MDMA EXPOSURE INDUCES BDNF AND HDAC I ALTERATIONS: POSSIBLE CORRELATION WITH LATER NEUROPSYCHIATRIC DISORDERS

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Introduction: A relationship between drug addiction and the development of psychiatric disorders has been suggested. In this regard, different factors such as genetic vulnerability, psychosocial experiences and environmental influences could favor this comorbidity. The abuse of "ecstasy" that is 3,4-methylenedioxymethamphetamine (MDMA) has been associated with the onset of psychological disorders and with a number of psychiatric symptoms which persist after the cessation of drug abuse.
The neurotrophin brain-derived neurotrophic factor (BDNF) seem to play a relevant role both in addiction-related neuroplasticity and in neurochemical alterations observed in neuropsychiatric disorders. In addition, epigenetic processes which represent a mechanism able to modulate long-term gene expression changes could be involved in this comorbidity and, in particular, an involvement of histone deacetylase (HDAC) class I enzymes has been suggested. On this basis, our purpose was to evaluate the effects of the acute or chronic MDMA administration on the HDAC class I enzyme gene expression as well as on the mRNA levels for the neurotrophic factor BDNF and its TrkB receptor.

Materials and methods: Male Sprague-Dawley rats received the acute or chronic (twice daily for 7days) intraperitoneal administration of 8mg/kg MDMA. After treatments, the mRNAs of interest were analyzed by qRT-PCR in the hippocampus (HIPPO) and prefrontal cortex (PFCX) of MDMA- or vehicle-treated rats.

Results: An up-regulation of BDNF gene expression was observed after both treatment regimens in the PFCX whereas a down-regulation was assessed in the HIPPO.
In the PFCX, class I HDAC mRNA levels were reduced by the acute MDMA treatment; on the contrary, the repeated MDMA exposure increased HDACs gene expression in the same area. Similarly, the acute or chronic MDMA administration caused differential alteration of HDACs gene expression in the HIPPO.

Discussion and conclusions: Interestingly, the opposite direction of BDNF gene expression changes in the PFCX and in the HIPPO mimic a similar pattern of alteration observed for the tryptophan-hydroxylase (TPH) gene expression after MDMA exposure, in the same areas. Moreover, since an increase of PFCX BDNF levels has been observed in serotonin-deficient mice (TPH knock out), the BDNF gene expression increase here reported in the same area suggest an elevation of the serotonergic signaling caused by the MDMA treatment that could favor the later development of psychiatric disorders. The increase of HDAC I enzymes induced by the prolonged MDMA exposure could be related to the potential development of later neuropsychiatric disorders in MDMA abusers since a possible neuroprotective action of HDAC inhibitors has been proposed.
In conclusion, our data provide new information on the involvement of HDAC enzymes and BDNF neurotrophic factor in the effects induced by exposure to MDMA, highlighting that different brain regions respond specifically to the substance. Furthermore, these results support the involvement of HDACs and BDNF in a possible comorbidity between drug addictions and neurological disorders.