

ALZHEIMER'S DISEASE CAUSES AND MANGEMNT**Hanaa H.Ahmed¹ and Hanan F. Aly^{2*}**¹Hormones Department, National Research Center, Cairo, Egypt^{2*}Therapeutic Chemistry Department, National Research Center, Cairo, EgyptArticle Received on
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Egypt.**ABSTRACT**

Alzheimer's disease is a progressive disease that destroys memory and other important mental functions. It's the most common cause of dementia, a group of brain disorders that results in the loss of intellectual and social skills. These changes are severe enough to interfere with day-to-day life. In Alzheimer's disease, the connections between brain cells and the brain cells themselves degenerate and die, causing a steady decline in memory and mental function. Scientists are still trying to fully understand the cause or causes of Alzheimer's disease. In the meantime, it's helpful to understand the hallmarks of Alzheimer's plaques and tangles as well as the risk factors that affect a person's likelihood of developing the disease. Scientists are still

studying how plaques and tangles are related to Alzheimer's disease. One theory is that they block nerve cells' ability to communicate with each other, making it difficult for the cells to survive. Autopsies have shown that most people develop some plaques and tangles as they age, but people with Alzheimer's develop far more than those who do not develop the disease. Scientists still don't know why some people develop so many compared to others. However, several risk factors for Alzheimer's disease have been uncovered. Age, advancing age is the number one risk factor for developing Alzheimer's disease. One out of eight people over the age of 65 has Alzheimer's disease, and almost one out of every two people over the age of 85 has Alzheimer's. The probability of being diagnosed with Alzheimer's nearly doubles every five years after age 65. Family history, people who have a parent or sibling that developed Alzheimer's disease are two to three times more likely to develop the disease than those with no family history of Alzheimer's. If more than one close relative has been affected, the risk increases even more.

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List of abbreviations

AD	Alzheimer's disease.
Ach	Acetylcholine
AchE	Cholinesterase
AchT	Acetylcholinetransferase
AICD	Amyloid precursor protein intracellular domain.
Al	Aluminum.
AND	Androstenedione.
ApoE	Apolipoprotein-E.
Apo-E₄	Apolipoprotein E epsilon 4.
APP	Amyloid precursor protein.
APPsα	Large soluble extracellular amino-terminal portion of APP.
APPsβ	Short soluble amino terminus of APP.
AR	Androgen receptor.

Aβ	Amyloid- β .
Aβ25–35	A β fragment 25–35.
BACE1	β -site APP-cleaving enzyme.
BMI	Body mass index.
C83	Carboxy-terminal fragment that consists of 83 residues.
C99	Carboxy-terminal fragment that consists of 99 residues.
cdk-5	Cyclin dependent kinase-5.
CNS	Central nervous system.
CRH	Corticotropin-releasing hormone.
CSF	Cerebrospinal fluid.
DAT	Dementia of the Alzheimer type.
DHEA	Dehydroepiandrosterone.
DHEAS	Dehydroepiandrosterone sulfate.
DHT	Dihydrotestosterone.
DS	Down Syndrome.
E1	Estrone.
E2	Estradiol.
E3	Estriol.
EEG	Electroencephalogram.
ER	Estrogen receptor.
ERs	Estrogen receptors.
ERT	Estrogen replacement therapy.
ERβ	Estrogen receptor β .
fAβ	Beta-amyloid fibrils.
FSH	Follicle-stimulating hormone.
fT₄	Free thyroxin.
GABA-A	Gamma aminobutyric acid-A.
GCs	Glucocorticoids.
GDX	Gonadectomy.
GH	Growth hormone.
GHRH	Growth hormone releasing hormone.
GNRH	Gonadotropin-releasing hormone.
GPCR	G-protein coupled receptor.
GSH	Reduced glutathione.
GSK3β	Glycogen-synthase kinase 3 β .
H₂O₂	Hydrogen peroxide.
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal.
HPG	Hypothalamic pituitary gonadal.
IGF-1	Insuline-like growth factor-1.
IL-1	Interleukin 1
IL-6	Interleukin 6
ip	Intraperitoneal.
4kDa	4 kilo Daltons
LH	Luteinizing hormone.
LHR	Luteinizing hormone receptor
LTD	Long-term depression.
LTP	Long-term potentiation.
MAPK	Mitogen-activated protein kinase-signaling.
MCI	Mild cognitive impairment.

MDA	Malondialdehyde.
mRNA	Messenger ribonucleic acid
NEP	Neprilysin
NFTs	Neurofibrillary tangles.
NGF	Nerve growth factor.
NGFR	Nerve growth factor receptor.
NMDA	N-methyl-D-aspartate.
$^1\text{O}_2$	Singlet oxygen.
ONOO⁻	Peroxynitrate.
rhGH	Recombinant Human Growth Hormone.
sAPPα	Soluble Amyloid precursor protein alpha.
T₄	Thyroxine.
TGN	Trans-Golgi network.
TNF-α	Tumor necrosis factor- α
TRH	Thyrotropin-releasing hormone.
TSH	Thyroid stimulating hormone.
TSH-R	Thyroid stimulating hormone-receptor.
3xTg-AD	Triple transgenic mouse model of AD.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive degenerative disease of the brain that affects memory, thought, reasoning and language (**Fig. 1**). Eventually, patients may develop changes in personality and behavior and become unable to care for themselves. Most patients live about 8 to 10 years after their diagnosis, though some may live for as long as 20 years. AD is considered as the most common cause of dementia in elderly and it is characterized by a progressive memory decline as well as serious cognitive disability due to the progressive dysfunction and death of nerve cells that are responsible for the storage and processing of

information (Ramos et al., 2006). AD is characterized by a deficit in cholinergic neurotransmission affecting cholinergic neurons of the basal forebrain (Kasa et al., 1997). Evidence has demonstrated that the enzyme involved in synthesis [acetylcholinesterase (AChT)] of acetylcholine (ACh) has reduced activity and may be responsible for this defect (Dekosky et al., 1992). Moreover, cholinesterase (AChE) has been found to be present in brains from AD patients and this suggests that AChE could have a role in the pathogenesis of AD (Guillozet et al., 1997). AD remains perhaps the most devastating disease of old age and constitutes a large social and economic burden to both the families and society as a whole (Driscoll and Resnick, 2007). Although our knowledge and understanding of the disease continues to grow, infusing a sense of optimism, no treatments have proven effective thus, so far in reversing or even stabilizing the disease process (Thung et al., 2014).

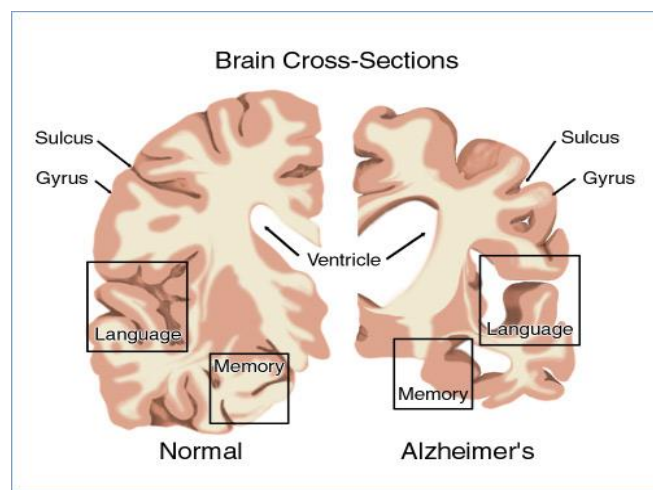


Fig. (1): Normal and Alzheimer's disease brain cross-section

http://www.hoinews.com/news/news_story.aspx

Epidemiology of Alzheimer's disease

Since it was first described in 1906 by Alois Alzheimer, this neurodegenerative disease is affecting an increasing number of individuals each year with the number of patients reaching upwards of 30 million worldwide in 2004 and the incidence increases from 0.5% to 8% per year at the age of 65–85 years. The peak incidence of the initial development of AD is individuals in between the ages of 65 and 74 years (Selkoe, 2004).

By 2025, about three-quarters of the estimated 1200 million people aged 60 years and older will be living in developing countries (WHO, 2003). Taking into account the increase in life expectancy and the fact that the incidence of AD increases with advancing age (Kalaria, 2003), and AD considered as the fourth most common cause of death in developed nations (Yates and McLoughlin, 2008).

Epidemiological studies of dementia of the Alzheimer type (DAT) have rarely been reported in Arab populations and there were unexpected differences in prevalence rates of Alzheimer's disease, such as between Arabs in Upper Assiut, Egypt at 1.4% (**Farrag et al., 1998**) and those of Wadi-Ara, Israel who have the same paternal origin, at 20.5% (**Bowirrat et al., 2001**) .

Although, the overall number of studies is small, pooled results suggest that a higher adherence to the Mediterranean diet (MeDi) is associated with a reduced risk of developing mild cognitive impairment (MCI) and Alzheimer's disease (AD), as well as a reduced risk of progressing from MCI to AD (**Singh et al., 2014**).

Pathology of Alzheimer's disease

The pathological hallmarks of AD are neuritic plaques, neurofibrillary tangles (NFTs), gliosis and neuronal degeneration (**Selkoe et al., 2002; Wang and Wang, 2006; Bojarki et al., 2008**). Neuritic plaques (**Fig. 2**) are largely formed from the aggregation of the 4 kDa beta-amyloid peptide (a39–43 amino acid peptide), which is released into the extracellular space following the metabolic breakdown of the larger amyloid precursor protein (APP).

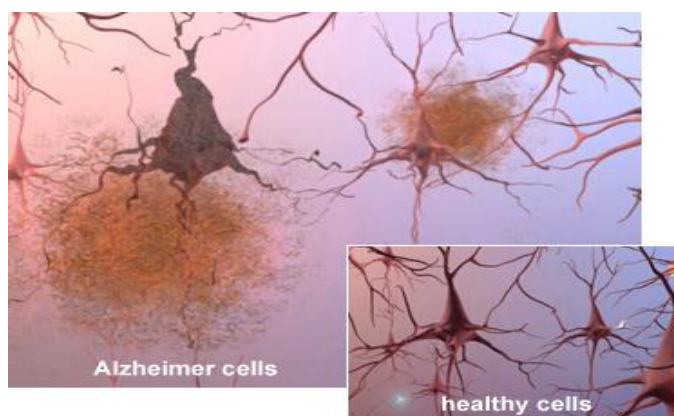


Fig. (2): Amyloid- β plaques

<http://www.alz.org/brain/10.asp>

APP is a type 1 transmembrane protein in which the carboxy-terminal portion of amyloid- β ($A\beta$) peptide is embedded within the cell membrane. Multiple isoforms of APP are derived by differential splicing, with the predominant variants containing 695, 751 or 770 residues, although other minor species of different lengths also exist. The 751- and 770-residue isoforms are distinguished from each other by an OX-2 antigen domain (which is absent in APP_{751}), and from the 695-residue isoform by the presence of a kunitz protease-inhibitor domain. These three isoforms have in common the same $A\beta$, transmembrane and intracellular

domains; however, within the brain, APP₆₉₅ is the main species present in neurons, whereas APP₇₅₁ and APP₇₇₀ are expressed predominantly in glial cells.

APP undergoes two endoproteolytic cleavage events that either preclude or cause the formation of the amyloidogenic A β peptide. Cleavage by α -secretase- a membrane-associated metalloproteinase, the activity of which is probably elaborated by several distinct enzymes, occurs within the A β domain (between residues 16 and 17), precluding the liberation of an amyloidogenic species, and resulting instead in the release of the large soluble extracellular amino-terminal portion of APP (APPs α) and a carboxy-terminal fragment that consists of 83 residues (C83). C83 can undergo further proteolysis by γ -secretase to liberate the P3 peptide, which is considered to be non-amyloidogenic (Lalowski et al., 1996; Tekirian et al., 1998). To liberate the A β species, APP must undergo two sequential endoproteolytic steps that are mediated by distinct enzymatic activities known as β - and γ -secretase. β -secretase, which is the enzyme known as β -site APP-cleaving enzyme (BACE1), cleaves APP at the amino-terminal region of the A β sequence (Vassar et al., 1999). Cleavage by β -secretase generates a slightly shorter soluble amino terminus (APPs β) and the amyloidogenic carboxy-terminal fragment (C99). Cleavage of C99 by γ -secretase occurs at the recently elucidated ϵ -site within the transmembrane domain, liberating the carboxy-terminal 50 residues of APP, known as the APP intracellular domain (AICD). This is then followed by cleavage of the A β -containing fragment at the γ -secretase site after residue 40 or 42 of A β (Fig. 3).

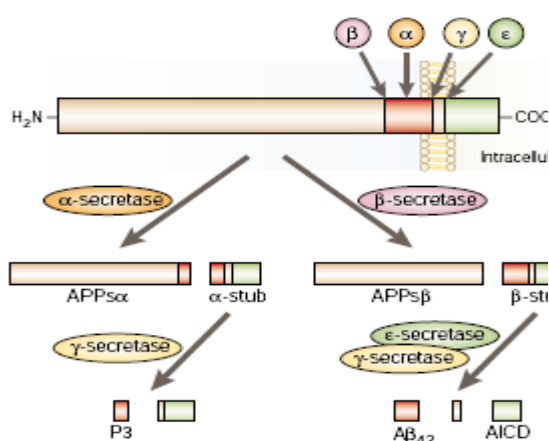


Fig. (3): Proteolysis of APP
(Laferla, 2002)

These aggregates may form high molecular weight insoluble fibrils, 10 nm in diameter, which can be observed radiating from the dense core of the neuritic plaques (**Fig. 4**). In AD, the amyloid deposits are largely spherical, reaching up to 200 μ m in diameter and are prevalent throughout the cortex and hippocampus of brains from affected individuals (**Glenner et al., 1984**).

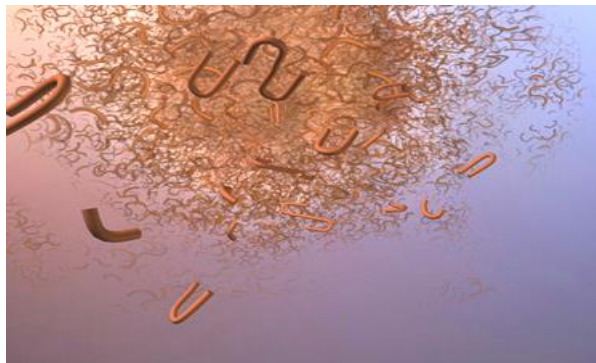


Fig. (4): High molecular weight insoluble amyloid- β fibrils

<http://www.alz.org/brain/11.asp>

A β fragments are neurotoxic to hippocampal and cortical neurons (**Nakamura et al., 2001 ; Shen et al., 2002a**). This effect of A β is considered to be localized to amino acid residues 25–35 of the full-length peptide which are known as the neurotoxic domain of the parent A β peptide. Moreover, Inflammation has been implicated in the pathogenesis of AD, although the exact mechanisms by which A β impairs cholinergic signaling and injures vulnerable neurons in the AD brain are not fully understood. Accumulating evidences indicated that A β deposition and phagocyte activation participate in inflammatory reactions in the brain during the course of AD (**Meda et al., 1999**). A β , as a triggering factor of inflammatory events in AD, may promote or exacerbate the inflammatory responses by activating glial cells to release proinflammatory mediators (**Gitter et al., 1995 ; Lorton et al., 1996**). A number of inflammatory mediators closely associated to A β deposits have been detected in the brains from AD patients including cytokines such as IL-1, IL-6, TNF- α , complement proteins and acute phase proteins (**Griffin et al., 1995 ; Eriksson et al., 1998**).

NFTs are formed as a result of abnormal aggregation of proteinaceous material. NFTs develop within neurons, gradually filling the intracellular space. Eventually, these aggregates (often referred to as ‘inclusions’) are believed to kill the affected neurons (**Yates and McLoughlin, 2008**). The main constituent of NFTs is the microtubule-associated protein tau (**Ballatore et al., 2007**). Under normal, conditions tau is bound to microtubules (key components of the neuronal cytoskeleton) stabilizing their structure and the internal cellular

architecture. However, in AD, tau becomes detached from microtubules and aggregates. Notably, this pathology is associated with aberrant phosphorylation of the individual tau molecules, which may be crucial for initiating NFT formation. The presence of ever-larger NFT inclusions combined with destabilization of the microtubules is likely to seriously impair neuronal function long before cell death occurs (**Fig. 5**).

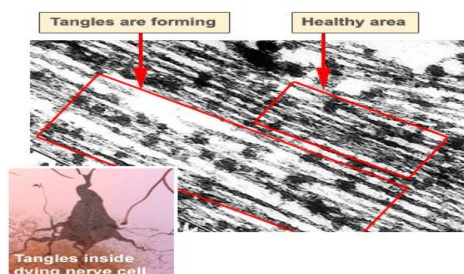


Fig. (5): Neurofibrillary tangles

<http://www.alz.org/brain/12.asp>

The association between an AD-like signature using the established biomarkers amyloid β 1-42, biomarkers total tau, and P-tau with increased levels of neurofilament light provides *in vivo* evidence of an association between AD and subcortical axonal degeneration in this uniquely large dataset of cerebrospinal fluid samples tested for dementia biomarkers (**Skillbäck et al., 2013**).

Risk factors for Alzheimer's disease

The precise cause of AD is unknown and AD is considered as multifactorial disease which may be caused by a combination of more than one risk factors. Advancing age is the first risk factor for AD (**Elwan et al., 2003**). Repetitive mild brain trauma also accelerates amyloid plaque formation and cognitive impairment (**Uryu et al., 2002**). Researchers have found a number of environmental factors that have been associated with the development of AD, including chronic exposure to toxins that leads to free radical generation (**Rosler et al., 1998**) as well as long-term exposure to silicon or aluminum (Al) (**AbdEl-Rahman, 2003; Solfrizzi et al., 2006**). **Ling et al. (2007)** reported that, $A\beta$ inserts into the neuronal membrane bilayer and generates oxygen-dependent free radicals that then cause lipid peroxidation and protein oxidation. Loss of membrane integrity leads to cellular dysfunction, such as loss of Ca^{2+} homeostasis, disruption of signal pathways, and activation of nuclear transcription factors and apoptotic pathways. Neuronal death is the ultimate consequence of these cellular dysfunctions (**Varadarajan et al., 2000**). Oxidative damage may be responsible for the cognitive and functional decline observed in AD (**Engelhart et al., 2002; Solfrizzi et al.,**

2006). Some circumstantial evidence has linked chronic exposure to Al with the development of AD (Shin, 1997; Abd El-Rahman, 2003; Solfrizzi et al. 2006). Alzheimer's disease patients have significantly higher levels of Al in their brains than healthy individuals or those with dementia caused by alcohol abuse, stroke or atherosclerosis (Zapatero et al., 1995). Al emanates from a variety of sources including deodorants, toothpaste, antacids, water supplies and food. Unfortunately, these Al compounds are readily absorbable by humans. Also, several beverages and foods such as coffee and some types of tea as well as tomatoes and hydrogenated or partially hydrogenated vegetable oils may increase the amount of Al that's absorbed (Abd El-Rahman, 2003). According to Rao (1992), the direct effect of Al depends on its binding to different brain cells causing inhibition of membrane-bound Na^+ , K^+ , Ca^{2+} ATPase activity. These enzymatic disturbances would result in cellular alterations and may cause death. High levels of exposure to mercury and silver have also been associated with the development of Alzheimer's disease (Lorscheider et al., 1995). Many studies have found that individuals with a genetic marker called the apolipoprotein E epsilon 4 (Apo-E₄) allele are at increased risk for developing AD (Friedland et al., 2000). Also, this gene lowers the age of onset of AD (Roses, 1997) as an association was found between Apo-E₄ genotype and memory function (Bondi et al., 1995). Several studies have found evidence that AD is a disease that is caused by or resulted from a decreased metabolic activity in the brain (Salehi and Swaab, 1999). It has been speculated that Apo-E₄ may be involved in the development of decreased metabolic activity that is associated with AD. Researchers have proposed that genetic mutations may alter the mechanisms by which amyloid proteins in the brain are processed. The risk of developing AD is increased in first-degree relatives of affected individuals. The familial types of Alzheimer's disease are associated with less than 7% of all cases of Alzheimer's disease. Most cases are classified as being sporadic (ie, not inherited). The available epidemiological data indicated the contribution of type 2 diabetes mellitus to cognitive impairment and AD- type neurodegeneration (de la Monte and Wands, 2005; Haan, 2006). Several mechanisms could help to explain the link between type 2 diabetes mellitus and increased risk of AD. These include insulin and insulin resistance, inflammatory cytokines, and oxidative stress. Obesity or physical inactivity might also influence AD through effects on hypertension, insulin sensitivity or inflammation (Martins et al., 2006). Regarding education, low levels of education are considered risk factors for AD as the years of education contributed significantly to cognitive status. There is an association between education in early adult life and cognitive status in late life, which may be an important factor

in evaluating risk factors for cognitive decline in the elderly (Stern et al., 1994; Plassman et al., 1995). Thus, the risk of AD has been claimed to be reduced by education attainment.

Several risk factors have been discovered that are associated with AD. The most well-known genetic risk factor for late-onset AD is apolipoprotein E4 (ApoE4) (Verghese et al., 2011 ; Potter and Wisniewski ,2012). Recently, it has been reported by two groups independently that a rare functional variant (R47H) of TREM2 is associated with the late-onset risk of AD. TREM2 is expressed on myeloid cells including microglia, macrophages, and dendritic cells, as well as osteoclasts. Microglia are a major part of the innate immune system in the CNS and are also involved in stimulating adaptive immunity. Microglia express several Toll-like receptors (TLRs) and are the resident macrophages of the central nervous system (CNS). In this review, we will focus on the recent advances regarding the role of TREM2, as well as the effects of TLRs 4 and 9 on AD (Boutajangout and Wisniewski, 2013).

Pathogenesis of Alzheimer's disease

Three main stages can be clinically characterized in AD (Kryger et al., 1999).

The first stage is the so-called **amnesia stage**, which involves initial loss of short-term memory and lack of emotional spontaneity (Fig. 6).

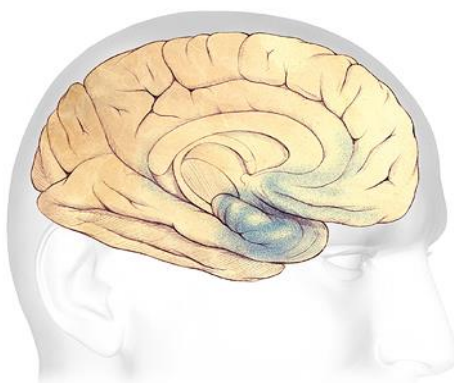


Fig. (6): Earliest Alzheimer's disease

<http://www.alz.org/brain/14.asp>

In the second stage, **the confusion stage**, the patient exhibits time and space disorientation, severe mental confusion and personality changes (Fig. 7).

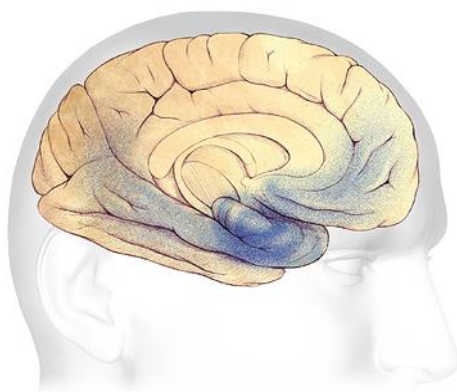


Fig. (7): Mild to moderate Alzheimer's disease

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The last stage, **the dementia stage**, involves the total mental incapacity and full dependence of the patient (**Fig. 8**).

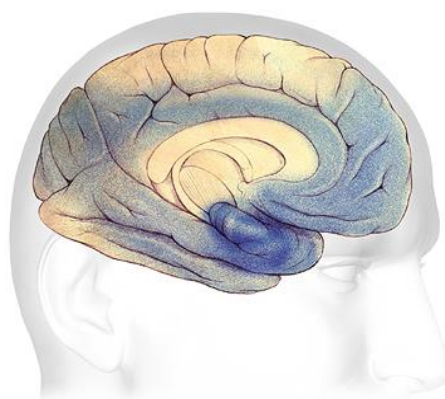


Fig. (8): Severe Alzheimer's disease

<http://www.alz.org/brain/16.asp>

Most relevant pathogenic events in AD can be classified into four main categories. **Primary events:** genetic alterations, neuronal apoptosis-like processes leading to premature neuronal death and brain dysfunction. **Secondary events:** A β deposition in senile plaques and brain vessels, neurofibrillary tangles due to hyperphosphorylation of proteins and synaptic loss. **Tertiary events:** neuroimmune dysfunction, neuroinflammatory processes. **Quaternary events:** accelerated neuronal death due to excitotoxic reactions and cerebrovascular dysfunction (**Barril et al. 2001**).

Apoptosis signal regulating kinase 1 (ASK1) is a mediator of the MAPK pathway, which regulates various cellular responses such as apoptosis, cell survival, and differentiation. Accumulating evidence indicates that ASK1 plays a key role in the pathogenesis of neurodegenerative disorders such as Huntington's disease and AD. Of particular interest,

ASK1 is associated with many signaling pathways, which include endoplasmic reticulum (ER) stress-mediated apoptosis, A β -induced neurotoxicity, tau protein phosphorylation, and insulin signal transduction. Here, we review experimental evidence that links ASK1 signaling and AD pathogenesis and propose that ASK1 might be a new point of therapeutic intervention to prevent or treat AD (Song et al., 214).

Diagnosis of Alzheimer's disease (<http://www.naturalhealthvillage.com/ML250FA-REP.2007>).

- 1- The diagnosis of AD is based mainly on the clinical picture of the disease, so the physicians have to confirm the presence of memory impairment and one or more of the following four cognitive deficits: 1.) apraxia (impaired ability to carry out certain motor activities), 2.) aphasia (language impairment), 3.) agnosia (failure to recognize or identify objects in the environment) and 4.) impairment in executive functioning (the ability to plan, organize, sequence and abstract). Physicians need to confirm that these deficits are not caused by other central nervous system conditions such as Parkinson's disease, cerebrovascular disease, brain tumor, Huntington's disease, or others.
- 2- Lumbar puncture if a chronic central nervous system infection is suspected.
- 3- Standard laboratory tests in patients presenting with suspected AD include complete blood cells counts, serum electrolyte levels, glucose levels, kidney function tests, liver tests, thyroid tests, HIV test, syphilis test, and serum vitamin B12, folic acid and homocysteine levels.
- 4- A computed tomography scan or magnetic resonance imaging may also be performed to rule out mass lesions, hydrocephalus and to confirm the presence of the atrophy of brain tissue associated with Alzheimer's disease (Figs. 9,10).

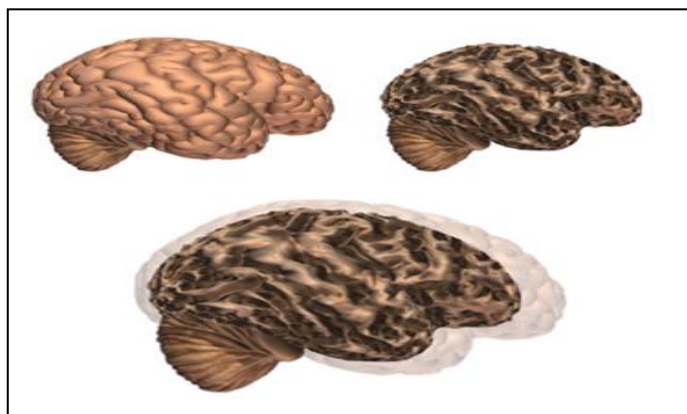


Fig. (9): Atrophy of brain tissue

<http://www.alz.org/brain/8.asp>

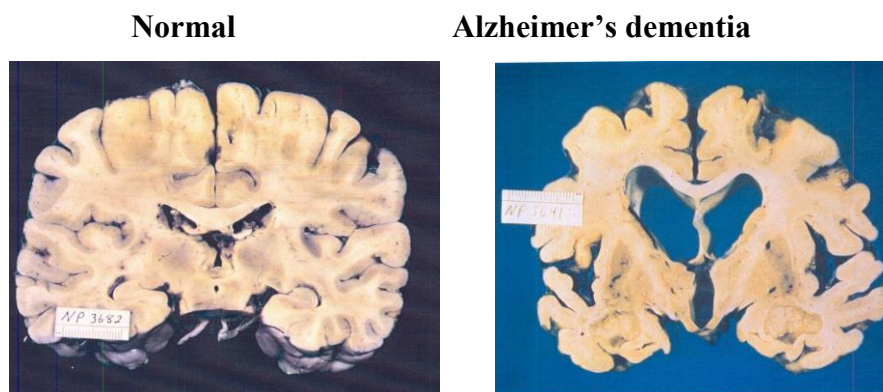


Fig. (10): Sections of normal brain tissue and one from Alzheimer's dementia

<http://alzheimers.about.com/library/blbrain.htm>

5- The electroencephalogram (EEG) is a useful tool in the diagnosis of Alzheimer's disease. Patients with the disease have a diffuse and symmetrical slowing of the brain waves that register on the EEG.

6- Hair mineral analysis may also be done to evaluate the levels of heavy metals.

Alzheimer's disease and hormones

Dysregulation of the hypothalamic pituitary gonadal (HPG) axis during aging has been associated with the risk of cognitive decline and developing AD (**Verdile et al., 2008**). The hormones of the HPG axis include gonadotropin-releasing hormone (GNRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, progesterone, testosterone, activin, inhibin, and follistatin. Each of these hormones is involved in regulating reproductive function by participating in a complex feedback loop that is initiated by the hypothalamic secretion of GNRH (**Genazzani et al., 1992**). GNRH stimulates the anterior pituitary to secrete the gonadotropins, LH and FSH. Then, these gonadotropins bind to receptors on the gonads and stimulate oogenesis/spermatogenesis as well as the production of the sex steroids. Sex steroids complete the negative feedback loop by decreasing gonadotropin secretion from the hypothalamus and pituitary gland. Menopause/andropause shifts the balance of the HPG axis feedback loop and this shift leads to an increase in the production of gonadotropins. In women, these changes can be attributed to the loss of negative feedback by estrogen (**Couzin et al., 1993**) and result in a 3-4-fold increase in the concentration of serum LH and a 4-18-fold increase in the concentration of serum FSH (**Chakravarti et al., 1976**). Likewise, men also this played a greater than 2- and 3-fold increase in LH and FSH, respectively, as their reproductive function deteriorates during andropause (**Neaves et al., 1984 ; líviaRobusto-Leitao and Ferreira, 2006**).

1- Gonadotropins

Barron et al. (2006) reported that, in addition to the classical role of gonadotropins as a modulator of sex hormone production, it is now becoming apparent that the gonadotropins may have actions within the central nervous system. Evidence is also mounting that age-related increases in levels of the gonadotropins may exert neurodegenerative effects such as those seen in AD. Evidence in the literature suggested that gonadotropins may be involved in processes that contribute to the etiology/pathogenesis of AD such as inflammation, cholesterol homeostasis, and insulin status. Furthermore, there is growing evidence supporting a role of gonadotropins, particularly LH, in the pathogenesis of AD, beginning with the finding of a 2-fold increase in circulating gonadotropins in individuals with AD compared with age-matched control individuals (**Bowen et al., 2000; Short et al., 2001**).

Potential progressive involvement of LH and testosterone in the early preclinical stages of AD was detected. Furthermore, these hormones should be considered while attempting to predict AD at the early stages of the disease (**Verdile et al., 2014**).

1.1 Luteinizing hormone (LH)

Despite the increase of both LH as well as FSH in the serum of AD patients, only LH receptors have been detected in the brain and the highest density of which are found within the hippocampus (**Lei et al., 1993; Casadesus et al., 2006C**). Furthermore, LH was significantly elevated in vulnerable neuronal populations in individuals with AD compared to age-matched controls (**Bowen et al., 2002**). Notably, such increases in neuronal LH appear to be a very early change in disease history serving to predict the neuronal populations at risk of degeneration and death. In fact, the elevations in LH parallel the ectopic expression of neuronal cell cycle and the oxidative markers, which represent the initiating pathological changes preceding neuronal degeneration (**Harris et al., 2000; Nunomura et al., 2001; Ogawa et al., 2003**). Furthermore, while LH did not alter APP expression as in the study of **Bowen et al. (2004a, 2004b)** using M17s, a neuroblastoma cell line, this hormone did alter APP processing toward the amyloidogenic pathway as evidenced by increased secretion and insolubility of amyloid and decreased levels of soluble APP_α. This event is greatly supported by the study of **Verdile et al. (2008)**. Further, LH may also play a role in regulation of Aβ levels through changing expression of presenilins, which are important mediators of Aβ production (**Barron et al., 2006**).

Casadesus et al. (2007) examined hippocampal-associated cognitive performance, as measured with the Y-maze task, in two strains of transgenic mice, one (Tg-LHbeta) which over-expresses LH and another (LHRKO) which has increased circulating LH levels, but its receptors are silenced. Their results demonstrated that Tg-LHbeta, but not LHRKO mice, show decreased Y-maze performance when compared to aged-matched wild-type animals. These findings indicated that increased LH levels, in the presence of functional receptors may, at least in part, be responsible for cognitive decline after menopause. Therefore, LH could be an important causative factor in the development of AD (**Gregory et al., 2006; Verdile et al., 2014**).

1.2. Follicle stimulating hormone (FSH)

Similarly, FSH was found to be significantly higher in patients with AD than controls (**Short et al., 2001**). This could be a result of falling estrogen levels after menopause, as estrogen has been shown to lower circulating levels of LH and FSH. It was further hypothesized that elevated FSH levels may have a role in A β protein production. It is plausible, therefore, that elevated FSH levels may contribute to the pathogenesis of AD (**Tsolaki et al., 2005; liviaRobusto-Leitao and Ferreira, 2006**).

2. Estrogen

It has been known for over a quarter of a century that estrogen influences numerous aspects of brain structure and function. These hormones are synthesized not only by ovaries, but also by glia in central nervous system (CNS) and Schwann cells in peripheral nervous system. Therefore, they create microenvironment having a wide spectrum of effects such as neuroprotective and antiapoptotic or supporting neurogenesis and regeneration (**Malinowska-kolodziej et al., 2006**). Estrogen replacement therapies have been extensively studied as a way to improve the cognition and to lower the risk of AD. Aromatase enzyme is a key player in this context as it controls estrogen biosynthesis and, therefore, it may exert neuroprotective effects via increasing the local estrogen levels in injured neurons. Consistent with this idea, brain injury in mice and rats rapidly up-regulates aromatase enzyme expression in glial cells at the injury site suggesting that aromatase may be involved in protection of injured neurons through increased estrogen levels (**Hiltunen et al., 2006**).

Estrogen receptors (ERs) have been found in the hypothalamus, the pituitary and the hippocampus (**Pfaff, 1980**) and thus estrogens may play a central protective role against AD (**Smith et al., 2003; Webber et al., 2004; Webber et al., 2007**). **Sundermann et al. (2006)**

suggested that benefits of estrogen replacement therapy could help to ameliorate the earliest symptoms of AD, olfactory dysfunction, and memory impairment. Moreover, **Carroll et al. (2007)** mentioned that in gonadally intact female triple transgenic mouse model of AD (3xTg-AD), AD-like neuropathology was apparent by 3 months of age and progressively increased through age 12 months, a time course that was paralleled by behavioral impairment. Ovariectomy-induced depletion of sex steroid hormones in adult female 3xTg-AD mice significantly, increased A β accumulation and worsened memory performance. Treatment of ovariectomized 3xTg-AD mice with estrogen prevented these effects.

Xu et al. (2006) reported that estrogen replacement therapy (ERT) at an early stage, especially when given prior to menopause, reduced the risk of AD in postmenopausal women. Experimental study of **Sohrabji (2007)** supported this event in young animals.

Estrogen affects a wide variety of cellular processes that can protect neuronal health. One of its protective effects is maintaining the integrity of the blood-brain barrier. Multiple lines of evidence have proven the neuroprotective effects of estrogen, via enhancing neurotrophin signaling and synaptic activities related to memory functions and protecting neurons against oxidative injuries and A β toxicity. **Viña et al. (2007)** stated that A β caused intracellular toxicity *via* the increased production of oxidant species. Reactive oxygen species generated by mitochondria act as a signal to start the mitochondrial apoptotic pathway. Indirect evidence shows that estrogenic compounds may increase the expression of antioxidant enzymes, leading to a lowering of oxidative stress and thus protection against intracellular toxicity of A β peptide. In addition, estrogen decreased generation and secretion of A β peptides in cultured cells and primary neurons *in vitro*. Moreover, the administration of estrogen in estrogen-deprived mice reversed the elevated levels of brain A β . Estrogen could increase the intracellular trafficking of APP and hence reduce maximal A β generation within the trans-Golgi network (TGN), a subcellular compartment in which APP is known to be cleaved by the secretase enzymes to generate A β (**Xu et al., 2006**). Also, the beneficial effect of estrogen on aspects of cognition in women includes its ability to increase the concentration of choline acetyltransferase, the synthetic enzyme for acetylcholine (**Luine et al., 1975**).

Morinaga et al. (2007) examined the effects of estrogen (estrone (E1), estradiol (E2), and estriol (E3) and related sexual steroids androstenedione (AND) on the polymerization, extension and destabilization of beta-amyloid fibrils [fA β (1-42) and fA β (1-40)] *in vitro*, using fluorescence spectroscopic analysis and electron microscopic studies. E1, E2 and E3

dose-dependently inhibited the formation as well as destabilization of $\text{fA}\beta$. The overall anti-amyloidogenic activity of these molecules was in the order of: $\text{E3} > \text{E2} = \text{E1} > \text{AND}$.

Interestingly, progesterone significantly reduced tau hyperphosphorylation when administered both alone and in combination with estrogen. Estrogen and progesterone independently and interactively regulate AD-like neuropathology and suggested that an optimized hormone therapy may be useful in reducing the risk of AD in postmenopausal women (**Carroll et al., 2007**).

Progesterone is commonly considered as a female reproductive hormone and is well-known for its role in pregnancy. It is less appreciated that progesterone and its metabolite allopregnanolone are also male hormones, as they are produced in both sexes by the adrenal glands. In addition, they are synthesized within the nervous system. Progesterone and allopregnanolone are associated with adaptation to stress, and increased production of progesterone within the brain may be part of the response of neural cells to injury. Progesterone receptors (PR) are widely distributed throughout the brain, but their study has been mainly limited to the hypothalamus and reproductive functions, and the extra-hypothalamic receptors have been neglected. This lack of information about brain functions of PR is unexpected, as the protective and trophic effects of progesterone are much investigated, and as the therapeutic potential of progesterone as a neuroprotective and promyelinating agent is currently being assessed in clinical trials. The little attention devoted to the brain functions of PR may relate to the widely accepted assumption that non-reproductive actions of progesterone may be mainly mediated by allopregnanolone, which does not bind to PR, but acts as a potent positive modulator of γ -aminobutyric acid type A (GABAA) receptors (**Schumacher et al., 2014**).

3. Androgen

The hippocampus is integral for normal spatial learning and memory (**Nadel and Moscovitch, 2001**). It is a target structure for gonadal steroids (**Juraska, 1991; Roof and Havens, 1992**) with a relatively high concentration of androgen receptors (**Kerr et al., 1995**) suggesting a likely relationship between androgen receptors (AR) and hippocampus-dependent cognition.

Beneficial actions of androgens such as neuron viability and modulation of $\text{A}\beta$ levels support the hypothesis that age-related androgen depletion by aging may increase the risk of

developing AD (Gillet et al., 2003). Several studies have identified androgens as endogenous regulators of A β (Gouras et al., 2000; Gandy et al., 2001; Gillett et al., 2003; Rosario et al., 2006). The mechanism(s) by which androgens regulate A β is not known, but presumably involves one or more of three general pathways; direct actions through AR-dependent pathways, indirect actions through estrogen pathways via testosterone aromatization to estradiol, indirect actions through gonadotropin pathways via testosterone modulation of the hypothalamic–pituitary–gonadal axis (Fig. 11).

Decreases of the sex steroids, testosterone and estrogen, are associated with increased risk of Alzheimer's disease. Testosterone and estrogen supplementation improves cognitive deficits in animal models of Alzheimer's disease. Sex hormones play a role in the regulation of amyloid- β via induction of the amyloid- β degrading enzymes neprilysin and insulin-degrading enzyme. To mimic the effect of dihydrotestosterone (DHT), we administered a selective androgen receptor agonist, ACP-105, alone and in combination with the selective estrogen receptor β (ER β) agonist AC-186 to male gonadectomized triple transgenic mice. We assessed long-term spatial memory in the Morris water maze, spontaneous locomotion, and anxiety-like behavior in the open field and in the elevated plus maze. We found that ACP-105 given alone decreases anxiety-like behavior. Furthermore, when ACP-105 is administered in combination with AC-186, they increase the amyloid- β degrading enzymes neprilysin and insulin-degrading enzyme and decrease amyloid- β levels in the brain as well as improve cognition. Interestingly, the androgen receptor level in the brain was increased by chronic treatment with the same combination treatment, ACP-105 and AC-186, not seen with DHT or ACP-105 alone. Based on these results, the beneficial effect of the selective ER β agonist as a potential therapeutic for Alzheimer's disease warrants further investigation (George et al., 2013).

1- Androgen regulation of A β through direct androgen pathways

A β levels revealed significant increase following gonadectomy (GDX) and this effect was completely blocked by dihydrotestosterone (DHT) treatment (Ramsden et al., 2003b). Because DHT is not aromatized to estradiol, these data indicated that the mechanism is independent of ER α and likely involves AR. However, recent observations of Lund et al. (2006) demonstrated that the DHT metabolite 5 α -androstane-3 β ,17 β -diol can act as an agonist for estrogen receptor β (ER β) leaving open the possibility that DHT actions may be mediated indirectly through ER β . However, in the Ramsden et al. (2003b) study, the treatment of

gonadectomized male rats with estradiol did not reverse the GDX-induced elevation in A β , suggesting that androgen rather than estrogen pathways regulate A β levels. In a recent study by **Rosario et al. (2006)** about androgen regulation of neuropathology in male 3xTg-AD mice, it has been found that DHT blocked increased A β accumulation resulting from GDX. Initial evidence suggests that estradiol treatment of GDX male 3xTg-AD mice can partially reduce A β accumulation in a region-specific manner. Recent cell culture studies have identified a novel AR-dependent mechanism in which androgens reduce A β levels by increasing expression of neprilysin, an important A β -catabolizing enzyme (**Rosario and Pike, 2008**).

2. Androgen regulation of A β through estrogen pathways

Similar to androgens, estrogens have also been found to be endogenous regulators of A β . In cell culture models, 17 β - estradiol has been shown to reduce A β levels directly by assay of soluble A β or indirectly as evidenced by demonstration of increased levels of sAPP α , a proteolytic product of nonamyloidogenic APP metabolism (**Xu et al., 1998; Vincent and Smith, 2000**). These studies indicated that estrogen regulation of A β is likely mediated by regulation of APP processing and/or APP trafficking (**Greenfield et al., 2002**) and perhaps through activation of mitogen-activated protein kinase-signaling (MAPK) pathway (**Manthey et al., 2001**). Although the precise mechanism remains to be fully elucidated, cell culture studies suggested that estrogen modulates A β levels by regulating its production from APP. The study of **Huang et al. (2004)** indicated that estrogen may increase the activity of the A β -catabolizing enzyme neprilysin, suggesting a possible effect of estrogen on A β clearance rather than on A β production.

3. Androgen regulation of A β through gonadotropin pathways

In addition to direct activation of AR-dependent signaling and indirect activation of estrogen pathways, androgens may affect A β levels indirectly by regulation of the HPG axis and the gonadotropin LH. Testosterone loss results in diminished negative feedback on the HPG axis that leads to elevated LH levels theorizing that it participates in increasing risk of AD (**Casadesus et al., 2004**). Consistent with this idea, recent data demonstrated that treatment of female mice with the GnRH agonist, leuprolide acetate, which presumably suppressed LH levels, results in reduced levels of A β (**Bowen et al., 2004b**). In a transgenic mouse model of AD, 3 months treatment with leuprolide acetate resulted in a decreased A β accumulation and a reduction in cognitive impairments (**Casadesus et al., 2006b**).

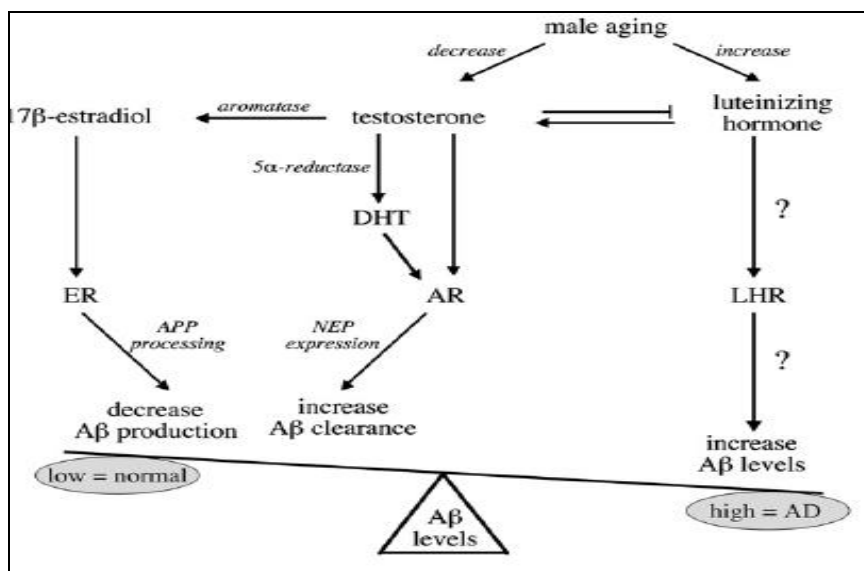


Fig. (11): Androgen regulation of A β may involve three general pathways. Aging decreases testosterone, which can reduce A β levels directly by androgen receptor (AR)-dependent regulation of the A β -catabolizing enzyme neprilysin (NEP) and indirectly by aromatization to 17 β -estradiol, which has been shown to reduce amyloidogenic processing of the A β precursor protein (APP). Through regulation of the hypothalamic-pituitary-gonadal axis, age-related testosterone depletion also elevates LH levels, which have been associated with increased A β by an incompletely defined mechanism that may include the LH receptor (LHR). (Rosario and Pike, 2008)

3.1. Testosterone

Recently, testosterone and its effects on the nervous system have received attention in the area of research on age-related cognitive decline and AD (Driscoll and Resnick, 2007). Testosterone undergoes a gradual but steady age-related decline with a loss of 100ng/dl per decade (Morley et al., 1997). There is an evidence suggesting that testosterone loss constitutes a risk for cognitive decline and possibly AD (Rosario et al., 2006) and those elderly men might benefit from exogenous supplementation of testosterone. Testosterone upregulates AR messenger RNA and increases nerve growth factor (NGF) levels in the hippocampus and nerve growth factor receptors (NGFR) in the forebrain (Tirassa et al., 1997) which seem to play a role in promoting fiber outgrowth and sprouting and in turn may aid in recovery after brain injury (Morse et al., 1992). Studies in non-human animals repeatedly report neuroprotective properties of testosterone and enhanced memory performance after acute or chronic treatment. Effects of testosterone supplementation in older men have reported in several but not all studies (Driscoll and Resnick, 2007). The study of Rosario et al. (2006) on adult male 3xTg- AD mice showed that in comparison to gonadally

intact 3xTg-AD mice, gonadectomized mice exhibited robust increases in the accumulation of A β in both hippocampus and amygdala. In parallel to elevated levels of A β , gonadectomized mice exhibited significantly impaired spontaneous alternation behavior, indicating deficits in hippocampal function. Importantly, DHT treatment of GDX 3xTg-AD mice for 4 months attenuated both A β accumulation and behavioral deficits (**Fig. 12**). Furthermore, testosterone inhibits expression of A β in the rat brain (**Gouras et al., 2000**) reduces A β -induced neurotoxicity in culture (**Pike, 2001**), prevents hyperphosphorylation of tau (**Papasozomenos, 1997**), and protects against oxidative stress (**Ahlbom et al., 2001**) and apoptosis (**Hammond et al., 2001**). These data demonstrated that testosterone depletion accelerates the development of AD-like neuropathology, suggesting that a similar mechanism may underlie the increased risk for AD in men with low testosterone. In addition, their finding that DHT protected against acceleration of AD-like neuropathology predicts that androgen-based hormone therapy may be a useful strategy for the prevention and treatment of AD in aging men.

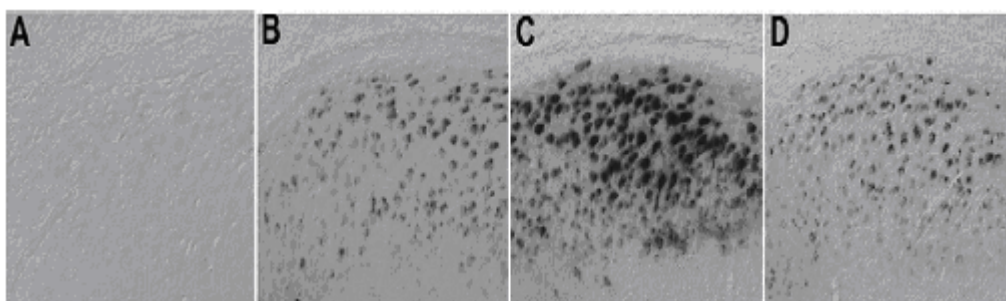


Fig. (12): Androgen regulates accumulation of A β in the triple transgenic model of AD (3xTg-AD). Immunostaining with anti-A β antibodies in adult (age 7 months) male mice shows absent A β immunoreactivity in subiculum of wild-type mice (A), but significant intracellular accumulation in 3xTg-AD mice (B). 3xTg-AD mice that were androgen depleted by gonadectomy (GDX) at age 3 months show a robust increase in A β accumulation at age 7 months (C), an effect prevented by DHT treatment beginning immediately after GDX(D) (Rosario and Pike, 2008)

Clinical studies on men showed that administration of testosterone for 3 months to healthy old men results in enhancement of spatial cognition but no change in other cognitive domains (**Janowsky et al., 1994**). A similar positive effect of testosterone for 6 weeks as compared to placebo on spatial memory and spatial ability in normal old men has been reported by **Cherrier et al. (2001)**. Recent clinical trials suggested that testosterone can improve cognitive function in andropause. Although such improvement in cognitive function is subtle, patients on testosterone replacement therapy have reported memory improvements in both

declarative and procedural domains (**Fuller et al., 2007**). Only a small number of supplementation trials in men with mild cognitive impairment (MCI) or AD have been reported. When ten male AD patients were given testosterone (200mg) every two weeks and tested on a battery of cognitive tests at baseline, 3, 6, and 9 months, cognitive improvement, especially in visuo-spatial ability, was noted at all the time points examined compared to baseline and to the placebo group (**Tan and Pu, 2003**). The efficacy of 6 weeks testosterone supplementation on cognition in a sample of men with AD (N=15) or MCI (N=17) found improvements in spatial memory, constructional abilities, and verbal memory (**Cherrier et al., 2005c**).

Pike et al. (2006) reported that there are two candidate mechanisms by which testosterone may affect AD pathogenesis. First, testosterone has been identified as an endogenous regulator of A β . Second, findings from several different paradigms indicated that testosterone has both neurotrophic and neuroprotective functions (**Fig. 13**). It should be kept in mind that testosterone is aromatized to estradiol in both the brain and periphery. Therefore effects of exogenous (or endogenous) testosterone on behavior could be due to direct testosterone effects on specific testosterone receptors in brain or indirectly through estradiol effects. An "experiment of nature" in a man with a genetic aromatase deficiency suggested that some physiological effects of testosterone may indeed be attributable to estradiol (**Carani et al., 1997**).

Butchart et al. (2013) showed that, the levels of sex hormones in men with AD differ from men without AD. Therefore, male sex hormones have been postulated as risk modifiers in AD, possibly through immunomodulatory effects on known inflammatory AD risk factors, such as tumor necrosis factor α (TNF- α). We conducted a cross-sectional study of sex hormones and TNF- α levels in 94 community-dwelling men with AD. Comparisons were made with normal values derived from the literature. Men with AD had lower free testosterone levels than non-AD men and higher luteinizing hormone (LH) levels. Within the cohort of men with AD, there was a positive correlation between LH and TNF- α and this remained significant after correcting for age. These data support the hypothesis that sex hormones and the immune system influence each other in AD. Furthermore, modulatory effects between LH and TNF- α may provide a mechanism for an effect of male sex hormones on AD risk.

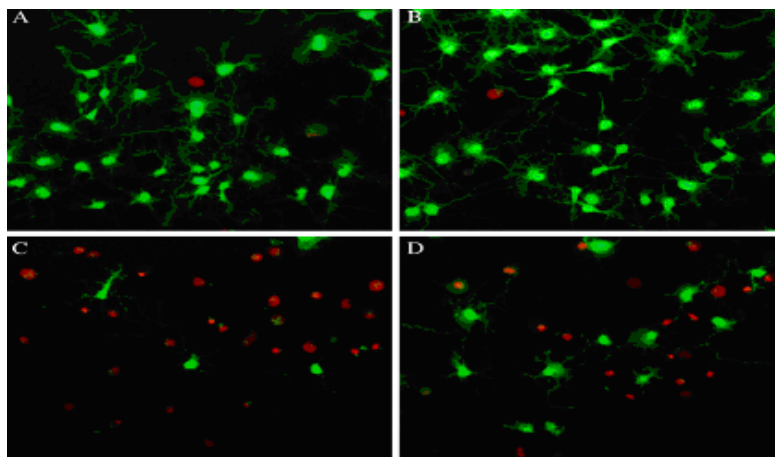


Fig. (13): Testosterone partially protects neurons from A β toxicity. Cultured rat hippocampal neurons were pretreated for 1 hour with 0 nM (A,C) or 10nM testosterone(B,D) then exposed for 24 hours to 0 μ M (A,B) or 25 μ M A β 1-40 (C,D). Images show fluorescent staining of live cells (green) labeled with calcein acetoxymethyl ester and dead cells (red) labeled with ethidium homodimer. The amount of A β -induced cell loss is less in cells treated with testosterone(D) than those treated with vehicle(C) (Pike et al., 2008).

4. Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is the most common hormone in the body. It is found in large quantities in the brain. DHEA levels decrease in the blood and brain with age and are thought to be associated with many of the symptoms of aging. **Farr et al. (2004)** found that chronic oral administration of DHEA sulfate (DHEAS) improves acquisition and retention in aged SAMP8 mice, a model of AD. Therefore, this study suggested an involvement of the age-related decline of DHEAS in the dementia of the Alzheimer's disease type. A case-control study found that subjects with AD had significantly lower levels of DHEAS in the plasma compared to matched healthy controls (**Carlson et al., 1999; Cho et al. 2006**). A study of 52 patients with Alzheimer's disease found that those with higher plasma DHEAS levels scored higher on a variety of cognitive tests than those with lower DHEAS level (**Bastianetto et al., 1999**).

Two separate studies suggested that DHEA can improve memory and enhance cognitive function in elderly persons with cognitive problems (**Kalimi and Regelson, 1990; Hillen et al., 2000**). DHEA has the ability to protect hippocampus from oxidative damage (**Wolkowitz et al., 2003**). DHEA is known to affect N-methyl-D-aspartate (NMDA) receptors (**Bergeron et al., 1996**) and to promote both memory formation (**Flood et al., 1992**) and hippocampal long-term potentiation (**Yoo et al., 1996**). DHEAS has been reported to protect hippocampal neurons against excitatory amino acid-induced neurotoxicity (**Kimondides et al., 1998**). DHEAS may exert some of its effects by acting as an antagonist at the gamma aminobutyric

acid-A(GABA-A) receptor complex (Sousa and Ticku, 1997; Hansen et al., 1999), possibly at the picrotoxin site (Sousa and Ticku, 1997). Peripheral administration of DHEAS can increase levels of acetylcholine in the hippocampus of male rats (Rhodes et al., 1996). This is consistent with the finding that decreasing GABA in the septum increases acetylcholine in the hippocampus (Farr et al., 1999).

Alzheimer's disease is a progressive, yet irreversible, neurodegenerative disease for which there are limited means for its ante-mortem diagnosis. The previously identified a brain- and cell-specific oxidative stress-mediated mechanism for dehydroepiandrosterone (DHEA) biosynthesis present in rat, bovine, and human brain, independent of the cytochrome P450 17 α -hydroxylase/17,20-lyase (CYP17) enzyme activity found in the periphery. This alternative pathway is induced by pro-oxidant agents, such as Fe²⁺ and amyloid- β peptide. Using brain tissue specimens from control and AD patients provided evidence that DHEA is formed in the AD brain by the oxidative stress-mediated metabolism of an unidentified precursor, thus depleting the levels of the precursor present in the blood stream. Serum oxidation resulted in a dramatic increase of DHEA level in control patients, whereas only a moderate or no increase was observed in the AD patients. The DHEA variation after oxidation correlated with the patients' cognitive and mental status. These results suggested that the comparison of serum DHEA levels in patient before and after oxidation could provide a useful diagnose tool for AD (Rammouz et al., 2011).

5. Corticotropin-releasing hormone (CRH)

A neuroprotective action of Corticotropin-releasing hormone (CRH) has come to light because a pathophysiological role for CRH and/or CRH-receptors in a number of neurodegenerative disorders, such as stroke models and ischaemia, has been demonstrated (Lyons et al., 1991; Strijbos et al., 1994). However, evidence for neuroprotective actions of CRH is strengthened by detecting that significant change in CRH concentrations in animal model studies of AD as well as in patients suffering from AD. Specifically, reductions in brain tissue CRH concentration have been detected in frontal and temporal cortex, caudate nucleus, with reciprocal increases of CRH-receptors (Bissette et al., 1985, DeSouza et al., 1986 ; Whitehouse et al., 1987).

Reduced CRH-levels in cerebrospinal fluid (CSF) from AD patients have been detected, and this decrease is even considered to be a surrogate marker for the disease (Mouradian et al., 1986, May et al., 1987 ; Davis et al., 1999). In general, a correlation between CSF-CRH

levels and global neuropsychological impairment ratings has been shown, suggesting that greater cognitive impairment was associated with lower CSF-CRH concentrations (**Pomara et al., 1989**). Furthermore, the rationale that increasing levels of CRH in the brain may be beneficial in treating AD was confirmed when CRH itself, as well as other molecules which displace CRH from its binding molecule, thereby increasing 'free' levels of CRH in the brain, exerted positive effects on learning and memory (**Behan et al., 1995**).

CRH could increase the secretion of sAPP α , in primary cerebellar neurons, in a CRH-R1-dependent manner (**Lezoualc'h et al., 2000**). However, the mechanism by which CRH promotes the α -secretase pathway of APP-processing is so far unknown. CRH action may involve an increase in expression and/or activation of the α -secretase or suppress the activity/expression of the β -secretase. This phenomenon may differ in neurons in different regions of the brain (hippocampus, cerebellum, cortex), considering that CRH mediates neuronal survival and induces intracellular signaling in a brain region-specific manner (**Bayatti et al., 2003**).

The tau protein contains a large number of identified phosphorylation sites and several kinases that mediate its phosphorylation (**Geschwind, 2003**). These kinases include cyclin dependent kinase-5 (cdk-5) as well as glycogen-synthase kinase 3 β (GSK3 β). These two kinases can phosphorylate tau at pathological sites. Interestingly, it has been recently identified that CRH is a molecule that inactivates basal levels of GSK3 β in primary neuronal cells (**Bayatti et al., 2003**) and deactivates cdk-5 activity in hippocampal neurons (**Tonelli et al., 2001**). This action of CRH raises the important implications for this hormone to the control of tau phosphorylation and subsequent tangle formation.

Isolation of glucocorticoids (GCs) from adrenal glands followed by synthesis led rapidly to their first clinical application, about 70 years ago, for treatment of rheumatoid arthritis. To this day GCs are used in diseases that have an inflammatory component. However, their use is carefully monitored because of harmful side effects. GCs are also synonymous with stress and adaptation. In CNS, GC binds and activates high affinity mineralocorticoid receptor (MR) and low affinity glucocorticoid receptor (GR). GR, whose expression is ubiquitous, is only activated when GC levels rise as during circadian peak and in response to stress. The mechanisms concerning pulsatile secretory pattern of GCs as well as various processes that tightly control their synthesis *via* hypothalamic-pituitary-adrenal (HPA) axis involving regulated release of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone

(ACTH) from hypothalamus and pituitary, respectively. GR modulates neuronal functions and viability through both genomic and non-genomic actions, and importantly its transcriptional regulatory activity is tightly locked with GC secretory pattern. There is increasing evidence pointing to involvement of GC-GR in neurodegenerative disorders. Patients with Alzheimer's or Parkinson's or Huntington's disease show chronically high cortisol levels suggesting changes occurring in controls of HPA axis. In experimental models of these diseases, chronic stress or GC treatment was found to exacerbate both the clinical symptoms and neurodegenerative processes. However, recent evidence also shows that GC-GR can exert neuroprotective effects. Thus, for any potential therapeutic strategies in these neurodegenerative diseases we need to understand the precise modifications both in HPA axis and in GR activity and find ways to harness their protective actions (**Vyas and Maatouk, 2013**).

6. Glucocorticoids (GCs)

Normally, GCs are required for various bodily functions but their excess is deleterious. Prolonged exposure to high glucocorticoid concentrations has been shown to impair cognitive function and to increase the vulnerability of cerebral neurons for toxic events. Hippocampus, which has the highest density of GC receptors in the brain, is particularly vulnerable to their damaging effects and undergoes reversible atrophy under their influence. Hippocampal atrophy is an initial event for the development of AD. Apart from atrophy, GCs are able to produce a variety of other initial structural and functional changes in hippocampus. GCs could down-regulate GC receptors, leading to disruption in negative feedback loop, alter dendritic morphology and impair axonal transport. Impaired axon transport is probably an initial event that leads to the formation of paired helical filaments (**Dhikav and Anand, 2007**). Additionally, they inhibit insulin-degrading enzyme, which degrades A β ; consequently reducing its clearance (**Landfield et al., 2007**).

Popp et al. (2007) mentioned that hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which results in elevated plasma cortisol levels, is a well-described feature in AD. The mean plasma cortisol concentration was significantly higher in AD patients compared to control subjects. Also, **Hoogendijk et al. (2006)** added that cortisol levels in CSF of AD patients were more than double those of controls. However, the role of cortisol in the pathogenesis of AD remains the subject of controversy (**Swaab et al., 2005**). A more recent longitudinal study has not found elevated baseline plasma cortisol levels in participants with

very mild AD compared to healthy subjects (Csernansky et al., 2006). Popp et al. (2007) found similar CSF cortisol concentrations in mild cognitive impairment and in cognitively healthy controls. These findings indicated that a marked cortisol increase does not arise early in AD. However, increased CSF cortisol was reported as an evidence for HPA axis dysfunction in AD (Swaab et al., 2005; Csernansky et al., 2006).

There is an association between the increased CSF cortisol levels and the presence of the ApoE₄ allele in AD patients (Peskind et al., 2001). Cortisol levels were found to be related to the ApoE genotype with ApoE₄ carriers showing higher levels than non-carriers in AD patients (Peskind et al., 2001; Popp et al., 2007).

In the subjects with dementia, higher plasma cortisol levels were associated with more rapidly increasing symptoms of dementia and more rapidly decreasing performance on neuropsychological tests associated with temporal lobe function. So, higher HPA activity, as reflected by increased plasma cortisol levels, is associated with more rapid disease progression in subjects with Alzheimer-type dementia (Csernansky et al., 2006).

Both clinically healthy elderly subjects and demented patients, particularly those with AD, have significantly higher cortisol levels at night time, i.e. at the moment of the maximal sensitivity of HPA axis to stimulatory or inhibitory inputs when compared to young controls. At the same time, a clear age- and disease-dependent reduction of DHEAS secretion was found. Thus the cortisol to DHEAS molar ratio was significantly higher in healthy old subjects and even more in demented patients, when compared to young controls and significantly linked to both age and cognitive impairment (Magri et al., 2006).

The cause and mechanism of development of Alzheimer's disease (AD) remain unexplained. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis denoted by adrenal cortisol hypersecretion, is a recognised feature of the condition but generally disregarded as causative, due to lack of association between AD and other hypercortisolemic states. However, a meta-analysis of published studies suggests a need for reappraisal. A specific circadian rhythm of cortisol hypersecretion pertains at mild-to-moderate AD stages, entailing increased levels at the circadian peak from a low nadir. This is in contrast to the continuously elevated levels that are characteristic of other hypercortisolemic states, e.g. Cushing's disease or major depression. This previously overlooked detail provides a starting premise here: that equating the form of hypercortisolism in AD with that in other states is inappropriate, as

phasic and chronic elevation elicits different neuroendocrine effects. Given the capacity of glucocorticoids and corticotropin-releasing hormone to induce AD-associated pathologies, suggesting a role for circadian cortisol hypersecretion in the initiation of sporadic AD; and propose a temporal mechanism for AD development featuring neuroinflammation-mediated suppression of central glucocorticoid receptor (GR) signaling. This latter may represent a critical phase in AD development, where the density of functional GR is proposed to underlie the "cognitive reserve". Supporting evidence for this mechanism is drawn from the brain regional locations of AD neuropathologies, and from risk factors for AD development (aging, ApoE-4 genotype, and hypertension). Thus, it is argued that basal hypercortisolemia merits further scrutiny regarding AD causation and development (**Notarianni, 2013**).

7. Growth hormone releasing hormone (GHRH)

Vitiello et al. (2006) provided the first clear evidence that GHRH treatment, with its resultant increases in growth hormone (GH) and insuline-like growth factor-1 (IGF-I) improves the cognitive function of healthy older men and women. They reported that the stimulation of the somatotrophic axis can influence cognition and they employed GHRH to augment the somatotrophic axis. The use of GHRH has several advantages. For one, GHRH, depending on its exact formulation, produces either a brief pulse of GH secretion or a train of pulses generally resembling physiological pulsatile GH secretion, rather than a prolonged rise in GH levels. Also when a secretagogue such as GHRH is used, the normal negative feedback regulation by IGF-I on pituitary GH secretion is preserved, offering at least some relative buffering against overdosing. Thus, GHRH provides a more "normal physiologic" boost to GH secretion than GH itself (**Merriam et al., 2000**).

GHRH treatment was associated with improved performance on a number of cognitive tasks. Six months of GHRH treatment resulted in significant improvement in cognitive functions, particularly those that involve problem solving and psychomotor processing speed and working memory of both healthy old men and women. The pattern of findings revealed that GHRH had no impact on motor reaction time per se. It is of particular interest that novel problem solving, cognitive processing speed and working memory all showed improvement with GHRH treatment, as these are three areas of cognitive function that demonstrated well documented age-related deficits (**Vitiello et al., 2006**).

It is unclear whether the observed effects are the result of increased microvascularity and related changes in cerebral blood flow per se, the direct paracrine actions of IGF-I (via

NMDA receptors) or both (Merriam et al., 2000; Lynch et al., 2001). However, given the density of type 1 IGF-I receptors in cortical areas supporting abilities such as declarative memory, it is conceivable that IGF-I supplementation via GHRH administration is a likely mechanism for these facilitatory effects on cognitive function (Vitiello et al., 2006).

The positive effects of GHRH on cognitive function were unaffected either by gender or by the estrogen status of the women who participated in the study. Further, there was no evidence to indicate that the effect of GHRH treatment was moderated by cognitive capacity, suggesting that GHRH may also improve cognitive function in those populations for whom cognitive function may be impaired, e.g., MCI or AD patients (Vitiello et al., 2006).

In cell cultures, the GHRH analog showed anti-oxidative and neuro-protective properties and inhibited the GHRH-growth hormone-insulin like growth factor axis (Jaszberenyi et al., 2012).

7.1. Growth hormone (GH)

Alzheimer's disease has been traditionally conceptualized as a clinicopathological entity, its definite diagnosis requiring the presence of characteristic pathology together with a dementia clinical picture. The fact that certain AD biomarkers show an acceptable sensitivity and specificity to detect AD pathology has shifted the diagnostic paradigm towards a clinicobiological approach. Neuropathological analysis of AD-affected brains reveals extensive atrophy due to neuronal loss, and accumulation of neurofibrillary tangles and neuritic plaques, surrounded by a tract of neuroinflammation and loss of neurons. Recently, emerging evidence supports the concept that AD is also a disorder of metabolic degeneration. Taken together, the neurochemical changes in the brain from patients with AD indicate multiple disturbances and it seems likely that the changes are secondary to more fundamental changes into the brain. There is a physiological decline of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis with aging and the possibility that the GH/ IGF-I axis is involved in cognitive deficits has been recognized for several years. The IGF-I is a potent neurotrophic as well neuroprotective factor found in the brain with a wide range of actions in both central and peripheral nervous system. IGF-I is a critical promoter of brain development and neuronal survival and plays a role in neuronal rescue during degenerative diseases. The investigations of GH releasing stimulation tests especially to GHRH in AD are equivocal and in some cases contradictory. When a cholinesterase inhibitor as rivastigmine, a drug for AD, is acutely administered the area under the curve of the GH response to GHRH doubled,

showing that rivastigmine is a powerful drug to enhance GH release. Starting with a more accurate diagnosis not of the clinical syndrome, but of underlying molecular defects, that may eventually lead to a personalized, more effective treatment. Hence, the development of novel therapeutic approaches is urgently **needed (Sáez,2012)**.

The central nervous system is a target for GH actions **(Nyberg, 2000)**. GH deficiency is associated with sleep disturbances, memory loss and other cognitive impairments **(McGauley et al., 1990; Hayashi et al., 1992; Rosen et al., 1994)**. In animal models, GH has been shown to protect the brain and the spinal cord from different forms of neurodegenerative stimuli and promote neuronal survival after hypoxic–ischaemic injury **(Scheepens et al., 2001; Nyberg and Sharma, 2002)**. These neuroprotective effects of GH suggested that decreases in the hormonal levels with age **(Lamberts et al., 1997)** may affect the brain and may contribute to the aging-associated deterioration of brain function **(Finch, 2002; Gallagher et al., 2003)**.

The mounting evidence indicated that the decline of cognitive functions with aging is paralleled with the decrease of circulating GH **(Azcoitia et al., 2005)**. GH replacement therapy could improve some of the age-dependent cognitive functions, such as memory, motivation, mental processing speed as well as the behavioral problems in the somatotropin – deficient patients **(Gibney et al., 1999; Stouthart et al., 2003)**.

The study of **Azcoitia et al. (2005)** indicated that GH may protect hilar hippocampal neurons from degeneration associated with aging. The stereological estimation of the total number of hilar neurons revealed that 24 month-old rats that have been treated with GH showed more neurons in the hilus than control animals. The neuroprotective effect of GH was observed in both sexes. They concluded that chronic treatment with GH for 10 weeks, between 22 and 24 months of age, prevented neuronal loss in the hilus in both sexes. Their findings indicated that GH may prevent some of the hippocampal alterations associated with aging, giving further support to the notion that GH is a neuroprotective hormone.

The mechanisms involved in the neuroprotective effect of GH on the hippocampus of old rats remain to be determined. In young animals the neuroprotective effects of GH appear to be mediated, at least in part, by the activation of GH receptors **(Scheepens et al., 2001)**. Furthermore, it is known that GH administration to old rats increases IGF-I expression in the brain **(Lopez-Fernandez et al., 1996)** and activates intracellular signaling pathways involved

in the promotion of neuronal survival in the hippocampal formation (**Frago et al., 2002**). Since IGF-I is a neuroprotective factor for hilar neurons (**Azcoitia et al., 1999; Carro et al., 2001**), the local production of this molecule may mediate neuroprotective effects of GH.

The antioxidant properties of GH have been shown in A β (22–35) model mice, in which malondialdehyde (MDA) increased; reduced glutathione (GSH) remarkably decreased, and the A β -mediated neuron apoptotic events appeared. However, GH by daily intraperitoneal (ip) injection for 7 days, could protect neurons by scavenging free radicals and decreasing lipid peroxidation (**Ling et al., 2007**). It has been demonstrated that GH could regulate cholinergic system and inhibit cell apoptosis by scavenge free radical induced by the aggregated A β , which finally leads to improving learning and memory deficits. This suggests the potential usage of the rhGH in AD patients (**Ling et al., 2007**). However, exogenous high dosage GH injection in healthy elderly subjects or AD patients has potential side effects. Thus, the method for increasing the endogenous GH secretion might be a better alternative (**Khorram, 2001**).

8. Insulin and IGF-1

Emerging evidence suggests that insulin and IGF-1 have important functions in the brain, including metabolic, neurotrophic, neuromodulatory and neuroendocrine actions (**Torres-Aleman, 2000**). Insulin and IGF-1 share a high degree of structural and functional homology and both bind to and activate the receptor of the other, thus sharing several physiological functions.

IGF-1 has well documented neuroprotective effects (**Venters et al., 2001**) and promotes neurogenesis (**Aberg et al., 2000; Trejo et al., 2001**), development, differentiation, synapse formation and glucose utilization throughout the brain (**Venters et al., 2001**).

There is a growing interest in the possible links between impaired insulin signaling and the pathogenesis of AD. Insulin and insulin-signaling mechanisms are important for neuronal survival. Moreover, the neurodegeneration of the central nervous system is associated with the dysfunctional neuronal insulin receptors. Many important components of AD appear to stem from the imbalances in insulin signaling intrinsic to the brain, rather than systemic insulin imbalances, and thus the treatments aimed at redressing insulin imbalances in the brain could be effective therapies (**Revill et al., 2006**).

Clodfelder-Miller et al. (2006) found that insulin deficiency causes rapid and large increases in tau phosphorylation, thereby contributing to the increased susceptibility to AD caused by diabetes. Moreover, **Craft (2007)** mentioned that insulin resistance increases the risk of age-related memory impairment and AD.

Glucose uptake and energy metabolism in the brain are regulated by insulin and IGF (**Rivera et al., 2005**). Recent studies demonstrated progressive deficiencies in brain insulin and IGF production and responsiveness and these abnormalities were correlated to acetylcholine deficiency in AD (**De la Monte and Wands, 2006**).

Increased peripheral insulin is associated with reduced AD-related brain atrophy, cognitive dysfunction, and dementia severity, suggesting that insulin signaling may play a role in the pathophysiology of AD (**Burns et al., 2007**). Also, **Reger et al. (2006)** reported that raising insulin acutely in the periphery and in brain improves verbal memory and that intranasal insulin administration may have therapeutic benefit without the risk of peripheral hypoglycemia. However, **Craft (2007)** showed that raising plasma insulin in humans to levels that characterize patients with insulin resistance increases the levels of A β and inflammatory agents in the brain. These effects may impair memory and induce AD pathology. Therapeutic strategies focused on preventing or correcting insulin abnormalities may thus benefit a subset of adults with age-related memory impairment and AD.

Salkovic-Petrisic and Hoyer (2007) reported that alterations of the brain insulin system in experimental animals resembling those in AD were associated with tau protein hyperphosphorylation and A β -like aggregations in meningeal vessels. They suggested that insulin resistance in the brain might be the primary event which precedes the A β pathology in AD.

Circulating IGF-I enters the brain and promotes clearance of amyloid peptides known to accumulate in AD brains. Both patients and mouse models of AD show decreased level of circulating IGF-I enter the brain as evidenced by a lower ratio of cerebrospinal fluid/plasma IGF-I. Importantly, in presymptomatic AD mice this reduction is already manifested as a decreased brain input of serum IGF-I in response to environmental enrichment. To explore a potential diagnostic use of this early loss of IGF-I input, we monitored electrocorticogram (ECG) responses to systemic IGF-I in mice. Whereas control mice showed enhanced ECG activity after IGF-I, presymptomatic AD mice showed blunted ECG responses. Because nonhuman primates showed identically enhanced electroencephalogram (EEG) activity in

response to systemic IGF-I, loss of the EEG signature of serum IGF-I may be exploited as a disease biomarker in AD patients (**Trueba-Sáiz et al., 2013**).

Insulin, IGF-1 and cerebral amyloidosis

Compelling evidence indicates that insulin and IGF-1 have a direct effect on the metabolism and clearance of A β (**Carro et al., 2002; Adlerz et al., 2007**). The effect of insulin on A β metabolism is far complex. Insulin directly increases A β secretion and decreases the intracellular levels of A β peptides by stimulating their intracellular trafficking in neuronal cultures (**Gasparini et al., 2001**). The recent report by **Carro et al. (2002)** reported that IGF-1 has an important role in regulating A β load and its clearance from the brain. Administration of IGF-1 to aged rats by subcutaneous chronic infusion decreased the levels of A β in brain parenchyma to the levels found in young rats. Importantly, IGF-1 had a similar effect on endogenous A β in a transgenic-mouse model of AD amyloidosis, the Tg2576 mouse (**Hsiao et al., 1996**). Administration of IGF-1 remarkably decreased the levels of A β peptides and reduced fibrillar amyloid deposits in the brain parenchyma of one-year-old Tg2576 mice. These studies provided evidence that the effect of IGF-1 on A β clearance is mediated by enhancing the transport of the A β carrier proteins albumin and transthyretin into the brain through the choroid plexus. Significantly, the increased entrance of albumin and transthyretin after IGF-1 administration was paralleled by increased levels of A β bound to these proteins in the CSF and blood, suggesting that albumin and transthyretin are involved in the transport of A β out of the brain (**Carro et al., 2002; Trueba-Sáiz et al., 2013**).

Insulin, IGF-1 and tau phosphorylation

Insulin and IGF-1 might also influence the development of neurofibrillary tangles, another hallmark of the AD brain. In fact, insulin and IGF-1 regulate the phosphorylation of tau in neuronal cultures (**Lesort and Johnson, 2000**) and in vivo (**Schubert et al., 2003**). Specifically, insulin and IGF-1 reduce tau phosphorylation and promote tau binding to microtubules in human neuronal cultures. These findings indicate that insulin and IGF-1 could play a pivotal role in regulating tau protein phosphorylation and assembly in neurons, suggesting a direct effect of insulin and IGF-1 on neurofibrillary-tangle pathology (**Lesort and Johnson, 2000; Trueba-Sáiz et al., 2013**).

9. Thyrotropin-releasing hormone (TRH)

Evidence for a neuromodulatory role of thyrotropin-releasing hormone (TRH) within the central nervous system has increased considerably over the past 25 years. TRH is associated

with regulation of the hypothalamic–pituitary–thyroid axis but also functions as a neuropeptide in certain key areas of the brain and other neural tissues **(Nillni and Sevarino, 1999; Gary et al., 2003)**. TRH is synthesized in neurons, packaged into and stored in vesicles along with classical neurotransmitters. It is released at synaptic terminals and binds, with high affinity, to specific TRH receptors on neurons **(Nillni and Sevarino, 1999)**. TRH and TRH receptors are found in abundance in certain extrahypothalamic brain loci, particularly in the hippocampus, and it has been suggested to have a potential role in neuromodulation **(Nillni and Sevarino, 1999; Gary et al., 2003)**.

An increasing body of evidence implicated TRH as a neuroprotective agent against AD **(Luo et al., 2002; Reisberg et al., 2003 ; Luo et al., 2006)**, neurotrauma **(Faden et al., 2005)** and brain ischemia **(Urayama et al., 2002)**. **Veronesi et al. (2007)** demonstrated that TRH/analogs facilitate neuronal viability and protect against neuronal overexcitability. This finding supports the previous one of **Jaworska-Feil et al. (2001)** who reported that TRH and RGH 2202, a TRH analog, significantly reduced the effects of kainate-induced excitotoxicity and neuronal loss in two specific regions of the mouse hippocampus. The mechanism of TRH's neuroprotective role in the CNS is not well understood. However, it has been suggested that TRH may act through its own selective G-protein coupled receptor (GPCR) **(Faden et al., 1999)**. In addition, AD was found to be associated with abnormal function of the hypothalamic-pituitary-thyroid axis **(Yong-Hong et al., 2013)**.

9.1. Thyroid stimulating hormone (TSH)

Labudova et al. (1999) reported that thyroid hormone abnormalities are strongly associated with Down Syndrome (DS) with elevated thyroid stimulating hormone (TSH) levels as the most consistent finding. They found significant overexpression of mRNA levels for the thyroid stimulating hormone-receptor (TSH-R) in brain of a fetus with DS. Based upon this observation they determined TSH-R protein levels in five brain regions of patients with DS, AD and controls. These results revealed significantly elevated immunoreactive TSH-R protein(s) 40 kD and 61 kD in temporal and frontal cortex of patients with DS and, unexpectedly, in AD. Their results showed that elevated brain immunoreactive TSH-R is not specific for DS and maybe reflecting apoptosis, a hallmark of both neurodegeneration.

The circadian rhythm of serum TSH levels in AD patients did not appear, and their serum TSH levels were significantly lower than those in normal controls. Thus, the circadian rhythm

in serum TSH a level in AD patients differs greatly from that of the general populationenerative disorders (**Chen et al., 2013**).

9. 2. Thyroid hormones

Clinical thyroid disorders are associated with cognitive impairment and dementia. A very recent study indicated that there is a possible association between AD and thyroid dysfunctions (**Mafrica and Fodale, 2008**). Experimental studies indicated that the thyroid hormones induce changes in amyloid precursor processing or deposition of A β (**Belandia et al., 1998; Latasa et al., 1998**). This suggested that there may be a role for thyroid hormones in the etiology of AD (**de Jong et al., 2007**), but it remains unclear how thyroid function is related to AD. These authors demonstrated that, higher levels of free thyroxine (fT₄) and thyroxine (T₄) are associated with an increased risk for both dementia and AD in their population-based study of very old men. **Stuerenburg et al. (2006)** reported that high levels of plasma fT₄ might result in a worsening of cognitive impairment in AD. T₄ was also associated with more neurofibrillary tangles and neuritic plaques in the cerebral cortex (**Belandia et al., 1998 ; de Jong et al., 2007**).

In addition, **de Jong et al. (2007)** stated that higher thyroid hormone levels are associated with a smaller hippocampal volume which is a putative marker of AD in the Rotterdam Scan Study in subjects who were not demented. The hippocampus is involved in the setting of the basal activity of the thyroid axis through hippocampal-hypothalamic connections. By decreasing thyroid-hormone-releasing hormone gene expression in the hypothalamus, the hippocampus exerts a negative effect on this axis (**Shi et al., 1993**). If the affected hippocampus in AD leads to less feedback on the hypothalamo–pituitary–thyroid axis, higher levels of fT₄ could follow. The finding that higher serum fT₄ levels were associated with smaller hippocampal volumes of non-demented elderly (**de Jong et al., 2006**) may offer support for this hypothesis.

de Jong et al. (2007) suggested that higher thyroid function is a marker of sub-clinical disease rather than causal factor in the development of AD. Sub-clinical dementia might lead to higher thyroid hormone levels through several mechanisms. First, higher T₄ levels may be due to neurodegeneration. Second, higher T₄ levels may result from dementia through concomitant nonthyroidal illness. Evaluation of thyroid function in the elderly is complicated by an increased prevalence of non-thyroidal illness (**Chiovato et al., 1997**) in which thyroid hormone and thyrotropin concentrations are altered, without overt thyroid dysfunction being

present. Also, **Johansson et al.(2013)** found that patients with AD as well as other dementias had signs of mild brain hypothyroidism, which could be only to detected in serum.

10. Melatonin

Wang and Wang (2006) demonstrated that melatonin, an indoleamine secreted by the pineal gland, may play an important role in aging and AD. Under normal physiological conditions during youth, brain tissue contains equimolar levels of melatonin and A β in the dark phase of the circadian cycle (**Pang et al., 1974**). This molar ratio is the optimal one for melatonin to inhibit A β aggregation/fibril formation (**Pappolla et al., 1998**), suggesting that melatonin maintains anti-amyloidogenic environment to prevent A β aggregation/fibril formation.

The level of melatonin in the pineal gland declines progressively with age, and this may contribute to a proamyloidogenic microenvironment in the aging brain (**Shen et al., 2007**). Interestingly, it has been shown that patients with Alzheimer's disease have more profound reduction of this hormone (**Reiter, 1992; Mishima et al., 1994; Magri et al., 1997**).

Melatonin supplementation has been shown to slow down the progression of cognitive impairment in Alzheimer patients. Melatonin not only inhibits A β generation but also arrests the formation of amyloid fibrils by a structure-dependent interaction with A β . Also, melatonin efficiently attenuates Alzheimer-like tau hyperphosphorylation. Although the exact mechanism is still not fully understood, a direct regulatory influence of melatonin on the activities of protein kinases and protein phosphatases is proposed. Additionally, melatonin also plays a role in protecting cholinergic neurons (**Wang and Wang, 2006**).

Melatonin possesses antiinflammatory action, so it could repress proinflammatory factor expressions triggered by A β (**Shen et al., 2007**). Due to its blood-brain barrier penetration, it interacts directly with A β and inhibits spontaneous formation of β -sheets and amyloid fibrils (**Pappolla et al., 1998; Reiter, 1998**). It also improved the impairment of hippocampal and cortical neurons exposed to A β fragment 25–35 (A β 25–35) by inhibition of apoptosis and oxidative stress (**Shen et al., 2002a**).

Naismith et al.(2014) demonstrated that circadian misalignment and sleep disruption is evident in patients with mild cognitive impairment (MCI), and is consistent with changes observed in Alzheimer's disease. Such findings could be a marker for disease trajectory, and may even be implicated in disease pathogenesis

1- Neuroprotective effect of melatonin

Effects of melatonin on neurons, as a neuroprotective agent, are presumably because of the unique character of melatonin, which made it totally different from other agent, such as the high lipid solubility of indoles that allows melatonin to move into the lipid bilayer of cell membranes and gain free access to the interior of the cell (**Shen et al., 2007**). Thus neuroprotective action of melatonin on A β -mediated toxicity do not require binding of melatonin to a membrane receptor (**Pappolla et al., 2002**). It is carried into the ventricular system via choroid plexus portals and passes through cell membranes and inhibits the aggregation and deposition of misfolded A β protein (**Cheng and Van Breemen, 2005; Naismith et al., 2014**).

2- Antioxidant properties of melatonin

Oxidative stress is one of key features in the AD brain, and it has been demonstrated that the micro-aggregated amyloid is sufficient to produce oxidative stress (**Pappolla et al., 1998**). **Praticò et al. (2001)** reported that increased lipid peroxidation precedes amyloid plaque formation in Tg2576 AD transgenic mice, suggesting that brain oxidative stress contributes to A β amyloidosis before its deposition in affected brain. Melatonin has been shown to be a very efficient scavenger of peroxynitrate (ONOO⁻) (**Gilad et al., 1997; Cuzzocrea et al., 1998**), hydrogen peroxide (H₂O₂) (**Behl et al., 1994**), and singlet oxygen (¹O₂) (**Zang et al., 1998**) that have been implicated in the pathogenesis of AD. Among them, ONOO⁻ is the strongest candidate for AD pathology (**Good et al., 1996; Smith et al., 1997**). Melatonin also acts as an indirect antioxidant in that it stimulates several important antioxidant enzymes such as superoxide dismutase or glutathione peroxidase (**Cheng et al., 2006; Naismith et al., 2014**).

3- Anti-amyloidogenic activity of melatonin

The anti-amyloidogenic property of melatonin has been shown via its inhibitory effects on the formation of secondary β -sheet structures through the disruption of the imidazole-carboxylate salt bridges between the side chains of the His⁺ and Asp⁻ residues in A β peptides that are critical to the formation and stabilization of β -sheet structure (**Pappolla et al., 1998**). Thus melatonin could reduce the neurotoxic β -sheet-rich conformer of amyloid peptide (**Simmons et al., 1994; Harrigan et al., 1995**).

Melatonin has been found to have many beneficial effects against AD, including improvement of cognitive function, anti-oxidative injury, anti-apoptosis, inhibition of A β deposition and A β fiber

formation as well as inhibition of tau protein hyperphosphorylation, via inhibition of cyclin-dependent kinases 5 (cdk5). In Alzheimer's disease, these actions may potentially slow down or stop the progression of dementia (**Cheng et al., 2006; Wang et al. 2007; Naismith et al., 2014**).

11. Leptin

Leptin is a protein, secreted predominantly by adipocytes, that regulates appetite, energy balance and neuroendocrine function. It has also been implicated in bone and brain development (**Harvey, 2003**). A growing body of evidence indicates that leptin may play a role in learning and cognition (**Holden et al., 2008**).

Leptin receptors and mRNA are widely expressed in the human brain, including the hippocampus and neocortex (**Funahashi et al., 2003**). A role for leptin in neurogenesis and neurodevelopment is strengthened by the study of **Udagawa et al. (2006)** who demonstrated that leptin stimulates the proliferation of precursor cells committed to neuronal differentiation and promotes neuronal terminal differentiation. Recent work by **Guo et al. (2007)** suggested that leptin serves a neurotrophic function in the developing and adult hippocampus by enhancing mitochondrial resistance to apoptosis and excitotoxicity. Leptin has also been shown to be neuroprotective against ischemic cell injury as well as dopaminergic cell death (**Weng et al., 2007 ; Zhang et al., 2007**).

Aging is associated with declining serum leptin levels, independent of body mass index (BMI), as well as with the development of leptin resistance (**Wang et al., 2001; Ma et al., 2002; Nogalska et al., 2003**). In case-controlled studies, patients with AD have lower leptin levels than controls, also independent of BMI (**Power et al., 2001**). **Holden et al. (2008)** examined the relationship between serum leptin level and cognitive decline in a large population of well-functioning, community-dwelling, elderly individuals. At 5 years, they observed less cognitive decline in individuals with high leptin versus low leptin levels. After adjustment for potential confounding factors, this association remained statistically significant, with the high leptin group nearly 50% less likely to develop cognitive decline compared to the low leptin group.

There is a positive role for leptin in memory and learning processes in rodents. Molecular mechanisms implicated in this process include actions that modulate synaptic plasticity. Genetically obese rodents with dysfunctional leptin receptors had impaired hippocampal long-term potentiation (LTP) and long-term depression (LTD) and performed poorly on

spatial memory tasks (**Li et al., 2002; Gerges et al., 2003 ; Holden et al., 2008**). Moreover, direct administration of leptin into the dentate gyrus enhanced LTP in rats (**Wayner et al., 2004**), while direct leptin administration into the hippocampus improved spatial memory and learning in mice (**Farr et al., 2006**). At the cellular level, leptin has been shown to enhance NMDA receptor function (**Shanley et al., 2001**) possibly through rapid trafficking of NMDA receptors to the plasma membrane (**Harvey et al., 2006**) in a manner analogous to insulin (**Skeberdis et al., 2001**). Thus leptin may enhance memory and learning through mechanisms that modulate synaptic plasticity in the hippocampus (**Shanley et al., 2001; Li et al., 2002**).

In addition to leptin's role in modulating synaptic plasticity, recent work by **Fewlass et al. (2004)** demonstrated that leptin modulates brain A β production and clearance. The modulation of A β production is apparently through a reduction in β -secretase activity, and A β clearance through an increased apolipoprotein-E (ApoE)-mediated clearance of A β fibrils. Moreover, leptin decreased the total brain A β load in rodents by up to 50%. These findings suggest that leptin levels may play a role in the pathogenesis of AD.

The data suggested that plasma leptin deficiency provides an indication of potential CNS leptin deficiency, further supporting the exploration of plasma leptin as a diagnostic marker for MCI or AD. The important question is whether leptin deficiency plays a role in the causation of AD and/or its progression. If this is the case, individuals with early AD or MCI with low plasma leptin may benefit from leptin replacement therapy. Thus, these data indicate that trials of leptin in low leptin MCI/early-stage AD patients should be conducted to test the hypothesis (**Johnston et al., 2013**).

CONCLUSION

In conclusion, hormones have a potential importance in Alzheimer's disease. Some hormones have neuroprotective effects which may help to lower the risk of Alzheimer's disease. Hormonal changes may play a major role in initiation, progression and clinical changes associated with Alzheimer's disease. The frequent co-occurrence of hormonal decline in patients with Alzheimer's disease indicates that such hormonal disturbance could be considered as direct and/or indirect risk factor for this disease. Hormonal profile may be helpful in diagnosis of Alzheimer's disease especially in the presence of confirmed memory impairment and cognitive deficits. Also, hormonal tests may be useful for prediction of Alzheimer's disease in subjects at risk for developing such disease. Hormonal therapy may have a clear positive role in slowing the progression of Alzheimer's disease.

Recommendations

1. Further potentially fruitful directions for new research on the relationship between hormones and Alzheimer's disease must be done.
2. Hormonal profile must be included in the standard laboratory tests in patients presented with suspected Alzheimer's disease.
3. Since one of the hallmarks of Alzheimer's disease is inflammation in the brain, epidemiologic evidence strongly suggests that anti-inflammatory agents and the popular pain relievers including ibuprofen are associated with a decreased risk of Alzheimer's. Studies in animal models of Alzheimer's disease suggest that anti-inflammatory agents can limit plaque production in the mouse brain.
4. It may be advantageous for subjects of age 40 years to increase their physical activity to reduce the risk of Alzheimer's disease since exercise preserves brain blood flow and reduces A β production.
5. Supplementation with antioxidants protects against Alzheimer's disease via reducing oxidative stress through their effects as free radical scavengers. Also, the antioxidant can activate neurons and preserve cellular viability.
6. Eating fish once a week is recommended for reducing the risk of Alzheimer's disease due to its polyunsaturated fatty acids contents. These types of fatty acids may suppress brain inflammation and have a role in brain development and protecting nerve cells degeneration.

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