Cardiovascular Side Effects of Antiobesity Drugs
A Yellow Flag in the Race to Safe Pharmacotherapy for Obesity
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The global surge in obesity with its attendant increase in diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease is provoking alarm. Fortunately, the surge in obesity has been paralleled by a revolution in understanding the biological regulation of appetite, metabolism, and adiposity.1,2 Mushrooming discoveries are identifying new pathways regulating appetite and metabolism. These pathways are potential new therapeutic targets, but we still lack safe effective pharmacotherapy for obesity. Consequently, the effort to develop safe, effective pharmacotherapy goes on, fueled by the discovery of new biological mechanisms and new therapeutic targets regulating appetite and metabolism.

Notwithstanding the Fen-Phen (fenfluramine and phentermine) debacle with heart valve disease and pulmonary hypertension,3 the major concern with side effects of antiobesity drugs has been neuropsychiatric.4 Cardiovascular side effects merit greater attention. Many of the brain regions and pathways involved in regulation of appetite and metabolism also participate in regulation of sympathetic neural activity and arterial pressure. Several interventions that inhibit appetite and stimulate metabolism act to increase (not decrease) sympathetic activity and arterial pressure.5–9 This brings the cardiovascular system into focus in evaluation of potential antiobesity drugs.

In this issue, Belin de Chantemèle et al10 from Stepp’s laboratory present an interesting and important study of adverse sympathetic and arterial pressure responses to genetic deletion of protein-tyrosine phosphatase 1B (PTP1B), a leptin and insulin inhibitor. Leptin, a hormone secreted by white adipocytes, acts in the brain to promote satiety and increase energy expenditure and thereby decrease adiposity.1 Among its pleiotropic effects, it influences glucose metabolism, reproductive biology, immune function, and, of note for this discussion, sympathetic and arterial pressure regulation.1,3–6

In rats and mice, leptin acts in the brain to increase sympathetic nerve activity to brown adipose tissue.5 This produces sympathetically mediated increases in thermogenic metabolism, ie, a metabolic action of leptin. Leptin also increases sympathetic nerve activity to the kidney, hindlimb, and adrenal gland that regulates cardiovascular function.5 The renal sympathetic action of leptin increases arterial pressure in rodents.6 This has prompted suggestions that leptin contributes to hypertension in diet-induced obesity. In children with complete leptin deficiency and severe obesity, treatment with leptin decreases adiposity and body weight. In a child with congenital leptin deficiency and severe obesity, leptin did not produce overt increases in arterial pressure, but arterial pressure also did not decrease, as is expected with profound weight loss.11 This suggests a latent pressor action of leptin in humans. Because leptin is not widely available to investigators for human investigation, we lack systematic experimental studies on the arterial pressure actions of leptin in humans.

In common human obesity, there is partial resistance to leptin1,2 analogous to insulin resistance in Type 2 diabetes mellitus. Partial leptin resistance is thought to occur mainly in central neural leptin signaling pathways downstream of the leptin receptor.1,2 This limits the effectiveness of leptin in the treatment of common human obesity. Consequently, there has been an intensive search for the mechanisms and treatment of partial leptin resistance in human obesity.1,2

Attention has focused on 2 endogenous leptin inhibitors acting in the brain: PTP1B12–14 and suppressor of cytokine signaling-3 (SOCS-3).15,16 The latter increases in the hypothalamic arcuate nucleus during a high-fat diet and has been implicated in the pathogenesis of diet-induced leptin resistance.15 Protein-tyrosine phosphatase 1B is an endogenous leptin and insulin inhibitor, but it does not increase during a high-fat diet and may not be implicated in diet-induced leptin resistance.15

Genetic deletion of either PTP1B or SOCS-3 enhances leptin-mediated decreases in food intake and weight loss and protects against diet-induced weight gain.12,13,15,16 Deletion of PTP1B also increases insulin sensitivity.14 Not surprisingly, then, disruption of the formation or function of PTP1B has been considered a potential target for the development of antiobesity drugs.12–14

Belin de Chantemèle et al10 report the effects of genetic deletion of PTP1B on sympathetic and cardiovascular function in mice. The results are dramatic and suggest that sympathetic and cardiovascular effects may complicate the safety of disrupting PTP1B.

The PTP1B knockout mice had substantially higher arterial pressure than control mice despite having lower body fat. The higher arterial pressure was mediated by sympathetic activation. Hypertension commonly accompanies common human obesity, and traditional thinking has held that decreases in adiposity and body weight consistently lower arterial pres-
sure. This thinking would hold that an intervention, such as disruption of PTP1B, that decreases adiposity and protects against diet-induced obesity would lower arterial pressure. By contrast, Belin de Chantemèle et al. found that disruption of PTP1B in mice produced substantially higher arterial pressure than was observed in control mice despite lower body fat. This finding indicates that the effects of antiobesity interventions on food intake and adiposity are not necessarily paralleled by decreases in arterial pressure. Indeed, with deletion of PTP1B, there were qualitatively contrasting effects on adiposity and arterial pressure. Adiposity decreased, but arterial pressure increased.

Belin de Chantemèle et al. also observed that deletion of PTP1B enhanced the pressor response to leptin in addition to sensitizing the leptin-induced decreases in food intake and body weight. The augmented pressor response to leptin was reversed by ganglionic blockade, which suggests that it was sympathetically mediated. The authors conclude that PTP1B is a major physiological regulator (inhibitor) of the cardiovascular effects of leptin.

The authors’ discussion of these findings is thoughtful. I address a key point in the interpretation of the study.

Protein-tyrosine phosphatase 1B contributes to multiple physiological functions, including inhibition of insulin and leptin signaling. Consequently, as the authors indicate, it is not clear whether the hypertension in the PTP1B mice results from increased leptin signaling, other effects of deleting PTP1B, or both. Although PTP1B inhibits insulin signaling, deletion of PTP1B did not unmask a pressor response to insulin, whereas it did augment the pressor response to leptin. Nevertheless, it is possible that other mechanisms besides increased leptin signaling contribute to the hypertension in this model. This is a key point. The finding that increased leptin signaling caused by PTP1B deletion is accompanied by hypertension and augmented sympathetic and arterial pressure responses to leptin does not establish that increases in leptin sensitivity produced by other interventions will cause similar adverse cardiovascular consequences.

The study by Belin de Chantemèle et al. highlights the importance of evaluating the sympathetic and arterial pressure effects of potential antiobesity therapies to exclude adverse cardiovascular effects. Although antagonism of PTP1B was previously considered a promising target for treatment of obesity, the finding that deletion of PTP1B in mice leads to hypertension raises a yellow flag.

There is another recent example, another yellow flag, of sympathetic and arterial pressure actions complicating a potential new class of antiobesity drugs, namely, melanocortin-4 receptor (MC4R) agonists. Activation of MC4R in the hypothalamus inhibits appetite and increases energy expenditure. Rodents and humans with loss of function of MC4R are obese. This prompted interest in MC4R agonists for the treatment of common human obesity, but it now appears there is a problem with this idea. In rodents, stimulation of MC4R increases sympathetic nerve activity and arterial pressure in addition to inhibiting appetite and increasing metabolism.

Common polygenic multifactorial human obesity is often associated with increased sympathetic activity and arterial pressure. By contrast, Greenfield et al. reported that patients with obesity caused by loss of function mutations in the MC4R have lower arterial pressure and urinary norepinephrine than do control, weight-matched patients with common human obesity. This suggests that MC4R receptor agonists, which would logically be considered potential new antiobesity drugs, might produce increases in sympathetic activity and arterial pressure. Greenfield et al. confirmed this concern. In humans with common human obesity (who do not have mutations in the MC4R), treatment with an MC4R agonist led to dose-related increases in arterial pressure. This is another example, another yellow flag, of sympathetic and arterial pressure actions complicating potential antiobesity drugs. The study by Greenfield et al. further indicates that the sympathetic and arterial pressure actions of MC4R stimulation have pathophysiological and pharmacological significance in humans, not just in rodents.

In summary, Belin de Chantemèle et al. report in this issue of Circulation that genetic deletion of PTP1B, a leptin and insulin inhibitor, increases sympathetic activity and arterial pressure in mice in addition to enhancing leptin-mediated decreases in adiposity and body weight. This study and a recent study by Greenfield et al. on the arterial pressure responses to MC4R receptor stimulation raise a yellow flag in the race to develop safe, effective antiobesity drugs. Many of the central neural regions and pathways involved in the regulation of appetite and metabolism also participate in the regulation of sympathetic activity and arterial pressure. Unfortunately, several of the interventions that inhibit appetite, increase metabolism, and decrease adiposity may increase (not decrease) sympathetic activity and arterial pressure. This may complicate the safety of potential antiobesity drugs. This emphasizes the importance of evaluating the cardiovascular actions of potential and emerging antiobesity drugs.

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References

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