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# THE IMPORTANCE OF KI67, GLIAL FIBRILLAR ACIDIC PROTEIN AND VITAMIN D RECEPTOR IN THE CENTRAL NERVOUS SYSTEM OF POSTMORTEM SUICIDE CASES

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**Abstract:** Death by suicide is a tragic public health problem. Major depressive patients constitute some of these deaths. Although the etiology of major depression has not been clarified, there are studies suggesting that the hippocampus and caudate nucleus may be effective. In this study, it was aimed to compare vitamin D receptor (VDR), Ki67 and glial fibrial acidic protein (GFAP) antibodies in the brain tissues (hippocampus and caudate nucleus) of untreated major depression patients who died because of suicide with the control group. Left hippocampus and caudate nuclei of seven patients with untreated major depression who died of suicide in a one-year period and six psychiatrically normal patients were taken during autopsy. The hippocampus was stained with VDR, GFAP and Ki67 antibodies, and the caudate nucleus was stained with VDR and GFAP antibodies. There was no significant difference in the number of Ki67-positive cells in the anterior and posterior dentate gyrus between the major depression and control groups ($P > 0.05$). In the major depression group, a negative correlation was reported between the number of Ki67-positive cells in the anterior dentate gyrus and age ($r: 0.867$, $P < 0.05$). In the anterior dentate gyrus, posterior dentate gyrus and caudate nucleus, there was no significant difference between the suicide and control groups in the fraction of the immunoreactive area with GFAP antibodies ($P > 0.05$). While the percentage of immunoreactive granular cells for vitamin D receptor in the anterior dentate gyrus was significantly higher than the control group ($P <0.05$), no significant difference was reported in the posterior dentate gyrus. Vitamin D receptor immunoreactive neuron positivity in the caudate nucleus was not significantly different between the major depression and control groups ($P > 0.05$). In untreated major depression, additional immunohistochemical changes are observed in the anterior hippocampus, and the vitamin D receptor increases in the granular cells as a protective factor.

**Keywords:** Suicide, hippocampus, vitamin D receptor, caudate nucleus.

## INTRODUCTION

As a result of suicide, ~800,000 people die annually in the world [1]. There is ample evidence of a strong relationship between suicide and major depressive disorder (MDD) [2]. However, despite many studies, the etiopathogenesis of suicides caused by depression is still not understood [3]. There are multiple studies in the literature investigating the hippocampus, which is a part of the limbic system, and which is considered to be effective in depression. It has been reported that there is a decrease in the hippocampus volume in depression, and this decrease is caused by changes in the number of neurons, glia, and body size [4-6]. There are ongoing studies on the effect of neurogenesis that develops in the adult human hippocampus on multiple neuropsychiatric diseases including depression [7]. The precursor cells from which adult neurogenesis originates in the hippocampus are located in a narrow band called the subgranular zone in the tissue between the granular cell layer of the dentate gyrus and hilus [8]. Ki67 is a nuclear protein that is expressed in dividing cells in the hippocampus dentate gyrus and is used as a marker for dividing cells [9].

Astrocytes are among glial cells that have multiple functions in maintaining synaptic transmission such as buffering electrolytes and neurotransmitters in the extracellular area [10-11]. GFAP is an astrocyte-specific protein synthesized by astrocyte cells. There is evidence that astrocyte dysfunction is effective in

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major depression. In a study conducted on postmortem human tissue, the fraction of GFAP immunoreactivity in the prefrontal cortex of young patients with major depression disorder (MDD) was reported to be significantly higher compared to the control group [12].

Vitamin D is another factor that is considered to be effective in the pathophysiology of major depression. In a study involving 2070 people over 65 years of age, an increase in depressive symptoms was reported in vitamin D deficiency [13]. In a study conducted on 7970 people between the ages of 15 and 39, a strong correlation was reported between low vitamin D levels and the risk of depression [14]. Vitamin D performs its biological activities by providing target gene control through the VDR. Various studies have reported the presence of VDR in neuronal and non-neuronal cells in the central nervous system [15-16]. VDR has been described in many regions in the human brain that play a role in the pathophysiology of depression such as the prefrontal cortex, hippocampus, cingulat gyrus, thalamus, hypothalamus, and substantia nigra [17].

The aim of this study was to compare VDR, Ki67 and glial fibrial acidic protein (GFAP) antibodies in the brain tissues (hippocampus and caudate nucleus) of untreated major depression patients who died as a result of suicide with the control group.

## MATERIALS AND METHODS

A total of 16 cases autopsied in our center were included in the study. Written informed consent was obtained from the relatives of the patients before the autopsy. Suicide cases included in the study were selected with the DSM V major depression criteria scale as per the anamnesis obtained from their relatives. A control group was formed from patients without psychiatric disease based on anamnesis obtained from their relatives, blood toxicology results, and prescription information within the last six months. Before autopsy, blood samples of all cases were taken and the presence of antidepressant drugs was investigated. Antidepressant drugs were detected in two cases and cerebrovascular pathology was reported in the pathology results of one case. These three cases were excluded from the study. The study was conducted with seven suicide cases with untreated major depression and six control cases. Left hippocampus and head caudate nucleus were taken from all cases at autopsy. The left hippocampus was cut from the beginning of the lateral geniculate and divided into two as anterior and posterior. Note that eight sections were taken from each anterior and posterior hippocampus. Monoclonal Ki67 antibody was used for staining the left hippocampus, while monoclonal GFAP antibody and abcam 3805 Vitamin D receptor antibody were used for staining the left hippocampus and head caudate nucleus. Preparations stained with VDR and Ki67 were blindly counted at 40x magnification under the Olympus BX53 microscope. Ki67 was counted in the subgranular layer region in the hippocampus dentate gyrus. The number of Ki67-positive cells was expressed as cells/mm by dividing the cell count by the length of the granular cell layer, which was measured using the Olympus celsens standard program 1.13. The result was calculated as a percentage by taking the average of the positive cell count in 100 granular cells in 10 different areas in the VDR stained hippocampus dentate gyrus. Neurons with VDR positivity in seven different areas at 40x magnification in the caudate nucleus were compared to the total number of neurons counted and the results were expressed as a percentage. Serial images were taken at the hippocampus dentate gyrus (DG) at 4x magnification and at the caudate nucleus at 20x magnification. Photos were saved as JPEG and converted into eight-bit format using Image J 1.48v (National Institutes of Health https://imagej.nih.gov/ij/index.html). Hippocampus DG boundaries in the photographs were determined using Image J as the area between the hippocampal sulcus separating the striata molecular layer and where the CA 4 pyramidal neurons were detected. GFAP IR areas and the total area whose boundaries were determined were measured using the equivalent feature of Image J by taking the non-immunoreactive areas as background and using it as a reference. GFAP IR areas were calculated as the area fraction in proportion to the total area. Shots in the caudate nucleus were restricted to stained areas of cell heterogeneity. Permission was obtained from Fırat University Faculty of Medicine Ethics Committee for the study.

### *Statistical methods*

The data were transferred to the SPSS 22 (IBM) program and analyzed using the Mann–Whitney U test. The relationship between the parameters studied and age, postmortem interval (PMI), duration of tissue immersion in formaldehyde, the duration of depression, and the relationship between VDR IR and Ki67 positivity was examined using Spearman's correlation analysis. The level of significance was taken as $P < 0.05$.

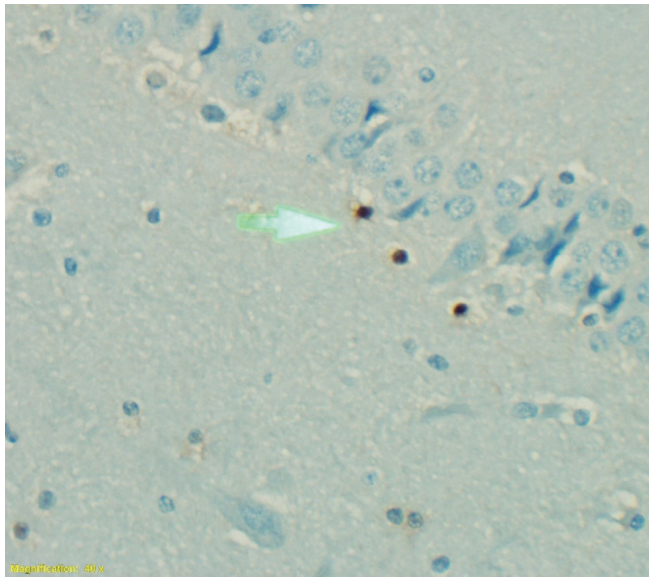

**Figure 1.** Ki67 cell positivity in Dentate Girus subgranular zone.

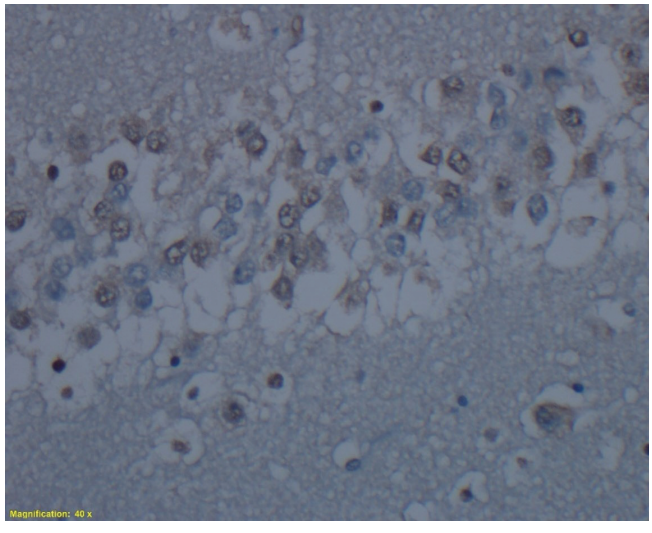

**Figure 2.** VDR IR granular cell appearance in Dentate Girus granular cell layer.

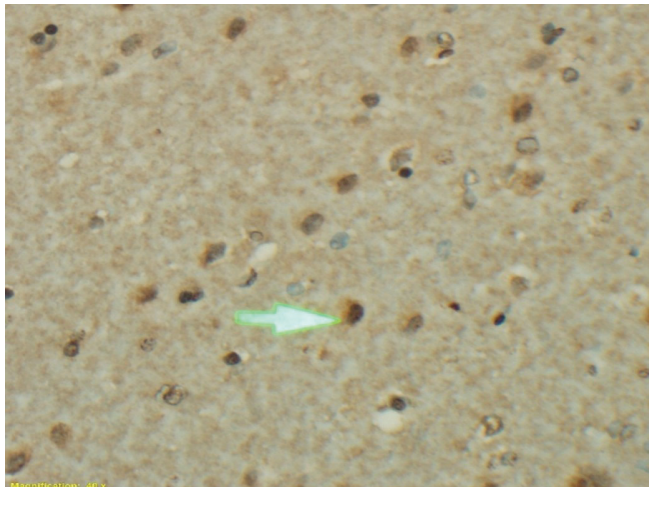

**Figure 3.** VDR IR positivity in caudate nucleus neurons.

## RESULTS

Note that 13 cases were evaluated in total; in fact, 7 were untreated MDD cases who died by suicide, and 6 were the healthy control group. The mean age of MDD patients was 44.0 ± 3.7 years, and the mean age of the control group was 41.6 ± 3.4 years. No antidepressant drug use was detected in the blood and prescriptions of the last six months in any of the cases included in the study. There was no difference between the control group and the suicide group in terms of age, PMI, and the duration of tissue immersion in formaldehyde (P = 0.774; P = 0.280; P = 0.886). In the dentate gyrus subgranular zone, the number of Ki67-positive cells (cells/mm granular cell layer (GCL)) was not statistically different in the anterior and posterior Dentate gyrus between the MDD group and control group (P = 0.098; P = 0.176) (Fig. 1). Furthermore, six of 13 cases had no Ki67 positivity. GFAP IR field fraction (%) in the anterior DG was median 28.9 (range = 13.5-34.1; mean ± standard error = 27.0 ± 2.4) in the MDD group, median 29.1 (25.4-38.4; 31.2 ± 2.2) control group, and no statistical difference was found between the groups (P = 0.391). GFAP IR field fraction in the posterior DG was median 26.7 (13.7-31.8; 26.0 ± 2.2) in the MDD group, median 29.7 (22.8-39.2; 29.9 ± 2.5) in the control group, and no significant difference was reported between the groups (P = 0.475). Median percentage (%) of VDR IR granular cells in the anterior DG granular layer was 13.2 (4.9-24.6; 14.9 ± 2.9) in the MDD group, 4.9 (1.1-6.5; 4.6 ± 0.8) in the control group, and it was significantly higher in the MDD group (P = 0.009) (Fig. 2). Median percentage (%) of VDR IR granular cells in the posterior DG granular layer was 10.6 (5.2-22.9; 11.8 ± 2.4) in the MDD group, 5.4 (4.2-20.5; 8.3 ± 2.5) in the control group, and there was no statistical difference between the groups (P = 0.116). GFAP IR field fraction (%) in the caudate nucleus was 16.7 (8.2-29.4; 17.9 ± 3.1) in the MDD group and 11.3 (5.6-24.8; 13.6 ± 3.4) in the control group, and no statistical difference was found between the groups (P = 0.252). The percentage of VDR IR-positive cells in caudate nucleus neurons was 22.3 (11.7-34.8 22.3 ± 2.8) in the MDD group, 19.5 (8.3-60; 28.3 ± 8.8) in the control group, and no statistical difference was reported between the groups (P = 0.99) (Fig. 3). In the untreated major depression case group, the number of Ki67-positive cells in the anterior DG showed a negative correlation with age (r = -0.867 P = 0.012). No correlation was reported between cell count and PMI and duration of tissue immersion in formaldehyde. No

correlation was reported between Ki67, GFAP IR and VDR immunoreactivity in posterior DG and caudate nucleus GFAP immunoreactivity and age, PMI, and duration of tissue immersion in formaldehyde. When the cases with Ki67 positivity were evaluated without grouping, a negative correlation was reported between anterior DG Ki67 positivity and VDR immunoreactivity ($r = -0.857$ $P = 0.014$) (Table 1).

## DISCUSSION

In their study, Reif *et al.* reported no difference in dividing cells in the anterior hippocampus in depressive patients compared to the control group [18]. In the study conducted by Boldiri *et al.*, although Ki67 positivity in the dentate gyrus was 50% less in patients with untreated major depression compared to the control group, the difference was not statistically significant [19]. In this study, no statistical difference was reported between suicide and control groups in terms of Ki67 positivity in the anterior and posterior dentate gyrus. This may be attributed to the number of cases in the study and the absence of Ki67 positivity in six cases. However, the absence of Ki67 positivity was reported in other studies. In the study conducted by Dennis *et al.*, Ki67 positivity was detected in only 2 out of 8 adult cases [20]. Another interesting finding in this study is the detection of a negative correlation between the number of anterior DG Ki67-positive cells and age in MDD cases. In addition, in a recent study in which neuropsychiatric patients were excluded, it was stated that Ki67 positivity did not change with age [21]. All this information suggests that neuropsychiatric diseases may be effective on the pool of DG proliferating cells in adulthood.

Miguel-Hidalgo *et al.* reported no significant difference between MDD patients and the control group in terms of GFAP IR field fraction in the dorsolateral prefrontal cortex; however, when the MDD cases were divided as per age groups, a significant decrease in GFAP IR was reported in the area fraction of the MDD group aged 45 and below compared to the MDD group over 45 years of age and the control group. In the same study, GFAP IR area fraction was reported to be non-significant higher in the elderly MDD group compared to the elderly control group [12]. In a study conducted by Si *et al.* using the Western Blotting method, a significant decrease was reported in the level of GFAP in the dorsolateral prefrontal cortex in the MDD group under 60 years of age compared to the control group of same age. However, no significant difference was reported between the MDD group over 60 years of age and the control group of same age [22]. In this study, no significant difference was reported between MDD and control group in GFAP levels in anterior and posterior DG. We believe that this is attributed to the wide age range and the insufficient number of cases.

Evidence regarding the role of 1αdihydroxyvitamin D3 in calcium homeostasis in bone tissue, as well as in central nervous system functions is increasing [23]. In one study, while 1αdihydroxyvitamin D3 increased the expression of nerve growth factor (NGF) and neurotrophin 3 in primary astrocyte culture, it reduced neurotrophin 4 expression [24-25]. In another study, 1αdihydroxyvitamin D3 was reported to be a strong inducer of glial-derived neurotrophic factor (GDNF) expression [26]. Furthermore, 1,25(OH)2D3 is an important factor in the modification of the synthesis of neuromeditors such as acetylcholine by increasing the gene expression of the choline acetyltransferase enzyme [27]. In a study, it was determined that VDR density was regulated by 1,25(OH)2D3 in several tissues [28]. Moreover, no change was reported in VDR in neonatal rats born from mothers with vitamin D deficiency [29]. In another study, no change was reported in VDR mRNA content in adult offspring deprived of vitamin D during gestation [30]. This suggests that it is a not vitamin D level alone that is effective in VDR regulation. In the present study, the percentage of VDR IR cells in the anterior DG was reported to be higher in suicide cases compared to the control group. However, there was no significant difference in the posterior DG. Different anatomical regions of the hippocampus may be differently affected because of their different functions. As a matter of fact,

**Table 1.** GFAP and VDR results in brain tissues

| Brain tissues | | MDB Median/Mean values | Control Median/Mean values | P |
|---|---|---|---|---|
| Anterior Dentate Gyrus | GFAP IR field fraction | 28.9/27.0 | 29.1/31.2 | 0.391 |
| Posterior Dentate Gyrus | GFAP IR field fraction | 26.7/26.0 | 29.7/29.9 | 0.475 |
| Anterior Dentate Gyrus | VDR IR granular cells (%) | 13.2/14.9 | 4.9/4.6 | **0.009** |
| Posterior Dentate Gyrus | VDR IR granular cells (%) | 10.6/11.8 | 5.4/8.3 | 0.116 |
| Caudate nucleus | GFAP IR field fraction (%) | 16.7/17.9 | 11.3/13.6 | 0.252 |
| Caudate nucleus | VDR IR positive cells (%) | 22.3/22.3 | 19.5/28.3 | 0.99 |

while the anterior part of the hippocampus plays a role in emotional regulation, the posterior part is mostly effective in cognitive functions [31]. In a postmortem study, the number of granular cells in the anterior and middle DG of depression patients was less than the control group, but no difference was found in the posterior DG [32]. Considering all these factors, it can be suggested that the anterior hippocampus, which plays an active role in the regulation of emotions, is negatively affected in suicide cases, and the VDR increase in the anterior DG may likely be a defense mechanism, considering the roles of VDR as a neuroprotective factor and in regulating neurotransmitter release. In animal experiments and cell culture studies, the anti-proliferative effect of vitamin D was shown [23, 33]. In the present study, the presence of a negative correlation between the number of anterior DG Ki67 positive cells and VDR IR supports the findings of studies the anti-proliferative effect of vitamin D.

In a meta-analysis study examining magnetic resonance imaging (MRI) studies, it was reported that the total caudate volume decreased in depressive patients [4]. In the study of Shah *et al.*, it was found that treatment-resistant depression patients had smaller caudate tissue compared to the patients who recovered and healthy individuals [34]. It was stated that all of these can be interpreted as changes in the caudate nucleus related to the persistence of depression [35]. In a study conducted with depression cases who committed suicide, GFAP mRNA and protein levels were reported to be lower in the caudate nucleus compared to the control group [36]. Furthermore, it was shown that the expression of some astrocyte specific genes was decreased in MD [37]. In this study, unlike the hippocampus, the fraction of GFAP area was found to be higher in the caudate nucleus, although it was not statistically significant. This may be due to the difference between patients who received treatment and those who did not.

Consequently, we believe that immunohistochemical changes occurred in the anterior hippocampus in MDD cases who committed suicide and VDR may have increased because of its neuroprotective functions in tissues under adverse conditions.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Limitation**

The limited study period and consequently the small sample size are the limitations of this study. The study is planned to be performed with a larger sample.

## References

1. Preventing suicide: aresource for media professionals, update 2017. Geneva: World Health Organization 2017 (https://www.who.int/mental_health/suicide-prevention/en/)
2. Roca M, Del Amo AR, Riera-Serra P, Pérez-Ara MA, Castro A, Roman Juan J, García-Toro M, García-Pazo P, Gili M. Suicidal risk and executive functions in major depressive disorder: a study protocol. BMC Psychiatry. 2019; 19(1): 253-259.
3. Rajkowska G, Stockmeier C. Astrocyte pathology in majör depressive disorder: Insigths from human postmortem brain tissue. Curr Drug Targets. 2013; 14: 1225-1236.
4. Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur Neuropsychopharmacol. 2012;22(1):1-16.
5. Cobb JA, Simpson J, Mahajan GJ, Overholser JC, Jurjus GJ, Dieter L, Herbst N, May W, Rajkowska G, Stockmeier CA. Hippocampal volüme and total cell numbers in majör depressive disorder. J Psychiatric Res. 2013; 47(3): 299-306.
6. Cobb JA, O'Neill K, Milner J, Mahajan GJ, Lawrence TJ, May WL, Miguel-Hidalgo J, Rajkowska G, Stockmeier CA. Density of GFAP-immunoreactive astrocytes is decreased in left hippocampi in major depressive disorder. Neuroscience. 2016; 316: 209-220.
7. Jacobs BL, Van Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry. 2000; 5(3): 262-269.
8. Kempermann G, Song H, Gage FH. Neurogenesis an the adult hippocampus. Cold Spring Harb Perspect Biol. 2015; 7(9): 1-14.
9. Scholzen T, Gerdes J. The Ki-67 protein: From the known and unknown. J Cell Physiol. 2000; 182(3): 311-322.
10. Gosselin RD, Gibney S, O'Malley D, Dinan TG, Cryan JF. Region specific decrease in glial fibrillary acidic protein immunoreactivity in the brain of a rat model of depression. Neuroscience. 2009; 159(2): 915-925.
11. Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. Nat Neurosci. 2007; 10(11): 1369-1376.
12. Miguel-Hidalgo JJ, Baucom C, Dilley G, Overholser JC, Meltzer HY, Stockmeier CA, Rajkowska G. Glial fibrillary acidic protein immunoreactivity in the prefrontal cortex distinguishes younger from older adults in major depressive disorder. Biol Psychiatry. 2000; 48(8): 861-873.
13. Stewart R, Hirani V. Relationship between vitamin D levels and depressive symptoms in older residents from a national survey population. Psychosom Med. 2010; 72(7): 608-612.
14. Ganji V, Milone C, Cody MM, McCarty F, Wang YT. Serum vitamin D concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey. Int Arch Med. 2010; 3(29): 10-16.
15. Langub MC, Herman JP, Malluche HH, Koszewski NJ. Evidence of functional vitamin D receptors in rat hippocampus. Neuroscience. 2001; 104(1): 49-56.
16. Baas D, Prüfer K, Ittel ME, Kuchler-Bopp S, Labourdette G, Sarlième LL, Brachet P. Rat oligodendrocytes express the vitamin D(3) receptor and respond to 1,25-dihydroxyvitamin D(3). Glia. 2000; 31(1): 59-68.
17. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat. 2005; 29(1): 21-30.
18. Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch KP. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry. 2006; 11: 514-522.
19. Boldrini M, Underwood MD, Hen R, Rosoklija GB, Dwork AJ, John Mann J, Arango V. Antidepressants increase neural progenitor cells in the human hippocampus. Neuropsychopharmacology. 2009; 34(11): 2376-2389.

20. Dennis CV, Suh LS, Rodriguez ML, Kril JJ, Sutherland GT. Human adult neurogenesis across the ages: An immunohistochemical study. Neuropathol Appl Neurobiol. 2016; 42(7): 621-638.
21. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V, Rosoklija GB, Stankov A, Arango V, Dwork AJ, Hen R, Mann JJ. Human Hippocampal Neurogenesis Persists throughout Aging. Cell Stem Cell. 2018; 22(4): 589-599.
22. Si X, Miguel-Hidalgo JJ, O'Dwyer G, Stockmeier CA, Rajkowska G. Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. Neuropsychopharmacology. 2004; 29(11): 2088-2096.
23. Marini F, Bartoccini E, Cascianelli G, Voccoli V, Baviglia MG, Magni MV, Garcia-Gil M, Albi E. Effect of 1alpha,25-dihydroxyvitamin D3 in embryonic hippocampal cells. Hippocampus. 2010; 20(6): 696-705.
24. Neveu I, Naveilhan P, Jehan F, Baudet C, Wion D, De Luca HF, Brachet P. 1,25-dihydroxyvitamin D3 regulates the synthesis of nerve growth factor in primary cultures of glial cells. Brain Res Mol Brain Res. 1994; 24(1): 70-76.
25. Neveu I, Naveilhan P, Baudet C, Brachet P, Metsis M. 1,25-dihydroxyvitamin D3 regulates NT-3, NT-4 but not BDNF mRNA in astrocytes. Neuroreport. 1994; 6(1): 124-126.
26. Naveilhan P, Neveu I, Wion D, Brachet P. 1,25-Dihydroxyvitamin D3, an inducer of glial cell line-derived neurotrophic factor. Neuroreport. 1996; 7(13): 2171-2175.
27. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab. 2002; 13(3): 100-105.
28. Darwish H, DeLuca HF. Vitamin D-regulated gene expression. Crit Rev Eukaryot Gene Expr. 1993; 3(2): 89-116.
29. Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin D3 and brain development. Neuroscience. 2003; 118(3): 641-653.
30. Eyles D, Almeras L, Benech P, Patatian A, Mackay-Sim A, McGrath J, Féron F. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial, cytoskeletal and synaptic proteins in the adult rat brain. J Steroid Biochem Mol Biol. 2007; 103(3): 538-545.
31. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron. 2010; 65(1): 7-19.
32. Boldrini M, Santiago AN, Hen R, Dwork AJ, Rosoklija GB, Tamir H, Arango V, John Mann J. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. Neuropsychopharmacology. 2013; 38(6): 1068-1077.
33. Brown J, Bianco JI, McGrath JJ, Eyles DW. 1,25-dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. Neurosci Lett. 2003; 343(2): 139-143.
34. Shah PJ, Glabus MF, Goodwin GM, Ebmeier KP. Chronic, treatment-resistant depression and right fronto-striatal atrophy. Br J Psychiatry. 2002; 180: 434-440.
35. Lorenzetti V, Allen NB, Fornito A, Yücel M. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J Affect Disord. 2009; 117(1): 1-17.
36. Torres-Platas SG, Nagy C, Wakid M, Turecki G, Mechawar N. Glial fibrillary acidic protein is differentially expressed across cortical and subcortical regions in healthy brains and downregulated in the thalamus and caudate nucleus of depressed suicides. Mol Psychiatry. 2016; 21(4): 509-515.
37. Ordway GA, Szebeni A, Chandley MJ, Stockmeier CA, Xiang L, Newton SS, Turecki G, Duffourc MM, Zhu MY, Zhu H, Szebeni K. Low gene expression of bone morphogenetic protein 7 in brainstem astrocytes in major depression. Int J Neuropsychopharmacol. 2012; 15(7): 855-868.