257

Essential amino acid restriction dictates the systemic metabolic response to dietary protein dilution

Yann Yap [1,*], Patricia Rusu [1], Dieter Schmoll [2], Bente Kiens [3], Matthew Piper [4], Mathias Heikenwälder [5], Stefan Bröer [6], Adam Rose [1]

[1] *Department of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria, Australia*
[2] *Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany*
[3] *Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark*
[4] *School of Biological Sciences, Monash University, Clayton, Victoria, Australia*
[5] *Division Chronic Inflammation and Cancer, German Cancer Research Center, Heidelberg, Germany*
[6] *Research School of Biology, The Australian National University, Canberra, Australia*

Dietary protein dilution (DPD) promotes metabolic health but the precise nutritional components driving this response remain ill defined. Here we definitely demonstrate that, independent of dietary carbohydrate supply, dietary amino acids (AA) are sufficient and necessary to drive the increases in metabolic inefficiency, systemic insulin sensitivity, and serum/liver FGF21 to DPD. In particular, the restriction of dietary essential AA (EAA) supply, but not non-essential AA, drives the systemic metabolic response to total AA deprivation. Furthermore, of the nine EAA, systemic deprivation of the strictly EAA, THR and TRP, are both adequate and necessary to confer the systemic metabolic response to both diet-, and genetic AA-transport loss-, driven AA restriction. Of note, serum THR is also lower in response to a naturally low-protein diet fed to humans, and THR was identified as the most limiting EAA in this diet according to exome matching analysis. Taken together, our studies demonstrate that the restriction of the strictly EAA, particularly THR and TRP, are sufficient and necessary to confer the systemic metabolic effects of DPD.

https://doi.org/10.1016/j.orcp.2018.11.180

258

Legacy effects of high fat preconditioning against metabolic syndrome with enhanced metabolic capacity in muscle and adipose tissue

Jiming Ye *, Xiu Zhou, Songpei Li, Eunjung Jo, Ali Mahzari, Sherouk Fouda

RMIT University, Bundoora, VIC, Australia

Postnatal overconsumption of fat has been shown to increase the susceptibility to metabolic disease in the later life. There is emerging evidence to suggest that certain interventions in the adulthood can have prolonged metabolic effects beyond the intervention duration, namely the legacy effect (*N Eng J Med*. 2008;359:1618–20; *PLoS One*. 2012;7:e42115). However, it remains unclear that whether prior exposure to high fat (HF) diets in adulthood also has long-term metabolic effects after the cessation of the HF feeding.

This study was set to test the hypothesis that prior intermittent exposures to a HF diet exacerbate the metabolic syndrome in response to subsequent feeding of the HF diet. To test this hypothesis, we pre-exposed adult mice (12 wks) a HF diet twice with each episode for 2 wks followed by 2 wks of washout with a chow (CH) diet. The mice were then challenged by feeding the same HF diet for 6 weeks to examine the legacy effect. In contrast to our hypothesis, the results showed that prior exposures to the HF diet significantly lessened body weight gain and visceral adiposity during the period of subsequent HF feeding. Along with the reduced obesity, both glucose tolerance and insulin tolerance were improved. Interestingly, these protective legacy effects were not observed in high fructose diet under the same conditions and they occurred without a reduction in calorie intake. Further analysis revealed that these legacy effects were associated with persistent increases in plasma FGF21 and enhanced metabolic capabilities in both muscle and adipose tissue.

These findings indicate that HF diet preconditioning induces protective legacy effects against subsequent consumption of the HF diet. The mechanism involves enhanced metabolic capacity in muscle and adipose tissue. This paradoxical legacy effect may offer a unique paradigm to explore novel factors with anti-obesity properties.

https://doi.org/10.1016/j.orcp.2018.11.181

259

Do exercise and NMN provide synergistic benefits in obese mice?

Josephine Yu *, Margaret J. Morris, Neil A. Youngson

School of Medical Sciences, UNSW Sydney, Kensington, NSW, Australia

Obesity is a growing epidemic with almost two thirds of Australian adults classified as overweight or obese. Exercise is known to be beneficial as an intervention in obesity, possibly due to increases in mitochondrial activity and the concomitant increases in nicotinamide adenine dinucleotide (NAD^+). Recent studies have tried to pharmacologically increase NAD^+ levels through supplementation with precursors such as nicotinamide mononucleotide (NMN). Our previous work comparing effects of NMN and exercise in the context of high fat diet (HFD)-induced obesity showed that both interventions were able to improve glucose tolerance but were associated with differing tissue-specific effects on mitochondrial function. Here we aimed to examine whether NMN and exercise could synergise in the management of obesity. Eighty 5-week old female C57BL/6J mice were split across 5 groups: Control (Con), HFD, HFD with NMN (HN), HFD with exercise (HEx) and HFD with both NMN and exercise (HNEx). After 11 weeks of diet, the exercise groups started treadmill exercise (15 m/min for 45 min, 6 days/week), while NMN groups received NMN in drinking water (400 mg/kg body weight/day). These interventions continued for 8 weeks during which metabolic measures were performed before collection of tissues. As expected, HFD feeding increased body weight and adiposity, with no significant impact of any intervention. Interestingly while impaired glucose tolerance caused by HFD-feeding was improved in the HEx group, this was not observed in the HNMN nor the combination HNEx groups. Both NMN groups had significantly increased liver NAD^+ levels. Muscle mitochondrial DNA (mtDNA) copy number was increased in both exercise groups compared to HFD group. Overall, these data suggest that although NMN was able to increase liver NAD^+ and exercise was able to improve glucose tolerance and increase muscle mtDNA copy number, there was no evidence for synergistic benefits of NMN supplementation and exercise.

https://doi.org/10.1016/j.orcp.2018.11.182