Review Paper:

Oral-Gut Dysbiosis: Causative for the Initiation of Brain Cognitive Memory Decline

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Abstract

Oral passage and intestinal tract are some of the important microecosystems present in humans. In these microecosystems, approximately 10^{14} bacterial colonies are present with 2000 known bacterial species. These bacterial colonies are responsible for the maintenance of normal oral and gut microbiota. The presence of these common oral and gut microbiomes results in the regulation and development of cognitive functions in the brain. Imbalance in this normal flora, results in the development of impaired cognitive functions. In a healthy state, oral and gut microbiomes are present in a balanced state (BS) and do not have any impact on cognitive functions. Whenever this BS is affected by internal or external microorganisms, it may result in the formation of dysbiosis in oral and gut microflora. Later on, it results in the development of impaired cognitive functions.

In the present review, we presented the impact of normal oral and gut microflora in the development of cognitive functions and discussed the reversal of oral and gut dysbiosis-induced impaired cognitive functions with the help of probiotic microorganisms. Recent research studies showed that oral beneficial flora plays a major role in the reversal of impaired cognitive functions through the secretion of neurotransmitter precursors chemical compounds (NPCs) (short-chain fatty acids [SCFAs], tyrosine, levodopa [L-DOPA], tryptophan and 5-hydroxytryptophan [5-HTP]). Secreted NPCs are further transmitted to the brain for the formation of neurotransmitters like dopamine, glutamate, gamma-aminobutyric acid (GABA), serotonin and norepinephrine. Further, these synthesized neurotransmitters result in the reversal of cognitive memory formation by strengthening the synaptic connections present in the brain through the molecules involved in neuronal signaling pathways.

Keywords: Cognitive Decline, Gut Microbiota, Learning, Memory, Oral Microbiota.

Introduction

The oral microbiome is a diverse microbiota with an approximate amount of 700 bacterial species including bacteria, fungi, viruses and protozoa. It acts as a complex habitat for invading microorganisms and serves as a crucial region for the maintenance of oral and systemic health[16,22,63]. It acts as the second-largest microbial community in a human host. This human microbiome (HM) consists of two different microbiomes i.e. core microbiome (CM) and variable microbiome (VM). CM is common for all individuals whereas VM differs from person to person based on their lifestyle and differences in their physiological conditions.

For the colonization of microorganisms, two different surfaces of the oral cavity (OC) were used by the microorganisms for their colonization, they are classified as teeth surfaces (TS) and oral mucosa (OM). TS consists of hard and soft tissues provides a platform for the anchorage of microorganisms in the OC. Other than TS and OM, tongue, hard palate, cheeks, soft palate, gingival sulcus and tonsils may provide a nutrient-rich medium for the growth of microorganisms in the OC. Colonization and multiplication of bacterial species in the OC result in the formation of biofilm structures[16,54,73,79].

These microbial communities present in the OC play a major role in physiological, immunological and metabolic functions like prevention of microbial invasion, digestion of food, absorption of nutrients, generation of energy, differentiation, maintenance and maturation of the host immune system. Interaction between different homeostasis mechanisms may result in the interaction between OC and host in varying scalar quantities[28,62,76]. The present review explores the role of normal oral/gut flora in synaptic plasticity formation through the gut-brain axis.

Role of Oral Microbiota in the Development of Cognitive Functions: During normal conditions, stimulus exposure (SE) results in the formation of long-term memory (LTM) with the help of synaptic plasticity changes. Formed synaptic plasticity refers to the stimulus-dependent active changes occurring in the presynaptic neurons which play a major role in the formation of cognitive memory including short-term memory (STM) and LTM[1,19]. These synaptic changes were observed in several animal models as a result of repeated stimulus exposure for a limited period and defined as long-term potentiation (LTP). In the initial phase of cognitive memory formation, LTP formation may depend on neuronal transcription factors and neuronal pathways for the development of long-term plasticity changes (LPC).

Recent reports have shown that LPC results in the formation of LTM through the recruitment of new proteins by the process of de novo protein synthesis[19,37].

Initially, LTP results in the release of neurotransmitters from the presynaptic neurons as a result of activity-dependent changes. The released neurotransmitter binds with the postsynaptic receptors and results in the activation of adenyl cyclase (AC), protein kinase A (PKA), extracellular signal-regulated kinase-1/2 (ERK-1/2) and mitogen-activated protein kinase (MAPK). Activation of ERK-1/2 and PKA may result in the activation and phosphorylation of cyclic AMP response element-binding protein (CREB)[20,21,50]. Phosphorylation of CREB further activates the immediate early gene (IEG) cascade (*Egr-1*, *C-fos* and *C-jun*) and other post-synaptic density proteins (PSDs) for the formation of LTM. Other than activation of IEGs and PSDs, CREB may also be needed for the regulation of certain microRNAs (miRNAs) during LTM formation[7,29,48,49,56,68].

Recent research studies showed that oral gut microbiota plays a major role in the formation of cognitive functions through the gut-brain axis (GBA). This GBA is a bidirectional communication network that links the enteric and central nervous systems (ENS and CNS). This communication is established with the help of the autonomic nervous system (ANS), hypothalamic pituitary adrenal (HPA) axis and nerves present within the gastrointestinal (GI) tract. The formed GBA axis may influence mood, cognition and mental health[5,24,44,45,60]. Recent studies showed that some bacterial strains may synthesize/regulate the production of neurotransmitter precursor compounds (NPCs) in the gut.

Several reports supported that various neurotransmitters (serotonin [5-HT], noradrenaline [NA], dopamine [DA] and γ-aminobutyric acid [GABA]) are possibly regulated bacterial species present in the oral/gut microbiome[9,13,17,42,52,60]. In normal conditions, these neurotransmitters initiate calcium influx and other associated molecules involved in cognitive memory formation. Thus, it is proved that oral/gut microorganisms play a major role in the development of cognitive functions[17,51,58-60,77]. The present review tries to present the impact of oral/gut dysbiosis in the development of cognitive impairment with the help of research in the field of gut-brain axis and cognition.

Impact of Oral-Gut-Brain Axis in the Development of Cognition Functions: Microbial species present in the oral and gut microbiota played a major role in the influence and development of host physiology and individual health maintenance. In healthy individuals, these microbial species present in the oral cavity play a major role in the partial digestion of nutrients along with the enzyme salivary amylase[15,36,78]. Other than digestion, it also played a major role in the development of oral hygiene by preventing the multiplication and colonization of pathogenic microorganisms in the oral cavity. The regulatory activity of this oral microbiota played a major role in the development of cognitive functions through the oral-gut-brain axis. This oral-gut-brain axis links the oral and gut microbiota with the brain and plays an unavoidable role in neuronal development, mental state, cognitive regulation, behavior, emotional regulation and various brain functions[2,14]. This oral-gut-brain axis can be regulated by top-down (TD) and bottom-up (BU) approaches.

Three different pathways are involved in this TD and BU approach including endocrine, neural and immune (ENI) pathways. Brain recruits ENI pathways to influence the composition of gut microbiota through the hypothalamus pituitary adrenal (HPA) axis. During stress conditions, the HPA axis regulates the secretion of cortisol and thereby regulates cortisol activity against gut permeability (GP), gut microbiota composition (GMC) and barrier functions (BF). Unregulated cortisol activity affects GP, GMC and BF in an unimaginable state. Thereby, the TD approach is used by the brain to maintain GMC during stress conditions and other harmful conditions like gastritis[2,14,78].

In the BU approach, gut microbiota (GM) signals to the brain via the production of primary and secondary metabolites, cytokines and NPCs. During a healthy state, the BU approach may regulate the production of systemic tryptophan and stimulates the vagus and enteric nerves for establishing communication between GM and the brain[3,10,17,42,53]. Several shreds of evidence prove that GM produces a wide range of neuroactive metabolites including neurotransmitters and their precursors. These NPCs are collectively secreted by the enteroendocrine cells and gut microbiota in the bloodstream. Released NPCs are transmitted to the brain through the blood-brain barrier (BBB) via the enteric nervous system (ENS)/vagus nerve[34,46,70]. In a healthy state, a balanced state of oral and gut microbiota plays an important role in the maintenance of relationships with the brain.

The equilibrium of oral and gut microbiota is mainly affected by lifestyle changes like alcohol consumption, diet, smoking, pathogenic infections and alterations in the sleep cycle[12,23,61,72]. Alterations in this microbiota result in brain activity changes and the development of neurodegenerative/ neurological disorders resulting in oral and gut dysbiosis. Thus altered/dysbiosed microbiota plays a major role in the development of cognitive memory impairment. Developed cognitive impairment may be reversed with the help of probiotics and symbiotic supplementation. Thus the oral-gut-axis plays a major role in the development of cognitive functions in a healthy/disease-free state[25,32,35,38,47,65].

Interrelationship between Neurodegenerative Disorders and Oral-gut dysbiosis: Most neurodegenerative disorders (ND) are characterized by a gradual diminishing of cognitive functions especially the formation and retrieval of memory. Among the ND, Alzheimer's disease (AD) is caused by the earlier symptoms termed mild cognitive impairment (MCI). Few studies reported that probiotics can be used for the improvement of cognition during the early stages of AD[26,31,66,67,80]. These studies proved that oral/gut dysbiosis

plays a major role in the development of MCI and also stated that oral passage was chosen as a possible route for the treatment of MCI with the help of probiotic microorganisms. Other than probiotic microorganisms, fecal microbial transplants are also used as non-drug interventions for the treatment of cognitive loss during the early stages of AD[6,18,27,30,46,57,69].

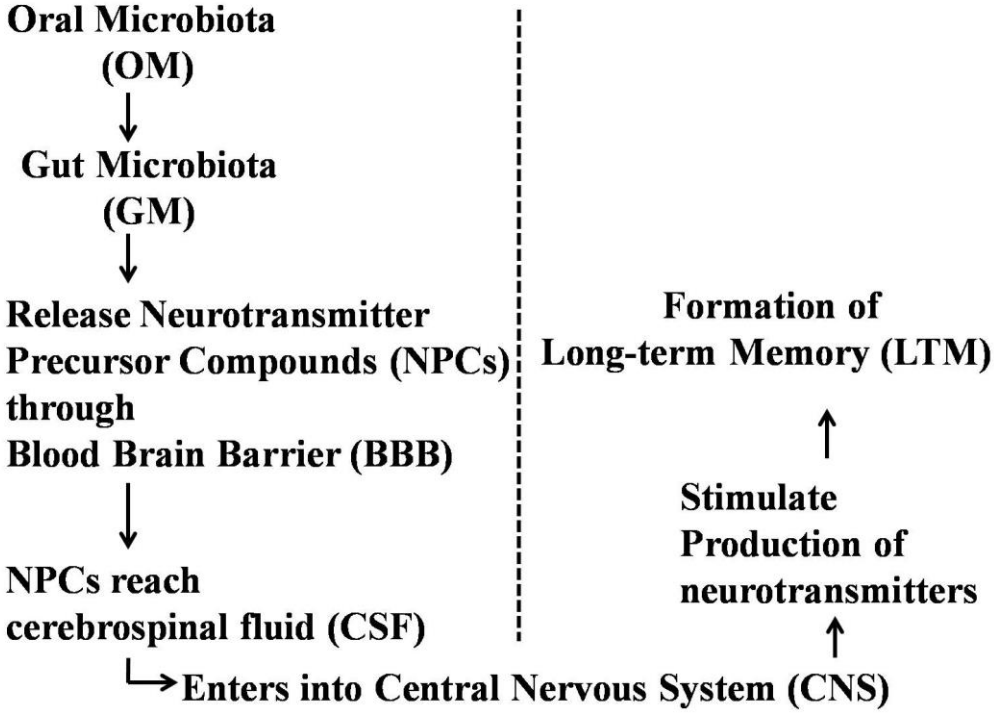

Figure 1: Role of Oral-Gut-Brain Axis in the development of cognitive memory during healthy conditions

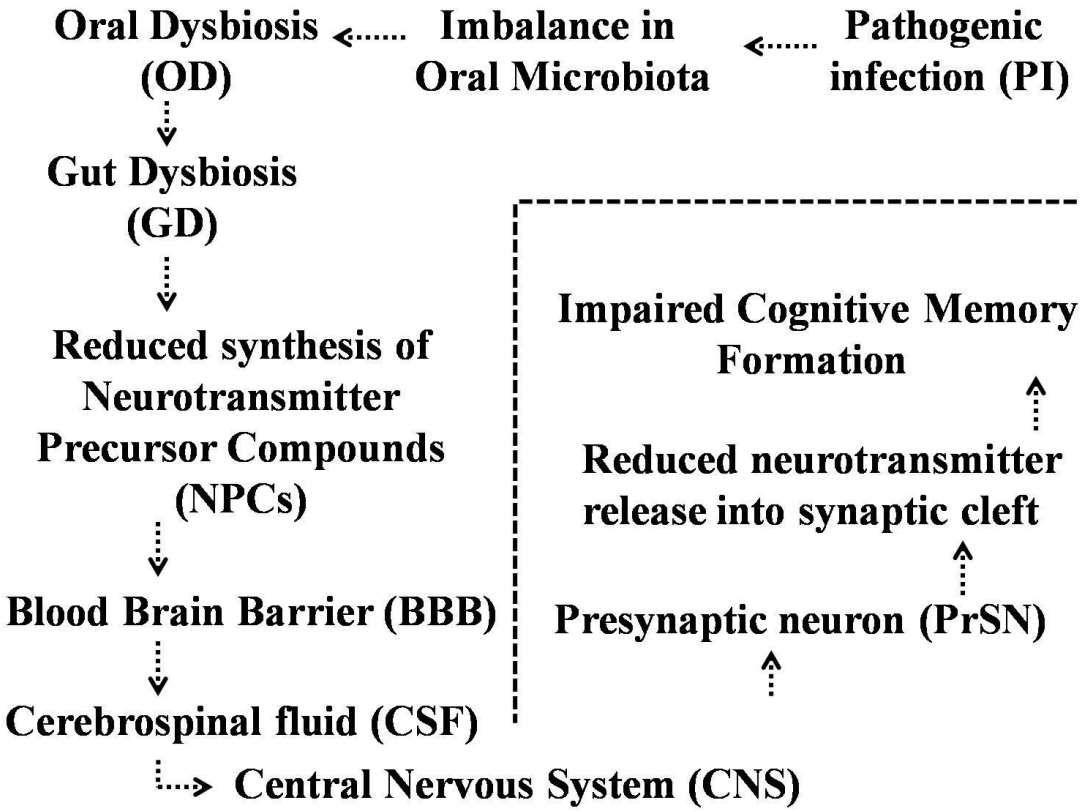

Figure 2: Effect of pathogenic infection on Oral-Gut dysbiosis which results in the development of impaired cognitive memory formation

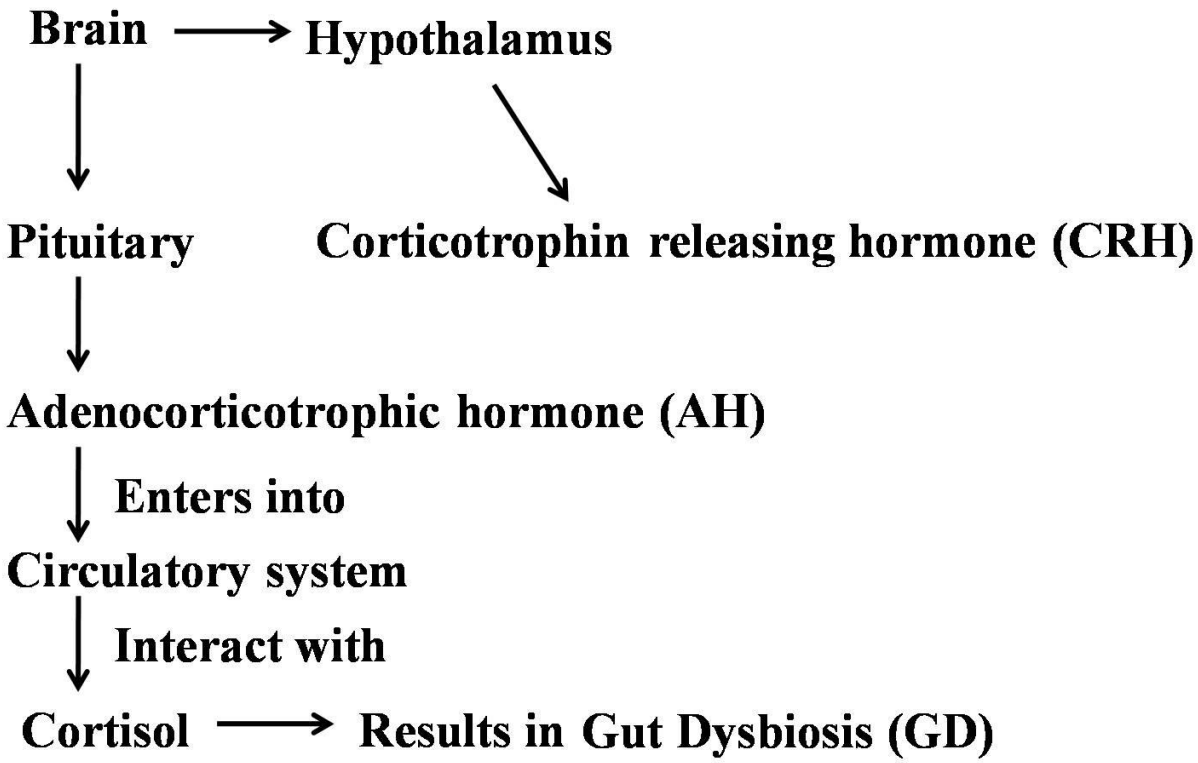

Figure 3: Flow cyclic diagram of the top-down pathway between the gut microbiota and the brain. The top-down pathway shows the impact of the oral-gut-brain axis in cognitive memory formation.

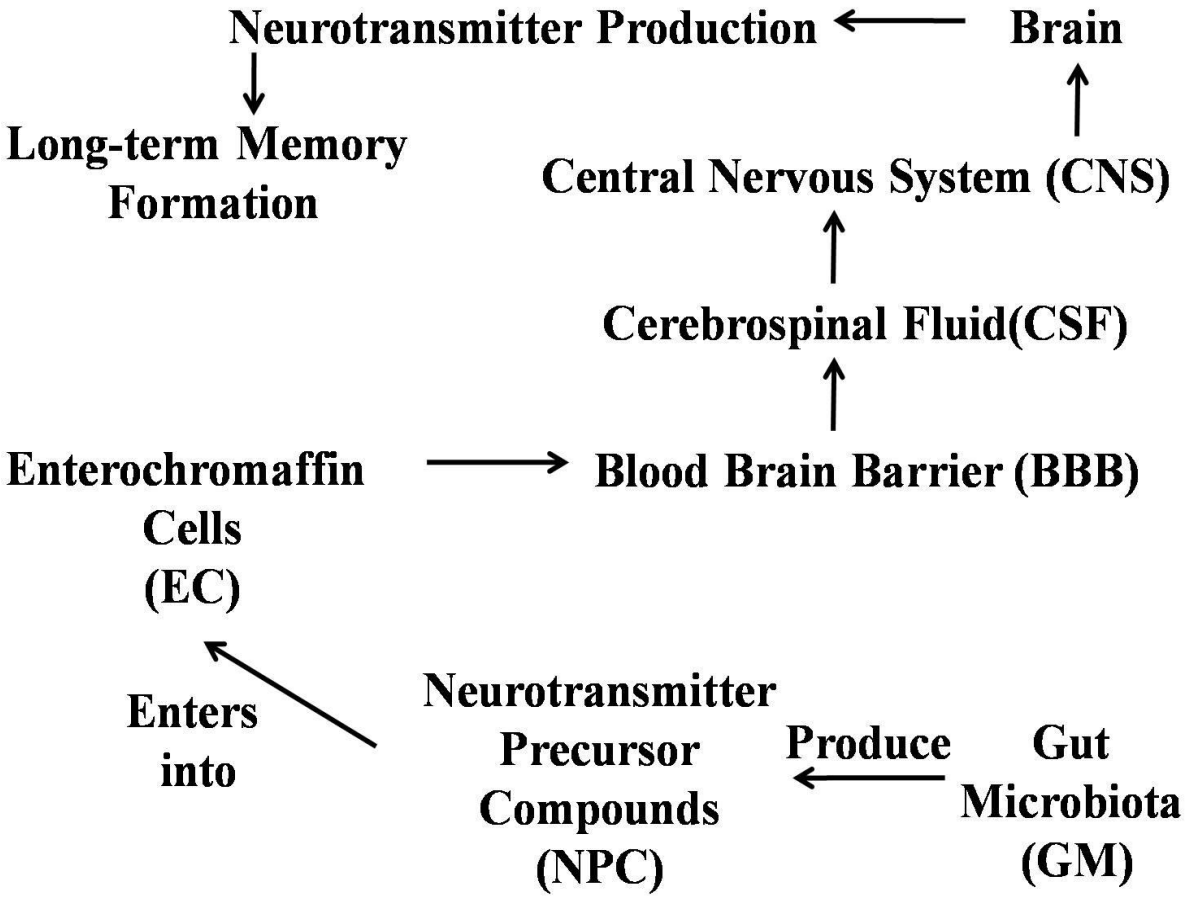

Figure 4: Bottom-up pathway showed the role of the oral-gut-brain axis in the development of cognitive memory formation

Recent research findings showed that oral hygiene plays a major role in the development of cognitive memory formation through the BBB via the vagus nerve. To prove this concept, Murugan[46] used oral infusions of *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli* in an animal model (*Carassius auratus*). Oral infusion studies revealed that *P. aeruginosa* played a major role in the development of cognitive decline during MCI. The outcome of this study proved that poor oral hygiene caused by oral dysbiosis plays a major role in the aberration of gut microflora which results in the development of impaired cognitive memory formation. Formed cognitive impairment may be result of a 'leaky gut' due to the translocation of small bacterial metabolites from the gut to the brain through the cerebrospinal fluid (CSF).

Few studies have reported that gut microbiota can influence the development of BBB and can influence its permeability through gastrointestinal hormonal secretion (GHS). This GHS allows certain drugs, metabolites and amino acids to enter the central nervous system (CNS) which also plays a major source for the brain's neuronal amyloid production. Other than amyloids, some bacterial lipopolysaccharides may also act as stimulators of neuroinflammation in MCI and AD[8,46,51,55]. Thus oral-gut dysbiosis plays a major role in the development of cognitive decline in MCI, AD and other NDs via poor oral hygiene, pathogenic infection and other bacterial toxin transport[46,74].

Role of Probiotic, Probiotic and Synbiotic Supplementations in the Reversal of Oral-gut Dysbiosis: Recent reports showed that three different types of supplementation (probiotic, probiotic and synbiotic) may reverse the impaired cognitive memory formation with the help of oral-gut-brain axis[4,11,43,47,58]. In cognitive reversal therapy, probiotics are most commonly used for the reversal of oral/gut dysbiosis. Probiotics taken in the form of food can retain the balance of normal gut flora. These probiotics are mostly bacterial species, used for the maintenance of good health in a host[25,40,71,75]. Some of these intestinal probiotic microorganisms are needed for the production of short-chain fatty acid (SCFA) by anaerobic fermentation of dietary fibers. Produced SCFA is made up of carboxylic acid which is present in the aliphatic tails of 1-6 carbon and contains acetate, propionate and butyrate at the 2, 3 and 4th carbon.

Among the six carbon molecules, acetate is the most abundant SCFA synthesized in the gut with the help of enzyme acetyl CoA. Other than acetyl CoA, propionate and butyrate are also formed from carbohydrate metabolism that happens during the process of glycolysis[39,64]. Produced SCFA is responsible for the transmission of NPCs from the gut to the brain through the BBB.

However, this SCFA declines with gut dysbiosis/microbial imbalance and age. Majorly, this gut dysbiosis/microbial imbalance is a result of increased pathogenic bacteria load which further results in the neuroinflammation in brain. In these conditions, the oral-gut-brain axis plays a dual role in the development and reversal of cognitive impairment and neurodegenerative disorders during oral/gut dysbiosis[22,33,39,41].

Formed impaired cognitive memory may reverse with the help of NPCs produced by the probiotic microorganisms. After production, formed precursors compounds cross the BBB and reach the central nervous system (CNS) to synthesize needed neurotransmitters and activate neuronal transcription factors within the brain neuronal system[17,81]. For example, serotonin (5-HT) is synthesized from the amino acid precursor (tryptophan). Initially, tryptophan is converted into an intermediate compound called 5-hydroxytryptophan (5-HTP) with the help of an enzyme (tryptophan hydroxylase). Finally, produced 5-HTP is reconverted to 5-HT with the help of aromatic amino acid decarboxylase (AACD)[17,57,81].

Produced 5-HT is further released into the synaptic cleft by the presynaptic neuron and binds with the specific receptors in the postsynaptic neurons to increase the calcium influx. An increase in calcium influx results in the activation of adenyl cyclase (AC), which may further increase the level of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). Increased levels of cAMP and PKA may result in the activation and phosphorylation of CREB. Phosphorylation of CREB further activates IEGs and PSD proteins which are responsible for cognitive long-term memory formation[7,29,46,48-50,56,68].

Conclusion

Recent studies showed that poor oral hygiene plays a major role in the development of impaired cognitive functions in the earlier stages of various neuronal disorders. The present review concisely represents the impact of oral-gut dysbiosis in the development of impaired cognitive memory formation with the help of CREB-mediated neuronal signaling pathways in the brain. Collective data presented in this review proved that normal oral and gut microbiota played a major role in the development of cognitive functions especially long-term memory formation by releasing serotonin (5-HT) from the presynaptic neuron.

For the production of 5-HT, presynaptic neuron needs an amino acid precursor tryptophan from the gut in the form of a neurotransmitter precursor compound. This precursor compound was produced by some beneficial microorganisms (probiotics) present in the gut. Synthesis of these precursor compounds was affected during pathogenic infection/microbiota imbalance which may result in oral-gut dysbiosis-formed oral-gut dysbiosis resulting in the development of cognitive impairment due to reduced synthesis and transportation of precursor compounds from gut to brain. Formed oral gut dysbiosis can be reversed with the help of probiotic microorganisms to restructure the synaptic plasticity during cognitive memory formation.

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