A Richness that Cures

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A study in *Nature* by Fischer et al. shows that environmental enrichment or increasing histone acetylation rescue the ability to form new memories and re-establish access to remote memories even in the presence of brain degeneration. Chromatin remodeling may be the final gate environmental enrichment opens to enhance plasticity and represents a promising target for therapeutical intervention in neurodegenerative diseases.

Exposure to enriched environment (EE) potently modulates synaptic plasticity and learning and memory processes. Effects of EE have been observed in developing, adult, and aging animals (Cancedda, et al., 2004; Nithianantharajah and Hannan, 2006). In laboratories, exposure to EE is achieved by housing animals (rodents) in large cages where exploratory activity is promoted by the presence of a variety of toys, tunnels, and climbing devices. A recent study in *Nature* by Fischer et al. suggests that these enrichment effects might be mediated, at least in part, by chromatin remodeling (Fischer et al., 2007).

Fischer et al. examined the beneficial effects of EE in a mouse model, the p25 transgenic mouse, which allows temporally and spatially restricted induction of neuronal loss. The p25 protein has been implicated in various neurodegenerative diseases, including Alzheimer's disease (Cruz and Tsai, 2004). The authors had previously demonstrated that, upon induction of the p25 transgene in adult mice, neurodegeneration is triggered, and animals also display both learning and memory impairments (Fischer et al., 2005). Six weeks after switching the transgene on, mice are not only unable to form new memories but they are also unable to retrieve memories acquired before the transgene was switched on. Now, Fischer et al. have used this model system to assess whether EE has beneficial effects in this transgenic animal model (Fischer et al., 2007). Six weeks after induction of p25, when anatomical and functional deficits are well established, the authors transferred the animals into an EE for 4 weeks. Surprisingly, the authors found that this rescued the mice's ability to form new memories (i.e., the mice learned a new fear conditioning and a new spatial task) and also allowed the mice to re-establish access to remote memories learned prior to brain degeneration, all of this despite the fact that the neuronal loss did not recover (Figure 1). It is important to note that the new memories formed by the mice required the hippocampus, while remembering the remote memories likely involved accessing neocortical networks, as these remote memories would have been progressively transferred from the hippocampus to the neocortex over time. Indeed, while recall of recent memories activates the hippocampus and hippocampal lesions impair this recall, remote memory retrieval is impaired by cortical lesions, and their recall activates cortical areas (Frankland and Bontempi, 2005). The fact that EE restores both new learning and access to remote memories suggests that the effects of EE are probably widespread within hippocampal and cortical areas.

What caused the effects reported by Fischer et al.? The authors demonstrated that synaptic-related proteins were increased in EE mice, indicating the presence of new dendritic branching and activation of synaptogenesis. This increase was seen in both the hippocampus and the cortex, strengthening the idea that the behavioral effects they reported might be related to these anatomical changes. Prior studies had also shown an effect of EE on neural connectivity, and these results had been taken as an indication that synaptic plasticity was induced. But the authors also went a step further. They first demonstrated that EE increased histone acetylation in the hippocampus and, to a lesser extent, in the cortex of wild-type mice. Histone post-translational modifications regulate chromatin susceptibility to transcription: high levels of histone acetylation on a specific DNA segment is generally correlated with increased transcription rates. The effects of EE on wild-type mice suggested that the effects of EE in the p25 transgenic mice might be mediated, at least in part, by histone acetylation. Indeed, the authors also found that promoting histone acetylation by means of administration of histone deacetylation inhibitors to these mice also promoted synaptogenesis and recovery from learning and memory deficits, similar to that seen with exposure to EE. Beneficial effects of histone acetylation in memory-related plasticity had previously been described both in WT animals and in animal models of human mental retardation (Alarcon et al., 2004; Korzus et al., 2004; Levenson and Sweatt, 2005). The importance of the Fischer et al. results is that they show, for the first time, that promoting histone acetylation restores learning and the access to long-term memories in a degenerated brain, after synaptic and neuronal loss had already occurred and in the absence of neuronal regeneration.

Similar beneficial relationships between histone acetylation states and EE effects have also recently been shown to exist in the visual system.

Histone acetylation can be modulated by visual experience, and this affects subsequent experience-dependent plasticity in the visual cortex (Putignano et al., 2007). Visual experience activates histone acetylation during the critical period for ocular dominance plasticity, but its action becomes downregulated in adult animals, in correlation with the lower levels of adult cortical plasticity: this suggests that, as it does with plasticity of visual cortical connections, visual experience progressively reduces its own effectiveness in regulating gene transcription and/or modifies the ensemble of regulated genes (Majdan and Shatz, 2006). Trichostatin treatment, which promotes histone acetylation in the visual cortex, also enhances adult visual cortical plasticity (Putignano et al., 2007). Similarly, EE in adult rats promotes recovery from a pathological reduction in visual acuity arising from a defective visual experience during development (amblyopia) (Sale et al., 2007). Monocular deprivation during the critical period causes strong modifications in visual cortical circuits and leads to loss of vision in the deprived eye. While visual acuity recovers if normal vision is restored to the deprived eye during the critical period, very little recovery is observed in adult animals. Sale et al. showed that when they reopened the deprived eye in adult rats and exposed these amblyopic animals to EE, these rats recovered normal visual acuity in the formerly deprived eye. The effects of enrichment seemed to be mediated by a reduction in the intracortical inhibitory tone in the visual cortex: EE animals showed a reduction in GABA release, while enhancing GABA action by diazepam infusion into the visual cortex prevented EE-induced recovery of visual acuity. This recovery was also associated with modulation of other factors known to be involved in visual cortical plasticity (e.g., BDNF and extracellular matrix components, chondroitin sulfate proteoglycans [CSPGs]; Pizzorusso et al., 2002). In particular, BDNF was shown to be upregulated in the visual cortex of enriched animals, and the assembly of CSPGs in perineuronal nets (PNNs) was reduced (Sale et al., 2007).

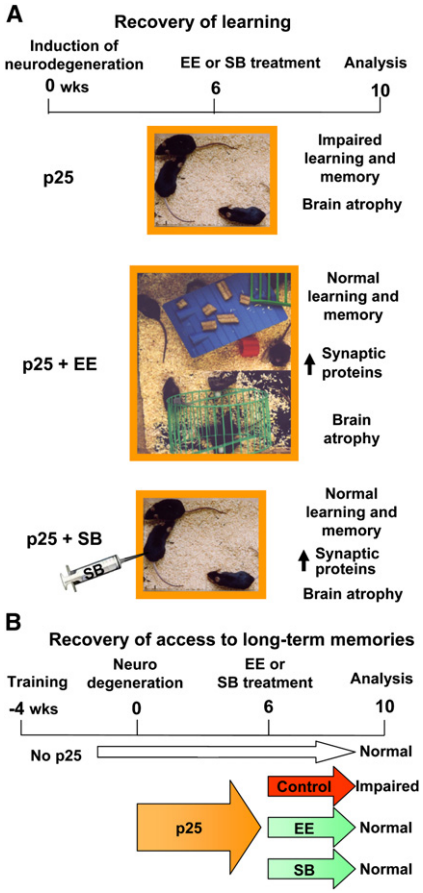

Figure 1. Induction of p25 for 6 Weeks (Starting at 11 Months of Age) Induces Brain Atrophy, Neurodegeneration, and Learning and Memory Impairments

(A) Exposure to EE for 4 weeks reinstates normal learning and memory despite the persisting brain atrophy. EE in WT mice increased histone acetylation (see text). Daily injections of histone deacetylase inhibitor sodium butyrate (SB) for 4 weeks determine effects similar to EE in non-EE p25 mice.

(B) Mice were trained in two learning tasks and then returned to their home cages. After 4 weeks, in some of the mice p25 was induced for 6 weeks, causing neurodegeneration. Mice were either put in an EE or kept in their home cages for 4 weeks. Non-EE p25 mice showed loss of memory of what they had learned 14 weeks before; EE p25 mice showed a marked recovery of long-term memory. Also in this case, brain atrophy was not affected by EE. The same effect was obtained in p25 mice treated with SB for 4 weeks.

The studies on the effects of EE on memory (Fischer et al., 2007) and adult visual cortical plasticity (Sale et al., 2007) nicely complement each other. It is possible that the cellular and molecular mechanisms proposed to mediate the effects of EE on adult visual cortical plasticity could be upstream of the histone acetylation effects reported by Fischer et al., thus filling the gap between EE and control of chromatin remodeling. Taken together, the results of these two papers allow one to draw a tentative scenario linking EE with the activation of gene transcription programs leading to plastic changes that subserve functional recovery (Figure 2). This interpretation is strengthened by the fact that the two very different models of plasticity used in Sale et al. and Fischer et al. share two common features, sensitivity to EE and to histone acetylation. Indeed, promoting histone acetylation enhances plasticity both in the visual cortex (Putignano et al., 2007) and in different learning and memory systems (Fischer et al., 2007; Alarcon et al., 2004; Korzus et al., 2004), as is the case for EE, which promotes recovery both in amblyopic rats and in p25 mice. This strongly suggests that epigenetic control of gene transcription through histone acetylation could be the final gate opened by EE to promote plasticity.

EE has been demonstrated to be beneficial in reducing cognitive deficits and the progression of the disease in several models of neurodegenerative pathologies related to human diseases, such as Huntington's and Alzheimer's, and in preventing neurodegeneration caused by different types of insults (ischemic, traumatic) (Nithianantharajah and Hannan, 2006; Berardi et al., 2007; Lazarov et al., 2005). In these models, many of the factors regulated by EE are neuroprotective, promote plasticity, and ameliorate behavioral and morphofunctional deficits. Could this be true also for histone acetylation? Fischer et al. provide some support for this idea by showing that histone deacetylation inhibitors allow cognitive recovery after behavioral and anatomical pathology are already established. It is hoped that studies such as these will eventually allow

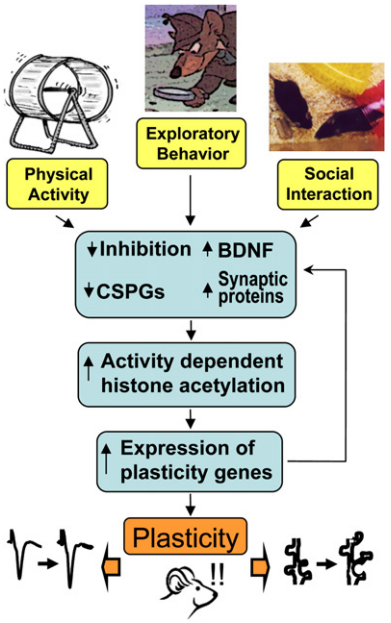

Figure 2. Diagram Showing the Possible Mechanisms of Action of EE on Functional and Structural Plasticity

sufficient understanding of the EE process such that this mechanism might be exploited to its full potential as a "behavioral therapy" in humans. In addition, EE animals can be viewed as potential models to fish out molecules that mediate the beneficial effects of EE and that might someday be used to develop possible therapeutic agents for humans. It should be stressed that the Fischer et al. (2007) study does not directly address whether promoting histone acetylation might be beneficial in human neurodegenerative pathologies, given that it remains unknown whether the elegant mouse model used in their studies truly recapitulates all the features found in patients affected by neurodegenerative diseases such as Alzheimer's disease. However, by increasing our knowledge on the cellular and molecular mechanisms underlying EE's beneficial effects, papers like those discussed here pave the way for the possibility that therapeutic applications for humans may well be developed in the future.

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