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Dottorato di Ricerca in "Scienze della Terra e della Vita"

Ciclo XVIII

"Effects of (Methylcyclopentadienyl) Manganese (I) Trycarbonil on dopaminergic neurons in zebrafish (*Danio rerio*)"

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ANNO ACCADEMICO 2016

ABSTRACT

Epidemiological and toxicological studies suggest a link between alterations of brain manganese (Mn) and neurodegenerative diseases such as Alzheimer, Amyotrophic Lateral Sclerosis (ALS) and Parkinson's Disease (PD). Moreover, cognitive and motor function deficits were reported among children following low level environmental exposure to Mn. Recently, strong concern was expressed over (Methylcyclopentadienyl) Manganese (I) Tricarbonyl (MMT), an organic Mn-containing gasoline additive, due to health risk from long-term exposure to environmental Mn. Despite evidence of structural and functional damage induced by Mn-containing chemicals on dopaminergic (DA) neurons, little is known about sub-lethal dose effects of chronic exposure during neurogenesis *in vivo*.

First, in the present study a gene expression analysis of transcription factors, enzymes and transporters involved in differentiation of DA neurons following MMT treatment (10–300 μM) has been performed. This analysis revealed that MMT treatment alters the proper specification (*lmx1b*), differentiation (*otp*) and maturation (*th*) of DA neurons transiently.

Second, MMT treatment is also able to alter the morphology of dopaminergic neurons increasing the number and size of tyrosine hydroxylase-positive cells of specific ventral diencephalic DA cluster 2 neurons. These data were also confirmed *in vivo* using the Tg(*dat*:EGFP) transgenic line, in which GFP protein is expressed under the control of dopamine transporter (*dat*). Interestingly, MMT treatment showed to induce the presence of ectopic tyrosine hydroxylase-positive neurons.

Third, the analysis of spontaneous locomotor pattern revealed an alteration of functional response following MMT treatment, translating in a hyperactive behavior.

Altogether, the present study is the first to show that sub-lethal MMT treatment may interfere with the transcription of many DA markers and that MMT treatment is able to alter

the morphology (number and shape) as well as, interestingly, to induce the ectopic position of few tyrosine hydroxylase-positive cells in a model of zebrafish.