Physical exercise- and stress-induced neuroplasticity changes in knock-in mice with the human BDNF Val66Met polymorphism

A. Ieraci[1], L. Musazzi[1], A. Mallei[1], A.I. Madaio[1], P. Tornese[1], N. Sala[1], F.S. Lee[2], M. Popoli[1]

[1]Laboratory of Neuropsychopharmacology and Functional Neurogenomics - Dipartimento di Scienze Farmacologiche e Biomolecolari and Center of Excellence on Neurodegenerative Diseases, University of Milano, Milano, Italy
[2]Dept. of Psychiatry, Weill Cornell Medical College of Cornell University, New York, New York 10065, USA

Brain-Derived Neurotrophic Factor (BDNF), the most abundant neurotrophin in the adult brain, has an essential role in the nervous system development and adult neuroplasticity. Due to its pleiotropic effects, BDNF has been involved in cognitive functions and in the pathogenesis of various neuropsychiatric disorders. Physical exercise (PE) and stressful experiences have been shown to exert opposite effects on behavioral functions and brain plasticity, partly by involving the action of BDNF. However, a considerable variability of individual responses to these environmental challenges has been reported. The reason for this is not known, but may be accounted for by individual genetic variants. A common single nucleotide polymorphism (SNP) has been identified in the BDNF human gene (BDNF Val66Met) that leads to decreased BDNF secretion and has been correlated with cognitive deficits and neuropsychiatric disorders. Recently, a knock-in mouse carrying BDNF Val66Met SNP, which replicates core phenotypes identified in Val66Met human carriers, has been generated. Despite the well-documented role of BDNF as mediator of the effects of PE and stressful experiences, it is still controversial whether the BDNF Val66Met SNP may moderate the individual response to these environmental challenges.
To study whether and how the BDNF Val66Met SNP impacts the neurobiological effects induced by different environmental challenges, we specifically assessed behavioral changes, hippocampal neurogenesis modifications and gene expression variations induced by 28 days of voluntary running in wild type ($BDNF^{Val/Val}$) and homozygous BDNF Val66Met knock-in ($BDNF^{Met/Met}$) male mice. Moreover, we measured plasma corticosterone levels and glutamate release from hippocampal synaptic terminals (synaptosomes) in superfusion, in $BDNF^{Val/Val}$ and heterozygous ($BDNF^{Val/Met}$) mice after acute restraint stress.
We found that PE decreased the latency to feed in the novelty suppressed feeding and the immobility time in the forced swimming test in $BDNF^{Val/Val}$ but not $BDNF^{Met/Met}$ mice. PE-induced hippocampal neurogenesis was reduced in $BDNF^{Met/Met}$ mice compared to $BDNF^{Val/Val}$ mice. PE significantly increased total BDNF mRNA, BDNF splice variants 1, 2, 4, 6 and mGluR2 in the dentate gyrus of $BDNF^{Val/Val}$ but not in $BDNF^{Met/Met}$ mice. $BDNF^{Met/Met}$ mice had lower basal BDNF protein levels in the hippocampus, which did not increase following 28 day-PE.
On the other hand, acute restraint stress promoted a higher release of glutamate in the hippocampus of $BDNF^{Val/Met}$ compared to $BDNF^{Val/Val}$ mice. Moreover, we found that acute restraint stress induced a similar increase of corticosterone plasma levels in both $BDNF^{Val/Met}$ and $BDNF^{Val/Val}$ mice.
Overall these results showed that BDNF Val66Met polymorphism impairs the beneficial effects of PE and favors a maladaptive stress response in adult male mice, suggesting that BDNF Val66Met polymorphism moderates the neuroplasticity effects and the behavioral outcomes induced by different environmental challenges. The present results are in line with the higher susceptibility to stress of human Val66Met carriers, and suggest that the BDNF SNP moderates the response to PE.