Obesity Paradox and Smoking Gun

A Mystery of Statistical Confounding?

Xi-Yong Yu, Ping Song, Ming-Hui Zou

The obesity paradox is a term coined for human conditions in which obesity is associated with a lower mortality than being underweight (ie, body below normal or healthy body weight). Smoking is often cited as a key confounder of obesity paradox, but how smoking causes obesity paradox is unknown. Here, we highlight that the obesity paradox can be attributed to insulin resistance (IR) and aberrant lipolysis in cardiovascular diseases (CVD).

Obesity Paradox in CVD

Obesity is an independent risk factor for the development of diseases associated with increased mortality in the general population, such as CVD, for which obesity increases the risk by ≈2-fold. However, for the elderly population or patients with specific conditions, such as cancer cachexia,[1] chronic obstructive lung disease, end-stage renal disease, or advanced chronic kidney disease (who are receiving hemodialysis therapy), a higher body mass index (BMI) is often found to be associated with reduced mortality, whereas lower body mass index is related to higher mortality in these patients. To describe these human conditions, a new term called obesity paradox is coined. The obesity paradox has also been reported in many patients with cardiovascular events; for example, class I obesity (BMI, 30–35 kg/m^2) patients who experience heart failure have lower short- and intermediate-term mortality than their leaner counterparts. Similarly, overall in-hospital mortality after acute myocardial infarction is dramatically lower in elderly obese patients (≥70 years) of all classes compared with patients with acute myocardial infarction without obesity. The obesity paradox has also been reported in cardiovascular therapy; for example, elderly patients who are obese or overweight have lower mortality with implantable cardioverter defibrillators than normal BMI patients.[2] Because the data to support obesity paradox are exclusively obtained from clinical observations, there are intense debates on whether or not obesity paradox is real or a bias/an artifact derived from observational studies.

Cigarette Smoking May Underlie the Obesity Paradox in CVD

Smoking is a critical independent risk factor for cardiovascular mortality and CVD, including peripheral arterial disease, stroke, coronary heart disease, and heart failure.[3] In addition, smoking cessation dramatically decreases the relative risk of cardiovascular mortality and coronary heart disease when compared with active smokers, although the risk of stroke is not lowered.[3] As smokers, who tend to be leaner, are subjected to higher mortality rates whereas smoking cessation is often linked to improved CVD conditions with body weight gain, several studies have unveiled that obesity paradox is the potential bias resulting from the confounding effects of illness-induced weight loss and smoking.[4,5] Obesity paradox is absent in cardiovascular events among never smokers. This outcome is not that surprising because failure to properly control for smoking cigarettes when in studies of the relationship between obesity and cardiovascular mortality is a classic example of confounding. Generally, smokers have lower body weights, and smoking is inversely correlated with BMI. In addition, patients who quit smoking (ie, former smokers) will frequently and substantially gain body weight. Hence, failure to adequately control for ongoing smoking is likely to result in artificially elevated mortality among the lean subjects, and failure to entirely control for smoking cessation or former smokers may lead to decreased measurements of mortality among the obese or overweight subjects. Overall, these epidemiological studies support that smoking is a mystery of statistical confounder for obesity paradox in CVD.

Lipolysis, IR, and Obesity Paradox in Smokers

Fat is a metabolically active and dynamic organ. Fat accumulation is determined by the balance between fat synthesis (lipogenesis) and fat breakdown (lipolysis/fatty acid oxidation). Lipogenesis is responsive to changes in the diet and is partly regulated by hormones (insulin, leptins, etc). Similarly, lipolysis is directly activated by sympathetic nervous system activation, glucagon, or growth hormone, etc.

Insulin is a key regulator for both lipogenesis and lipolysis. Insulin inhibits lipolysis and slows the breakdown of adipose tissue caused by lipolytic signals, such as sympathetic nervous system activation, glucagon, or growth hormone, etc. The impact of insulin on lipolysis is largely determined by the intensities of lipolytic signals. In IR state, insulin's inhibition on lipolysis is diminished. As a result, IR in hypertrophic adipocytes leads to increased lipolysis and the release of free fatty acid (FFA) into circulation. In return, FFA elevation has been postulated to play a critical role in the development of IR. Recent studies on both humans and mice indicate that high levels of FFA, which is associated with low body weight,

---

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Key Laboratory of Molecular Target and Clinical Pharmacology, School of Pharmaceutical Sciences and the Fifth Affiliated Hospital, Guangzhou Medical University, China (X.-Y.Y., M.-H.Z.); and Center for Molecular and Translational Medicine, Georgia State University, Atlanta (P.S., M.-H.Z.).

Correspondence to Ping Song, PhD, Center for Molecular and Translational Medicine, Georgia State University, 157 Decatur St SE, Atlanta, GA 30303. E-mail psong@gsu.edu

(*Circ Res*. 2018;122:1642-1644.
DOI: 10.1161/CIRCRESAHA.118.312897.)

***Circulation Research* is available at http://circres.ahajournals.org**
DOI: 10.1161/CIRCRESAHA.118.312897

impairs insulin sensitivity, whereas genetic inhibition of adipose tissue lipolysis by deletion of adipose triglyceride lipase, results in improved insulin sensitivity but with gain in body weights and fat levels (paradox).[6]

Cigarette smokers often have IR and compensatory hyperinsulinemia. In addition, long-term nicotine replacement therapy (nicotine gum or e-cigarettes), when used as a method of weight control, was reported to induce IR and other metabolic disorders.[7] Several mechanisms by which cigarette smoke or e-cigarettes cause whole-body IR have been reported. First, nicotine is the major bioactive component of cigarette smoke and e-cigarettes and activates sympathetic nervous system leading to increased lipolysis in white adipose tissue[8] and resultantly elevated FFA, which contributes to IR and weight loss (Figure). Second, nicotine acts through the α7nAchR (nicotinic acetylcholine receptor subunit α7) and causes increased levels of reactive oxygen and nitrogen species and selectively activates AMPK (5′ AMP-activated protein kinase) α2 in white adipocytes. Consequently, AMPKα2 phosphorylates MKP1 (mitogen-activated protein kinase phosphatase-1) at serine 334,[9] initiating its proteasome-dependent degradation. The nicotine-mediated reduction of MKP1 induces aberrant activation of both p38 mitogen-activated protein kinase and c-Jun N-terminal kinase, leading to increased phosphorylation of IRS1 (insulin receptor substrate 1) at serine 307, its degradation, and resultant IR (Figure). Third, nicotine induces IR through activation of mTOR (mammalian target of rapamycin) in skeletal muscle (Figure). Cigarette exposure-induced IR is highly associated with an increased risk of CVD, such as ischemic heart disease and coronary heart disease. Moreover, elevated FFA caused by IR contributes to myocardial dysfunction, which is associated with heart failure and acute coronary syndromes.

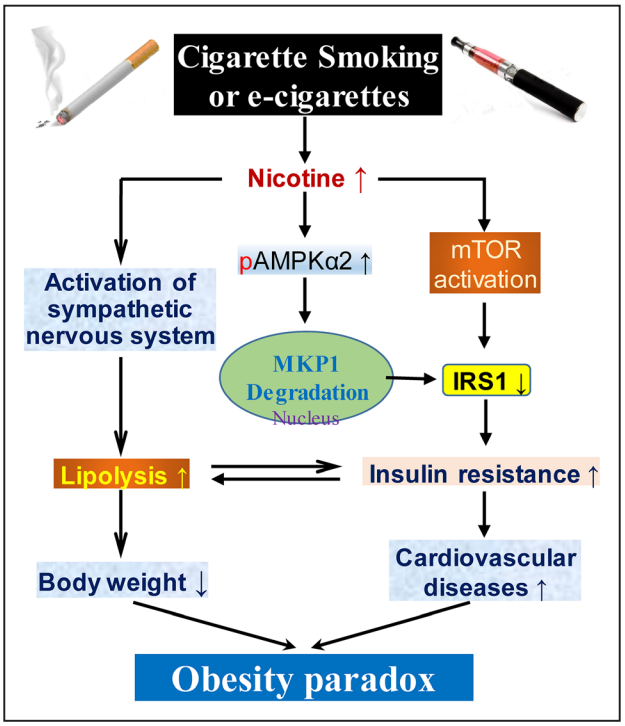

Figure. Schematic representation of the role of cigarette smoking–induced insulin resistance (IR) in the obesity paradox. First, nicotine-enhanced lipolysis by sympathetic nervous system activation contributes to IR and body weight loss. Second, nicotine acts via adipocyte α7nAchR (nicotinic acetylcholine receptor subunit α7) to induce ROS (reactive oxygen species) and activate AMPK (5′ AMP-activated protein kinase) α2. This subsequently enhances MKP1 (mitogen-activated protein kinase phosphatase-1) degradation, resulting in IRS1 (insulin receptor substrate 1) reduction and IR. Third, nicotine induces IR via mTOR (mammalian target of rapamycin) activation in the skeletal muscle. Hence, nicotine promotes both body weight loss and IR-induced cardiovascular diseases, which may underlie the so-called obesity paradox. pAMPKα2 indicates phosphorylated 5' AMP-activated protein kinase alpha2. →, induce or act on; ↑, increase; ↓, decrease.

Nicotine acts through numerous mechanisms to promote weight loss. For example, recent evidence has demonstrated that nicotine functions in the central nervous system by binding to the α3β4 nicotinic acetylcholine receptor and activating POMC (proopiomelanocortin) neurons in the arcuate nucleus of the hypothalamus to decrease food intake, thereby contributing to weight loss. Moreover, nicotine inhibits AMPK in the ventromedial nucleus of the hypothalamus to increase brown adipose tissue thermogenesis through the sympathetic nervous system, which also causes weight loss. Finally, nicotine-triggered IR exacerbates lipolysis in white adipose tissue, further enhancing weight loss. Taken together, nicotine replicates a condition in which low body weight is linked to high CVD.

On the contrary, smoking cessation causes obesity paradox because when people quit smoking, they undergo substantial weight gain,[10] improved insulin sensitivity, and decreased CVD. The fact that smoking cessation improves IR with body weight gains suggests that smoking's impacts on both cardiovascular health and insulin sensitivity are likely greater than body weight alone. Thus, obese smokers or former smokers, after smoking cessation, might have better insulin sensitivity and lower CVD risks than obese nonsmokers. That is to say, a former smoker who gains weight might have weaker IR than the obese general publics do. Thus, it is highly likely that removing CVD-reduced obese smokers or former smokers would epidemiologically increase CVD risk in the remaining nonsmoking obesity population—a typical phenomenon described as obesity paradox.

IR, Aberrant Lipolysis, and Obesity Paradox in Nonsmokers

The obesity paradox also has been reported in nonsmokers with cancer cachexia or cardiac cachexia[11]—a wasting syndrome primarily characterized by weight loss, including adipose tissues and skeletal muscle wasting. Although central nervous system– and inflammation-related anorexia regulate cancer cachexia, emerging data indicate that IR-accelerated lipolysis is a contributor.[12] For example, tumor-derived inflammatory cytokines, such as tumor necrosis factor and interleukin-6, induce IR, decrease lipogenesis, and increase lipolysis. Moreover, the sympathetic nervous system is also responsible for part of the visceral fat lipolysis in the fasting stage or anorexia. In addition, AMPKα1 reduction in cancer or stromal fibroblast cells[13] contributes to enhanced lipolysis in adipocytes and subsequent cancer cachexia.[14] Interestingly, the insulin sensitizer rosiglitazone attenuates adipose depletion, the consequent weight loss, and cancer cachexia.[15] Taken together, these findings indicate that IR is a key contributor to cachexia and suggest that IR is a potential therapeutic target.

Conclusions

Aberrant lipolysis accounts for the obesity paradox in smoking- and nonsmoking-related conditions. IR is a critical pathological factor for aberrant lipolysis. Therefore, insulin sensitizing drugs that attenuate IR might be a promising strategy to reduce CVD and related mortality in the patients with low and moderate body weights.

Sources of Funding

The laboratory of M.-H. Zou is supported by the grants from National Institutes of Health RO1 (HL079584, HL089920, HL08 0499, HL110488, HL128014, HL132500, HL137371, HL142287, HL140954, AG047776, and CA213022). P. Song is supported, in part, by HL140954. X.-Y. Yu is supported by the National Natural Science Foundation of China (81330007 and U1601227).

Disclosures

None.

References

1. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol*. 2013;10:90–99. doi: 10.1038/nrclinonc.2012.209.
2. Jahangir A, Mirza M, Shahreyar M, Mengesha T, Shearer R, Sultan S, Jahangir A, Choudhuri I, Nangia V, Dhala A, Bhatia A, Niazi I, Sra J, Tajik AJ. Presence of obesity is associated with lower mortality in elderly patients with implantable cardioverter defibrillator. *Int J Obes (Lond)*. 2018;42:169–174. doi: 10.1038/ijo.2017.211.
3. Pan A, Wang Y, Talaei M, Hu FB. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: a meta-analysis and systematic review. *Circulation*. 2015;132:1795–1804. doi: 10.1161/CIRCULATIONAHA.115.017926.
4. Di Angelantonio E, Bhupathiraju ShN, et al; Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016;388:776–786. doi: 10.1016/S0140-6736(16)30175-1.
5. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363:2211–9.
6. Ahmadian M, Abbott MJ, Tang T, Hudak CS, Kim Y, Bruss M, Hellerstein MK, Lee HY, Samuel VT, Shulman GI, Wang Y, Duncan RE, Kang C, Sul HS. Desnutrin/ATGL is regulated by AMPK and is required for a brown adipose phenotype. *Cell Metab*. 2011;13:739–748. doi: 10.1016/j.cmet.2011.05.002.
7. Eliasson B, Taskinen MR, Smith U. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation*. 1996;94:878–881.
8. Middlekauff HR, Park J, Moheimani RS. Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. *J Am Coll Cardiol*. 2014;64:1740–1750. doi: 10.1016/j.jacc.2014.06.1201.
9. Wu Y, Song P, Zhang W, et al. Activation of AMPKα2 in adipocytes is essential for nicotine-induced insulin resistance in vivo. *Nat Med*. 2015;21:373–382. doi: 10.1038/nm.3826.
10. Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM. The influence of smoking cessation on the prevalence of overweight in the United States. *N Engl J Med*. 1995;333:1165–1170. doi: 10.1056/NEJM199511023331801.
11. von Haehling S, Lainscak M, Springer J, Anker SD. Cardiac cachexia: a systematic overview. *Pharmacol Ther*. 2009;121:227–252. doi: 10.1016/j.pharmthera.2008.09.009.
12. Asp ML, Tian M, Wendel AA, Belury MA. Evidence for the contribution of insulin resistance to the development of cachexia in tumor-bearing mice. *Int J Cancer*. 2010;126:756–763. doi: 10.1002/ijc.24784.
13. Zhou Y, Xu H, Ding Y, Lu Q, Zou MH, Song P. AMPKα1 deletion in fibroblasts promotes tumorigenesis in athymic nude mice by p52-mediated elevation of erythropoietin and CDK2. *Oncotarget*. 2016;7:53654–53667. doi: 10.18632/oncotarget.10687.
14. Rohm M, Schäfer M, Laurent V, et al. An AMP-activated protein kinase-stabilizing peptide ameliorates adipose tissue wasting in cancer cachexia in mice. *Nat Med*. 2016;22:1120–1130. doi: 10.1038/nm.4171.
15. Asp ML, Tian M, Kliewer KL, Belury MA. Rosiglitazone delayed weight loss and anorexia while attenuating adipose depletion in mice with cancer cachexia. *Cancer Biol Ther*. 2011;12:957–965. doi: 10.4161/cbt.12.11.18134.

KEY WORDS: body weight ■ humans ■ insulin resistance ■ lipolysis ■ nicotine

Obesity Paradox and Smoking Gun: A Mystery of Statistical Confounding?

Xi-Yong Yu, Ping Song and Ming-Hui Zou

Circ Res. 2018;122:1642-1644
doi: 10.1161/CIRCRESAHA.118.312897
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571