Environmental Enrichment: A Cure for Cancer? It’s All in the Mind

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Environmental enrichment is used to enhance mental stimulation and physical activity and has been shown to delay onset and progression of a range of brain disorders. Now, Cao et al. (2010) report in Cell that this paradigm also exerts strong influences beyond the brain and is capable of suppressing tumor growth in mice.

The merits of enhanced mental stimulation are well-documented and range from staving off Alzheimer’s disease in the elderly to the improvement of memory. The benefits of cognitive stimulation, as well as physical activity, have been investigated extensively in the laboratory by studies involving rodents. The roots of this research can be traced back several decades to the observations of Donald Hebb who rather astutely noted that the rats living ‘in-house’ (quite literally, as he had brought several laboratory rats home) performed better on complex memory-demanding tasks than rats housed in laboratory cages. ‘Environmental enrichment (EE)’ in the context of rodent studies embodies the benefit of being housed in a complex environment where the subject is constantly engaging components within their surroundings when compared with the otherwise mundane conditions and limited space of standard laboratory cages. In fact, revelation and realization of the poor conditions associated with standard housing have led to a revolution of animal housing practices and it is not uncommon for standard housing to include ‘enrichment objects’ (e.g. tunnels) nowadays.

The benefits of EE have been specifically demonstrated in the study of models of neurological conditions (e.g. Alzheimer’s disease, Huntington’s disease, stroke) where it is capable of delaying the rate of progression and/or reducing the severity of disease symptoms and pathology (Nithianantharajah and Hannan, 2006). Until recently, it had been difficult to consolidate the means by which mental stimulation alone could possibly have a significant impact on any organ apart from the brain. In comparison, physical activities which directly engage muscle fibers, modify cardiac output and increase blood circulation would be more likely to exert a significant influence on peripheral organs. However, the intimate relationship between the brain and the rest of the body should not be overlooked.

Cao et al. (2010) have now provided evidence that EE is capable of modifying tumor growth in mice inoculated with cells that induce melanoma, colon and intestinal cancers while showing that this remarkable effect is driven by central brain regions. They reported that tumor growth in environmentally enriched mice took place at a significantly slower pace than in standard-housed control mice with significant reductions in tumor sizes. Importantly, this novel observation was proposed to be a unique effect of sensory and cognitive stimulation since encouragement of increased physical activity levels alone via access to a running wheel in the home cage was incapable of reproducing the benefits of enrichment in the melanoma model. One caveat here is that the mice were group housed, so it will be interesting to see in a future study repeated under single-housing conditions whether individual mice running large distances are protected from cancer using these models since there is certainly prior evidence for enhanced physical exercise protecting against certain cancers (Esser et al., 2009). In an attempt to identify how mental stimulation could affect peripheral organs, the levels of serum proteins were assayed and the major adipocyte hormone leptin leapt out as a potential candidate driving the enrichment benefits. Increased serum leptin levels have been widely associated with prostate, breast cancer and melanomas and it was remarkable to find that leptin levels in enriched mice were reduced to only 13% of standard housed controls. The investigators then focused on the hypothalamus—a brain region known to secrete neuropeptides that enter into the circulatory system. More specifically, they examined the arcuate nucleus, a discrete population of neurons that receive and process peripheral information through circulating hormones including leptin. The reduction of leptin levels was matched with a concurrent down-regulation in neuropeptide Y levels in the arcuate nucleus, an expected response based on previous studies of metabolism. Finally, the study identified that the hypothalamic levels of a protein more commonly associated with brain development and neuronal function, brain-derived neurotrophic factor (BDNF), were crucial in enrichment-
induced changes in leptin levels and the consequent limitation of tumor growth.

Although no astute scientist would find this initial evidence sufficient to start championing cognitive stimulation as the answer to cancer, this study has raised the profile and potential of EE, emphasizing the importance of mental stimulation by providing evidence for yet another benefit. The interaction between the environment and BDNF is well-documented in the fields of depression and anxiety and there is evidence from animal models that EE confers resilience to certain mental conditions (Laviola et al., 2008; D’Andrea et al., 2010). The potential of EE to modify the body’s host resistance, which has relevance to cancer formation, is associated with increased natural killer (NK) cell activity in enriched mice (Benaroya-Milshtein et al., 2004). This agrees with the established role of NK cells as the body’s natural protector against cancer development since carcinogenesis if facilitated by the suppression of NK cell activity (Ben-Eliyahu et al., 1999).

More recently, significant improvements in immunotherapy outcomes and overall survival in a mouse model of B-cell lymphoma were attributed to EE (Benaroya-Milshtein et al., 2007). However, until the present study, no mechanism of action had been described by which EE-induced brain stimulation could reduce tumor growth and inhibit cancer formation. Those gaps in our knowledge are only just beginning to be filled by the findings of Cao et al. (2010).

This study also highlights the substantial differences between EE and physical exercise, and their effects on peripheral physiology. In principle, it can be assumed that exercise (or running specifically) is reliant upon the activation and engagement of peripheral organs (e.g. the heart by increasing cardiac output) to a much greater extent than mental stimulation alone. One would therefore predict that exercising mice would show greater reductions in peripheral tumor growth. It is therefore very intriguing that an exercise-induced up-regulation of BDNF gene expression was absent in the hypothalamus of exercising mice since that was a robust response to enrichment. That finding was in contrast to previous findings that a similar period of wheel-running leads to significant up-regulation of BDNF in discrete brain regions such as the hippocampus (Zajac et al., 2010). This result is a clear demonstration of the complex nature with which the brain responds to mental and physical stimulation since specific brain regions respond independently to such stimuli and could potentially be signaling to the periphery to elicit different changes in peripheral physiology (e.g. metabolism). Furthermore, EE and wheel-running could be causing region-specific alterations in gene expression by the distinct subnuclei of the hypothalamus besides the arcuate nucleus such as paraventricular, ventromedial, dorsomedial and lateral hypothalamic areas.

Despite no observable benefits of wheel-running in the melanoma model, it would be premature to disregard the potential of aerobic exercise for improving treatment outcomes in other models of cancer. This study did not examine the effects of running on tumor growth in the models of colon or intestinal cancer despite previous reports of reducing prostatic carcinogenesis (Esser et al., 2009). However, it must also be pointed out that running is reportedly detrimental in at least one model of breast cancer (Colbert et al., 2009). The benefits of running on the brain (enhanced cognition linked with increased BDNF expression and hippocampal neurogenesis) have been associated with elevated levels of angiogenesis and vascular endothelial growth factor expression, both of which are altered in psychiatric conditions such as depression (Newton and Duman, 2004). The anti-tumorigenic effect of running has been suggested to be due to increased vascularization (angiogenesis) and blood flow within tumors. However, angiogenesis is initiated by an up-regulation of insulin-like growth factor 1 (IGF1) expression and that is in contrast with the decreased levels of IGF1 in both enriched and exercising mice. Therefore, further research will be required to determine if alteration of angiogenesis is the mechanism by which enrichment reduces tumor growth and establish whether this process is indeed IGF1-independent.

Environmental modulation of hypothalamic function and the neuroendocrine system is well-established, as physical exercise has been shown to modulate the immune system through interactions with the central nervous and endocrine systems. Why then did increased physical exercise (via running wheel access) not have any observable impact on tumor growth? This is interesting since enriched and wheel-running mice had similarly activated immune responses based on splenic lymphocyte and T-cell cytotoxicity assays, suggesting that the effects of hypothalamic BDNF are mediated by different signaling pathways acting independently of the immune response. This possibility could be addressed using mice with depleted hypothalamic BDNF levels which Cao et al. (2010) found to be resistant to the EE-induced benefits. In the absence of that information, there remains the possibility that BDNF is signaling in the hypothalamus to a discrete subpopulation of neurons that regulate the immune response independently of modulation of leptin.

It was surprising that the administration of propranolol and subsequent reduction of sympathetic drive by β-adrenergic receptors (β-ARs) antagonists ablated the positive effect of enrichment on reducing tumor growth. It was uncertain whether the route of administration affected hypothalamic function independently of the tumor, since melanomas have been shown to express these receptors. This finding needs to be interpreted carefully since it is in contrast with a previous report that systemic blockade of β-ARs promotes tumor growth and reduces resistance to tumor metastasis (Shakhar and Ben-Eliyahu, 1998).

From a translational point of view, the clinical relevance of this study is yet to be tested. It should be noted that this study was carried out in young mice between 6 and 9 weeks just as they reached sexual maturity whereas the cancers modeled are rare in humans at a young age. Furthermore, it is well-known that stress hormone levels increase with age. This could have a significant impact on the extent to which enrichment-driven increases in BDNF gene expression occurs. With that in mind, follow-up studies on aged mice may prove informative.

Regardless of the mechanisms by which tumor growth is suppressed, one key unanswered question is how EE and associated mental stimulation enhance hypothalamic BDNF expression. Addressing this major
question will have implications not only in the field of cancer research, as Cao et al. (2010) suggest, but also the multitude of mental disorders associated with alterations in BDNF signaling. The significance of this publication cannot be over-stated as it represents a giant step forward in the understanding of how the brain talks to the rest of the body. It also serves to re-emphasize the far-reaching influence of the nervous system by embodying a perfect marriage of two distinct fields of research—neuroscience and oncology. Hopefully, this study will open the floodgates to future endeavors exploring how the brain interacts with and influences the function and pathology of discrete organs that have historically been viewed as separable physiological systems.

References


