REVIEW DERLEME

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Combined Use of Probiotics and Vitamin D Against Neurotoxicity: Traditional Review

Nörotoksisiteye Karşı Probiyotik ve D Vitamininin Birlikte Kullanımı: Geleneksel Derleme

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This study was prepared based on the findings of Fatma Hazan Gül's doctoral thesis study titled "In vitro investigation of the neuroprotective effect of probiotics and vitamin D against neurotoxicity" (Kayseri: Erciyes University; 2023).

ABSTRACT Neurodegeneration caused by neurotoxicity is a condition influenced by many factors such as increased reactive oxygen species, protein misfolding, and ubiquitin-proteasome pathway dysfunction. The brain-gut axis is one of the primary systems affected by neurodegeneration. This axis is a bidirectional system consisting of neurological, endocrine, and immunological elements. Disruption of microbial balance in the gut leads to poor inflammation, increased oxidative stress, disruption of energy homeostasis, and cellular degeneration. Probiotics, which are important for maintaining this balance, are beneficial bacteria that, when ingested in sufficient quantities, positively affect host health and play an active role in maintaining microbial homeostasis in the gut. Another substance that impacts neurodegeneration is vitamin D. It is clearly stated in the literature that vitamin D supplementation, a fat-soluble micronutrient that falls into the steroid hormone category, or adequate sun exposure positively reduces the risk of developing/progressing neurodegenerative disorders. Vitamin D achieves this effect by inhibiting the synthesis of nitric oxide synthase and increasing the stimulation of gamma-glutamyl transpeptidase. Moreover, vitamin D exerts this beneficial effect by binding to vitamin D receptors in the intestine. It is known that probiotics and vitamin D have separate neuroprotective effects against neurotoxicity, but it is not well enough known that their beneficial effects are enhanced when probiotics and vitamin D are taken together. The aim of this study is to show that the beneficial effects of probiotics and vitamin D against neurotoxicity are enhanced when they are taken together.

Keywords: Probiotics; vitamin D; microbiota; brain-gut axis; neurotoxicity syndromes

ÖZET Nörotoksisitenin neden olduğu nörodejenerasyon, reaktif oksijen türlerinin artması, proteinlerin yanlış katlanması ve ubikitin-proteozom yolağının disfonksiyonu gibi birçok faktörden etkilenen bir durumdur. Nörojenerasyondan etkilenen sistemlerin başında beyin-bağırsak aksı gelir. Bu aks nörolojik, endokrin ve immünolojik unsurlardan oluşan çift yönlü bir sistemdir. Bağırsağın mikrobiyal dengesinin bozulması düşük dereceli inflamasyona, oksidatif streste artışa, enerji homeostazının bozulmasına ve hücresel dejenerasyonun artmasına neden olur. Bu dengenin korunmasında önemli olan probiyotikler, yeterli miktarda alındığında konakçı sağlığını olumlu yönde etkileyen ve bağırsaklarda mikrobiyal homeostazın sağlanmasında aktif rol oynayan yararlı bakterilerdir. Nörodejenerasyon üzerine etkisi olduğu bilinen bir diğer madde D vitaminidir. Steroid hormon kategorisine giren ve yağda çözünen bir mikro besin olan D vitamini takviyesinin veya yeterli güneş ışığına maruz kalmanın, nörodejeneratif bozuklukların gelişme/ilerleme riskini olumlu yönde azalttığı literatürde açıkça belirtilmektedir. D vitamini bu etkisini nitrik oksit sentazın sentezini inhibe ederek ve gama-glutamil transpeptidazın stimülasyonunu artırarak gerçekleştirmektedir. Ayrıca D vitamini bu yararlı etkisini bağırsaktaki D vitamini reseptörlerine bağlanarak gösterir. Probiyotikler ve D vitamininin nörotoksisiteye karşı ayrı ayrı nöroprotektif etkisi olduğu bilinmekle birlikte, probiyotikler ve D vitamini birlikte alındığında bu protektif etkinin arttığı yeterince bilinmemektedir. Bu çalışmanın amacı, nörotoksisiteye karşı probiyotiklerin ve D vitamininin birlikte kullanıldığında yararlı etkilerinin artığını ortaya koymaktır.

Anahtar Kelimeler: Probiyotikler; D vitamini; mikrobiyota; beyin-bağırsak aksı; nörotoksisite sendromları

NEUROTOXICITY

Neurotoxicity is defined as disruption of a nervous system function by an endogenous and exogenous compound or a combination thereof. Exposure to these acutely or chronically toxic chemicals during the fetal period may result in permanent damage that may cause neurodevelopmental disorders in the future.[1] Grandjean and Landrigan, identified 214 chemicals that damage the adult nervous system

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and 12 industrial chemical groups (toluene, lead, arsenic, manganese, methylmercury, fluoride, polychlorinated compounds, chlorpyrifos, biphenyls, brominated diphenyl ethers), dichlorodiphenyltrichloroethane/ dichlorodiphenidichloroethylene, trichloroethylene. More than 1,000 chemicals have been shown to be neurotoxic in *in vivo* studies.[2,3]

NEUROTOXINS AND THEIR TYPES

Any substance that causes atrophy or demyelination by damaging neurons, nerve fibers, glia, and myelin in the nervous system is considered a neurotoxin. These substances are usually of endogenous or exogenous origin. Endogenous are made by the human body, while exogenous are toxins that enter the human body from the external environment.[4] Endogenous toxins are primarily aging and genetic factors, exogenous toxins are pesticides and heavy metals.[4-6]

ENDOGENOUS NEUROTOXINS

Endogenous neurotoxins are substances that normally have a specific physiological function in the body but cause toxic effects in the central nervous system when produced in excess.

Glutamate, for example, is responsible for chemical transport at synapses and is one of the most important neurotransmitters in the nervous system. An increase in glutamate concentration causes toxicity in neurons by rising the permeability to calcium ions. As this increase in cellular calcium concentration stimulates calcium-related enzymes, apoptosis and necrosis occur in neurons.[7] Another example of this situation is nitric oxide (NO). NO is the secondary neurotransmitter synthesized by neuronal NO and is widely distributed in neurons. It also controls synaptic plasticity of the nervous system and muscular and neurovascular dilation in the nervous and vascular systems.[8] Abnormal NO concentration is associated with several neurological diseases (asthma, schizophrenia, and Huntington's disease). Endogenous neurotoxins inhibit ion channels of neurotransmitters (e.g., K^{+}, Ca^{+2}, Na^{+}), receptors (e.g., acetylcholine receptors) and enzymatic activities (e.g., tyrosine hydroxylase).[9-11]

EXOGENOUS NEUROTOXINS

Exogenous neurotoxins include heavy metals, microbial neurotoxins, biotoxins, and chemical toxoids. The mechanisms of action of each toxin in the nervous system are different. Heavy metals (lead, cadmium and aluminum) generally reach the brain via the bloodstream by disrupting the blood-brain barrier or inhibiting the blood-brain barrier.[12] After these neurotoxins cross the blood-brain barrier and reach the brain, they cause brain damage, resulting in learning difficulties, motor coordination disorders, and the onset of diseases such as Alzheimer diseases.[4,13,14] Microbial neurotoxins (botulinum, tetanus toxin, and lipopolysaccharide) are mostly produced by bacteria. These substances, which stimulate the nervous system, prevent the deliver of neurotransmitters from synaptic vesicles and block communication between neurons.[15] Bioneurotoxins are toxins such as tetrodotoxin, found in the puffer fish, snake venom, and chlorotoxin. Some of them inhibit neuronal communication by reducing the permeability of ion channels in neurons. The target ion channel of each bioneurotoxin differs from each other.[16-20]

PROBIOTICS

Probiotics are beneficial microorganisms that have a positive effect on human health when ingested in sufficient quantities and play a role in maintaining microbial homeostasis in the gut.[21] At the beginning of these beneficial microorganisms are bacteria, fungi, and algae that have the property of being probiotics. Probiotic microorganisms can be accepted with the characteristics defined by the European Food Safety Authority. These characteristics are: (i) colonize intestinal epithelial cells in the human body, (ii) have the ability to attach to mucus or intestinal epithelial cells, (iii) be non-pathogenic and non-toxic, (iv) have a proven effect on health, (v) interact with the target host being isolated from the same species, (vi) being viable while passing through the upper gastrointestinal tract.[22]

One of the systems affected by neurodegeneration is the brain-gut axis. This axis is a bidirectional system consisting of neurological, endocrine, and immunological elements. When the microbial balance of the gut is disturbed, communication between it and

the brain is impaired. This is accompanied by poor inflammation, increased oxidative stress, impaired energy homeostasis, and increased cellular degeneration.[23] Probiotics, which primarily provide gut microbial balance, are beneficial bacteria that have a positive impact on host health when ingested in adequate amounts and play a role in ensuring gut microbial homeostasis.[21] In an *in vitro* study, Lab4 (*Lactobacillus acidophilus* CUL21, *L. acidophilus* CUL60, *Bifidobacterium bifidum* CUL20, and *B. animalis subsp. lactis* CUL34) and Lab4b (*L. acidophilus* CUL08, *lactis* CUL34) and Lab4b co-incubated and post-incubated neuroprotective effects of two consortia of bacteria known as *B. bifidum* CUL20 and *B. animalis subsp. lactis* CUL34 were investigated. Looking at the post-incubation results of the study, cell viability was 70.9% in the rotenone group, while it increased to 86.7% in Lab4 and 90.3% in Lab4b. When bacterial consortia were used simultaneously, it was found that both strains reduced apoptosis and necrosis, with Lab4b having even a greater effect on reducing apoptosis and necrosis. In addition, the same consortia were found to reduce the upregulation of genes encoding antioxidant enzymes and the accumulation of intracellular reactive oxygen species (ROS) in SH-SY5Y cells.[24] SH-SY5Y is a human-derived neuroblastoma cell line used in experimental neurodegenerative studies. Because it morphologically resembles neuronal cells, it is used in *in vitro* neurodegenerative disease studies.[25,26] In another study, the effect of *L. fermentum* KU200060, *L. delbrueckii* KU200171, and *L. buchneri* KU200793 isolated from Korean fermented foods on SH-SY5Y cells were investigated. The cell line that caused neurotoxicity with MPP^+ was incubated with bacterial strains for about 4 hours. It was found that all strains showed neuroprotective effects on the SH-SY5Y cell line.[27] In another study, *L. plantarum* 200655 added to SH-SY5Y cells induced with H_2O_2 significantly decreased apoptosis-related Bax/Bcl-2 ratio and increased brain-derived neurotrophic factor and tyrosine hydroxylase mRNA expression. That's why, *L. plantarum* 200655 can be used as a prophylactic component to avoid neurodegenerative diseases.[28] In a study investigating the neuroprotective effects of *Ruminococcus albus*, which has probiotic properties, on SH-SY5Y cells and living organisms, neuronal proliferation was reduced in SH-SY5Y cells induced simultaneously with *R. albus* and H_2O_2 by inhibiting proteins related to cell proliferation, and *R. albus* by lowering ROS levels. It was observed to protect neurons from oxidative damage by increasing antioxidant enzyme levels.[29] The original probiotic formulation DSF has been shown to control the expression of various genes in the cerebral cortex of older animals, reducing inflammation and improving neuronal performance.[30] As can be seen, various probiotic formulations alleviate inflammation by producing cytokines in different ways and reduce oxidative stress by lowering ROS levels.[31,32] Administration of probiotics to mice with Parkinson disease has been shown to protect dopaminergic neurons and improve behavioral disorders.[33] This proves that probiotics can reduce the production of ROS by showing an antioxidant effect and have a neuroprotective effect by modulating the brain-gut axis in different ways.

VITAMIN D

Vitamin D is a fat-soluble steroid hormone and an anti-oxidant. It has two forms, D_3 (cholecalciferol) and D_2 (ergocalciferol). Cholecalciferol, the main source of vitamin D, is synthesized in the skin from 7-dehydrocholesterol by ultraviolet (UV) rays then converted to 25-hydroxyvitamin D_3 ($25(OH)D_3$) in the liver by the enzyme 25-hydroxylase, and then $25(OH)D_3$ is converted to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D$) in the kidneys. It undergoes hydroxylation to produce $1,25(OH)_2D$.[34] The effects on the immune system of the enzyme 1-α-hydroxylase, which converts the major form of vitamin D, 25-hydroxycholecalciferol, to its active form, calcitriol, are evidence that vitamin D has a broader spectrum of biological effects and acts as an antioxidant.[35] The body uses the cholecalciferol produced by UV light by either storing it in body tissues or activating it in the liver and kidneys to utilise it. Most of the vitamin D requirement in the body (90%) is met in this way. This situation is controlled by the parathyroid hormone, serum calcium and phosphorus levels. A small portion (10%) of vitamin D is absorbed through food (liver, egg yolk, fatty fish, etc.). Ergocalciferol, on

the other hand, is found in foods of plant origin and is formed in the presence of UV rays. The inability of people to adequately use sunlight due to lifestyle changes is leading to vitamin D deficiency in society.[36] Virtually all of the body's tissues and organs contain receptors that are influenced by vitamin D. The receptor-mediated mechanism of vitamin D activity is facilitated by the presence of active vitamin D.[37] The best known effect of vitamin D relates to the skeletal system. Vitamin D provides homeostasis in bone mineralization by balancing calcium and phosphorus absorption. Studies show that vitamin D supplementation can reduce the incidence of hip fractures and other non-vertebral fractures.[38] Vitamin D is thought to have a protective effect against neurological disease because of its immunomodulatory role. It controls calcium-mediated neuronal excitotoxicity in the nervous system by lowering oxidative stress and promoting synaptic structural proteins, neurotrophic factors, and neurotransmitters.[39] In the presence of vitamin D, it inhibits the synthesis of NO synthase, which acts as a catalyst for the free radical NO, which can damage cells. Vitamin D also increases the stimulation of gamma-glutamyl transpeptidase, an enzyme important for the synthesis of the antioxidant glutathione, which protects against cell damage by neutralizing free radicals.[40] In a study using rats, the fact that calcitriol reduces oxidative stress and increases the levels of antioxidant enzymes shows that its antioxidant effect is also valid in *in vivo* studies.[41] In another study conducted in rats with PD, it was shown that vitamin D administration increased glial cell line-derived neurotrophic factor expression and led to an increase in central dopamine levels compared to the control group.[42] An further mechanism through which vitamin D provides protection against neurological diseases is through its immunomodulatory function. By reducing oxidative stress and increasing synaptic structural proteins, neurotrophic factors, and neurotransmitters, vitamin D helps control calcium-mediated neuronal excitotoxicity in the nervous system.[39] In another study, the protective effect of calcitriol against 6-OHDA-induced dopaminergic neuron damage was investigated *in vivo* and *in vitro*. In the rat model (n=32) generated with 6-OHDA (8 µg), half of the animals received 1 µg/mL/kg/day vitamin D_3 for 8 days, while the other half received saline (154 mM NaCl, 1 mL/kg/day). It was observed that 6-OHDA decreased locomotor activity in the saline-treated group, while the lesions produced by 6-OHDA in the other group were significantly restored by vitamin D_3. Vitamin D_3 (10^{-10} M) has been found to have a neuroprotective effect against neurotoxicity induced by 6-OHDA or H_2O_2 in rat embryo cell cultures.[43] Vitamin D supplementation can also modulate the gut microbiota by regulating the host immune response.[44] $1,25(OH)_2D$, can be produced by colonocytes, and it is suggested that inadequate calcium intake or vitamin D concentration may cause inflammatory bowel disease and colon cancer development due to decreased synthesis in the gut.[45] In addition, vitamin D receptor (VDR) deficiency decreases intestinal tract T cells and the response of non-pathogenic bacteria to inflammation. Colonization with bacteria in the colon affects the distribution and expression of VDR, and intestinal VDR directly suppresses bacterial nuclear factor kappa B activation.[46]

COMBINED USE OF PROBIOTICS AND VITAMIN D

Probiotics and vitamin D have been shown to have independent neuroprotective effects on neurotoxicity in many studies.[24,40-42,47] However, there are very few studies that have investigated the protective effects of taking both substances together. The gut microbiota can be modulated by vitamin D/VDR pathway. Increased VDR expression has been shown to reduce microbial dysbiosis, improve gut barrier function, express more antimicrobial peptides, and produce more short-chain fatty acids in commensals.[48,49] There is no *in vitro* study in the literature in which vitamin D and a probiotic preparation were administered together. In clinical or *in vivo* studies, it has been found that co-administration of probiotics and vitamin D showed more effective results not only in neurodegenerative diseases but also in various disease groups. In a study of sixty patients diagnosed with chronic schizophrenia, subjects received 50.000 IU of vitamin D_3 every two weeks and 8×10^9 CFU/day of probiotics (*L. acidophilus, B. bifidum, L. reuteri,* and *L. fermentum*) (n=30) or placebo (n=30) for 12 weeks. Considering the results of the study, it was found that concomitant administration of probiotics

and vitamin D increased the total antioxidant capacity of plasma and decreased the levels of C-reactive protein (CRP) and malondialdehyde.[50] The effect of probiotics+vitamin D on mental health parameters and metabolic status in subjects with Type 2 diabetes mellitus (n=60; aged 45-85 years) with coronary artery disease was studied. Subjects received 50.000 IU vitamin D_3 every 2 weeks and 8×10^9 CFU/day probiotic (n=30) or placebo (n=30) for 12 weeks. After the intervention, significant improvements in Total Beck Depression and Beck Anxiety Inventory scores and general health questionnaire scores were observed in the vitamin D and probiotic-supplemented group compared with the placebo group. Serum insulin levels and insulin resistance decreased significantly; vitamin D levels and serum high-density lipoprotein (HDL) cholesterol increased. In addition, positive effects on serum CRP, plasma NO, total antioxidant capacity, and glycemic control were noted.[51] In an *in vivo* study, rats were separated into four groups: a control group, an obese control group, an obese group supplemented with probiotics, and an obese group supplemented with probiotics and vitamin D. The rats receiving probiotic and probiotic+vitamin D supplements had decreased levels of insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), triglycerides, interleukin 6 (IL-6), CRP, and leptin. The results of the study suggest that probiotics and vitamin D reduced weight gain more and had a more positive effect on fasting plasma glucose, insulin, HOMA-IR, triglycerides, IL-6, CRP, and leptin levels.[52] Glucose homeostasis, inflammation, oxidative stress, and pregnancy outcomes were investigated in another study that examined the effects of concomitant administration of vitamin D and probiotics on metabolism and pregnancy outcomes in women with gestational diabetes. Subjects participating in the study (n=87) received every 2 weeks 50.000 IU vitamin D_3+8×10^9 CFU/day probiotics (*L. acidophilus, B. bifidum, L. reuteri,* and *L. fermentum*) (n=30), 8×10^9 CFU/day probiotics (*L. acidophilus, B. bifidum, L. reuteri,* and *L. fermentum*) (n=29) were divided into 3 groups receiving placebo (n=28). The study intervention lasted 6 weeks. Vitamin D and probiotics supplementation significantly decreased fasting plasma glucose levels, serum insulin levels, and the HOMA-IR; it was found that the quantitative control index of insulin sensitivity significantly increased. In addition, this supplement decreased triglyceride levels, very low-density lipoprotein levels, HDL-to-total cholesterol ratio, CRP, and malondialdehyde levels; it was found to increase HDL cholesterol and total antioxidant capacity but did not alter NO and total glutathione levels. In addition, the incidence of hyperbilirubinemia and hospitalization was found to be lower in neonates born to mothers from this group after delivery.[53] Consistent with the results of this study, it was observed that 90-day supplementation with vitamin D and *L. reuteri* reduced bronchial inflammation in children with allergic asthma.[54] Ostadmohammadi et al., in a study of women with polycystic ovary syndrome, found that concomitant administration of vitamin D and probiotics had beneficial effects on hormonal, inflammatory, and antioxidant parameters, as well as mental health parameters such as depression, anxiety, and stress, compared with placebo.[55] The only study in which the simultaneous administration of probiotics and vitamin D was not found to be effective enough is the study by Tazzyman et al. According to this study, no statistically significant group differences were found that received probiotics and vitamin D together and the groups that received only vitamin D or only placebo.[56]

CONCLUSION AND RECOMMENDATIONS

In conclusion, neurotoxicity is a very serious condition that leads to neurodegenerative diseases. Since there is no definitive medical treatment to prevent these diseases, natural supplements are resorted to. It is known that probiotics and vitamin D have a positive effect on neurotoxicity. Recent studies have clearly shown that a stronger protective effect is obtained when the two agents are used together. In fact, studies conducted in the literature at the clinical level or *in vivo* have found that taking probiotics and vitamin D together shows more effective results not only in neurodegenerative diseases but also in different disease groups.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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