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Effect of Memantine on Expression of NAT-Rad18, Rad18 and Sorl1 Genes in Rat Model of Alzheimer's Disease

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ABSTRACT

Background & Objective: Dysregulation of long-term expression of non-coding RNAs (lncRNAs) has a potential role in progressive brain disorders such as Alzheimer's disease (AD). This study aimed to analyze the apoptosis and expression of *51A* and *NAT-Rad18* lncRNAs and their target genes in brain tissue and peripheral blood mononuclear cells (PBMCs) of the rat model of AD, before and after memantine treatment.

Materials & Methods: Twenty-eight male *Wistar* rats were divided into four groups: 1. Normal control (n = 4), 2. Sham-operated (n = 4), 3. Alzheimer's control (n = 10), and 4. The experimental group (n = 10) was treated with memantine. The qPCR and TUNEL tests were used to detect the lncRNAs expression and apoptosis.

Results: *Sorl1* gene was reduced in brain tissue of Alzheimer's control ($p = 0.016$) and PBMCs of Alzheimer's control and experimental groups ($p = 0.002$ and $p = 0.001$ respectively). The expression of *NAT-Rad18* and *Rad18* genes increased in brain tissue of Alzheimer's control group ($p = 0.002$ and $p = 0.04$ respectively) while reduced in PBMCs of Alzheimer's control and experimental groups ($p = 0.005$ and $p = 0.045$ for *NAT-Rad18*, $p = 0.01$ and $p = 0.006$ for *Rad18*).

Conclusion: ROC curve analysis showed 100% sensitivity and 85.7% specificity for the *Sorl1* gene with 0.911 under the curve area and 100% sensitivity and 100% specificity for *NAT-Rad18* and *Rad18*, separately with one under the curve area. Decreased expression in *Sorl1*, *NAT-Rad18,* and *Rad18* genes can be used as blood biomarkers for diagnosis independently. However, studies on Alzheimer's patients are needed.

Keywords: Alzheimer's disease, Rat, Biomarker, lncRNA, Memantine

Introduction

Alzheimer's disease (AD) is mild progressive memory loss with three features, extraneuronal amyloid beta (Aβ), intraneuronal neurofibrillary tangles (NFTs), and synaptic dysfunction due to Aβ accumulation. Amyloid plaques and NFTs change synaptic plasticity, leading to widespread synaptic loss neurodegeneration (1). Recent studies showed that dysregulation of long-term expression of non-coding RNAs (lncRNAs) plays a potential role in progressive brain disorders (2).

The 51A is located in an antisense configuration on intron 1 of the neuronal sortilin-related receptor gene (SORL1) (3, 4) and up-regulated in both in-vitro and AD brain models (3). In AD, over-expression of 51A causes down-regulation of SORL1 variant A via alternative splicing and subsequently increases Aβ formation in the brain (3, 4). The SORL1 is expressed in the central nervous system and has been predicted to be involved in AD pathogenesis (5). This gene localized to intracellular compartments in the cell soma of neurons, suggesting a role for this receptor in vesicular protein transport (6). The SORL1, as a sorting receptor for APP holoprotein, mediated APP localization and processing by 'trapping' APP in the Golgi and/or by directing APP into the endosome-to-Golgi retrieval pathway (3, 7). Absence or abundant expression of SORL1 in the neurons leads to modification APP from the retromer recycling pathway to the β-secretase cleavage pathway because more APP enters to late-endosome, where the enzymes BACE1 and

PS1 cleave neurotoxic Aβ (3, 8). The progression of AD disrupts SORL1 expression and its regulatory function (9).

Natural antisense transcripts versus Rad18 (NAT-Rad18) exerts a post-transcriptional control on Rad18 (10). There is an equilibrium relationship between NAT-Rad18 and its target gene, Rad18, in both mRNA and protein levels, with Rad18 showing a low expression level. Rad18 is an ubiquitin ligase involved in post-replication repair processes (11). Mammalian cells need the E3 ubiquitin ligase Rad18 for perpetuation after various types of DNA damage (12). Controlling the expression of DNA repair protein of Rad18, due to up-regulation of NAT-Rad18 in brain tissue of AD following exposure to Aβ, can make the neuron more sensitive to apoptosis (13). This document suggests NAT-Rad18 is probably involved in AD via its effects on the DNA repair system (2).

N-methyl-D-aspartate receptor (NMDAR) is a ligand of glutamate and the fast excitatory neurotransmitter in the human central nervous system, especially in the cortex and hippocampus (14). NMDAR activation plays a vital role in synaptic plasticity, learning, and memory (15). Inordinate NMDAR activity causes excitotoxicity and rising cell death which is associated with neurodegenerative disorders such as AD (16). Memantine, a non-competitive NMDAR antagonist (17), improves cognitive function and inhibits disease progression in the cortex and hippocampus by targeting NMDARs and APP protein translation (18).

The aims of the present study were: 1. The analysis of 51A and NAT-Rad18 lncRNAs and their target genes expression, Sorl1 and Rad18, before and after memantine treatment in brain tissue and peripheral blood mononuclear cells (PBMCs) in rats model of Alzheimer's disease 2. Detection of apoptosis with TUNEL test 3. The relationship between the expression of mentioned genes and the level of Aβ protein, measured in our previous study, will be discussed.

Materials and Methods

Twenty-eight male Wistar rats aged six weeks (mean weight 250-290gr) were purchased from the Animal Laboratory of Pasteur Institute, Tehran, Iran. The Ethics Committee principles and the Guide for the Care and Use of Laboratory Animals by the National Institute of Health (No. 85-23, revised in 1996) were followed in all the experiments. Ethics Committees approved this study with the ethical code of IR.IAU.SRB.REC.1397.170. In our previous study, surgical procedure, experimental design, histopathological examination, and RNA extraction were explained in detail (19).

ICV injection of STZ

According to the stereotaxic atlas, rats were kept in individual home cages for seven days after stereotaxic surgery (20). Rats received two bilateral intracerebroventricular injections (ICV) of STZ (Sigma, St. Louis, MO, USA) diluted in physiological saline at 3 mg/kg (1.5mg/kg on each side), on days 7 and 9 (21-23).

Experimental design

Rats were randomly divided into four groups: Normal control (n = 4), Sham-operated rats that underwent surgery (n = 4), Alzheimer's control rats that received STZ in a dose of 3 mg/kg (1.5mg/kg on each side) ICV-STZ bilaterally two times in day 7, and 9 (n = 10) and Experimental group that treated with memantine in a dose of 30 mg/kg/day using an intragastric tube for 28 days, starting with the first administration of the STZ (n = 10) (19).

Sampling

Three weeks after the first STZ or saline ICV injection at the doses of 3 mg/kg (24) (25), on the 28th day, all rats were anesthetized and sacrificed. 2 ml of blood was collected in Ethylene Diamine Tetra Acetic Acid-coated (EDTA) vials. Based on the test protocol, the left hemisphere was prepared for hematoxylin, eosin (H&E), and Bielschowsky staining (26). The right hemisphere was used for molecular detections. A Pilot Study of gene expression in the cortex and hippocampus, which are destroyed in Alzheimer's disease, showed no difference in gene expression, so whole brain tissue was used for the study.

RNA extraction and Gene expression

Ficoll (Cat No: GE17144003) was used to separate peripheral blood mononuclear cells (PBMCs). RNA was isolated by Trizol (cat no: YT 9066), and the Parstous cDNA Synthesis kit (cat no. A101161) was provided for reverse transcription. The Sorl1 gene primers were designed by the Gene Runner program and primer 3. The primers used for gene expression are 51A forward 5′-TGGGAGAGTCAGCATCTTGAAG-3′ and reverse 5′-TGTACAGTCAGACAAGAGGTGTGTGTAT-3′(27), Sorl1 gene forward, 5′-TGAGAAGCCTGTGTTTGTGTATG-3′ and reverse 5′-TCCTTGTTAGAGCCGAAGATGG-3′, NAT-Rad18 forward, 5′- CAGGCCACCAGCAGTTACT-3′ and reverse, 5′-TCAGAGGAAGGTGACTGTGC-3′ (10) and Rad18 forward, 5′-GCAGTAACAGAGCCAGACCT-3′ and reverse, 5′-GAGGTGGAAGACACAGGAGA-3′ (10) and Gapdh gene (as reference gene) forward, 5′-GAAGCTGGTCATCAACGGGA-3′ and reverse, 5′-GAAGGGGCGGAGATGATGAC -3′ (19). Amplification conditions were 95°C for 20 sec, 40 cycles of denaturation at 95°C for 5 sec, and annealing at 57°C for 20 sec.

TUNEL assay

In Situ Cell Death Detection Kit, fluorescein-dUTP, AP by Roche Applied Science (Cat no: 11684817910) was used to detect and quantify apoptosis cell death at the single cell level (TUNEL test). Image J software (Media version: 6.00) was used to analyze positive reactions (green stained pixels/total pixels) in 20-megapixel photos from cross-sections. The samples were assayed with a Nikon fluorescence microscope (Japan). Then, each

section's mean ± SD of pixel-based intensities was evaluated and compared among Alzheimer's control and experimental groups.

Statistical analysis

The gene expressions were measured by a relative quantification based on the relative expression of target genes against a reference gene (Gapdh). Statistical analyses were performed on the normalized data evaluated by ANOVA, Tukey, independent T-test, and ROC tests. The SPSS version 26 software package was used to analyze all statistical tests. The significance level was set at P-Value < 0.05.

Results

Gene Expressions

The expression of Sorl1 was significantly decreased in the brain tissue of Alzheimer's controls compared with normal control (p = 0.016). Although the expression of Sorl1 in the brain tissue increased in the experimental group in comparison with Alzheimer's control group (p = 0.000), the changes were not significant compared with normal control (p = 0.146) (Figure1.a). Furthermore, the expression of the Sorl1 gene in the PBMCs of Alzheimer's control and experimental groups was decreased compared to normal control (p = 0.002 and p = 0.001, respectively) (Fig1.b). The ROC curve analysis showed 87.5% sensitivity and 100% specificity for the Sorl1 gene in blood, with a 0.938 area under the curve (Figure 2).

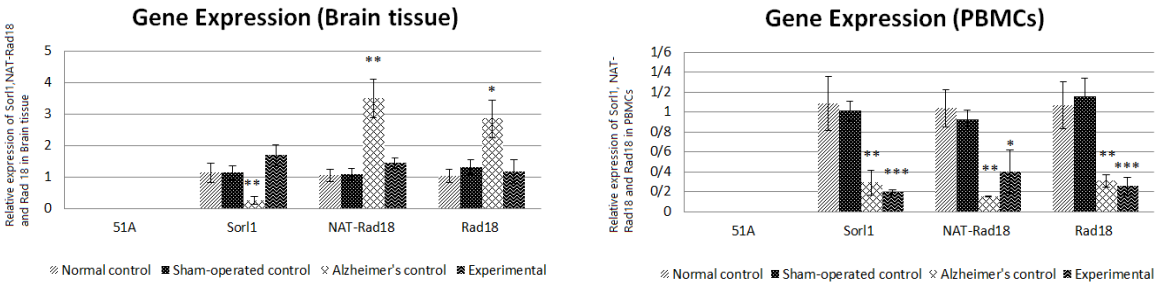

Figure 1. Expression of lncRNAs and their targets in brain tissue and PBMCs of normal control, sham-operated, Alzheimer's control and experimental groups. A value of P < 0.05 was considered significant. It is noted that * in the graphs indicates the significance of the Alzheimer's control and experimental groups compared to the normal control group. * , ** and * show P<0.05 , P< 0.01 and P<0.001, respectively. In brain tissue, the gene expression of Sorl1 significantly was down regulated in Alzheimer's control group. Expression of NAT-Rad18 and Rad18 genes, showed significant increases in brain tissue of Alzheimer's control group. In PBMCs, level of Sorl1, NAT-Rad18 and Rad18 genes expression indicated significant reduction in Alzheimer's control and experimental groups.**

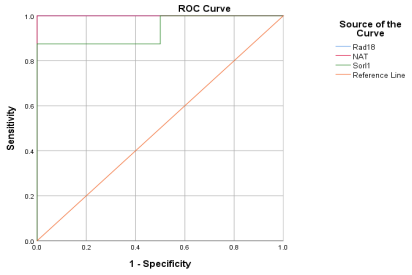

Figure 2. ROC curve analysis. Analysis showed 87.5% sensitivity and 100% specificity for Sorl1gene, with 0.938 area under curve and also, showed 100% sensitivity and 100% specificity for NAT-Rad18 and Rad18 genes in PBMC, separately, with 1 area under curve.

We couldn't find the sequence of the 51A gene in intron 1 of the Sorl1 gene in the rat genome. However, we used 51A primers based on the human genome. Our attempts failed to detect it.

The expression of NAT-Rad18 was significantly boosted in the brain tissue of the Alzheimer's control group compared with the normal control group (p = 0.002). Decreases in the brain tissue of the experimental group were significant compared to Alzheimer's control group (p = 0.006, Figure 1.a). On the other hand, the NAT-Rad18 expression level in PBMCs was reduced in the Alzheimer's control and the experimental groups compared to the normal control group (p = 0.005 and p = 0.045, respectively, Fig 1. b), while the changes in both the Alzheimer's control and experimental groups were not significant (p = 0.119).

The qPCR analyses indicated a significant increase in Rad18 expression in the brain tissue of the Alzheimer's control group compared to the normal control group (p = 0.04). The reduction of Rad18 in the experimental group was significant compared to Alzheimer's control group (p = 0.044, Figure 1.a). The expression of Rad18 significantly reduced in PBMCs of the Alzheimer's control and experimental groups compared with the control group (p = 0.01 and p = 0.006, respectively). In contrast, Alzheimer's control and experimental groups' changes were insignificant (p = 0.991, Figure 1.b).

The ROC curve analysis showed 100% sensitivity and 100% specificity for NAT-Rad18 and Rad18 genes in blood, with one area under the curve (Figure. 2).

TUNEL test

The cortex section in Alzheimer's control (a) and experimental (b) groups showed that the numbers of apoptotic neurons (green color, Figure. 3) in the Alzheimer's control were more than the experimental group in mean value, but the changes were not significant (p = 0.39).

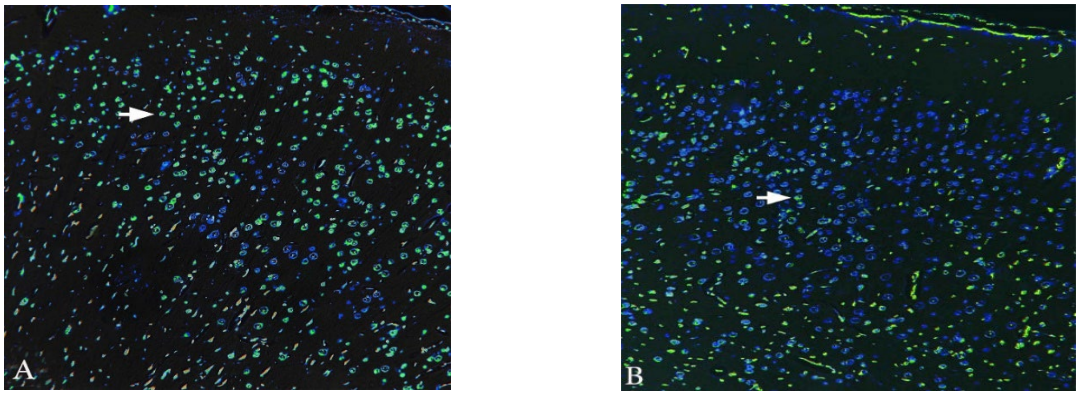

Figure 3. TUNEL assay in the cortex section in (a) Alzheimer's control and (b) experimental groups: Apoptotic neurons were shown with green color (arrow) (Immunofluorescent antibody staining, 40X).

Discussion

In this study, the gene expression of Sorl1 was significantly down-regulated in the brain tissue of the Alzheimer's control group and significantly increased in the experimental group compared to the Alzheimer's control group. Expression of NAT-Rad18 and Rad18 genes showed significant increases in brain tissue of the Alzheimer's control group and a significant reduction in the experimental group compared to the Alzheimer's control group. In PBMCs, levels of the Sorl1, NAT-Rad18, and Rad18 genes expression indicated a significant reduction in the Alzheimer's control and the experimental groups. Aβ protein level, according to our previous study (19), and apoptotic neurons in brain tissue of the Alzheimer's control group showed insignificant increases compared with the experimental group.

The SORL1 gene is mainly expressed in neurons, and the loss of APP binding to SORL1 leads to AD (28). The expression of the Sorl1 gene was decreased in the brain tissue of the Alzheimer's control group, while it was significantly boosted in experimental groups compared to the Alzheimer's control group. In the mice model of AD, a reduction of Sorl1 (29) and decreases in Aβ production via up-regulation of Sorl1 gene expression was reported. Conversely, the knock-out of the Sorl1 gene in cell lines and mouse models demonstrated the increases in Aβ generation (30). Our finding explained that memantine probably reduced AD progression by increasing the expression of the Sorl1 gene in the brain without affecting the Aβ protein level. The level of Aβ protein showed decreases in mean value, which were insignificant. Perhaps significant changes in Aβ protein levels could be observed by extending the length of the study, more than 28 days.

The 51A gene expression increases Aβ formation by reducing the SORL1 variant A via alternative splicing (3, 4). We were unable to detect the 51A expression because of the lack of 51A sequence in Wistar rats. However, due to the opposite relationship between 51A and Sorl1 genes expression, and based on the Sorl1 gene expression, we expected to see up-regulation of 51A expression in the brain tissue of Alzheimer's control group, and a reduction of 51A expression in the experimental group compared to Alzheimer's control group. Therefore, it seems that the expression of 51A is changed in response to memantine treatment. This is why Ciarlo et al. reported significant individual variations in their AD brain (0.049). Their samples were chosen from different stages of AD, without mention of memantine treatment or not. Maybe patients in severe and moderate stages have been treated with memantine (3). We think that 51A expression due to AD progression should be increased in the brain tissue with high significance and show decreases after memantine treatment.

NAT-Rad18 is differentially boosted in brain tissues, especially in cortical neurons, following exposure to Aβ (10, 31). Expression of both NAT-Rad18 and Rad18 genes significantly elevated in brain tissue, while significantly decreased followed memantine treatment compared to Alzheimer's control group. Similarly, Parenti et al. found that at the cellular level, the expression of NAT-Rad18 and Rad18 was counterbalanced using in-situ hybridization and immunohistochemistry (10). Based on the experiments, they suggested the existence of a NAT- Rad18 that exerts post-transcriptional control on Rad18. A prevalent discordant regulation was proposed due to counterbalanced expressions of NAT-Rad18 and Rad18, both at mRNA and protein levels. However, it was impossible for NAT-Rad18 to act at the level of

Rad18 translation, possibly due to antisense interaction with upstream sequences of Rad18 mRNA. This may mainly affect the stability of Rad18 mRNA **(10)**. According to our TUNEL assay, we think that increased in Rad18 protein levels followed by increases in NAT-Rad18 and Rad18 in the AD brain decreases the activity of Rad18 protein. Accumulating Rad18 protein in brain tissue can probably lead to the unavailability of the active site or limitation in physical interactions. It seems that memantine increases the activity of the Rad18 protein by decreasing NAT-Rad18, Rad18, and Rad18 protein in brain tissue. Therefore, the translation of the Rad18 protein was reduced via the reduction of Rad18 mRNA. Although insignificant, the reduction of the mean value of apoptotic neurons in the experimental group emphasizes the validity of this claim. It seems that by increasing the duration of memantine treatment to more than 28 days, the results of the TUNEL assay can be significant.

Different studies tried to measure lncRNAs expression and their targets in CSF and AD subjects' blood contents as a biomarker **(27) (4, 32)**. In PBMCs, we are unable to detect 51A expression, while Sorl1, NAT-Rad18, and Rad18 genes expression was significantly reduced in both Alzheimer's control and experimental groups. In the plasma of AD patients, Deng reported stable and significant increases in the expression of 51A **(27)**; in contrast, Feng found no significant changes **(32)**. These conflicting reports could be a reflection of the type of treatments, such as memantine, while they didn't mention the patient's medications. According to our results in blood, the ROC curve analysis showed 100% sensitivity and 85.7% specificity for the Sorl1 gene with 0.911 under the curve area and 100% sensitivity and 100% specificity for NAT-Rad18 and Rad18, separately with one under the curve area. So, the low expression of Sorl1, NAT-Rad18, and Rad18 genes can probably be used as non-invasive and effective blood biomarkers for prognostic or diagnostic of AD. However, human studies are needed to achieve certainty.

Conclusion

For the first time, the effect of memantine on the expression of Sorl1, NAT-Rad18, and Rad18 genes was investigated in both brain tissue and blood in the rat model of AD. Western blot experiments, in addition to gene expression studies, are suggested. It seems that the Sorl1, NAT-Rad18, and Rad18 expressions can be used as a non-invasive and effective blood biomarker for prognostic or diagnostic approaches. Also, Sorl1 and Rad18 expression can probably be used for monitoring AD progression. However, further studies on patients with mild cognitive impairment (MCI) and patients in different stages of Alzheimer's are needed.

Acknowledgments

None.

Conflict of Interest

The authors declare that they have no competing interests.

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