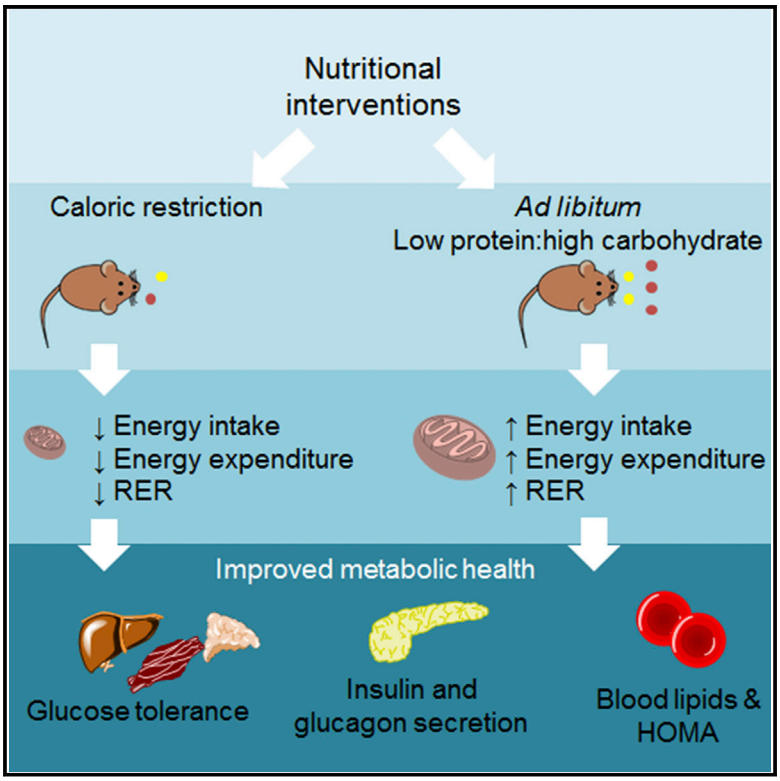
Cell Reports

Report

Dietary Protein to Carbohydrate Ratio and Caloric Restriction: Comparing Metabolic Outcomes in Mice

Graphical Abstract



Highlights

- Ad libitum low-protein, high-carbohydrate diets (LPHC) improve metabolic health
- Caloric restriction combined with LPHC diet does not provide added health benefits
- Energy intake and energy expenditure are increased on LPHC diets

Authors

Samantha M. Solon-Biet, Sarah J. Mitchell, Sean C.P. Coogan, ..., Rafael de Cabo, Stephen J. Simpson, David G. Le Couteur

Correspondence

samantha.solon-biet@sydney.edu.au (S.M.S.-B.), stephen.simpson@sydney.edu.au (S.J.S.)

In Brief

Nutritional interventions improve metabolic health in mice. Solon-Biet et al. find that short-term ad libitum low-protein, high-carbohydrate (LPHC) diets improve levels of insulin, glucose, lipids, and HOMA. LPHC diets under ad-libitum-fed conditions generate the metabolic benefits of caloric restriction without a 40% reduction in total caloric intake.

Solon-Biet et al., 2015, Cell Reports *11*, 1529–1534
June 16, 2015
http://dx.doi.org/10.1016/j.celrep.2015.05.007

CellPress

Cell Reports
Report

Dietary Protein to Carbohydrate Ratio and Caloric Restriction: Comparing Metabolic Outcomes in Mice

Samantha M. Solon-Biet,[1,2,4,*] Sarah J. Mitchell,[3] Sean C.P. Coogan,[1,4] Victoria C. Cogger,[1,2] Rahul Gokarn,[2] Aisling C. McMahon,[1,2] David Raubenheimer,[1,4,5] Rafael de Cabo,[3] Stephen J. Simpson,[1,4,*] and David G. Le Couteur[1,2]
[1]Charles Perkins Centre, University of Sydney, Sydney, NSW 2006, Australia
[2]Ageing and Alzheimers Institute and ANZAC Research Institute, Concord Hospital, University of Sydney, Sydney, NSW 2139, Australia
[3]Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA
[4]School of Biological Sciences, University of Sydney, Sydney, NSW 2006, Australia
[5]Faculty of Veterinary Science, University of Sydney, Sydney, NSW 2006, Australia
*Correspondence: samantha.solon-biet@sydney.edu.au (S.M.S.-B.), stephen.simpson@sydney.edu.au (S.J.S.)
http://dx.doi.org/10.1016/j.celrep.2015.05.007

SUMMARY

Both caloric restriction (CR) and low-protein, high-carbohydrate (LPHC) ad-libitum-fed diets increase lifespan and improve metabolic parameters such as insulin, glucose, and blood lipids. Severe CR, however, is unsustainable for most people; therefore, it is important to determine whether manipulating macronutrient ratios in ad-libitum-fed conditions can generate similar health outcomes. We present the results of a short-term (8 week) dietary manipulation on metabolic outcomes in mice. We compared three diets varying in protein to carbohydrate ratio under both CR and ad libitum conditions. Ad libitum LPHC diets delivered similar benefits to CR in terms of levels of insulin, glucose, lipids, and HOMA, despite increased energy intake. CR on LPHC diets did not provide additional benefits relative to ad libitum LPHC. We show that LPHC diets under ad-libitum-fed conditions generate the metabolic benefits of CR without a 40% reduction in total caloric intake.

INTRODUCTION

Caloric restriction (CR) of ~30%–50% increases healthspan, delays the onset of aging and age-associated diseases, and improves metabolic health in most species (Everitt et al., 2010; Masoro, 2005; Mattison et al., 2012; McCay et al., 1935; Mercken et al., 2012; Weindruch et al., 1986). It is generally thought that CR is mediated directly by the reduction in energy intake impacting on cellular substrates such as NAD^+ and AMP, with subsequent downstream effects on nutrient-sensing pathways such as sirtuin (SIRT1), AMP-activated protein kinase (AMPK), mechanistic target of rapamycin (mTOR), and insulin/insulin growth factor 1 (IGF-1) (Brunet et al., 2004; Fontana et al., 2010; Le Couteur et al., 2012). Although beneficial, CR is unsustainable in the vast majority of humans (Fontana and Partridge, 2015).

More recently, it has been demonstrated in studies using nutritional geometry that the balance of macronutrients has a profound impact on healthspan and lifespan in animals with ad libitum (AL) access to food (Lee et al., 2008; Piper et al., 2011; Solon-Biet et al., 2014). In these studies, CR induced by dietary dilution did not increase lifespan (Solon-Biet et al., 2014). In AL-fed mice and *Drosophila melanogaster*, diets low in protein and high in carbohydrates (LPHC) maximized lifespan, while a reduction of total energy intake had no positive impact on longevity (Lee et al., 2008; Solon-Biet et al., 2014). Moreover in mice, LPHC diets were associated with improved late-life cardiometabolic health (Solon-Biet et al., 2014) and a younger immune profile (Le Couteur et al., 2014). Low protein intake has also been associated with better health and reduced mortality in observational studies of humans (Levine et al., 2014), while high-protein, low-carbohydrate (HPLC) diets are associated with higher mortality, cardiovascular disease, and diabetes mellitus (Fontana and Partridge, 2015; Fung et al., 2010; Lagiou et al., 2012; Simpson et al., 2015).

Thus, a diet with altered macronutrient composition may be a more feasible intervention than severe CR for managing metabolic health in humans. However, there is a downside: whereas LPHC diets have beneficial effects later in life, they are associated with increased food intake, driven by compensatory feeding for protein (Gosby et al., 2011; Huang et al., 2013; Raubenheimer et al., 2015; Simpson and Raubenheimer, 2005). The clinical consequences of overconsumption are well established, including obesity, metabolic syndrome, type 2 diabetes mellitus, and fatty liver (Dietrich and Hellerbrand, 2014; Nseir et al., 2014; Simpson et al., 2015). Overall, reducing food intake and body weight improves the manifestations of metabolic syndrome and fatty liver (Ajala et al., 2013; Nseir et al., 2014). Effects of macronutrients on these outcomes in humans are less clear, but, in general, high-carbohydrate diets are thought to contribute to fatty liver and metabolic syndrome, while high-protein diets might be protective (Nseir et al., 2014), in part through aiding reduced energy intake (Gosby et al., 2014).

The question arises as to which dietary intervention is more effective at improving metabolic health and whether there is any synergy between these dietary regimens. In this study, we directly compared CR with diets differing in protein to