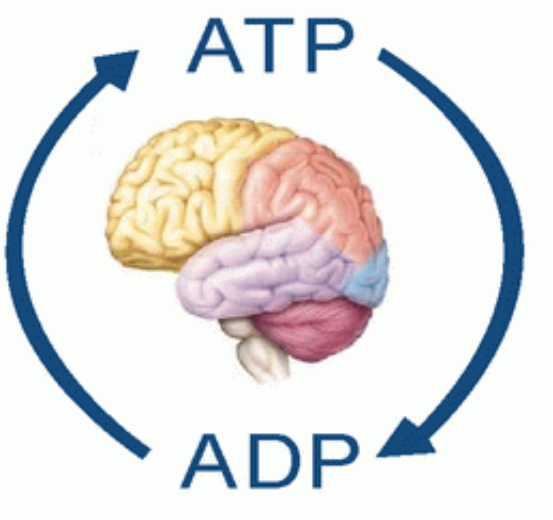
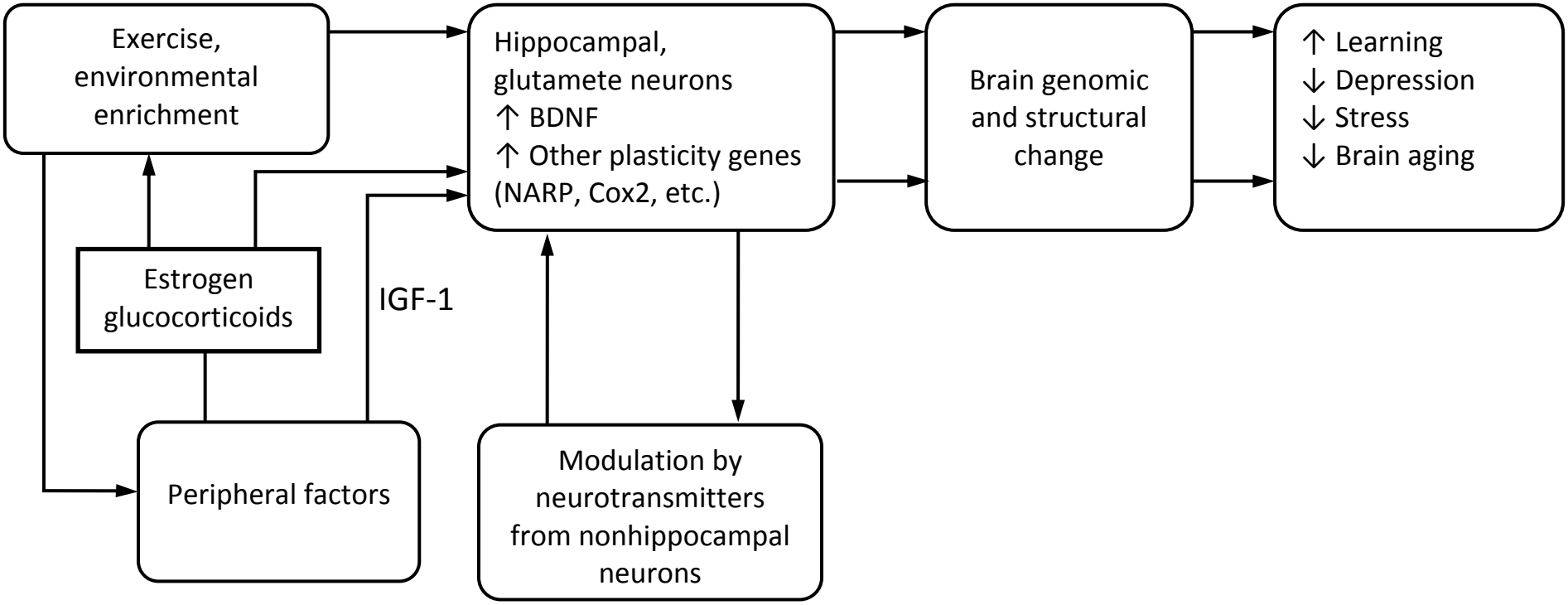


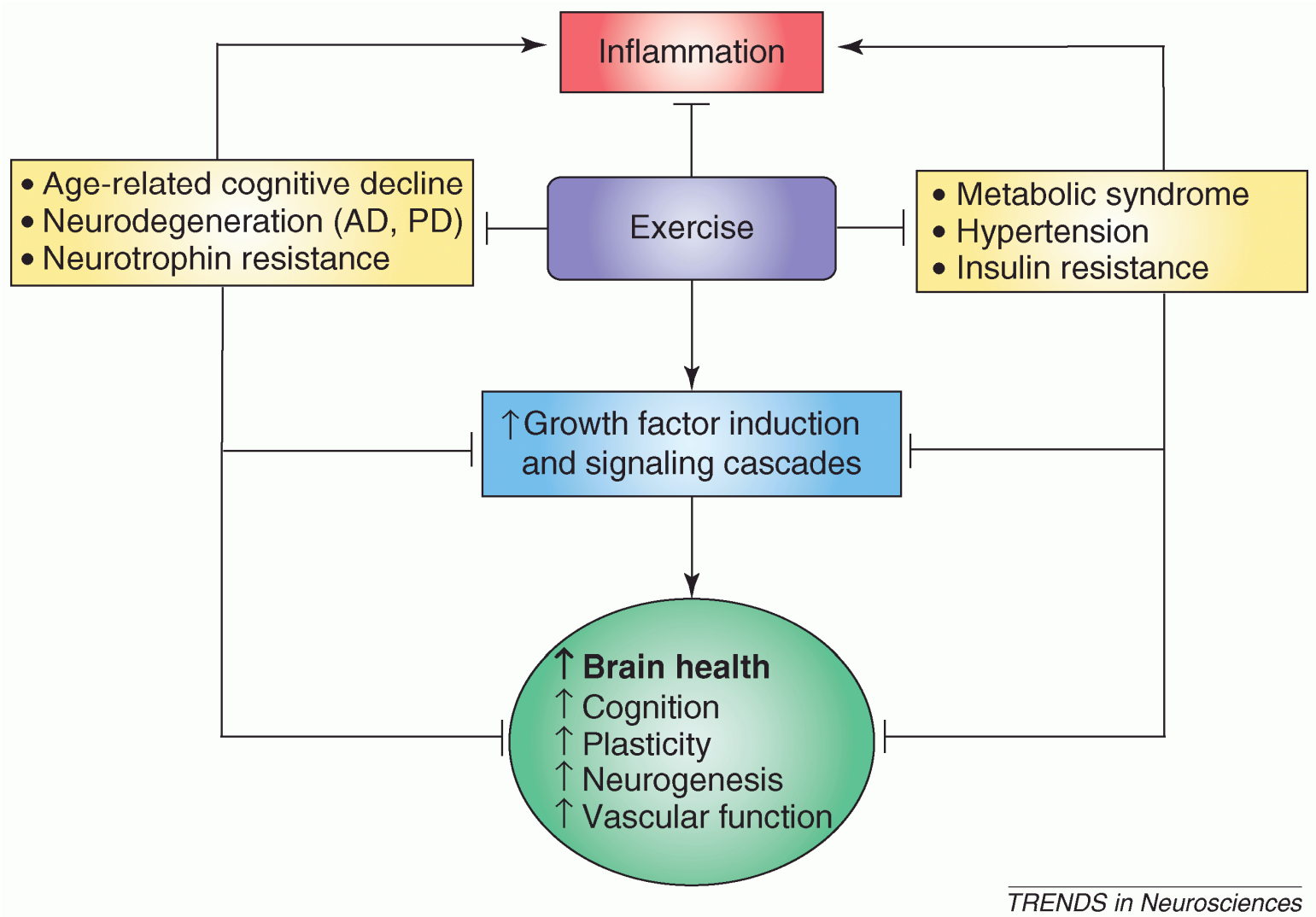
International Brain Awareness Week
March 16-22, 2009

Initiative on neurosciences and exercise promoted by Ginetto Bovo
In memory of my beloved wife Laura

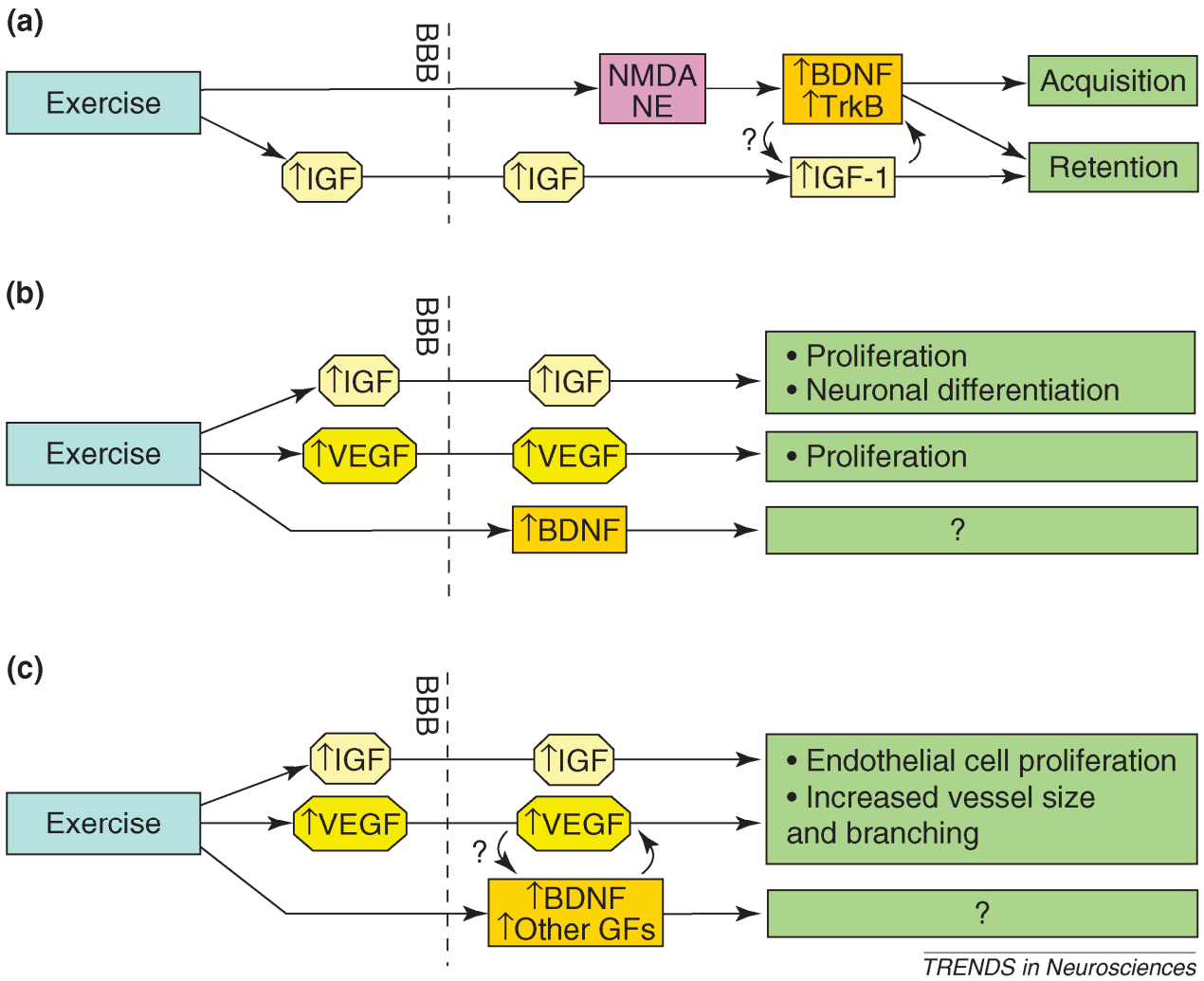
Figures reproduced with kind permission of Professor Carl W. Cotman, Institute for Brain Aging and Dementia, University of California-Irvine (USA), and Elsevier, Amsterdam (The Netherlands).
From Trends in Neuroscience, "Exercise a behavioral intervention to enhance health and plasticity", Vol. 25 (2002)



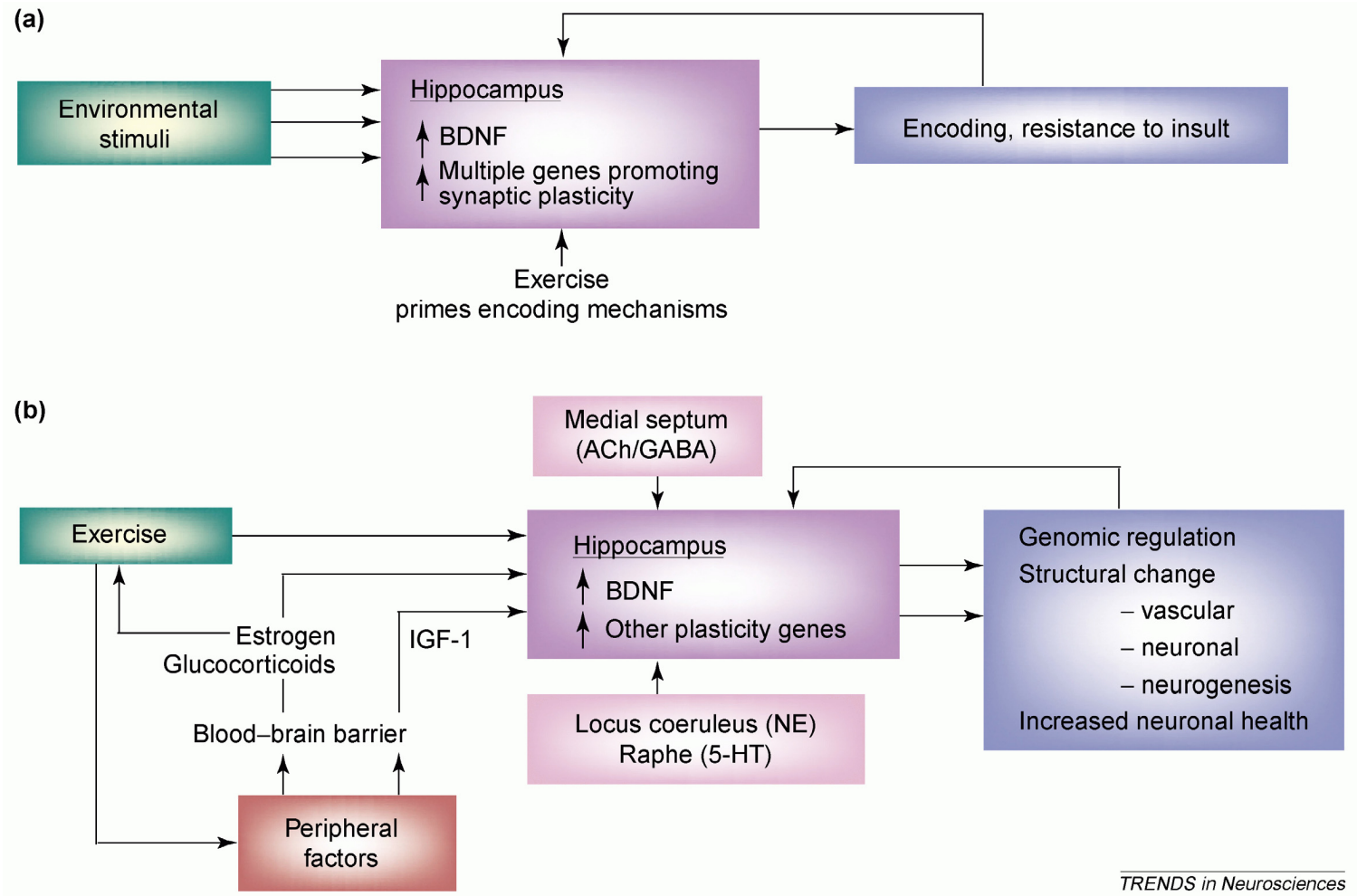
Mechanisms by which exercise and environmental enrichment prime the brain to enhance brain function by improving resistance to injury and age-related decline. Exercise and enrichment act on glutamate neurons in the hippocampus to increase levels of protective and plasticity factors such as BDNF. BDNF up-regulates NARP and COX-2, suggesting that BDNF may be one of the initiating molecules regulating some of the beneficial effects of exercise. Multiple factors control BDNF expression in the hippocampus, including neurotransmitters from nonhippocampal neurons and peripheral circulating factors such as estrogen, glucocorticoids, and IGF-1 (which is itself increased by exercise). Regulation of protective and plasticity factors results in further downstream genomic changes and structural changes in the brain that ultimately improve brain function.



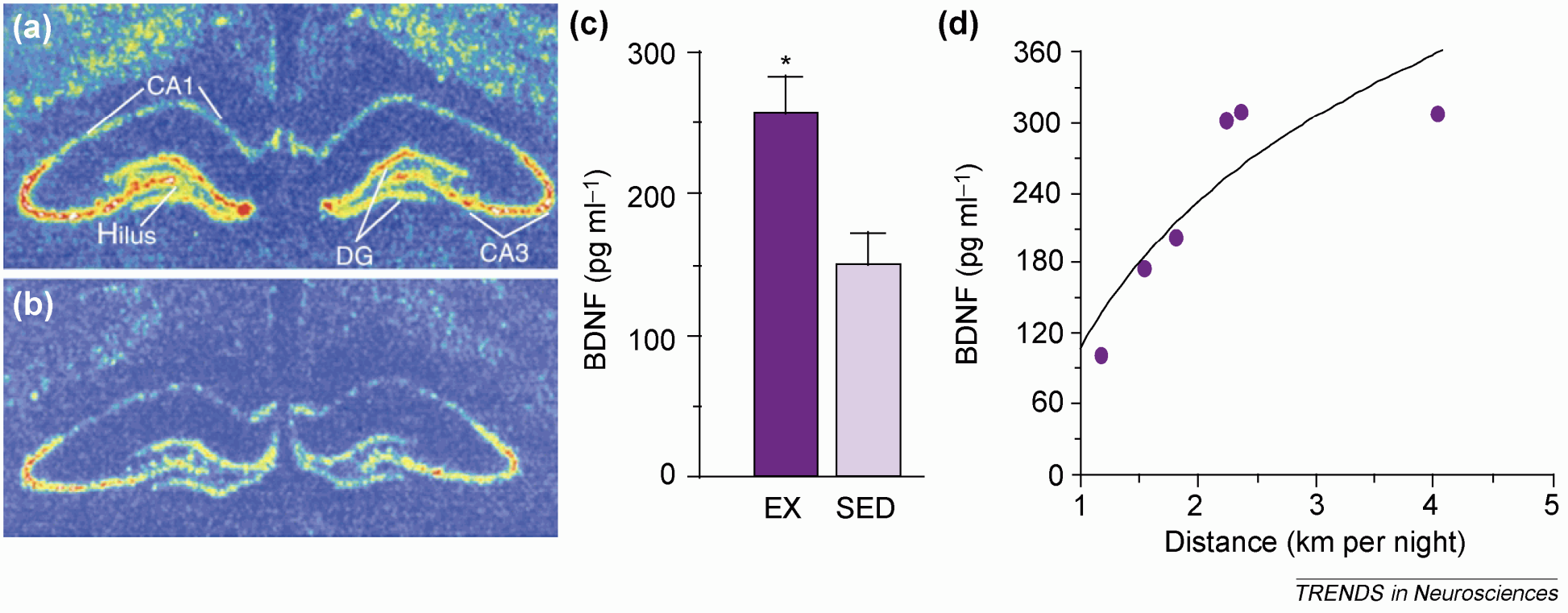
Exercise induces growth factor cascades, a central mechanism mediating exercise-dependent benefits in cognition, synaptic plasticity, neurogenesis and vascular function. In addition, exercise reduces peripheral risk factors for cognitive decline such as hypertension and insulin resistance, components of the metabolic syndrome that converge to increase the risk for brain dysfunction and neurodegeneration. Inflammation, which can impair growth factor signaling, exacerbate the metabolic syndrome and accelerate cognitive decline, is reduced by exercise. Overall, exercise induces growth factor cascades and reduces peripheral risk factors for cognitive decline, all of which converge to improve brain health and function, and to delay the onset of and slow the decline in neurodegenerative diseases including Alzheimer disease (AD) and Parkinson's disease (PD).



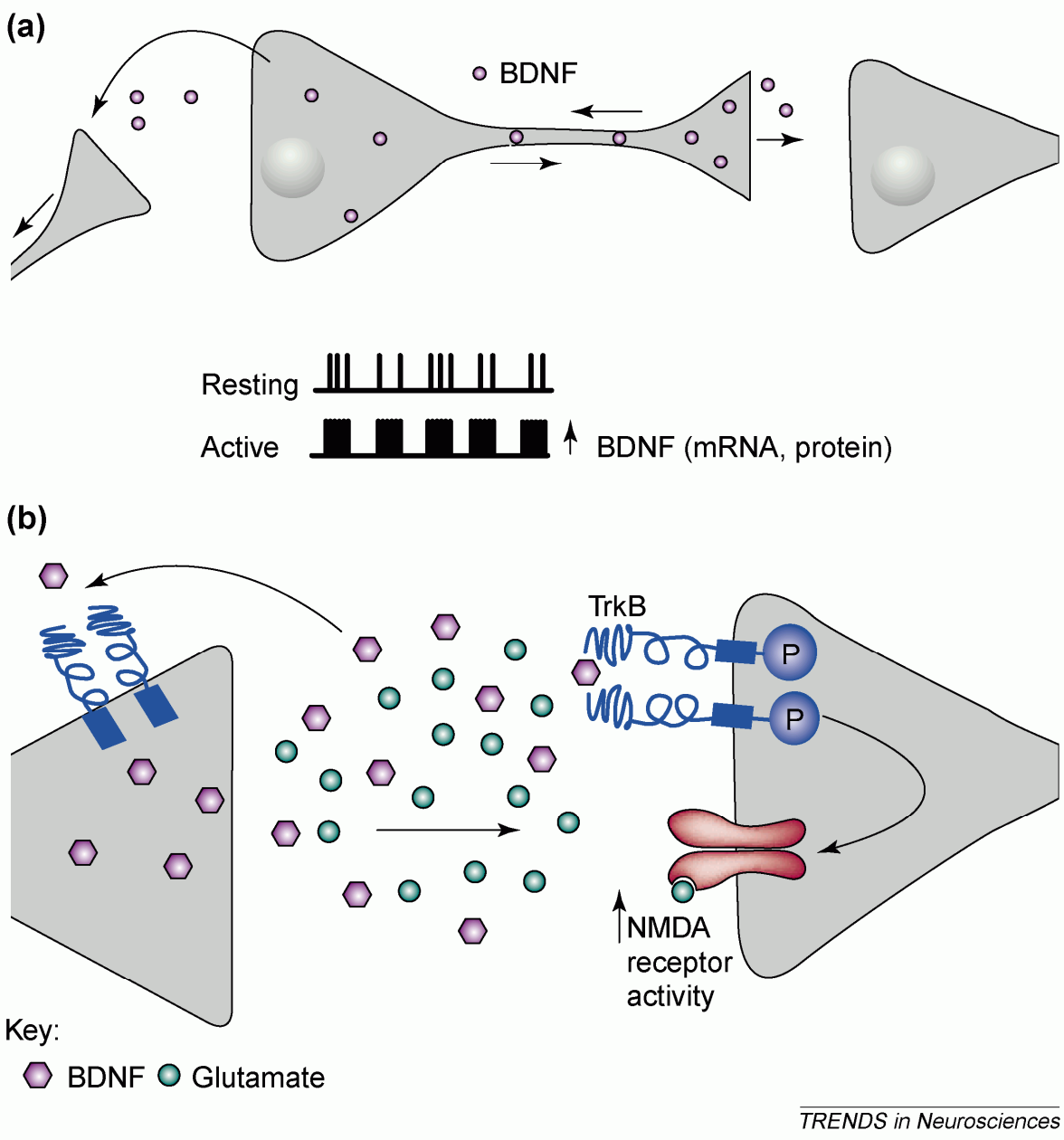
Exercise regulates learning, neurogenesis and angiogenesis through growth factor cascades. Insulin growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) derived from central and peripheral sources act in concert to modulate exercise-dependent effects on the brain. (a) Exercise enhances learning by induction of BDNF and IGF-1. Neurotransmitters, including NMDA receptors and the noradrenergic (NE) system [54,55], peripheral IGF-1 and possibly centrally derived IGF-1, mediate the induction of hippocampal BDNF with exercise. In turn, BDNF signaling is likely to be a hub foreffects of exercise on learning, including acquisition, retention and LTP. (b) Exercise stimulates neurogenesis in the hippocampus through the interactive effects of IGF-1 with VEGF. Peripheral IGF-1 and VEGF cross the blood-brain barrier (BBB) and drive enhanced proliferation and survival. (c) Exercise stimulates angiogenesis through the effects of IGF-1 and VEGF on endothelial cell proliferation and vessel growth. Peripheral sources of the growth factors (and possibly also central sources) mediate the effects. The role of BDNF in exercise-mediated neurogenesis and angiogenesis has not been directly tested.



Mechanisms by which voluntary running primes the brain to encode meaningful information from the environment. (a) Exercise might act as a gate that primes the hippocampus to respond to environmental stimulation, while simultaneously ensuring the viability of neurons to resist insult. These responses, in turn, feed back to strengthen the brain in a use-dependent fashion. (b) Exercisemediated enhancement of the encoding of information and neural resistance could involve factors such as brain-derived neurotrophic factor (BDNF), a prototypical candidate molecule that can help us to understand how exercise benefits the brain. Multiple factors control BDNF expression in the hippocampus. BDNF is expressed in glutamatergic neurons and its levels are modulated by neural activity and neurotransmitter input from the medial septum, raphe and locus coeruleus. Exercise-dependent BDNF gene changes are modulated by combined septal ACh and GABA inputs, noradrenaline (NE) and peripheral factors. BDNF gene expression is also dependent on steroid hormone (estrogen and corticosterone) status and peripheral entry of insulin-like growth factor 1 (IGF-1) into brain (which is itself modulated by exercise).



Effects of exercise on hippocampal brain-derived neurotrophic factor (BDNF) mRNA and protein levels. (a) *In situ* hybridization shows that expression of BDNF mRNA in the rat dentate gyrus (DG), hilus, CA1–CA3 regions and cortex is greater following exercise (seven days of voluntary wheel-running) than in sedentary animals (b). (c) ELISA quantification of hippocampal BDNF protein levels in the hippocampus in sedentary (SED) and exercising (EX) animals, after five days of wheel-running (*P <0.05). (d) Rats and mice acclimate rapidly to the running wheel and progressively increase their extent of daily running, in some cases up to a startling 20 kilometers (~12–13 miles) per night. BDNF protein levels correlate with running distance (average over 14 days running; $R^2 = 0.771$).



Characteristics of brain-derived neurotrophic factor (BDNF) that make it a natural candidate to mediate the benefits of exercise on brain health. (a) BDNF is transported retrogradely and anterogradely to synapses, where it potentiates synaptic transmission, participates in gene transcription, modifies synaptic morphology, and enhances neuronal resilience. BDNF mRNA and protein levels increase in an activity-dependent manner. (b) Released BDNF binds to its receptor (TrkB) presynaptically to modify transmitter release and postsynaptically to modify postsynaptic sensitivity, for example, via interaction with NMDA receptors [69,70].

Recent literature documenting the benefits of exercise on human brain health and function. IGF-1 = insulin-like growth factor; NARP = neuronal activity-regulated pentraxin; COX-2 = Cyclooxygenase-2.

- Improved cognitive function-executive function, memory (Colcombe & Kramer 2003)
- Protection from depression (DiLorenzo et al. 1999; Lawlor & Hopker 2001)
- Prevention of age-related declines in cerebral perfusion (Rogers et al. 1990)
- Prevention of age-related brain tissue loss (Colcombe et al. 2003)
- Decreased risk and incidence of Alzheimer's disease and general dementia (Friedland et al. 2001; Laurin et al. 2001)