measured in the present experiments, these results strongly indicate that cAMP plays a fundamental role in regulating insulin stimulation of leptin secretion. Although the role of cAMP appears to be merely modulatory because, in the absence of insulin, all the above lipolytic agents either did not alter or slightly inhibited basal leptin secretion.

Perspectives

The present study has shown that catecholamines, β-agonists, lipolytic hormones, cAMP analogs, or other agents activating adenylate cyclase inhibit insulin-stimulated leptin secretion. Norepinephrine, the physiological effector of lipolysis, inhibits leptin secretion not only via the low-affinity β₃-adrenoceptors, as previously shown (11), but also via the high-affinity β₁/β₂-adrenoceptors. Significantly, the neurohormone modulates insulin-stimulated leptin secretion in a reversible manner, most probably by stimulating adenylate cyclase activity. Experiments with phosphodiesterase inhibitors revealed that activation of phosphodiesterase III by insulin represents an important metabolic step in stimulation of leptin secretion. Thus it is likely that, under physiological conditions, norepinephrine and other lipolytic hormones competitively counterregulate the stimulatory effects of insulin on leptin secretion by activating the adenylate cyclase system. In rodents, several studies have shown that central administration of leptin increases the activity of the sympathetic nervous system, norepinephrine turnover in various tissues, and glucose uptake in brown adipose tissue and striated muscles, but not in white adipose tissue (26). By inhibiting leptin secretion from white adipose tissue, norepinephrine may decrease plasma leptin levels and consequently reduce the activity of the sympathetic nervous system. Thus norepinephrine may participate in a negative feedback loop preventing excessive activation of the sympathetic nervous system and energy expenditure. The fact that selective β₁- and β₂-adrenergic antagonists entirely reverse the effects of norepinephrine may help develop new drugs for controlling leptin levels in humans where β₂-adrenoceptors play a minor role in modulating lipolysis and leptin secretion (17, 30). Indeed, in humans, dysregulated leptin levels have been associated not only with obesity and diabetes but also with a series of physiopathologies, such as leptin-induced anorexia, cardiovascular diseases, and hematopoietic dysregulation (14).

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REFERENCES


