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Hippocampal overexpression of cerebral dopamine neurotrophic factor (CDNF) affected the behavior of mice with genetically-defined depressive-like behavior

Kaminskaya Y.*, Ilchibaeva T., Naumenko V., Tsybko A.
Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia
** yanka2410@gmail.com*

Dopamine neurotrophic factor (CDNF) is a promising target in the treatment of Parkinson's disease. However, the role of CDNF in the regulation of non-motor behaviour, including different kinds of psychopathologies, remains unclear. So, the aim of present work was to study the effect of CDNF overexpression in the hippocampus on the behaviour of mice with a genetic predisposition to depression-like behaviour. Overexpression of CDNF in hippocampal neurons of ASC (Antidepressant Sensitive Cataleptics) mice, characterized by genetically-defined depressive-like behaviour, was induced using an adeno-associated viral vector. Four weeks after stereotactic delivery of AAV-CDNF into dorsal hippocampus the locomotor activity, anxiety, exploratory and depressive-like behaviour were analysed in open-field (OF), elevated plus-maze (EPM) and tail-suspension (TST) tests. The Morris water maze (MWM) was used to test spatial learning and memory. In the MWM we have found significant improvements in the dynamics of learning in animals with CDNF overexpression. The animals of the experimental and control groups demonstrated approximately the same learning abilities. However, overexpression of CDNF boosted the dynamics of learning, which resulted in a decrease of distance covered, total path, and time spent even on the second day of training. At the same time CDNF overexpression failed to produce any significant changes in OF, EPM and TST suggesting that locomotor activity, anxiety, exploratory and depressive-like behavior were not affected. In addition we made an attempt to define underlying molecular basis for changes mentioned above. We have found the increase in mRNA level of unfolded protein response (UPR) marker IRE1α and spliced form of XBP1 known to be spliced by IRE1α. In its turn it is known that spliced XBP1 act as transcriptional regulator for different neuroplasticity-related genes.
Thus, we have shown for the first time that hippocampal CDNF improved learning of mice with genetically-defined depressive-like behavior. This effect may be linked with UPR signalling.
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