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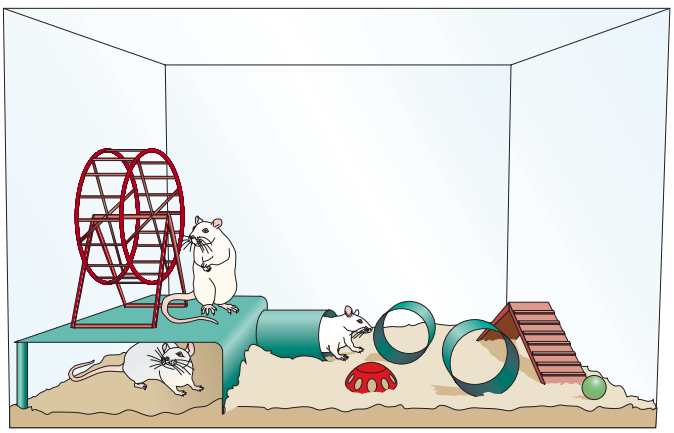
NEUROENDOCRINOLOGY

Housing conditions affect tumour growth

Environmental enrichment has been shown in rodents to have positive effects — on learning and memory, and in models of mood and neurodegenerative disorders. A paper published recently in *Cell* shows that mice living in an enriched environment (EE) are also more resistant to tumour growth through a pathway involving brain-derived neurotrophic factor (BDNF), leptin and adiponectin.

Cao and colleagues found that the growth rate of transplanted malignant melanoma cells in mice exposed to environmental enrichment (EE mice) was significantly reduced compared with mice housed in standard (control) conditions. Mice in EE cages weighed less than control mice despite identical diets, prompting the authors to examine systemic metabolic changes. Levels of insulin-like growth factor 1 and leptin were reduced in EE mice and serum from EE mice reduced the growth of melanoma cells *in vitro*. Increased levels of both of these factors have been associated with an increased risk of cancer development and progression, as they can stimulate the growth of cancer cells.



Expression of BDNF, an important component of the hypothalamic pathway that regulates energy homeostasis, was increased in mice after 2 weeks of enriched housing. Overexpression of BDNF in mice had a similar effect on melanoma growth to housing mice in EE cages. In addition, the effect of EE on melanoma growth was lost in mice when *Bdnf* levels were reduced through miRNA-mediated knockdown or *Bdnf* heterozygosity.

How does BDNF that is produced by the hypothalamus influence the levels of leptin and adiponectin? Both leptin and adiponectin are predominantly synthesized by white adipose tissue and suppression of leptin expression is thought to be influenced by sympathetic tone through β-adrenergic receptors (β-ARs). The expression of β-ARs, as well as noradrenaline levels, were increased in white adipose tissue from EE mice. Use of a β-blocker prevented the EE-mediated changes in leptin and adiponectin levels and the reduced growth of the transplanted melanoma cells. Moreover, leptin deficient (*ob*/*ob*) mice did not show reduced melanoma growth when housed in EE cages.

These results were not restricted to melanoma; mice that were injected with colon cancer cells and transgenic mice that spontaneously develop colon cancer ($Apc^{Min/+}$ mice) had reduced tumour burden in EE cages compared with mice that were housed in control conditions. Moreover, exposure of mice with established tumours to EE cages led to prolonged survival.

Overall, these data indicate that exposure to environmental enrichment induces activation of the hypothalamic–sympathoneural–adipocyte axis, resulting in the suppression of leptin expression and in increased adiponectin levels. This, combined with an increase in the immune response in EE mice, suggests that exposure to 'positive stress' reduces the growth of tumours in mice.

Nicola McCarthy, Chief Editor,
Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Cao, L. *et al.* Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis causes cancer remission and inhibition. *Cell* 142, 52–64 (2010)

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