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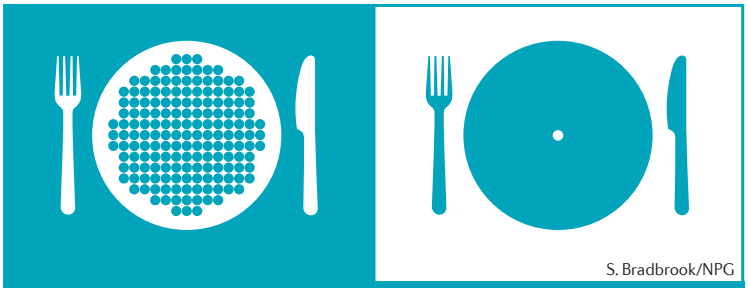

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IMMUNOMETABOLISM

Feast or famine to combat infection

Infections are associated with a range of altered behavioural responses such as lethargy, anorexia and social withdrawal, but how the metabolic state of an infected organism contributes to host defence is unclear. Now, Medzhitov and colleagues show that infection-induced anorexia improves survival during bacterial infection whereas it has detrimental effects during viral infection. These discrepancies suggest that different inflammatory responses are coupled to specific metabolic requirements to support distinctive tissue tolerance mechanisms.

The authors used *Listeria monocytogenes* to investigate the role of anorexia in infection. Mice displayed a dose-dependent decrease in food intake following infection, and force-feeding mice with nutrient supplements 8 hours post-infection was lethal. Glucose administration had the same effect and inhibition of glucose metabolism by administration of 2-deoxy-D-glucose (2DG) protected mice from mortality. A similar effect was seen in a lipopolysaccharide (LPS)-induced sepsis model, in which mortality is only due to a systemic inflammatory response. There was no difference in the magnitude of the inflammatory responses between glucose-treated and 2DG-treated LPS-challenged mice, which indicated that glucose use affects tissue tolerance to inflammatory damage rather than altering the magnitude of the inflammatory response. Furthermore, histopathological analyses of different organs from LPS-challenged mice treated with 2DG and controls were compared to identify any pathological changes including inflammation, necrosis and apoptosis. However, only one difference was found: 2DG-treated LPS-challenged mice had fewer shrunken neurons. Thus, anorexia protects mice against sepsis owing to inhibited glucose use that seems to alter tissue tolerance mechanisms mediated by the brain.

So, does anorexia have the same effect on the response to viral infections, which induce a different type of immune response compared with that induced by bacterial infections? Interestingly, the opposite effect was seen in mice infected with influenza virus or polyI:C (a synthetic mimic of viral double-stranded RNA); force-feeding these mice nutrient supplementation or glucose protected against influenza virus-associated mortality, whereas co-administration of virus or polyI:C together with 2DG was detrimental. In addition, these effects were independent of viral titres and the magnitude of inflammation, which indicated that protection was mediated by tissue tolerance. 2DG-treated polyI:C-challenged mice had decreased heart rate, respiratory rate and body temperature, suggesting perturbed central autonomic control. Thus, the protective effects of nutrient supplementation during influenza virus infection are mediated by altered tissue tolerance mechanisms.

Next, the authors were interested in investigating the signs of neural damage seen following viral inflammation. As endoplasmic reticulum (ER) stress-mediated apoptotic pathways are important for the response to viral infections, the authors hypothesized that these pathways could link viral inflammation to neural damage. Indeed, expression of the ER stress-induced transcription factor CHOP (CEBP homologous protein) was increased in the hindbrains of mice treated with polyI:C and 2DG, and CHOP-deficient mice were protected from influenza virus and 2DG challenge independently of viral load and inflammatory magnitude. Thus, glucose use mediates tissue tolerance to virus-induced inflammation by maintaining ER stress responses.

Finally, the authors showed that lethality due to glucose supplementation during bacterial sepsis is caused by increased reactive oxygen species (ROS) and brain damage. Ketogenesis was necessary to limit ROS-induced antibacterial inflammation, and impaired ketogenesis during bacterial infection was detrimental, whereas the opposite was seen during viral inflammation.

This study shows that glucose is required to survive viral infections, whereas it has detrimental effects during bacterial infections. Thus, different inflammatory responses seem to have specific metabolic requirements to provide protection.

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> “anorexia protects mice against sepsis”

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