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# GBA-related diseases and the application in Tourette syndrome treatment

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**Abstract.** This paper discusses the gut-brain axis (GBA) and how it takes part in various neurological diseases, including Alzheimer's disease (AD), Attention-deficit hyperactivity disorder (ADHD), and Tourette syndrome. The gut microbiota, inducing vital communications with the brain through the GBA, is not to be neglected in maintaining physiological balance, with the potential to become a source of new therapeutic opportunities for treating these diseases. Current studies show that methods such as personalized diets, oral bacteriotherapy, and multi-strain probiotics like SLAB51 and DEX have promising results in treating AD and ADHD through manipulation of the biotas. Based on the analysis of previous research, this paper finds how changes in gut microbiota amount in feces between healthy and TS mice, in particular the decrease in Firmicutes and Actinobacteria, and the increase in Bacteroidetes and Proteobacteria. However, future studies and experiments are required to evaluate potential side effects of microbiome alterations in humans, and potential treatments for Tourette's syndrome based on gut microbiota analysis. The GBA is a promising area for developing new therapeutic approaches for neurological diseases, and future research in this field holds great potential for advancements in the treatment of these disorders currently with no verified cures.

**Keywords:** GBA, AD, ADHD, Tourette Syndrome.

## 1. Introduction

The GBA is an essential communication channel providing a link between the central nervous system (CNS) and the enteric nervous system (ENS), which are responsible for transmitting messages to and fro the brain and the gut. The latter contains almost half a billion neurons, and it communicates with the brain through various means, including the vagus nerve, hormones released from the pituitary gland, and neurotransmitters. An extensive community of commensal bacteria, archaea, fungi, and viruses constitute the gut microbiome, which carries out various vital physiological functions, including the production of metabolites, the fermentation of indigestible carbohydrates, and the regulation of both the immune system and the nervous system. The microbiota is crucial to maintaining physiological balance and has significant potential as a source of new therapeutic opportunities, including targeting and influencing the microbiota-GBA in curing diseases similar to Alzheimer's disease (AD) of the central nervous system, one that severs nerve connections in patients' brain and greatly hinders their most basic muscle movements, and disorders of gut-brain interaction (DGBIs).

Currently, for AD, there is a potential to use personalized diets and oral bacteriotherapy to manipulate the gut microbiota and its byproducts, such as the amyloid protein, studies have indicated that this

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manipulation can produce positive results on the neuronal pathways, which can ultimately slow down the advancement of this disease [1]. Promising results from the study on the effect of dexmedetomidine (DEX) on behavior resembling Attention-deficit hyperactivity disorder (ADHD) in spontaneously hypertensive rats (SHRs) indicated that DEX may be an effective treatment for ADHD due to how it alters the gut microbiota's composition while lowering gut and brain inflammation. After the administration of DEX, the gut pathological scores, permeability, and inflammation in the gut and brain improved significantly [2]. Similarly, researchers have shown that innate, adaptive systemic immune pathways, and neuroinflammatory-relating mechanisms, are becoming increasingly evident that the microbiota-GBA is also involved in Tourette syndrome, a chronic neurological disease since at least a subset of individuals with Tourette syndrome and related neuropsychiatric disorders are influenced by gut microbes in the development of their conditions. This lasting disorder which causes involuntary tics and spasms in patients appears to bring notable impacts to microbiota in the gut and may be the prime factor for the development of corresponding plausible treatments.

In both AD and ADHD, GBA is a presence to be reckoned with, therefore, it is crucial to explore the mechanism of GBA in neurological diseases. This paper aims to discuss and evaluate the mechanism and treatments for GBA-related neurological diseases based on the two-way communication from the brain to the gut as a second brain, as well as current limitations and future improvement methods. The link between microbes and treatments for brain functions based on Tourette's disorder will also be discussed.

## 2. GBA-related diseases and their corresponding treatments

### *2.1. The relationship between GBA and AD*

Alzheimer's disease resulted from the atypical amyloid and tau protein accumulations both in and surrounding the brain cells, the build-up of amyloid forms plaques around the cells and the enmeshed tau proteins lead to shrinkage of healthy brain cells, while natural accumulations in smaller degree do occur during normal cell senescence [3]. Specifically, these plaques are formed between nerve cells in the cerebral cortex by over accumulation of β-amyloid, causing distorted neuron connections [4]. How the gut microbiota is a significant source providing these amyloids shows the link of the GBA with AD, these amyloids assist in binding between bacterial cells to form biofilms and prevent destruction by the immune system[5]. Due to the similarity in their tertiary structures between bacterial amyloids and CNS amyloids, immune system priming may be activated after exposure to the former, causing intensified endogenous production which leads to cumulation of neuronal amyloid in the brain [5].

### *2.2. The multi-strain probiotic formulation SLAB51 plays a positive role in AD treatment*

As gut microbiota is so tightly related to AD, given the context of high concentration of pro-inflammatory bacteria in the gut triggers more secretion of amyloids, and thus promoting neuroinflammation, oxidation, amyloid-beta deposition, neuronal degeneration and such, oral supplemented formulation of SLAB51 multi-strain probiotic can be effective in reducing amyloid load and tau hyperphosphorylation concentration, stimulating more production of neuroprotective gut hormones and triggering antioxidant mechanisms, based on studies of a transgenic murine model of AD on treated 8 weeks old 3xTg-AD and wild-type mice under hypoxia. This study investigates how SLAB51 affects hypoxia-inducible factor-1α (HIF-1α), a target for neurological pathology and a crucial protein controlling host-microbial interaction. The results showed that mice with continued full treatment with SLAB51 improved HIF-1α activity in cerebral expression, as well as decreased levels of its oxygen-dependent regulator—prolyl hydroxylase 2 (PHD2) [6].

Additionally, PHD2 regulates oxygen-dependent HIF-1α without the presence of repressor proteins and causes HIF-1α to be degraded by proteasomes under normoxia or after a brief exposure to hypoxia. Overall the results corroborated that this model could be protected based on the neroprotective and anti-inflammatory nature of SLAB51. Therefore it is demonstrated that in this transgenic murine model of AD, oral bacteriotherapy could manipulate neurochemical pathways through the increase of] fatty acids

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with less than 6 carbon atoms in the plasma and hormones in the gut designed to safeguard the nervous system. This could further repair proteolytic pathways and trigger antioxidant mechanisms, leading to decreased amyloid load and tau hyperphosphorylation. amyloid load and tau hyperphosphorylation [6]. However, it is worth noticing that the treated mice were not completely cured, instead gaining improved memory and attention. It is necessary for future studies to evaluate potential side effects of microbiome alterations since their structures and genetic and epigenetic factors may all alter results, while the use of SLAB51 could cause brain swelling and bleeding [6].

### *2.3. ADHD and its treatments*

ADHD, by contrast, is identified as a neurodevelopmental disorder (NDD) occurring in 5.9% to 7.1% of children and 1.2% to 7.3% of adults, including the following characteristics: inattention, hyperactivity, and impulsivity [7]. It has three subtypes, categorized based on the varying severities of the symptoms — predominantly hyperactive–impulsive, inattentive or mixed [7]. With its increasing occurrence among both teenagers and adults, affecting work and life, treatment methods such as the usage of Dexmedetomidine (DEX) have been more actively researched. As an alpha-adrenergic agonist, DEX has sedative, analgesic, and sympatholytic effects and it utilizes these properties by preventing norepinephrine release through hindering central sympathetic outflow with blockage of alpha receptors from the brainstem. When compared to alpha1, its selectivity for the alpha2 receptor is 1600 against 1. Clonidine, on the other, inhibits the release of sympathetic neurotransmitters from the CNS by triggering alpha-2 adrenoceptors as well as inhibitory neurons. Thus peripheral resistance is diminished, as well as renal vascular resistance and heart rate, and compared to DEX, its selectivity of 220 to 1 is significantly lower [8].

Studies using Male Wistar rats and the spontaneously hypertensive rat model (SHR/NCrl) show that DEX can attenuate ADHD-like behaviors and enhance brain function through modulation of the makeup of the gut microbiota, lowering gastrointestinal harm and inflammatory conditions, and repairing the functionality of the intestinal barrier in SHRs. The specific doses of relative medicines are included in table 1, including data based on the ICU sedation standard, amount to reach the desired amount, dosage range that brings no additional benefits as well as the amount which can act as an adjutant for peripheral nerve block. Thus DEX administration, which reconstructs the microbiota-gut-brain axis within the host, shows potential for ADHD intervention [9].

**Table 1.** Medication dose [10]

| | ICU sedation standard | Desired sedation level | Increase risk of side effects with no benefits | Adjunct for peripheral nerve block |
|---|---|---|---|---|
| Dosage range mcg/per hour | 0.2 to 0.7 | 1.5 | 2.5 | 1.0 |

Side effects may occur when using DEX for treatment, the most common ones being the most frequent ones are hypertension and hypotension, as well as bradycardia. When alpha subtypes of receptors in vascular smooth muscles are stimulated, hypertension can occur, it is relatively considered nonlethal and can be prevented by slowly administering the loading dose or by complete removal of it. On the other hand, regardless of the method of delivery, presynaptic alpha receptor stimulation results in less release of norepinephrine and, in addition, a decrease in the central sympathetic outflow, causing hypotension and bradycardia [10].

## 3. Possible relationship and treatment relating to Tourette's syndrome

The rapid, repetitive, non-rhythmic movements or vocalizations are clean signs indicating to Tourette Syndrome (TS) in a patient, being more common in males with a prevalence of 0.85-1%. Symptoms include consistent tics, compulsion and impulsive behaviours, leading to more severe subtypes like the Obsessive-Compulsive Tic disorder (OCTD) and tic-related OCD [11].

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The use of gut microbiota in the therapy of TS was prompted by the association between the microbes in the intestinal tract and neurological system disorders as autism spectrum disorder (ASD), Parkinson's disease (PD), epileptic seizures and depressive disorders. Enzyme activities and synthesis of neurotransmitter can be influenced by microorganisms in the intestines. Their metabolism has the potential ability to shield the dynamic semipermeable interface between the brain and blood and restore the neurological system. The immune cells are also under latent influence of these microorganisms, resulting in fluctuations in the secretion levels of pathogenic factors which may lead to inflammations and alteration of the inflammatory state of both the nervous and intestinal systems.

In an experimental case involving microbiota in the gut and the TS conducted by Xiaoge Wang and Xinmin Li, a relationship was found. Wang and Xi (conducted studies on the gut microbiota in children suffering from tic disorders (TS and TD) while comparing the results with those of healthy children. The previous discovered that Firmicutes's abundance had a relatively lower occurrence in TS patients while there was an increase in the relative abundance of Proteobacteria. In comparison to healthy children, treatment-naive TD children showed reduced abundances of Prevotella stercorea and Streptococcus lutetiensis and greater abundances of Bacteroides plebeians and Ruminococcus lactaris. Ruminococcus lactaris was significantly more prevalent in TS children, whereas Bacteroides plebeius was more commonly found in children with chronic tic histories. The study also discovered that fecal microorganisms in TD children approach those of healthy children after drug use. Finally, the level of GABA degradation was shown to be considerably higher in TD children, impacting the gut microbiota as well. The deterioration of TD symptoms was positively connected with Klebsiella pneumonia, whereas the YGTSS score was significantly more negatively correlated with Eubacterium spp, Bifidobacterium spp, and Akkermansia muciniphila. They later carried out an animal experiment with 3,3'-iminodipropiononitrile (IDPN) to create TS mouse models and examined the fecal microbes of both TS and normal mice in order to validate this link. Fecal microbiota transplantation (FMT) using TS mouse (HTSM) excrement was involved in this experiment. The findings demonstrated that, in comparison to healthy mice, the amounts of Turicibacteraceae and Ruminococcaceae were considerably reduced in TS animals. Regarding HSTM, Bacteroidetes and Proteobacteria showed a rise in their levels, while a decrease was exhibited in Firmicutes along with Actinobacteria. In the end, their findings matched the clinical outcome. However, Li didn't find existing twitch behaviour in HTSM after transplantation of TS mice faeces into normal mice, thus making it unclear whether the abnormal changes in gut microbiota is the primary cause of TS and more studies are required. Therefore bringing out the potential research orientation regarding specific gut microbiota in humans [12]. A further experiment of comparing faeces samples from a group of TS patients and TS-free patients, to see whether if there are seemingly abnormal differences between the proportion of specific microbiota while trying to balance out the uncertainties acquired from outer influences such as congenital genes and dietary patterns.

## 4. Conclusion

In conclusion, the GBA plays a critical role in various neurological diseases such as AD, ADHD, and TS. The gut microbiota is indispensable in maintaining the physiological balance of the GBA, and targeting and influencing the microbiota-GBA has great therapeutic potential in treating these diseases. The use of personalized diets, oral bacteriotherapy, and multi-strain probiotics such as SLAB51 and DEX have shown promising results in treating AD and ADHD by manipulating the gut microbiota. However, it is crucial to conduct further studies to evaluate the potential side reactions obtained from microbiome alterations, and potential treatments for Tourette's syndrome based on gut microbiota analysis require further research to verify current findings as well as for investigating new methods. In summary, the GBA is a promising area for the development of new therapeutic approaches for neurological diseases, and future research in this field holds great potential for advancements in the treatment of these disorders. Please follow these instructions as carefully as possible so all articles within a conference have the same style to the title page. This paragraph follows a section title so it should not be indented.

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