Archives of Advances in Biosciences

Review Article:

The Role of some miRNA Contribution in Alzheimer's Disease: Possible Role of miRNA_132, miRNA_124, miRNA_125 in Learning and Memory

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Cite this article as: Najar F, Afaghi A. The Role of Some miRNA Contribution in Alzheimer's Disease: Possible Role of miRNA_132, miRNA_124, miRNA_125 in Learning and Memory. Archives of Advances in Biosciences. 2023; 14:E43533. https://doi.org/10.22037/aab.v14i. 43533

https://journals.sbmu.ac.ir/aab/article/view/43533

Article info:
Received: 11 Oct 2023
Accepted: 07 Nov 2023
Published: 12 Nov 2023

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Abstract

Context: Alzheimer's disease (AD) is an advanced and devastating neurodegenerative illness. It is an important reason for dementia in the world's quickly aging population. The spread of AD cases positions serious problems on relations, society, and the family. MicroRNAs are endogenous ~22 nucleotides non-coding RNAs that could control gene expression nearby a length of RNA or DNA that has been transcribed respectively from a DNA or RNA template or translation suppression. AD is a multifactorial disorder and a progressive disease beginning with mild memory loss that micoRNAs show a serious character in the pathogenesis of AD. In this review, we will focus on the outcome of microRNAs in diverse pathological manners during AD development.

Evidence Acquisition: miRNAs are small noncoding endogenous RNA sequences active in the regulation of protein expression; change of miRNA expression can cause abnormal adjustment in key genes and pathways that contribute to disease development. The role of exosomal miRNAs has been proven in various neurodegenerative diseases, and this opens the possibility that dysregulated exosomal miRNA profiles may influence AD disease. However, most abnormally expressed miRNAs recognized in AD are not triggered by synaptic activity. Some findings showed that synaptic-related miRNA mediates synaptic/memory deficits in AD via the protein signaling pathway, illuminating a potential therapeutic strategy for AD. Data were obtained by inhibiting miRNA and blocking the phosphorylation on mediated protein.

Results: The pieces of evidence show that microRNAs play a critical role in the pathogenesis of AD, but they do not have the same role in the disease. For example, miRNA-134 and miRNA-146 show downregulation in the brain of AD mice while miRNA-138 can regulate the evolution of synapse and size of the spine.

Conclusion: The data on miRNAs in *in vitro* and *in vivo* AD animal models must be established by educations in the human brain. This feature is critical for forming the real the role of micRNA in AD miRNAs in AD.

Keywords: Alzheimer, Learning, Memory, MicroRNAs

1. Contex

As many studies proved the certain role of miRNA in Alzheimer, the main question of this review is, "which miRNA has more roles in the pathways of memory and learning?" Alzheimer's Disease (AD) is an irreversible advanced neurodegenerative disorder. The physical characteristics of AD are intellectual damage and memory defeat, causing most AD patients to lose the capacity to do everyday actions self-sufficiently [1]. By considering hyperphosphorylation, tau also undergoes abnormal glycosylation, ubiquitination, glycation, and other posttranslational modifications.

These abnormalities cause the aberrant aggregation of tau in the synaptic loci in AD [2]. Major neuropathology research of postmortem AD brain confirms the presence of senile plaques primarily containing β-amyloid (Aβ) peptide aggregates and tangles comprising highly phosphorylated τ proteins. The "Aβ hypothesis" examines whether the spread of that spread of AD is driven by the accumulation and deposition of Aβ peptide aggregates in the brain. The amyloid precursor peptide (APP) is degraded by several proteases, α-, β-, and γ-secretases. A sustained imbalance between production and clearance of Aβ40–42 fragments by β- and γ-secretases leads to the accumulation of Aβ peptide monomers, oligomers, and finally large aggregated Aβ plaques that "gum up" the parenchymal space between neurons in the brain [3]. An endogenous high molecular weight (HMW) complex (~5 MD) containing β- and γ-secretases and holo-APP with catalytical potential in vitro and generate a full array of Aβ peptides, with physiological Aβ42/40 ratios. The isolated complex reacts correctly to γ-secretase modulators. Alzheimer's-creating mutations in presenilin change the Aβ42/40 peptide ratio produced by the HMW β/γ-secretase complex indistinguishably from that apperceived in all cells. So, Aβ is generated from holo-APP by a BACE1–γ-secretase complex that prepare sequential, efficient RIP processing of full-length substrates to terminal products [4].

MicroRNAs, a class of non-coding RNAs, have been known as vital controllers for post-transcriptional gene expression by either suppressing translation or unbecoming target miRNA [5]. In the simplest way, microRNAs act to decline the expression of messenger RNAs that include stretches of sequence complementary to the microRNA. This function is assumed to be the function of endogenous or synthetic short involving RNA. However, microRNA function is more complicated and exactly accurate than what this "on–off" model would propose [6].

2. Evidence Acquisition

A bulk of research has confirmed the changes of several microRNAs between AD patients and age-matched control, further demonstrating that microRNAs might be involved in the pathogenesis of AD [7]. AD is driven by two processes: extracellular deposition of beta-amyloid (Aβ) and intracellular accumulation of tau protein. Aβ is the main component of senile plaques and tau is the component of neurofibrillary tangles. Aβ deposition is specific for AD and is thought to be primary. A few microRNAs, involved in the guideline of genes causally linked to Alzheimer's disease, are dysregulated in social AD patients [8]. Upregulated miRNAs contain miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a, and miRNA-155 [9]. MicroRNAs involved in Aβ production, include miR-34a, miR-146 [10] , microRNA-125b [11], miR-330 [12], miR-24, miR-186, and miR-455 [13]. The AD-like method was performed on rats using hydrated aluminum chloride (AlCl3.6H2O) solution that was injected orally at a dose of 75 mg/kg daily for 6 weeks. Morris water maze (MWM) behavioral test was performed to confirm the cognitive dysfunction; then, AD-like rats were orally behaved with different doses of ATX (5, 10, and 15 mg/kg) dissolved in dimethyl sulfoxide (DMSO) for six weeks. The results showed that ATX significantly and dose-dependently recovered the performance of AD-like rats treated with ATX during MWM and unseat the accumulation of amyloid β1-42 and malondialdehyde. Of course, ATX significantly inhibited acetylcholinesterase and monoamine oxidase activities and the expression of β-site amyloid precursor protein cleaving enzyme 1 (BACE 1). ATX also significantly elevated the content of acetylcholine, serotonin, and nuclear factor erythroid-2-related factor 2 (Nrf2) and miRNA-124 expression [14]. NF-κB, a pro-inflammatory transcription factor, could be stimulated by Aβ, and the activation of NF-κB could lead to the upregulated of six inducible miRNAs: miR-7, miR-9, miR-34a, miR-125b, miR-146a, and miR-155 [15]. Neurofibrillary tangles were mainly collected of hyper-phosphorylated Tau as a result of the imbalance between Tau phosphorylation and de-phosphorylation through regulating the expressions and events of a number of interrelated kinases and phosphatases [16]. NOP2/Sun RNA methyltransferase 2 (NSun2) is one of the few realized brain-enriched methyltransferases able to methylate mammalian non-coding RNAs. In particular, AβO-induced tau phosphorylation and cell toxicity in human neurons could be set free by overexpression of NSun2. In all, these results indicate that neuronal NSun2 deficiency promotes dysregulation of miR-125b and tau phosphorylation in AD and highlights a novel way for therapeutic targeting [17]. Smith et al. (2015) found that the expression of Tau could be in a straight line synchronized by miR-132, and the deletion of miR-132/212 in mice could raise the expression, phosphorylation and amass of Tau [18]. Wang et al. (2017) also reported that the downregulation of miR-132/212 could encourage Tau phosphorylation and interruption of the imbalance between Tau phosphorylation and de-phosphorylation via the NOS1-dependent pathway in primary human neurons and neural cells [19]. The expression levels of miR-124b were diminished in the brain of AD patients and N2a/APP695swe cells. It was recommended that miR-124-3p could prevent abnormal phosphorylation of tau through targeting Caveolin-1 and regulating the

pathway Caveolin-1-PI3K/Akt/GSK-3β [20]. Many miRNAs have been recognized as critical components for the regulation of cognitive functions and memory courses lost in AD, through the by-law of activity-mediated protein synthesis at the synaptic level [21].

3. Results

How do miRNAs contribute to neural plasticity and memory?

Based on latest findings, we propose that miRNAs donate to neural plasticity and memory in three individual, but connected, ways: (i) miRNAs might influence cognitive ability by regulating dendrite morphogenesis during primary development; (ii) miRNAs influence fine-tune gene function by regulating translation near within synapses of distinct dendrites; and (iii) miRNAs might aid to oblige or destabilize memory upon retrieval to permit new knowledge or memory updating to happen [22]. The Hippocampal miR-132 expression is stopped by the time-of-day, with peak levels happening during the circadian night. Moreover, in miR-132 knockout mice and in transgenic mice, where miR-132 is constitutively expressed by affecting the control of the tetracycline regulator system, researchers detected that time-of-day dependent memory recall (as assessed via novel object location and contextual fear conditioning paradigms) was unseated [23]. The principal function of miR-132 in reply to neural activity is to work for as a proteome change, broadly controlling the translation of proteins serious for the formation or keeping of memory [24]. As mentioned in the table 1, the fact that

Table 1. Summary of studies demonstrating miRNA activity associates with learning and memory (▲: Increased, ▼: decreased, MWM: Morris water maze, CFC: contextual fear conditioning, TFC: trace fear conditioning, SOR: spontaneous object recognition, CPP: conditioned place preference, FC: auditory fear conditioning, EXT: auditory fear extinction)

miRNA	Encoding	Consolidation	Ref
Armitage Dicer miR-132	▼Armitage= ▲Olfactory learning ▼Dicer=▲MWM, CFC, TFC learning ▲mi-132= ▼SOR learning	CFC, Cocaine or Odor exposure ▲ miR-132 expression	Ashraf et al. (2006) Konopka et al. (2010) Nudelman et al. (2010) Hansen et al. (2010)
miR-134	▲miR-134=▲ CFC learning		Gao et al. (2010)
miR-124, miR-181, Let-7d	▼miR-124, miR-181, or Let-7d alters Cocaine-CPP learning		Chandrasekar and Dreyer (2009, 2011)
Ago2 miR-181a,miR-324, miR-369	▼ Ago2= ▼Cocaine self-administration learning	Cocaine self-administration ▲ miR-181a, miR-324, miR 369 expression	Schaefer et al. (2010)
miR-212	▲miR-212=▼ Cocaine self-administration learning	Extended access to cocaine	Hollander et al. (2010)
miR-9 miR-128b	▲miR-9= ▲FC learning	▲miR-212 expression EXT ▲ miR-128b expression	Im et al. (2010) QL, unpublished, observations TWB, unpublished observations

AD patients are described by miRNA variations in the brain and biological fluids, containing serum, plasma, and cerebrospinal fluid (CSF), has stimulated the idea to use these noncoding sequences as biomarkers of the sickness [25]. At current, the only biomarkers documented for AD are Aβ peptides and tubulin-associated unit (tau) proteins [26]. MiRNAs, not like mRNAs, are constant sufficient in biological liquids, containing serum, plasma, and CSF [27]. If we compare miRNAs to unoriginal protein-based biomarkers of AD, the level of sensitivity the level of successful sensitivity of miRNAs due to extension by PCR is far larger than what is presently accessible for proteins [28]. The miRNA quantification was completed with Affymetrix[2]

microarray analysis and confirmed using RT-qPCR [29]. In another research, it was reported that miR-93 expression measured by RT-qPCR significantly declined in AD patients' serum compared with that of the control [30]. Remarkably, it was displayed that the vaccination of ASO into the CSF of nonhuman primates affects the decrease of the target RNA (tau) in the brain areas analyzed, containing the hippocampus [31]. Using miRNA microarray investigation of cortical tissue from Tg2576 transgenic mice, miRNAs of the miR-200 family (miR-200b and miR-200c) were known as down regulators of Aβ secretion by modulation of mTOR[3] in murine principal neurons and human neuroblastoma cells [32]. Correspondingly, in a study aimed to discover the character of miR-124 in the pathogenesis of AD, miR-124 expression was tested using RT-qPCR analysis in 35 occasions of random AD brain tissues and 35 cases of healthy regulator subjects [33]. MiR-124 expression was considerably brought down in AD brain tissues compared with that of the control group [33]. In addition, inhibition of miR-124 significantly improved BACE1 levels in human neuroblastoma (SH-SY5Y) cells though miR-124 overexpression pointedly blocked BACE1 expression [33]. In a brain tissue under examination taken from patients with AD and those with plain major age-related tauopathy, it was found that miR-219 measured by RT-qPCR analysis is downregulated [34]. Neuronal restoration can be achieved by overexpressing other miRNAs. In AD animal models, it was revealed that miR-302/367 adapt astrocytes to neurons that substitute dead ones [35]. MiR-125b [36] and miR-146a [37] overexpression encourages neuronal apoptosis and tau phosphorylation in AD cellular models. Furthermore, other adverse outcomes on neuronal survival produced by miRNAs are related to the downregulation of neurotrophic factor expression, as proved in human neuroblastoma cells [38] and AD transgenic mice [39]. For instance, it was revealed that anti-inflammatory drugs could be of profit in stopping the progression of AD via inflection of miRNA expression [40]. Also, natural composites identified for their potential as neuroprotective causes in AD, such as resveratrol [41] seem to apply their action by modulating particular miRNAs and stimulating manners such as autophagy and neuronal rejuvenation [42]. Moreover, recent data hold up the hypothesis that exosomes, small vesicles concealed by neurons and glial cells, could help as therapeutic causes to deliver miRNAs and, or little obstructing RNA (siRNA) in AD patients [43]. Each only miRNA may have very pleiotropic properties to the genome, and therefore the change of miRNA expression in humans may guide to undesired side special effects in AD patients [44]. Corticolimbic overexpression of miRNA-137 or -let-7a declined the MAGL gene expression that encodes the MAGL enzyme to enhance the endocannabinoids. Thus, according to the molecular mechanisms and signaling pathways involved in the pathophysiology of Alzheimer's disease (AD), it is valuable considering the role of endocannabinoids in the corticolimbic regions. CB1 receptor agonists, miRNA-137 or -let-7a, may be potential therapeutic targets against cognitive decline in AD [45]. Fan and his colleague's showed that scopolamine-induced amnesia has relation with downregulated expression of miR-210/miR-183 and upregulated expression of SIN3A. Additionally, treatment with EA decreased scopolamine-induced amnesia in rats and was associated with upregulated expression of miR-210/miR-183 and downregulated expression of SIN3A [46]. Moreover, the role of cancer drugs must be considered in memory and learning. The data of a study has shown the expression of Let-7a, b and e miRNAs in association with Letrozole[2] injection, and relations between the expression of the studied Let-7 miRNAs and both condition of working memory and the hippocampal p-Tau levels [47].

5. Conclusion

The pieces of evidence show that microRNAs play a critical role in the pathogenesis of AD, but they do not have the same contribution to the disease. For example, MiRNA-134 and MiRNA-146 show downregulation in the brain of AD mice, while MiRNA-138 can regulate the evolution of synapse and size of the spine. Thus, the highlight effect of microRNAs in different pathological processes throughout AD progression needs more research.

Ethical Considerations

Compliance with ethical guidelines

As the format of article is review and we have not used any animal sample for getting data so the ethical considerations are according principles of this concept. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written consent has been obtained from the subjects.

Funding

As I mentioned in the first part for review article, it did not receive any grant from funding agencies in the public, commercial, or nonprofit sectors.

Author's contributions

Farzaneh Najar is a main writer and corresponding author from department of basic science, Medicine Branch, Islamic Azad University, Tehran, Iran and Azam Afagh is my colleague from department of

Biology, Sofian Branch, Islamic Azad University, Sofian, Iran. She has helped me during selecting best references for article.

Conflict of Interest

The Authors declare that there is no conflict of interest.

Acknowledgements

We would like to extend our appreciation and thanks to all participants specially Dr. Rasta Haddadi and her colleagues those who made this study is accepted in Bioscience archive successfully.

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