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Commentary

COMMENTARY

Commentary on the study of Roy et al. Amygdala Based Altered mir-128-3p in Conferring Susceptibility to Depression-like Behavior via Wnt Signalling

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Abstract

The study of Roy and colleagues recently accepted for publication in *International Journal of Neuropsychopharmacology* is a very interesting report investigating the role of specific microRNAs (miRNAs) in vulnerability or resistance to major depressive disorder in a specific brain region (e.g., amygdala). MiRNAs may act as a mega-controller of gene expression being involved in the pathogenesis of major neuropsychiatric conditions. Interestingly, some of the altered miRNAs (e.g., hsa-miR-425-3p, miR-425, miR-674-3p, and miR-873-3p) identified in this study were found to be dysregulated even in existing studies, but several methodological issues may hamper the translation of basic research findings in clinical studies. MiRNAs are proposed as possible biomarkers of disease and treatment response to disentangle the biological complexity underlying major affective disorders. The main implications regarding the present findings are discussed.

Keywords: amygdala, major depressive disorder, miRNAs, resistance, vulnerability

The study of Roy and colleagues that was recently accepted for publication in the *International Journal of Neuropsychopharmacology* is a very interesting report investigating the role of specific microRNAs (miRNAs) in vulnerability or resistance to major depressive disorder (MDD). MiRNAs are generally responsible for the posttranscriptional repression or degradation of target mRNA (Bartel, 2009) and are proposed as a mega-controller of gene expression (Dwivedi, 2018), being involved in the pathogenesis of neuropsychiatric conditions or representing possible biomarkers of response to treatment (Dwivedi, 2016). Abnormalities of specific miRNAs may play a critical role in the translational regulation at the synapse and are able to affect important functions, including synaptic plasticity, neurotrophic activity, and stress response, critically involved in stress-related disorders and complex multifactorial conditions (Serafini et al., 2012, 2014).

Roy et al. (2020) reported that, relative to tested control rats and based on transcriptome-wide miRNA analysis in

amygdala, the differential regulation of 53 miRNAs (37 up- and 16 downregulated) in learned helpless (LH) rats might be linked to a molecular maladaptive stress response, while abnormalities in 70 miRNAs (60 upregulated and 10 downregulated) might be associated with stress resilience. The authors also stated that, according to a comparison between LH vs non-LH rats, abnormalities in 25 miRNAs (17 up- and 8 downregulated) could be the first molecular changes of susceptibility to stress-induced depression. In their analysis, miR-128-3p was found to be the most significantly upregulated miRNA in LH rats. The major strength of this paper is, in our opinion, that it is the first report, to our knowledge, to explore the role of miRNAs in both vulnerability or resistance to MDD in a specific brain region (e.g., amygdala). Other additional strengths are (1) the identification of upregulated miR-128-3p in the amygdala of LH rats, which is proposed as a possible target for pharmacological intervention; and (2) the epigenetic perturbation of Wnt signaling in the brain of depressed rats. However, brain regions other than amygdala are involved in memory modulation, stress response, as well as emotional regulation, which are frequently altered in MDD; thus, miRNA abnormalities that are presumably implicated in the pathophysiology of MDD need to be investigated in brain regions other than amygdala. In addition, while the authors correctly suggested that amygdala is a salient brain area under miRNA-mediated epigenetic control for mood dysregulation and the implication of Wnt signaling in stress-induced conditions is well recognized by existing evidence, MDD susceptibility might be mediated by other additional biochemical mechanisms (e.g., a β-catenin–independent mechanism downstream of glycogen synthase kinase 3, regulating cytoskeletal proteins) (Ciani et al., 2004).

Some of the altered miRNAs (e.g., hsa-miR-425-3p, miR-425, miR-674-3p, and miR-873-3p) identified in the study of Roy and colleagues were found to be dysregulated even in the peripheral blood of patients with MDD. For instance, Maffioletti and colleagues (2016) reported the alteration of hsa-miR-425-3p as a potential MDD peripheral biomarker. Fang et al. (2018) suggested that miR-124 plasma levels in treatment-free MDD and citalopram-treated MDD groups were 1.8-fold and 4-fold higher than in the control group, respectively, while Balakathiresan and colleagues (2014) found, in an animal model of posttraumatic stress disorder, a specific panel of 9 dysregulated stress-responsive miRNAs, including miR-674-3p in the amygdala, and proposed these circulating miRNAs as potential biomarkers of posttraumatic stress disorder. In addition, Lopez and colleagues (2014) used real-time reverse transcription-polymerase chain reaction and reported a relation between the abnormal expression of 10 miRNAs (including the upregulated miR-873-3p) and polyamine gene expression in the prefrontal cortex (BA44) of suicide completers (n = 15) and controls (n = 16), hypothesizing a specific role for spermidine/spermine N1-acetyltransferase 1 and spermine oxidase downregulation by miRNA posttranscriptional activity in the predisposition to suicidal behavior. However, changes in circulating miRNAs may be not similar to brain miRNA modifications, and several methodological issues may hamper the translation of basic research findings in clinical studies. Thus, robust studies aimed to compare both peripheral and brain central miRNA levels and improve the translational of molecular targets/mechanisms identified from preclinical studies to clinical studies need to be carefully conducted to overcome these caveats and provide a better understanding of the mechanisms directly linked to depression and suicide.

From a clinical point of view, MDD and suicidal behavior (which is frequently associated with MDD) are very heterogeneous phenomena with multiple endophenotypes; thus, caution is required when interpreting data. Importantly, whether different cell-specific miRNA abnormalities are related to specific clinical phenotypes and differential illness trajectories is unclear to date and needs to be further explored in the near future. The results of existing studies displayed a great variability between study cohorts, suggesting that the effects of miRNAs as possible biomarkers of neuropsychiatric conditions and treatment response are presumably influenced by many variables that are usually not investigated or sufficiently taken into account in currently available studies (Fiori et al., 2017). We propose that establishing a coordinated network of dysfunctional miRNAs linked to peculiar clinical characteristics considered as specifiers of illness severity (e.g., anhedonia, alexithymia, melancholia, seasonality, trauma-related dissociation, etc.) might be a valid strategy to identify vulnerable or resistant individuals.

Overall, cell type-specific miRNA-mediated regulation of amygdala Wnt signaling and its participation in inducing LH behavior (supported in the study of Roy et al., 2020) are promising aspects towards the potential use of miRNAs as biomarkers of disease and response to treatment. However, further additional evidence is required to clarify the exact role of miRNAs in stress-related conditions, major affective disorders, and suicidal behavior as we are only at the beginning of a fascinating journey towards the identification of miRNAs as diagnostic and therapeutic biomarkers in patients with depression. We firmly believe that the detailed knowledge of these endogenous molecules, acting as elegant fine-tuners and on-off switches of gene expression, is of critical importance to disentangle the biological complexity underlying major affective disorders.

Statement of Interest

In the last 3 years, Prof. Serafini received lecture honoraria as a speaker from Neuraxpharm, Janssen-Cilag, Angelini, and Lundbeck. Prof. Amore received lecture honoraria as a speaker from Angelini, Lundbeck, Otzuka, and Pfizer. Dr Aguglia, Dr Amerio, and Dr Trabucco have no relevant interests to declare.

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