Early and time dependent modulation of hippocampal microRNAs and associated target genes by antidepressants

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MicroRNAs (miRNAs) have recently emerged as key regulators of complex patterns of gene/protein expression changes in the brain, where they have a crucial role in the regulation of neuroplasticity, neurogenesis, and neuronal differentiation. Recent studies showed that miRNAs could be involved in the pathophysiology of mood disorders and in the action of some psychotropics, but much remains to be discovered (1,2). Main aim of the present work was to verify whether and how treatments for 3 and 7 days with two different antidepressants, the tricyclic antidepressant desipramine and the selective serotonin reuptake inhibitor fluoxetine, could affect rat hippocampal miRNome. Nine male Sprague–Dawley rats were used for each group: 3 and 7 day- treatment with fluoxetine, desipramine (both at 10 mg/kg/die), or water as vehicle. Each hemi-hippocampus from right or left hemisphere was taken separately and randomly assigned for RNA or protein analysis. miRNAs expression was assessed by using TaqMan Array Rodent MicroRNA A+B Cards Set v3.0 on Applied Biosystem Fast 7900HT. In order to identify miRNA putative target genes and molecular pathways potentially involved, bioinformatic analyses were performed by integrating and filtering the results of different miRNA target prediction algorithms, followed by annotation analyses with Gene Ontology subcategories and KEGG pathways. Expression analysis by means of RT-PCR and western blot was performed on selected putative target genes in order to validate putative functional miRNA::mRNA interactions.

We found that, although in a specific way, both antidepressants induced early and time-dependent modifications in miRNA expression. Indeed, desipramine increased the levels of eight miRNAs and of thirteen additional miRNAs, after 3 and 7 days respectively. Fluoxetine downregulated eight miRNAs after 3 days, and modulated thirty-five miRNAs (seven reduced and twenty-eight increased) after 7 days of treatment. Interestingly, after 7 days of treatment, eight miRNAs were similarly modulated by both drugs, thus suggesting a common action on hippocampal miRNome. Bioinformatic analysis highlighted enrichment of miRNA targets in different pathways, some related to neuronal functions previously associated to pathophysiology and pharmacotherapy of mood disorders, and others, particularly at early times to gene transcription and epigenetic mechanisms. Moreover, we validated also early changes in the expression of some putative target genes, such as Galr1, Kv4.2, Bmp7, Smad2 and Tgfbr1, which could be of interest in unraveling antidepressant action.

Overall, in conclusion, our data showed that miRNAs may be early mediators of antidepressant effects and identified new possible target genes that could contribute to the antidepressant mode of action through different patterns, thus paving the way for better therapies for mood disorders.

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2) Tardito D, Mallei A, Popoli M. Lost in translation. New unexplored avenues for neuropsychopharmacology: epigenetics and microRNAs. Expert Opin Investig Drugs. 2013 Feb;22(2):217-33