Evaluation of the Toxic Effects of Dichloroacetic Acid on Hippocampus of Adult Male Albino Rats

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Abstract

Background: Dichloroacetic acid (DCAA) is a prevalent disinfection byproducts (DBPs) formed during the chlorination process of drinking water disinfection. Owing to its well-documented toxicological properties, DCAA has attracted substantial scientific attention. Extensive experimental studies in rodent models have demonstrated that DCAA exposure induces multiple organ toxicities, including pronounced nephrotoxicity and testicular toxicity. Moreover, accumulating evidence indicates that DCAA may also exert neurotoxic effects, highlighting its potential impact on the nervous system. **Aim:** This study aims to critically evaluate the toxicological impact of dichloroacetic acid on the hippocampal region of adult male albino rats. **Conclusion:** DCAA administration elicited neurotoxicity manifested with impaired cognition, learning, and memory functions, oxidative stress, neuro inflammation, disturbed synaptic plasticity and marked histopathological alteration in the hippocampus.

Keywords: Dichloroacetic acid, hippocampus, disinfection byproducts, neurotoxicity.

Introduction

Water disinfection byproducts

Water is essential to life. Water pollution and the introduction of toxic substances to water bodies such as lakes, rivers, oceans, and so on, which get dissolved in them, lie suspended in the water, or deposit on the bottom, represent one of the most serious ecological threats. Industrial waste discharge, city sewage disposals, contamination from groundwater bodies, human agricultural practices, and improper waste disposal systems have been noted as the most contributing factors to water pollution **(1).**

The water supply systems are being contaminated by emergent pollutants such as pesticides, synthetic fertilizers, chemical compounds like dyes, heavy metals, hormones, personal care products, detergents, waterborne pathogenic microorganisms such as bacteria, fungi, viruses, protozoa, and pharmaceuticals. These pollutants can enter the aquatic system and ultimately have an impact on human health **(2).**

Approximately half of the population in developing countries suffers from one or more of the six major water and sanitation diseases (diarrhea, ascariasis, dracunculiasis, hookworms, schistosomiasis, and trachoma). A large number of children under the age of 5 in the world die every hour from an acute intestinal infection transmitted through water **(3).**

In this regard, one of the most important stages of water treatment is disinfection, which is the most

effective way to prevent these diseases. Disinfection is an effective barrier to many pathogens (especially bacteria) in the treatment of drinking water, and it should be used for surface water and groundwater. The destruction of pathogens and parasites through disinfection has greatly contributed to the reduction of the incidence of diseases transmitted through water and food **(4).**

Various methods are employed for water disinfection against various pathogens, such as chlorine, chloramine, chlorine dioxide, peracetic acid, ozone, and ultraviolet radiation (UV) **(5).**

Chlorination has been widely used in resource-constrained settings because it is inexpensive, does not require electricity, and provides free chlorine residual to protect stored water from recontamination for a period of time **(6).**

Chlorination is highly effective at inactivating most microorganisms in water. However, it does not readily inactivate certain pathogens (e.g., *Cryptosporidium* and *Giardia*) or remove chemical contaminants. Additional disadvantages of chlorine include the formation of disinfection byproducts (DBPs) and a taste or odor that can reduce user adoption rates **(7).**

The reaction between the different types of precursors and disinfection agents in raw water leads to the formation of DBPs **(8, 9).**

Many precursors, such as natural organic matter, algal organic matter, anthropogenic contaminants (e.g., pesticides, pharmaceuticals, detergents, etc.), operational parameters (disinfection agent type and/or dose, pH, contact time, temperature), may contribute to the development of DBPs **(10).**

In Egypt, large amounts of agricultural waste drainage water are pumped into the Nile River without treatment in all governorates in the Delta region. The wastewater contents of organochlorine pesticides and polychlorinated biphenyls, as the source of total organic carbon compounds, are oxidized by chlorine to produce DBPs **(11).**

Disinfection byproducts are classified as "harmful to human health," and their occurrence in raw water sources imposes special monitoring and efforts for the water companies **(12).**

Out of a total of 600 DBPs, only 11 of them are most commonly included under the regulation **(10).** The most important DBPs are trihalomethanes (THMs), haloacetic acids (HAAs), haloacetonitriles, halophenols, and halopropanoles **(13, 14).**

According to **(10)**, the two important DBPs, namely:

A) Trihalomethanes (THMs): such as trifluoromethane, trichloromethane, and dibromochloromethane.
B) Haloacetic acids (HAAs): such as monochloroacetic acid, dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid, and dibromoacetic acid.

Dichloroacetic Acid

Introduction:

Dichloroacetic acid (DCAA) is produced as a by-product during the chlorination of water containing humic substances and may occur in drinking water or swimming pools after chlorine-based disinfection of raw water that contains natural organic substances **(15).**

Dichloroacetic acid is classified in the disinfection byproducts (DBPs) group of haloacetic acids (HAAs), which are regulated with a drinking water standard of 60 µg/L according to WHO **(16).**

According to the Egyptian Ministry of Health, the maximum level of DCAA in Egyptian standards for drinking water and domestic uses is 50 µg/L **(17)**.

Changes in treatment conditions and temperatures in different seasons of the year directly impact DCAA levels in processed water. It was found that DCAA values increased during the autumn, indicating the increased chlorine dosages and other disinfectant byproducts in the water in the Delta region, Egypt **(11).**

Dichloroacetic acid compound was used in agriculture as a fungicide and consequently was detected in vegetables, fruits, and grains, and can be taken up into foodstuffs from the cooking water. Therefore, human exposure to this compound can occur via food consumption **(18)**.

Some studies proved that DCAA can be used for some therapeutic purposes, especially for the treatment

of lactic acidosis in patients with mitochondrial dysfunction, shock, sepsis, ischemia, and diabetes **(19).**

Physical and chemical characteristics of dichloroacetic acid:

Dichloroacetic acid has a molecular formula of C-H-Cl-O^{-} and **a** molecular weight of 128.94 g/mol **(Figure 1) (20)**.

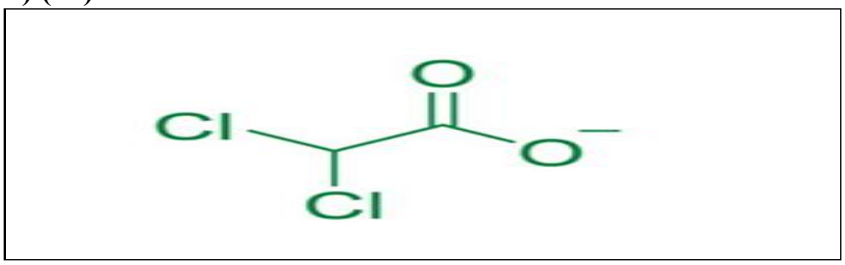

Figure (1): Chemical structure of dichloroacetic acid **(21).**

Dichloroacetic acid is a colorless or white crystalline powder with a pungent, unpleasant odor. Its melting point is 13-14°C and its boiling point is 194-195°C. DCAA has a density of 1.57 g/cm³ and is soluble in water, ethanol, and other organic solvents**.** It is a strong acid with a pKa of 1.29. DCAA is stable under normal conditions but may decompose in the presence of strong bases or heat. It reacts with strong bases, metals, and other reactive substances **(22).**

Sources and routes of exposure to dichloroacetic acid:

According to **23),** haloacetic acids like DCAA, as one of the most abundant DBPs groups, have raised public concern due to their high frequency of occurrence, considerable concentrations, and potent toxicity, so the most important ways of exposure to DCAA are:

1) Daily drinking water
2) The swimming pool water

Chlorine is used in food production and processing, including the following: disinfection of chicken in poultry plants; processing of seafood, poultry, and red meats; and oxidizing and bleaching in the flour industry. It is also used in sanitizing equipment and containers and in cooling heat-sterilized foods. Therefore, dichloroacetic acid is likely to be found as a disinfection by-product in meat and other food products. It was found that DCAA was stable in water during boiling and was taken up by foods during cooking in water **(24).**

Dichloroacetic acid exhibits great potential as an herbicide, but its application in agriculture has scarcely been investigated. Since DCAA readily undergoes photolysis when exposed to natural light or UV irradiation, there is a large activity loss in controlling weeds **(25)**

Some studies support dichloroacetic acid's role in cancer therapy. It enhances the cytotoxic effects of chemotherapy agents like cisplatin, carboplatin, and etoposide against various cancers, including small-cell lung cancer and ovarian cancer **(26).**

It has been used clinically for over 30 years in human hereditary mitochondrial metabolic diseases and lactic acidosis **(27).** DCAA also showed an effect as a lipid-lowering and antidiabetic agent with potential benefits for myocardial and cerebrovascular ischemia **(21).**

Dichloroacetic acid may be used in the production of allantoin, a skin conditioner that is added to some skin lotions and other cosmetic products. It may be used to remove warts and corns. People may be exposed to DCAA in cosmetics. It is a strong irritant to the skin, eyes, nose, throat, and lungs **(22).**

The routes of exposure for DCAA are ingestion, dermal contact, and inhalation, generally in that order. Ingestion is more common in water systems, while dermal is more common in industrial applications **(28).**

Dermal absorption of DCAA may occur when bathing or swimming in chlorinated pools or upon atmospheric exposure **(29).**

Pharmacokinetics of dichloroacetic acid :

Absorption

Dichloroacetic acid enters the human body mainly through ingestion. After oral administration, DCAA is absorbed rapidly and completely **(30).**

Distribution

Dichloroacetic acid has a plasma half-life of approximately one hour and inhibits its own metabolism. Over time, after repeated administration of DCAA, the plasma level and elimination half-life increase **(31).**

Dichloroacetic acid is initially distributed to the liver and muscles, and then to the remaining body organs **(28).**

Metabolism

The zeta-1 glutathione transferase (GSTz1) is the only known enzyme that metabolizes dichloroacetic acid**.** During the biotransformation of DCAA, a part of the GSTz1 is inhibited in a dose-dependent manner by the formation of adducts **(32)**.

This GSTz1 enzyme primarily resides in hepatocytes and proximal tubule cells of the kidney**.** The metabolism of DCAA involves oxidative dechlorination to form glyoxylate by glutathione transferase zeta-1, which is further oxidized to oxalate, carbon dioxide, or incorporated into amino acids, nucleophiles, and other cellular molecules **(33 ,19).**

Elimination

Only a small fraction of unmetabolized DCAA (1-2%) is found in the feces, and about 1% is excreted in urine as the parent compound. As the DCAA dose increases, the amount of parent compound in the urine also increases **(34).**

Elimination is due almost entirely to biotransformation. In rodents, 30–50% of an oral gavage dose is converted to CO_2 within 24 h. Urinary metabolites may account for an additional 25% of an administered dose. Renal clearance of parent DCAA is typically low, ranging from 0.3 to 2% of the dose **(35).**

There is evidence that the clearance of DCAA decreases with age **(30).**

Mechanism of dichloroacetic acid toxicity:

Dichloroacetic acid exerts its toxicity through several mechanisms, primarily by altering cellular metabolism and inducing oxidative stress. It inhibits pyruvate dehydrogenase kinase, leading to the activation of pyruvate dehydrogenase and increased oxidative phosphorylation **(36).**

Dichloroacetic acid can also interfere with the metabolism of certain amino acids and heme synthesis, potentially leading to the accumulation of reactive molecules and further oxidative stress. In addition, DCAA can interfere with the catabolism of the amino acids phenylalanine and tyrosine, and with heme synthesis, resulting in reactive molecules that form adducts with DNA and proteins, also causing oxidative stress **(37).**

The toxicity of dichloroacetic acid:

Acute toxicity

The following acute health effects may occur immediately after exposure to DCAA. Contact can cause severe skin and eye irritation and burns with possible permenant eye damage. Breathing DCAA can irritate the nose, throat and the lungs causing coughing or shortness of breath. Higher exposures can cause a build-up of fluid in the lungs (pulmonary edema), a medical emergency, with sever shortness of breath **(38).**

Chronic toxicity

- **Neurotoxicity of dichloroacetic acid :**

In patients treated chronically with DCAA, the nervous system appears to be most commonly affected. The most problematic effect from chronic DCAA treatment is reversible peripheral neuropathy and is considered the major limiting factor in clinical DCAA use **(39).**

According to **(40),** DCAA at 25 mg/kg/day is associated with peripheral nerve toxicity. It is known that

DCAA can produce dose-dependent demyelination through the reversible inhibition of myelin-related proteins **(41).** Based on some evidence, it was speculated that DCAA-induced inhibition of glycolysis is the cause, and studies have shown that glycolysis is required by myelinating Schwann cells **(42).**
Case studies have also reported peripheral neuropathy from oxalate deposition in peripheral nerves and other tissues in primary hyperoxalurias, highlighting the metabolism of DCAA to oxalate as a clinically significant event **(43).**
It was posited that the reversible polyneuropathy seen with DCAA may be due to thiamine deficiency, as thiamine stores are depleted during DCAA transformation into glyoxylate in its metabolic pathway. Glyoxylate is readily oxidized to oxalate via lactate dehydrogenase. The oxalate is further metabolized via glyoxylate carboligase in a thiamine-dependent reaction **(19).**

- **Hepatotoxicity of DCAA:**

Oral intoxication of the DCAA to male Wistar rats at 0.5 and 2 g/L for 2 months demonstrated a significant increase in the levels of hepatic marker enzymes [aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase, and gamma-glutamyl transferase(GGT)], conjugated bilirubin, and changes in the histological architecture of the rat liver. DCAA induced oxidative stress by increasing the extent of hepatic thio barbituric acid reactive substances formation, changing the activities of superoxide dismutase, catalase, and glutathione peroxidase, and by elevating the hepatic DNA fragmentation (**44**).
Early-life exposure to DCAA increased the incidence and number of hepatocellular tumors in male and female mice compared with controls. Both males and females showed significant dose effects. 10 weeks of high-dose DCAA led to tumor outcomes similar to lifetime exposure (≥85% incidence) **(45)**.
According to (**46),** there was an association between urinary DCAA and increased liver injury risk, ALT level, as well as lower AST/ALT among women. Another relation was observed between urinary DCAA and high GGT.

- **Reproductive toxicity of dichloroacetic acid :**

Dichloroacetic acid, as a chlorinated disinfection byproduct, may be a cause of male infertility. (**47)** found that DCAA has a deleterious impact on the quality of spermatozoa, resulting in a decrease in spermatozoal number and an increase in abnormal forms of spermatozoa in the testis.
According to **(48),** there were a histological changes in testes after exposure to DACC as epithelial layer shrinkage, the acini and fibromuscular tissues affected, and clumping in glandular ducts. Pathological changes seen in the prostate gland have been correlated with the possible alteration in the gonadal hormone. These changes confirmed the testicular and reproductive toxicity in male rats after exposure to DACC **(49).**
The subchronic treatment of rats with DCAA showed that testosterone, follicle-stimulating hormone, and luteinizing hormone levels were decreased. Severe histopathological changes in the testes were observed, including degeneration of seminiferous tubules and depletion of germ cells. These changes were associated with alterations in oxidative stress markers **(18).**
Based on existing experimental studies, there is sufficient evidence showing that HAAs, including DCAA, are male reproductive toxicants, including reduced epididymal weight, decreased semen parameters and sperm protein 22, and declined testosterone levels **(50).**
According to **(51),** DCAA can cause adverse effects on female reproductive function, which includes delayed puberty, elevated estrogen production, impaired ovarian steroidogenesis, and induced pregnancy loss. The high level of DCAA was associated with high serum progesterone and prolactin levels among women undergoing assisted reproductive technology.

- **Nephrotoxicity of dichloroacetic acid:**

Nephrotoxicity was induced in male Wistar rats by the administration of DCAA. After two months of experiment, DCAA administration caused elevated levels of renal malondialdehyde (MDA), significant

depletion of glutathione (GSH) levels, altered the antioxidant enzyme activities, and deteriorated the renal functions as assessed by the increased plasma urea, uric acid, and creatinine levels compared to control rats **(52).**

- **Carcinogenicity of dichloroacetic acid :**
  Disinfection byproducts could cause most types of cancers, including gastrointestinal, renal, bladder, breast, liver, and thyroid cancers. Liver and renal cancers are the most common target organs for toxicity by DBPs. Haloacetic acids such as TCAA and DCAA have been known as one of the most significant risk factors. DBPs can result in cancer development, especially in the liver and kidneys **(53).**
  Studies performed in mouse models associate DCAA early-life exposure with an increased incidence of hepatocellular tumors **(54).** A disturbance in the fat and carbohydrate metabolism, mitochondrial dysfunction, increased oxidative phosphorylation, and oxidative stress are mechanisms considered to be responsible for the carcinogenicity in the liver **(45, 55).**
  Dichloroacetic acid induces xenobiotic-metabolizing enzymes in the liver and has a tumor-promoting effect. There is considerable interference with the energy metabolism, particularly in the liver cells, and probably also, due to their high energy requirement, in the nerve cells. The inhibition of apoptosis, together with the selective advantage of spontaneously initiated cells, has been suggested as the mechanism of action for the formation of liver tumors **(56).**
- **Ocular dysplasia effect of dichloroacetic acid:**
  Maternal exposure to high doses of trichloroethylene and its oxidative metabolites, TCAA and DCAA, has been implicated in eye malformations in fetal rats, primarily micro-/anophthalmia. Mean fetal lens and globe areas were significantly reduced in the DCAA treatment groups. Mean medial canthus and interocular distances were reduced among the TCAA and DCAA treatment groups **(57).**

The hippocampus

The hippocampus is situated in the hippocampal sulcus, immediately below the floor of the temporal horn of the lateral ventricle and above the parahippocampal gyrus, and can be divided into three parts: the head, body, and tail **(Figure 2) (58)**.

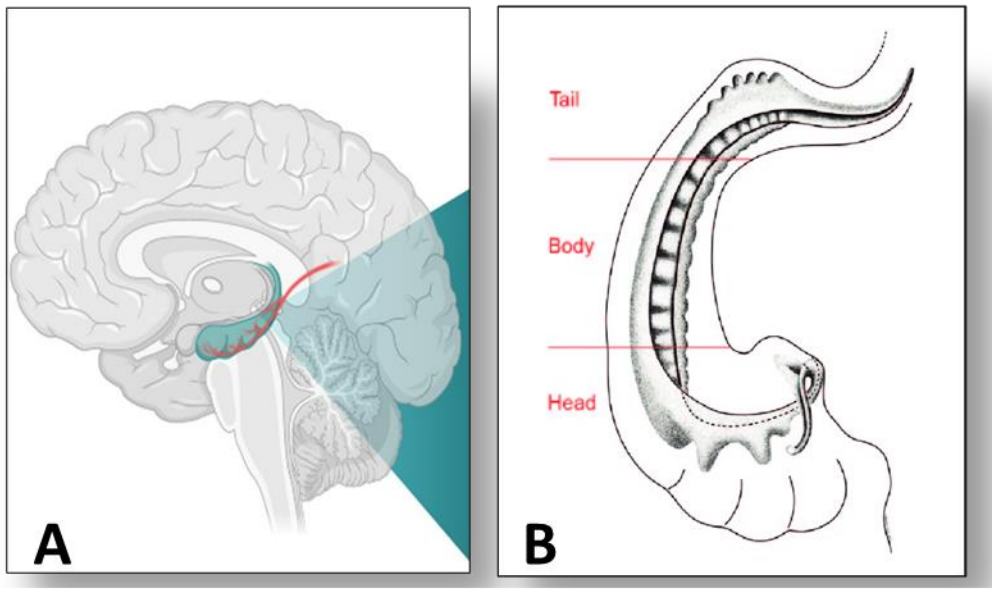

Figure (2): A: The site of the hippocampus **(59); B:** the parts of the hippocampus **(60).**

Subdivisions and microanatomy of the hippocampus :

The subdivisions of the hippocampus include the dentate gyrus (DG), the subiculum, and the hippocampus proper (cornu ammonis) (CA1, CA2, CA3, and CA4 regions). The dentate gyrus and hippocampus proper form two C-shaped rings that interlock. The subiculum is a transition zone, linking the hippocampus proper with the dentate gyrus **(Figure 3) (61).**

The dentate gyrus of the hippocampus contains tightly arranged small granule cells. The cornu ammonis regions contain densely packed pyramidal cells **(62)**.

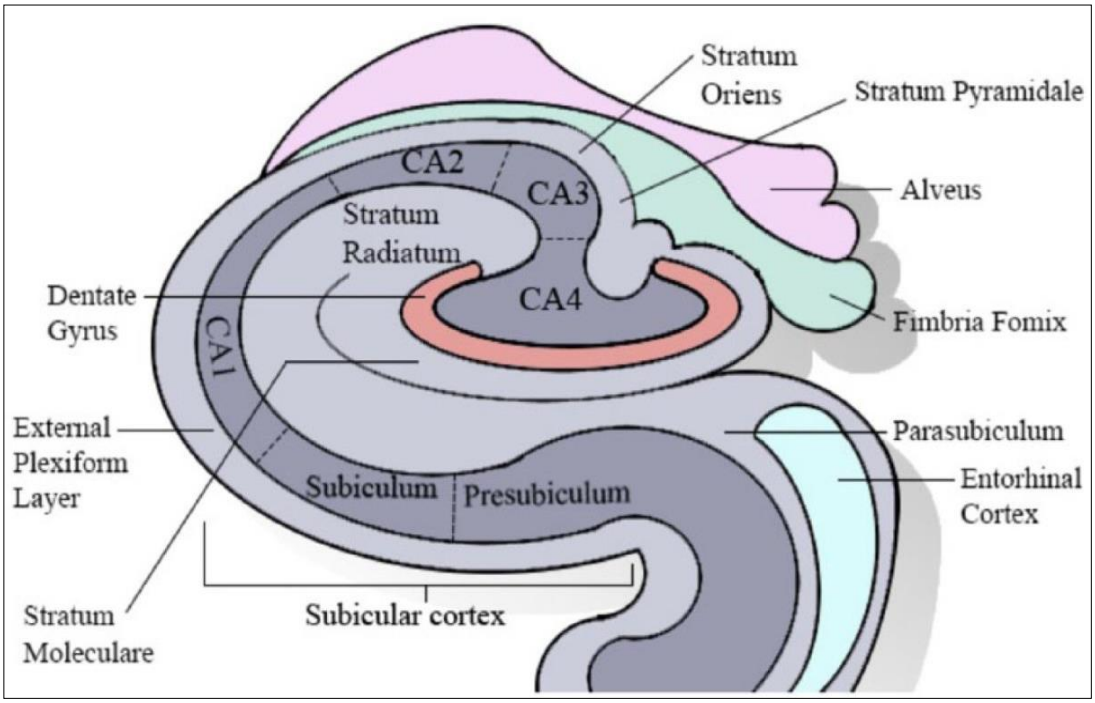

Figure (3): Subdivision of hippocampus **(63).**

The hippocampus is a trilaminate archicortex, which is made up of upper and lower plexiform layers, and in between these, there is a pyramidal cell layer. The CA1, CA2, CA3, and CA4 are the four fields of the hippocampus **(64).** The CA3 region receives mossy fibers from the DG, and it contains about ten layers of pyramidal cells; these cells are the largest among the hippocampal pyramidal cells. The CA2 region has compactly arranged pyramidal cells, which receive significant inputs from the supramammillary areas of the hypothalamus. The CA1 region overlaps the subiculum, and about 10% of the neurons present in the CA1 region are interneurons. The three layers of the hippocampus are included in the six strata **(Figure 4) (61).**

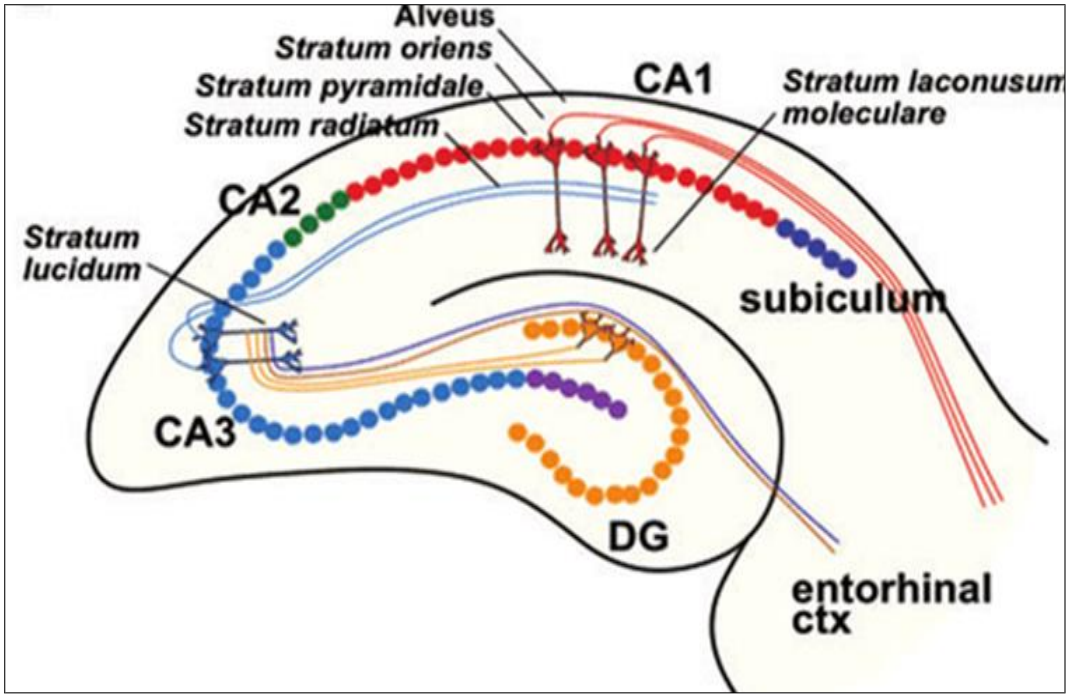

Figure (4): Microanatomy of the hippocampus **(65).**

Blood supply of the hippocampus:

The hippocampus is usually supplied by the branches of the posterior cerebral artery, a branch of the basilar artery, and the anterior choroidal artery, an extension of the internal carotid artery. However, the central part of the hippocampus is supplied by the posterior cerebral artery. It is also reported that the arterial supply of the hippocampus may vary in some people **(66).**

The arteries of the hippocampus are named according to their area of distribution. The anterior hippocampal artery supplies the head and uncus; the body is provided by the middle hippocampal artery, whereas the posterior hippocampal artery supplies the tail of the hippocampus **(Figure 5) (67).**

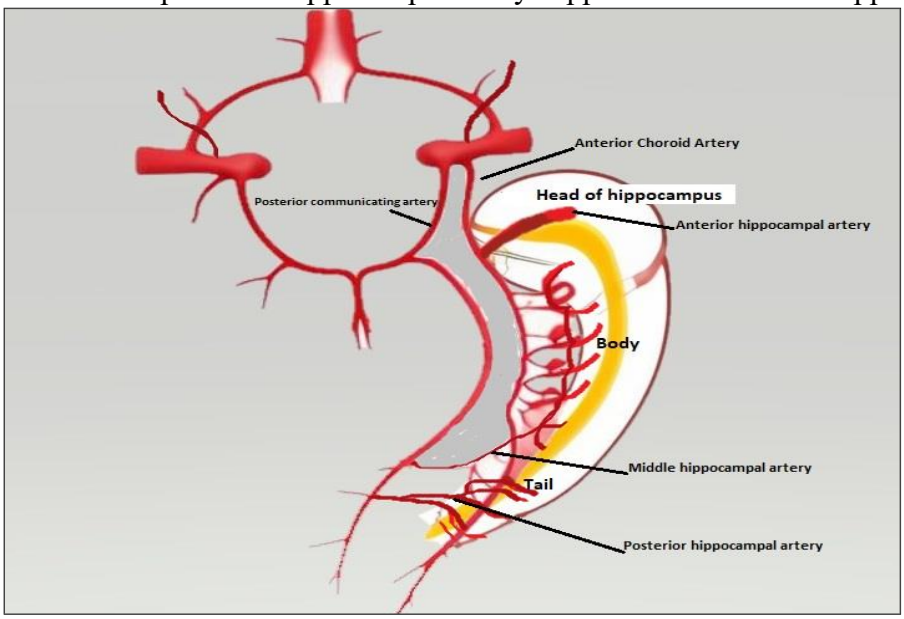

Figure (5): Blood supply of the hippocampus **(67).**

Function of the hippocampus:

Hippocampus is a vital region of the memory, cognitive function and adult neurogenesis in the brain **(68).**

The hippocampus is now known not just to be important in learning and memory but also in spatial navigation, emotional behavior, and regulation of hypothalamic functions. Connections between the hippocampus and neocortex are important for awareness about conscious knowledge **(69).**

The hippocampus is a part of the ventral striatal loop and, hence, can affect motor behavior. Though emotional behavior is regulated mainly by the amygdala, both the hippocampus and amygdala have reciprocal connections and thus can influence each other **(70).**

Hippocampal dysfunction :

The hippocampus is involved in various processes ranging from learning and memory to control of emotions and motivation. It is also responsive to stress hormones and is implicated in the pathogenesis of various disorders such as depression, post-traumatic stress disorder, schizophrenia, epilepsy, and neurodegenerative diseases (**71).**

Progressive memory impairment in Alzheimer's disease (AD) patients is associated with degeneration of the hippocampus. The dentate gyrus of the hippocampus, a region critical for learning and memory functions, is a site of adult neurogenesis in mammals. Recent evidence in humans indicates that hippocampal neurogenesis likely persists throughout life but declines with age and is strikingly impaired in AD **(72).**

Hippocampal dysfunction is a robust feature in the pathophysiology of psychosis. In patients with psychotic disorders such as schizophrenia, hippocampal volume is reduced and function is abnormal **(73).**

Temporal lobe epilepsy is thought to be associated with neuronal hyperexcitability in the hippocampal-entorhinal cortical circuit. Due to the complexity of the hippocampal-EC network connections, the biophysical mechanisms of the different circuits in epilepsy generation and propagation are still not fully established **(74).**

Transient global amnesia, a transient memory disorder in clinical neurology, is a unique clinical model for the study of hippocampal dysfunction and its implications for memory processes **(75).**

Synaptic Plasticity

Introduction:

A fundamental property of neurons is their ability to modify the strength and efficacy of synaptic transmission through a diverse number of activity-dependent mechanisms, typically referred to as synaptic plasticity. Indeed, studies into synaptic plasticity have not only been an important driving force in neuroscience research but are also contributing to the well-being of our societies, as this phenomenon is involved in learning and memory, brain development and homeostasis, sensorial training, and recovery from brain lesions **(76).**

Definition of synaptic plasticity:

Synapses between neurons are malleable biochemical structures, strengthening and diminishing over time depending on the type of information they receive. This phenomenon is known as synaptic plasticity. It performs varied cognitive roles in reinforcement, relearning, and associating memories **(77).**

After learning, memory is initially encoded in the hippocampus but subsequently stabilized in other brain regions, such as the cortex, for long-lasting storage. This process is known as systems memory consolidation **(78).**

Types of synaptic plasticity:

Throughout life, synapses remain plastic by altering their structure and strength. Such synaptic adaptations in neuronal circuits are critically dependent on experience-driven neuronal activity changes. Synaptic plasticity has multiple forms, including Hebbian plasticity, heterosynaptic plasticity, and

homeostatic plasticity **(79).**

The first form, homosynaptic plasticity (Hebbian plasticity), is a positive feedback mechanism that facilitates the reinforcement of synaptic connections and includes two major forms: long-term potentiation (LTP) and long-term depression (LTD) (**80**)

The second form is heterosynaptic plasticity, which is not limited to active synapses but can be induced at synapses that were not active during the induction of homosynaptic plasticity. Heterosynaptic modulation could have one of two forms: non-associative or associative. The non-associative form is purely heterosynaptic, whereas associative, activity-dependent heterosynaptic modulation combines features of homosynaptic and heterosynaptic mechanisms **(81).**

The third form, homeostatic plasticity (also known as 'synaptic scaling'), is a negative feedback mechanism whereby neurons counteract excessive excitation or inhibition in response to prolonged neuronal activity changes **(82).**

Different forms of synaptic plasticity interact to facilitate the network functions of the adult brain. Meanwhile, synaptic plasticity impairment is implicated in several neurological and cognitive disorders, notably AD **(83, 84).**

Synaptic plasticity markers:

1) Immediate early genes

- **C-fos**

C-fos is one of the first neuronal transcription genes whose induction is activity-dependent due to cAMP and Ca2+ stimulation by activating the cyclic AMP response element-binding protein complex (CREB). Increased c-fos expression is an indicator of neural activation, as demonstrated by behavioral training in learning, cognitive performance, and memory formation **(85).**

- **Activity-Regulated Cytoskeleton-associated protein (ARC)**

This gene is one of the most characteristic molecules that play a key role in memory formation. ARC encodes proteins involved in synaptic functions related to serotonin, glutamate, and dopamine, distinguishing it from c-Fos and early growth response 1(EGR-1) . ARC expression is regulated by EGR-1 , and its mRNA is transported to dendrites, making it a marker of neural activity **(86).**

- **Early growth response 1 (EGR-1)**

Early growth response 1, known by various names such as zif268, NGFI-A, Krox 24, or ZENK, is a transcription factor whose expression is induced by various factors, including injury, stress, and cell differentiation. EGR-1 expression exhibits a distinct pattern in the brain compared to c-Fos. It plays a crucial role in mediating the expression of multiple genes involved in neural processes. EGR-1 is relatively highly expressed during neural activity, particularly in the hippocampus and the dentate gyrus **(87).**

2) Structural proteins

- **Postsynaptic density protein (PSD-95):**

Postsynaptic density -95 (PSD-95) is a critical synaptic protein that binds to the N-methyl-D-aspartate receptor C-terminal domain. It requires palmitoylation to remain at synapses and controls synaptic transmission and plasticity. Overexpression of PSD-95 increases synaptic transmission and blocks ion-flux-independent LTD. Importantly, PSD-95 is reduced in brain tissue from AD mouse models in neural tissue exposed to beta-amyloid and in brain tissue from individuals with AD **(88).** Recently, variants in the discs large subfamily encoding PSD-95 were found to cause a neurodevelopmental disorder with a variety of clinical features, including intellectual disability, developmental delay, and epilepsy **(89).**

- **Synapsin-1**

Synapsin-1 is a phosphoprotein localized to the synaptic vesicle membrane in presynaptic terminals, and regulates the number of vesicles available and neurotransmitter release in presynaptic terminals. Learning and memory processes require synapsin-1**(90).**

- **Synaptophysin**

  Synaptophysin is the first cloned marker of synaptic vesicles and the second most abundant synaptic vesicle glycoprotein. This protein is the main component of the small vesicles of neuroendocrine cells and neurons and modulates the synaptic vesicle cycle. The level of synaptophysin is an agreeable indicator of the number of synapses and the efficiency of synaptic connections **(91).**

- **Growth-associated protein (GAP-43)**

  The growth-associated protein, also known as neuromodulin, is a presynaptic protein strongly involved in synaptic plasticity and neuronal development that is expressed in medial temporal lobe regions that are particularly vulnerable to the earliest AD-associated tau pathology. GAP-43 has been found to play a key role in axonal growth and the formation of new synaptic connections; its expression is associated with neuronal activity (**92).**

3) Neurotrophic factors and kinases

- **Nerve growth factor (NGF):**

  Nerve growth factor (NGF) was the first member of a family of neurotrophic factors to be discovered and is an essential neurotrophic factor for the development and maintenance of the central and peripheral nervous systems **(93).**

  It induces neuroprotective effects on the differentiation, growth, nutrition, and support of neurons. Some studies have confirmed that NGF deficiency in the brain induces neuronal aging, dysfunction, and apoptosis. Some previous studies have shown that NGF deficiency leads to neuronal apoptosis in the brain **(94).**

- **Brain-derived neurotrophic factor (BDNF):**

  The brain-derived neurotrophic factor (BDNF) is a key mediator of neuronal plasticity within the central nervous system, acting on both pre-synaptic and post-synaptic sites and affecting dendritic spines and adult neurogenesis at different levels **(95).**

  It plays multiple roles in the nervous system, including neuronal development, long-term synaptic potentiation in different brain regions, and neuronal survival. Alterations in these regulatory mechanisms account for several diseases of the nervous system **(96).**

- **Cyclic AMP response element-binding protein (CREB)**

  The cyclic AMP response element-binding protein is a transcription factor that binds to specific DNA sequences and regulates gene expression, and its activation has been shown to enhance LTP. CREB plays a key role in regulating synaptic plasticity, a fundamental process in learning and memory **(97**). The signaling pathways that lead to CREB activation and subsequent gene expression changes have been extensively studied and include the cyclic adenosine monophosphate pathway, as well as calcium-dependent pathways involving the activation of calcium/calmodulin-dependent protein kinases **(98).**

- **Ca^{2+}/calmodulin (CaM)-dependent protein kinase II (CaMKII)**

  The Ca^{2+}/calmodulin (CaM)-dependent protein kinase II plays a fundamental role in learning and possibly also in memory. CaMKII autophosphorylation at Thr286 does not provide the molecular basis for long-term memory, as long believed. Instead, pThr286 mediates the signal processing required for induction of several distinct forms of synaptic plasticity, including Hebbian long-term potentiation and depression and non-Hebbian behavioral timescale synaptic plasticity **(99).**

4) Synaptic receptors

- **N-methyl-d-aspartate receptor (NMDAR)**

  The N-methyl-d-aspartate receptor is a major type of ionotropic glutamate receptor in the central nervous system, and plays a fundamental role in both synaptic transmission and plasticity. NMDAR-dependent synaptic plasticity is a key cellular model for studying central brain functions, including learning and memory, chronic pain, and drug addiction. For example, NMDAR-dependent LTP in the hippocampus contributes to the formation of long-term memory **(100).**

- **α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)**
  Tetrameric AMPA-type ionotropic glutamate receptors are primary transducers of fast excitatory synaptic transmission in the central nervous system, and their properties and abundance at the synaptic surface are crucial determinants of synaptic efficacy in neuronal communication across the brain. Disruptions in the trafficking of AMPA receptors to and from the synaptic surface attenuate both forms of synaptic plasticity **(101).** AMPA receptors are critical for the formation and consolidation of various types of memory, and alterations in their function are intimately associated with cognitive dysfunction in aging and several neurological and psychiatric diseases **(102).**
- **Metabotropic glutamate receptors (mGluRs)**
  Metabotropic glutamate receptors are G-protein-coupled receptors that exhibit enormous diversity in their expression patterns, sequence homology, pharmacology, biophysical properties, and signaling pathways in the brain. In general, mGluRs modulate different traits of neuronal physiology, including excitability and plasticity processes. Particularly, group I mGluRs located at the pre- or postsynaptic compartments are involved in spike timing-dependent plasticity at hippocampal and neocortical synapses **(103).**

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