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Review

Gastrointestinal hormones in regulation of memory

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ABSTRACT

The connection between the gastrointestinal hormones and the brain has been established many years ago. This relation is termed the gut-brain axis (GBA). The GBA is a bidirectional communication which not only regulates gastrointestinal homeostasis but is also linked with higher emotional and cognitive functions. Hypothalamus plays a critical role in the regulation of energy metabolism, nutrient partitioning and control of feeding behaviors. Various gut hormones are released inside the gastrointestinal tract on food intake. These hormones act peripherally and influence the different responses of the tissues to the food intake, but do also have effects on the brain. The hypothalamus, in turn, integrates visceral function with limbic system structures such as hippocampus, amygdala, and cerebral cortex. The hippocampus has been known for its involvement in the cognitive function and the modulation of synaptic plasticity. This review aims to establish the role of various gut hormones in learning and memory, through the interaction of various receptors in the hippocampus. Understanding their role in memory can also aid in finding novel therapeutic strategies for the treatment of the neurological disorders associated with memory dysfunctions.

1. Introduction

The gut-brain interaction has revealed a complex ongoing communication which not only establishes regulation of gastrointestinal homeostasis but is expected to have multiple effects on affect, motivation and higher cognitive functions. This relation between brain and gut is defined as the Gut-brain Axis (GBA) [1]. The role of GBA is to monitor and integrate the functions of the gastrointestinal system, as well as to link the emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as enteric reflexes, intestinal permeability, immune activation and entero-endocrine signaling [2]. This is a bidirectional communication network which consists of the central nervous system (CNS), both brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS) and the hypothalamic pituitary adrenal (HPA) axis [3]. The GBA is responsible for the transfer of information from the digestive system to the subcortical regions of the brain such as limbic system, the autonomic and neuroendocrine centers in the hypothalamus and the brainstem. These connections between the gut and the brain are associated with a number of psychiatric disturbances including anxiety, neuroticism, depression, cognitive disorders. The GBA uses four major information carriers for communication between the gut and the brain: (i) neural messages carried by vagal and spinal afferent neurons, (ii) immune mediations by cytokines, (iii) endocrine messages by gut hormones and (iv) messages by gut microbiota-derived signaling molecules [4–7]. These messengers transmit information from the gut to the brain, while autonomic neurons and neuroendocrine factors carry outputs from the brain to the gut.

The gut microbiota is considered as a powerful communication system in signaling to distant organs including the brain. The gastrointestinal immune system interacts with the gut microbiota via the gastrointestinal mucosa (cytokines released during this process), thus maintaining homeostasis among the microbial community living in the intestine. Also, it modulates the release of lipopolysaccharide (LPS) and peptidoglycan components [8] that can directly act on the CNS. Thus the gut micro flora plays a role not only in the regulation of the digestion, nutrition, mucosal function and intestinal immunity but also in the systemic immunity, metabolic homeostasis and brain function such as cognition, mood, anxiety, emotions. The gut is the body's largest hormone-producing organ with more than 20 gut hormones being released after the ingestion of food [7]. However, prior to food intake, many gut hormones are released into the digestive system and then act on the hypothalamus. The hypothalamus represents the control center for hunger and satiety. It consists of the arcuate nucleus (in humans, called as the infundibular nucleus) which allows the entry of peripheral peptides and proteins to directly act on neurons. These neurons co-express peptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP) which stimulate the food intake and weight gain. Neurons in this region also express proopiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART) which inhibit food intake

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and thus promote weight loss [9]. The hypothalamus coordinates activity in the gut and integrates visceral function with limbic system structures such as hippocampus, amygdala and cerebral cortex [10]. This review gives an insight how some gut hormones can be used as an in the potential treatment of memory-related disorders.

2. Role of hippocampus in memory

Hippocampus is a part of human limbic system along with amygdala, thalamus, hypothalamus, basal ganglia, and cingulate gyrus. The function of the entire structure is driven by circuits of interconnected layers. The main structure of hippocampus consists of the dentate gyrus and Ammon's horns or Cornus Ammonis (CA) consisting of CA 1, 2 and 3 regions [11]. The hippocampus is involved in the spatial and episodic memory whereas parahippocampal structures (entorhinal and perirhinal cortices) are involved in the stimulus recognition or association stimulus. The hippocampus exhibits a phenomenon termed Long-term potentiation (LTP) which is responsible for memory formation [12]. The cellular basis for LTP induction depends on the various regulatory pathways in the CA1 region of the hippocampus. Extensive studies have shown that *N*-methyl-D-aspartate receptor (NMDA) activation is required for the LTP in the hippocampus, amygdala and medial septum [13–15]. Induction of LTP in the hippocampus is brought about by the repeated synaptic activation of the glutamate receptor (NMDA receptor) as well as simultaneous depolarization of the postsynaptic cells which is mediated by the opening of the Na^+ channels. This, in turn, enables the opening of the voltage and ligand-gated calcium channels. The influx of calcium also leads to the signaling of calcium-dependent kinase activity resulting in the structural and functional modification in the postsynaptic cell [12]. LTP activity is also dependent on various other pathways, such as the phosphoinositide 3-kinase (PI3K) signaling pathway, CREB signaling pathway and ERK/MAPK signaling pathway.

3. Signaling pathways in memory

A neuron has a known structural and functional plasticity (synaptic plasticity) which is responsible for cellular learning. There are various mechanisms/pathways involved in learning and memory, of which some major systems will be discussed in this review, e.g. the glutamatergic signalling system, cholinergic system, and some secondary messengers systems.

3.1. The glutamatergic signaling system

Transmission through glutamate is associated with LTP and is an essential signalling process involved in cognitive processes [16]. There are two different types of glutamate receptors: ionotropic (AMPA, kainate, and NMDA receptors) and metabotropic receptors present on the pre- and postsynaptic sites of the neuron. NMDA receptors are mainly responsible for learning and memory, while the AMPA receptors are involved in synaptic transmission [16]. The NMDA receptors are distributed abundantly in the hippocampus, cortex, and thalamus and allow the transmission of $Ca^{+2,}$ Na^+, and K^+ channels. The receptor being a dual voltage and ligand-gated channel, combines with the Mg^{2+} channels, which upon activation lead to the release of the glutamate neurotransmitter from presynaptic membrane (while the postsynaptic membrane is depolarized) [17]. This binding of the neurotransmitter to the receptor leads to the influx of calcium into the brain [18], and this phenomenon is amplified in some cases by simultaneous activation of metabotropic glutamate receptors. The increase in the calcium levels in the cytoplasm leads to the activation of protein kinases, which in turn induce LTP [19]. Hyperactivity of glutamate receptors leads to oxidative stress which is responsible for cognitive dysfunction, e.g. in the case of Alzheimer's disease [20]. AMPA receptors are found in cortex, hippocampus, basal ganglia and cerebellum. These receptors are known to modulate the fast and immediate postsynaptic response to glutamate release, thus contributing to synaptic plasticity. They play a role in maintaining the short term memory.

3.2. The cholinergic system

The cholinergic system comprises of two different families of receptors: muscarinic receptors (G Protein Coupled Receptors) [21] and nicotinic receptors (ligand-gated ion channels) [22] The muscarinic receptors are sub-grouped further into 5 subtypes (mainly M1–M5), while there are nine subtypes of nicotinic receptors (α2–α7 and β2–β4). These subtypes are distributed all over the brain areas including the hippocampus, neocortex, hypothalamus, corpus striatum and ventral tegmental area [21,22]. Acetylcholine is a main neurotransmitter which is responsible for the regulation of cognitive functions. There are around ten populations of cholinergic neurons, Ch1-Ch10, of which the impairment of the Ch4 cholinergic neuron is associated with Alzheimer's disease [23]. The nicotinic receptors are activated by acetylcholine, which stimulates release of glutamate and establishes hippocampal synaptic transmission [24]. Glutamate release is mediated by calcium dependent influx from the intracellular stores which subsequently on phosphorylation maintain the unregulated glutamate release necessary for LTP [25].

3.3. Secondary messenger systems

3.3.1. Calcium/calmodulin-dependent protein kinase II signaling pathway

The process of LTP is induced by high-frequency synaptic transmission in the CA1 region of the hippocampus. The glutamate receptors located at these synapses activate postsynaptic NMDA receptors and AMPA receptors. This opening of NMDA receptor leads to the influx of calcium which triggers a biochemical cascade, ultimately leading to LTP of postsynaptic current by AMPA receptor. A major synaptic protein, calcium/calmodulin-dependent protein kinase II (CaMKII), is responsible for the entry of calcium which activates the enzyme to modify the synapse. Thus CaMKII is important for the proper functioning of memory. It consists of two subunits: αCaMKII and βCaMKII. Once calcium entry occurs, the CaMKII is activated, however sometimes becomes partially autonomous upon phosphorylation at T286 [26]. αCaMKII and βCaMKII plays different roles in synaptic plasticity. Calmodulin when binding to βCaMKII, detaches the kinase from F-actin, which to CaMKII translocation to the postsynaptic density [27]. CaMKII activation occurs via auto-phosphorylation of the αCaMKII at threonine-286 that prolong its kinase activity. This, in turn, activates the AMPA receptor causing an increase in synaptic transmission [28].

3.3.2. MAPK/ERK signalling pathway

The mitogen – activated protein kinase (MAPK) family consists of seven kinases: ERK 1, 2 and 5, c-Jun N-terminal kinases (JNK's) 1–3, and p-38 [29]. Each MAPK signaling axis comprises at least three components: a MAPK kinase kinase (MAP3K), a MAPK kinase (MAP2K), and a MAPK. MAP3Ks phosphorylate and activate MAP2Ks, which in turn phosphorylate and activate MAPKs. Activated MAPKs phosphorylate various substrate proteins including transcription factors such as Elk-1, c-Jun, ATF2, and p53. ERK1 and ERK 2 is activated by MAPK/MEK. This occurs upon elevation of the Ras-GTP, which in turn activates the protein kinase Raf and then phosphorylates and activates MAPK/MEK [30]. ERK activation leads to the continuous phosphorylation of the K^+ channel in the postsynaptic membrane, causing excitation of the membrane ultimately leading to the activation of the NMDA receptors [19]. ERK 1/2 is also important for the memory consolidation process [31]. Signaling through ERK 1/2 is essential for the activation of Long-term memory (LTM) [32,33].

3.3.3. PI3K signalling pathway

Activation of the catalytic PI3K pathway leads to the phosphorylation of phosphatydylinositol-4,5-bisphosphate (PIP2) to generate