Peripheral blood BDNF alterations in adult subjects exposed to childhood trauma experiences

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Several evidences support causal relations between early life stress and psychiatric disorders. Indeed, exposures to childhood trauma experiences are associated with increased vulnerability for several kinds of disorders, including mental illnesses [van Winkel et al., 2013]. This increased vulnerability is due to the fact that childhood is a critical period for the brain development, where the brain is not completely developed yet and thus high vulnerable to adverse events. The Brain-Derived Neutrotrophic factor (BDNF) is a neuronal growth factor, which plays pivotal roles in the brain, regulating neurogenesis, neuronal maturation and survival, and synaptic plasticity [Tsankova et al., 2007]. It has been proposed that BDNF could be the link between early life stress and the vulnerability to psychiatric disorders [Schroeder et al., 2010].
The focus of this work was to investigate BDNF levels in the peripheral blood of control subjects characterized for exposures to stressful experiences during childhood. By using Real Time PCR we measured total BDNF mRNA levels and the results indicated a strong reduction of total BDNF mRNA levels in individuals exposed to stress early in life versus not exposed individuals (-32%, $p<0.01$ vs not exposed subjects). Then, we assessed the contribution of the different BDNF transcripts on BDNF total mRNA modulation, and we found that transcripts IV and IX were significantly reduced (-71%, $p<0.05$; -35%, $p<0.05$, respectively, all vs not exposed subjects). In order to investigate the molecular mechanisms underlying these long lasting changes in BDNF expression, we evaluated the role of DNA methylation and miRNAs as possible epigenetic mechanisms. We assessed the DNA methylation levels of specific CpGs in both the transcripts IV and IX, however, no significant changes in association to stress exposures were observed. Then, we focused on miRNAs targeting BDNF and we identified, by using biostatistical tools, a panel of predicted and validated miRNAs targeting the BDNF 5' UTR region, the CDS region and the 3' UTR region. Due to the high number of possible miRNAs targeting BDNF that we identified, we decided to use a whole genome approach and we run a miRNome analysis. We found that 26 of the 805 miRNAs targeting BDNF are significantly up regulated in response to stress early in life (Fold Change>1.2; $p<0,05$). Bioinformatic analysis, using the DIANA miRPath program (v.2.0), identified, among the most significant pathways modulated by the significant miRNAs, the signal transduction, the neurotrophin signalling and the long-term potentiation related pathways.
In conclusion, we found that total BDNF mRNA levels are reduced in the peripheral blood of subjects exposed to stressful experiences during childhood and that miRNAs could be, at least in part, responsible for these long lasting changes in BDNF expression. In the future, a better characterization of miRNAs modulation may identify novel targets for preventative therapies in subjects with a history of childhood trauma, which are at higher risk to develop psychiatric disorders in the adulthood.

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