Exercise and brain neurotrophins

SIR — Physical activity has emerged as a predictor of high mental function in ageing[1]. Exercise has been shown to affect several neurotransmitter systems[2,3], but it remains to be shown whether it can influence other key molecular systems which serve the maintenance and plasticity of the brain. Brain-derived neurotrophic factor (BDNF), a growth factor of the neurotrophin family, supports the function and survival of many neurons[4–6], and may help protect neurons from free-radical damage[7]. Ample evidence indicates that production of BDNF in the brain is regulated by neuronal activity[8–11]. Here we report evidence that physical exercise can increase BDNF gene expression in specific brain regions. These data open the encouraging possibility that exercise may increase the availability of trophic support, and thus resilience against insult, in certain neuronal populations.

Rats seem to find physical activity inherently rewarding; most will voluntarily run 1–2 km during the night, given access to a running wheel. Once acclimatized to running, each rat tends to maintain a characteristic activity level, running a similar total distance each night.

We used a nuclease protection assay to measure BDNF messenger RNA in distinct brain structures of adult rats following 0 (control), 2, 4 or 7 nights with free access to running wheels. BDNF mRNA in the hippocampus and caudal 1/3 of the neocortex (P = 0.05) was significantly increased over control levels after 2 nights with exercise, and remained elevated for 7 nights.

We next examined BDNF mRNA hybridization in specific cell populations within these structures via *in situ* hybridization (Fig. 1). Within the hippocampus, the pyramidal cells of Ammon's horn areas 1 and 4 (CA1, CA4) showed the largest upregulation, whereas CA3 and the dentate gyrus granular layer (DG) sustained smaller, later increases. In the caudal neocortex, labelling in layers II–III and V–VI rose progressively with length of exposure to exercise .

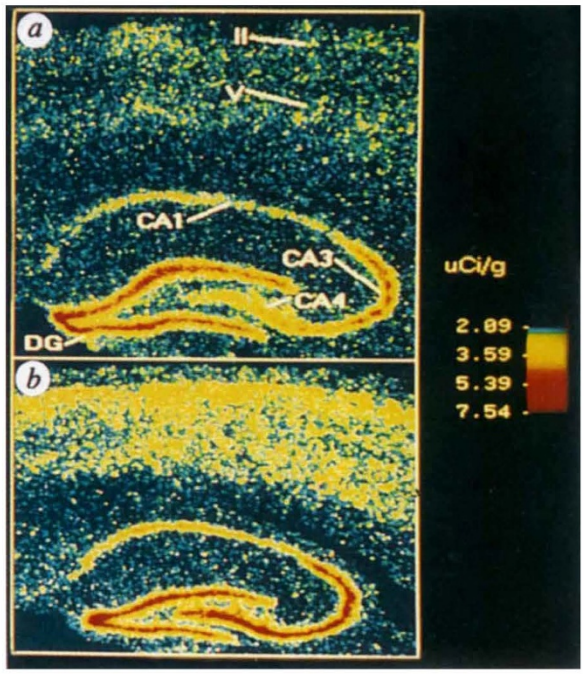

FIG. 1 Colour-enhanced image of autoradiograms from *in situ* BDNF mRNA hybridization in rat brain (sagittal plane). Increasing hybridization (ROD) is represented by green, yellow, then red. *a*, Control; *b*, 7 nights with exercise. Neocortical layers II and V, and hippocampal areas CA1–4 and dentate gyrus (DG), are identified. Methodological details can be obtained from the authors.

Because individual rats in the study maintained different activity levels, we compared BDNF mRNA levels with distance run per night by each rat. We found a significant, positive correlation between mean distance run per night and BDNF mRNA in hippocampus (Fig. 2*a–c*) and caudal neocortex (data not shown) in all exercise groups. One rat in the 2-night group did not run, and had BDNF mRNA measurement (Fig. 2*a*) close to control levels.

Interestingly, the greatest effects of exercise on BDNF occurred in highly plastic, or changeable areas, responsive to environmental stimuli[11–13]. This result supports previous suggestions that BDNF is involved in brain plasticity. A second relevant consideration is BDNF's potential involvement in neuronal survival and functional maintenance. For example, retrograde transport of BDNF from the hippocampus provides vital support to forebrain cholinergic neurons[14,15], a site of Alzheimer's disease and age-related degeneration. Physical activity could increase availability of BDNF to these cells by upregulating its expression in the hippocampus. Exercise-induced upregulation of BDNF could help increase the brain's resistance to damage and degeneration through BDNF's support of neuronal growth, function and survival.

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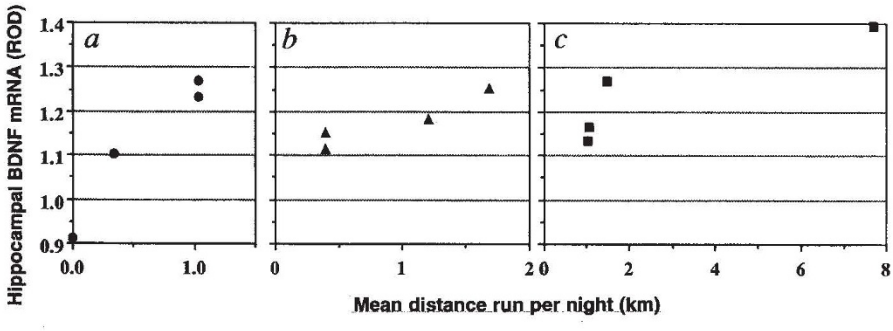

FIG. 2. Mean nightly distance run by each rat was significantly correlated with hippocampal BDNF mRNA (relative optical density measurements from the nuclease protection assay). *a*, Two-night (r=0.967, P=0.05); *b*, 4-night (r=0.95, P=0.05); and *c*, 7-night (r=0.892, P=0.2) groups. Wheel revolutions were monitored by computer (Ratrun, C. Hage Associates).

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