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Therapeutic Strategies for Ovariectomy-Induced Vascular Dementia: Current Insights and Future Directions

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Abstract

Background: *Ovariectomy-induced vascular dementia (OIVD) is a cognitive disorder that occurs as a result of estrogen deficiency causing neurovascular dysfunction, oxidative stress, neuroinflammation and BBB breakdown. These pathological alterations are related to the development of vascular dementia and this gives evidence to effective treatment strategies. Purpose: The aim of this analysis is to discuss the disease process in OIVD, and examine the use of different forms of treatment, such as hormone replacement therapy (HRT), neuroprotective agents, antioxidants, and lifestyle changes. Other methods of therapy like the stem cell therapy, neurotrophic factors and the aid of gene therapy are also being discussed, which will help alleviate OIVD.*

Procedures: *An extensive literature review was performed and focused on works on mental decline caused by estrogen deficiency and the corresponding therapy. Peer-reviewed journals and clinical trials that tested the efficacy of estrogen replacement methods, antioxidant treatments, neuroprotectants, and regenerative Snyder-Martin medicine as a remedy to OIVD were used to obtain data.*

Findings: *There is a close association between estrogen deficiency after ovariectomy and neurodegeneration and neurocognitive decline. HRT has been successful in easing such symptoms to the extent that it replenishes the estrogen. Several neuroprotective agents, especially the phytoestrogens such as biochanin A have shown effectiveness in enhancing memory by adopting the antioxidant and anti-apoptotic mechanism. Antioxidant treatment of oxidative pathways and lifestyle, including diet changes and physical exercise, are also beneficial, and they assist in managing the disease. Moreover, new medical procedures such as the transplantation of stem cells and the modification of genes provide new opportunities to conduct research in the future on the reversal of disease development rather than its symptoms alone.*

Conclusion: *Estrogen insufficiency is a key problem of management OIVD. The exploratory therapies have the possibility of a broader modification of the disease, compared to traditional therapies, which only provide symptomatic relief. Further studies are needed to define the effectiveness and safety of these new measures.*

Keywords: *Vascular dementia owing to ovariectomy; Deficiency of estrogens; Replacement therapy of hormones; Neuroprotection; Neuroprotection therapy with antioxidants; Neuroscutability or healing with stem cells; Homicidal therapy based on genes.*

INTRODUCTION

Ovariectomy-induced vascular dementia (OIVD) refers to a clinical condition where a decrease in thinking occurs due to the absence of estrogens and the effects it has to the brain blood system. There is a cascade of neurovascular changes that ensues after the sudden decline in estrogen levels due to ovariectomy and this includes oxidative damage, blood-brain barrier (BBB) disruption, and neuroinflammation that work together to initiate and promote vascular dementia [1].

Estrogen is needed to maintain cognitive ability and cerebrovascular health because it enhances cerebrovascular blood flow, reduces oxidative stress, and alters synaptic plasticity and has neuroprotective effects [2]. The loss of estrogen due to ovariectomy agitates these defence mechanisms and raises the production of reactive oxygen species (ROS) and sources oxidative damage to vascular and neural tissue through the facilitation of migration of peripheral immune cells into the CNS and escalation of neuroinflammatory responses and Redox imbalance contributes a principal role in BBB disruption [3]. Initial data support the notion that women who underwent both ovaries removal prior to natural hormone replacement therapy (HRT) are at greater risk of memory loss and early onset dementia this suggests the crucial role of naturally occurring estrogen in brain maintenance, especially, prior to age fifty on the one hand, beginning ET after age fifty and shortly after Menopause is associated with a lower risk or may even improve the risk of developing Alzheimers-related dementia, on the other hand [4,5. Such results support the significance of the so-called critical period when estrogen activates its neuroprotective functions, which ensures the fact that the manifestation of adverse cognitive effects of estrogen deficiency can be partially reduced through adequate intervention at the opportune time.

Next to hormonal treatment, non-pharmacological measures comprising diet and physical activities have also been tested to assess their capacity in reducing memory performance during menopause among women. The consumption of a mediterranean diet has been linked with the improvement of cognitive functions, it is defined by a superior consumption of fruits, vegetables, nuts, and olive oil [6]. Frequent sports activities are also associated with reduced incidence of cognitive decline, and it can be assumed that changes in lifestyles will be significant with regard to the prevention of cognitive health in the context of estrogen insufficiency [7].

New treatment strategies are also under exploration in an attempt to improve the multifactorial pathophysiology of OIVD. An example of this modified therapy is stem cell therapy which was successful in preclinical work making it appear promising by facilitating the growth of new neurons and improved cognitive functioning [8]. Choline acetyltransferase-overexpressing neural stem cells have been shown to enhance learning and memory deficiency in ovariectomized animal study models and offers a possible future treatment pathway [9]. Besides, phytoestrogen, biochanin A, has also shown its viability as an aid in learning and remembering because of its beneficial antioxidant and anti-apoptotic effects under an absence of estrogen conditions which makes it a possible candidate in the treatment of memory loss in post menopausal females [10]. Advanced neurotrophic factor and gene therapy methods also present promise of being able to improve neuronal survival and functionality with a hope that better modes of intervention of OIVD would be developed focusing on the same (Fig. 1)[11].

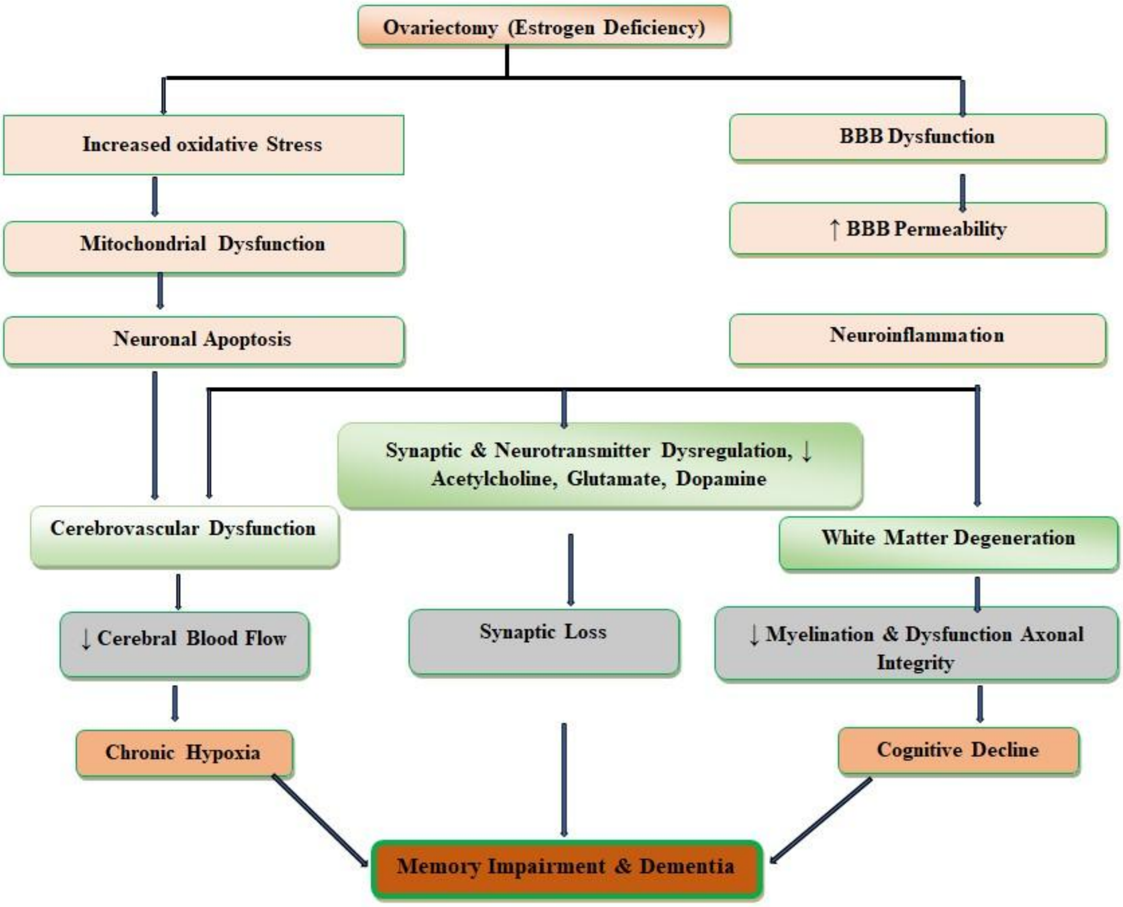

Fig 1: Memory Impairment & Dementia

2. Pathophysiology of Vascular Dementia associated with Ovariectomies (OIVD)

Its pathophysiology boils down to a complicated interplay between oxidative stress, inflammation, BBB dysfunction and cerebrovascular impairment.

2.1. Hormonal imbalance & Neurovascular malfunction

Evidence suggests that estrogen is important in protecting cerebrovascular integrity and neuronal functioning and deficiency induces severe neurovascular dysfunction following ovariectomy. Endothelial nitric oxide synthase (eNOS) is controlled by estrogen and this process is required to retain vasodilation and cerebral blood flow (CBF) [12]. The deficiency of estrogen interferes with this process and as a consequence of this reduction of vasodilation, stiffness of the vessels and impaired endothelium occurs [13]. Consequently, the brain is subjected to chronic hypoperfusion leading to degeneration of the neurons and deterioration of cognition. Also, estrogen insufficiency elevates the degree of oxidative stress because it decreases the activity of antioxidant enzymes and leads to the accumulation of ROS. Such ratio of permeability is also an aggravating factor in neuroinflammation and white matter degeneration, features of vascular dementia [14]. Moreover, estrogen has an influence on neurotransmitter communication systems, specifically, acetylcholine, dopamine, and serotonin, that play a role in learning, memory, and mood management [15]. With this deficiency of estrogens, these neurotransmitter pathways are disrupted resulting in synaptic dysfunction and poor communication amid the neurons, which further enhance the process of decay of cognitive abilities [16]. In general, estrogen deficiency initiates a cascade of neurovascular alterations that comprises cerebrovascular dysfunction, oxidative stress, the breakdown of the blood-brain barrier and neurotransmitter abnormalities[17,18].

2.2. Neuroinflammation and Oxidative Stress

Estrogen is critical to maintaining cerebrovascular health and aiding correct neuronal functioning. A decrease in it after ovariectomy may result in significant neurovascular dysfunction[19.20]. Discussing its major functions, one of them is the regulation of endothelial nitric oxidase synthase (eNOS) that is important in vasodilation and sufficient CBF. The presence of this regulatory mechanism occurs when the levels of estrogen fall, and a subsequent lessened vasodilation and augmented vascular stiffness and endothelial dysfunction are the repercussions[21]. This can result in chronically under perfused brain, as a result of which there is neuronal damage and gradual cognitive decline. Further, the loss of estrogens promotes the oxidative stress reducing the antioxidant enzyme activities and helps the buildup of ROS[22]. This oxidative load elevates permeability of the BBB to hyperinflate neuroinflammation and the degeneration of white matter, two hallmarks of vascular dementia. This is also because of the role of estrogen in neurotransmitter systems and especially the acetylcholine, dopamine, and serotonin which are essential to memory, mood and cognitive performance. Reductions in estrogen interfere with these pathways resulting in poor synaptic transmission and neuronal signalling thus increasing the rate at which a person undergoes cognitive decline. Overall, vascular dysfunction, oxidative stress, breakdown of the BBB, and neurotransmitter dysregulation are a chain of neurovascular disfunctions initiated by the lack of estrogen.

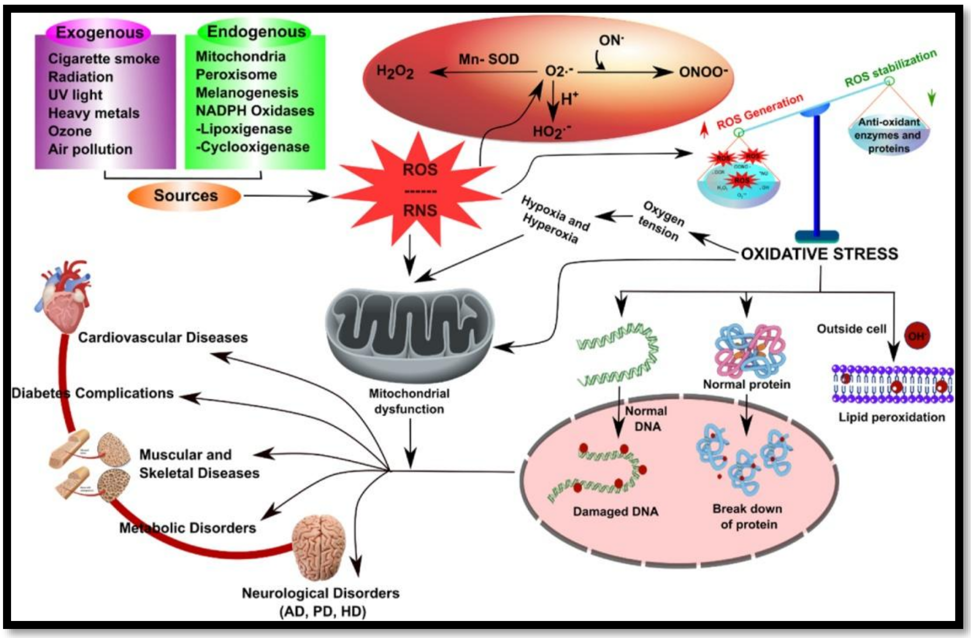

Fig 2: Oxidative stress and inflammation in the pathogenesis of neurological disorders [23]

2.3. Blood-Brain Barrier (BBB) Disruption

The BBB acts as a discriminatory passage that regulates the entry of vital nutrients towards the center of the nervous system (CNS) and prevents the invasions of potentially toxic materials [24]. Estrogen plays an essential role in ensuring the integrity of this barrier as it regulates the expression of tight-junction proteins including occludin, claudin-5 and ZO-1, the proteins that maintain the functional integrity of the barrier, and the integrity of the vascular leak. Ovariectomy leads to an estrogen deficiency resulting in the structural and functional compromise of the BBB [25]. This disturbance in hormonal balance favours the emergence of oxidative stress and stimulates inflammatory processes in weakening the barrier. Without the protective, anti-inflammatory effects of estrogen, astrocytes and microglia, and other glia, become activated in order to release inflammatory cytokines, such as TNF-alpha, IL-1, and IL-6 [26]. These pro-inflammatory molecules also compromise tight junctions permitting entry of immune cells and neurotoxic molecules towards the brain, which worsen neuroinflammation, and quicken neuronal death [27]. Moreover, BBB disruption in OIVD deteriorates the CBF regulation, resulting in hypoxia and the white damage and this is one of the major factors contributes to the vascular dementia [28]. The passage of flowing amyloid-beta (A o beta) peptide through BBB is increased, which also contributes to the development of neurotoxic plaques, in turn, spurring cognitive losses [29]. The disturbance of the BBB functionality in OIVD explains that early interventional measures or treatments may include the application of the therapy of estrogens, antioxidants, and anti-inflammatory medications to preserve the cerebral vascular system and minimize cognitive dysfunction.

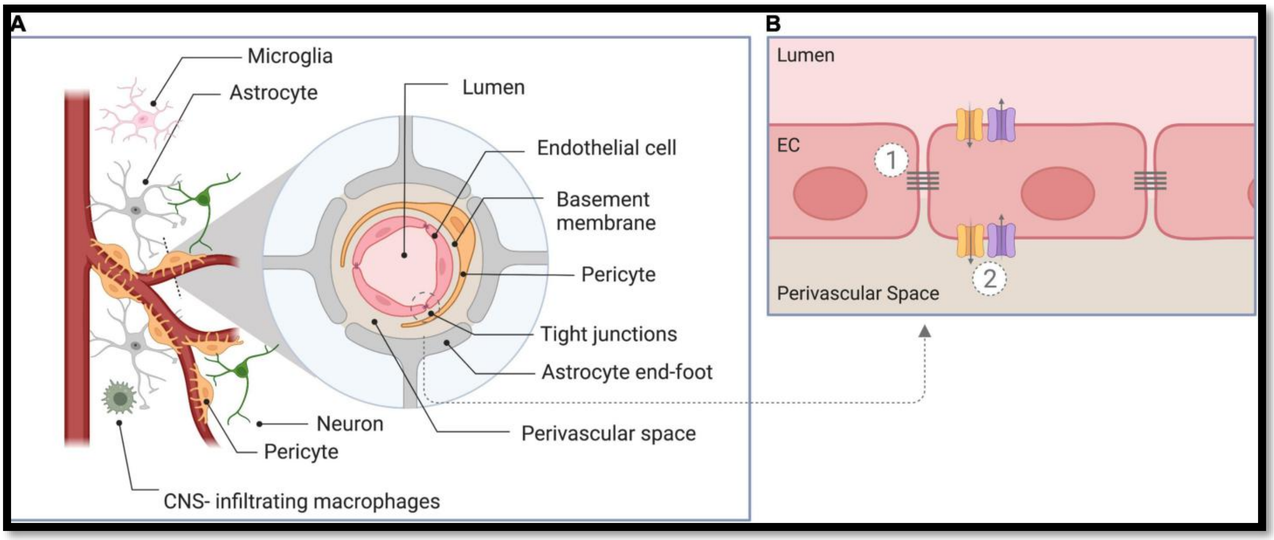

Fig 3: Blood-Brain Barrier (BBB) Disruption [30]

2.4. Mitochondrial Dysfunction and Synaptic Impairment

Mitochondria play important roles in energy production in neurons, synaptic performance, and general brain homeostasis considering that they stimulate mitochondrial biogenesis, and estrogen is necessary to maintain the well-being of the mitochondrion, oxidative phosphorylation, and antioxidant response [31]. Yet, the loss of estrogen due to ovariectomy triggers the dysfunction of mitochondria, a condition that contributes to energy shortage, oxidative stress and neurodegeneration, which are considered the principal pathological changes of OIVD [32]. The deficiency of estrogen reduces the activity of mitochondrial electron transport chain (ETC), causing a great decrease in production of ATP and an elevated accumulation of ROS [33]. Aberrant ROS production leads to excess of the oxidative stress of protein, lipid and mitochondrial deoxyribonucleic acid (mtDNA) which further decreases the functioning of the mitochondrion [34]. Such loss of mitochondria contributes to apoptosis, malfunctioning of synapses, and dementia. Besides, estrogen moderates via regulation of neural chemicals like acetylcholine, glutamate and dopamine that play an important role in learning and memory [35]. Reduced serum estrogen leads to impaired synaptic connections that lower dendritic spine density, expression of synaptic proteins and long-term potentiation (LTP) which is significant in cognition [36]. There is evidence that ovariectomized animal models have impaired synaptic plasticity, owing to downregulation of TrkB, the receptor of brain-derived neurotrophic factor (BDNF), although the latter is required both to maintain other cells and to maintain synapses [37].

Vascular erectile dysfunction, impaired eNOS expression and cerebral blood flow leads to vascular stiffness and under perfusion which are reflected in immunostain, MRI perfusion imaging and electron microscopy [38]. BBB disruption and neuroinflammation: The number of microglia associated with increased BBB permeability, microglial activation, and estrogen deficiency leads to extracellular neuroinflammation as pro-inflammatory cytokines are released (TNF-a, IL-2, and NF-kb), which aggravate BBB destruction and neuroinflammation process measured with Evans blue assay, RT-PCR, and GFAP/Iba1 staining [39]. The presence of oxidative stress and mitochondrial dysfunction, increased ROS, lipid peroxidation (MDA), and mitochondrial damage, were confirmed by biochemical assays, 8-OHdG staining and electron microscopy. Acetylcholine, dopamine, serotonin and synaptic protein (synaptophysin, PSD-95) imbalance and loss of synapse were assessed by HPLC, Western blot and Golgi staining [40].

3. Treatment Plan against Ovariectomy and Vascular Dementia (OIVD)

OIVD is a complicated neuro-inflammatory disease in which the defect of the estrogen scheme, oxidative stress, neuroinflammation, the dysfunction of the blood-brain barrier, impaired mitochondrial functions, and synaptogenesis contribute to its development. The existing treatment strategies revolve around, HRT, antioxidants and anti-inflammatory based treatment, lifestyle modifications, regenerative pharmaceuticals, gene therapeutics, and novel drug delivery systems. These treatments will prevent or prepare against neurodegeneration, increase circulatory products in the brain and boost cognition.

3.1. Hormonal Replacement Therapy (HRT)

Positive responses that support estrogen replacement therapy (ERT) are highlighted in the neuroprotective effects of estrogen in post-menopausal women and also in animals with ovarian cancer, resulting in regulation of cerebral blood flow and enhancement of synaptic plasticity, mitochondrial functionality, and neuroinflammatory syndrome [41]. The "critical window hypothesis" contributes to the effectiveness of ERT as early application after menopause is considered to grant cognitive advantages, late application can become ineffective or even damaging [42]. Also, selective estrogen receptor modulators (SERMs), exemplified by raloxifene, demonstrate some of the effects of the hormone estrogen in the brain but eliminate the dangers of hormone-related cancer [43]. So called phytoestrogens found in soy products like genistein are estrogen-like compounds of medical value within plants which have neuroprotective effects, but their clinical utility is yet to be more thoroughly examined [44]. Combination treatment with progesterone has been inconsistent and this implies that individualized treatment is required in order to maximize intercession management [45].

3.2. Anti-inflammatory and Antioxidant

Treatments Oxidative stress and neuroinflammation have been a key feature of the pathology of OIVD and so antioxidant agents and anti-inflammatory agents are a promising new treatment option. MitoQ and other mitochondrial-directed antioxidants (coenzyme Q10 and N- acetylcysteine) are effective in protecting against oxidative stress and improving mitochondrial outcome, neuronal survival and cellular energy metabolism [46]. The polyphenol curcumin, extracted out of turmeric, has shown high anti-inflammatory and antioxidant properties, lowering neuroinflammation and amyloid-beta plaques in preclinical models [47]. Secondly, non-steroidal anti-inflammatory drugs (NSAIDs) have also been studied on their role in microglial activation inhibition to decrease neuroinflammation, although, the efficacy of OIVD in clinical practice is not as clear in the long term [48].

3.3. Lifestyle Interventions

Such non-pharmacological measures as a diet and exercising help prevent cognitive deterioration. Diets such as a Mediterranean diet, high in both omega-3 fatty acids, polyphenols, and antioxidants have also been shown to positively impact in synaptic functionalities, decreasing neuroinflammation and neurodegenerative diseases [49]. Consistent aerobic exercise enhances cerebral blood flow, and neurogenesis as well as boosts the presence of brain-derived neurotropic factor (BDNF), which facilitates plasticity of the synapses and memory construction. Cognitive stimulation and resistance training have also been prescribed as other additions to limit cognitive impairment[50].

3.4. Regenerative Medicine approaches

Stem cell therapy has become a subject of consideration as an effective direction in the treatment of OIVD, mainly because of the ability to increase neurogenesis and support damage to synapses. All these findings have shown that both neural stem cells and mesenchymal stem cells have the capability of restoring cognitive functions through integrating into the damaged structured neural paths and secreting neuroprotective oncobes. In addition, such neurotrophic factors as BDNF, nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF) are significant to rescue neurons, keep the structure of synapses, and retain the functions of brain. Although the preclinical data are promising, clinical trials on a large scale are needed to prove the clinical worth and safety of stem cell based therapies[51].

3.5. Gene Therapy and Molecular Targeting

The technological development of gene therapy has offered new areas in treatment of OIVD which has been based on the neuroprotection, mitochondrial processes and estrogenic signalling genes. The gene therapy of BDNF has been found to promote cognitive flexibility and the synaptic plasticity [52]. Therapeutic approaches targeting the enhancement of estrogen receptor (ER) expression or affecting the SIRT1 and AMPK signalling pathways would help in augmenting the mitochondrial energy metabolism and neuronal survival [53]. These methods are the potential ways of personalized treatment in the future.

3.6. Complex Drug Delivery Systems

New technologies, such as nanotechnology based neuroprotective agent carriers and degradable arteriovenous brain implants are in development to help improve focused neuroagent delivery, maximizing the targeted neuroprotective effects with drug carriers and minimizing over-system exposure associated side effects [54]. Delivery systems based on liposome, polymeric nanoparticles, and exosomes enhance the bioavailability of the drug and can release it under control in the areas where the brain is damaged. Also, personalized medicine, such as that made possible by artificial intelligence, can promote optimal treatment outcomes through treatment customization according to a population, which is based on genetic and metabolic profiles.

4. Strategies in Ovariectomy-Induced Vascular Dementia (OIVD) based on Formulation

Treatment strategies based on the formulation aim at increasing the bioavailability, penetration in the brain, and long-term therapeutic benefits of drugs used to treat ovariectomy-induced vascular dementia (OIVD). These have been various approaches such as hormonal formulations, antioxidant, anti-inflammatory strategies, regenerative medicines and superior drug delivery systems with the intent of maximizing the treatment effectiveness and reducing the systemic danger.

4.1. Hormone-Based Formulations

ERT continues to be one of the main interventions in manifestations of OIVD, and the novel formulations are aimed at optimizing effectiveness and safety.

4.1.1 Transdermal, Micronized estrogen

Transdermal 17beta-estradiol patches (e.g. Estraderm Climara) and gels (e.g. EstroGel) keep estrogen levels at a stable level but avoid first-pass metabolism, so are less likely to have thrombotic risks than oral estrogen [55]. Micronized estradiol preparations enhance bioavailability and also provide a sustained release [56]. 1) Lightweight: Lightweight systems were used that contained only a few items of clothing in a small backpack.

4.1.2. Selective estrogen receptor modulators S.E.R.M.s and Tissue-selective estrogen complexes T.S.E.C.s (TSEC)

The SERMs including raloxifene are neuroprotective in addition to reducing the breast and uterine estrogenic risks [57]. TSECs, such as conjugated estrogens and bazedoxifene form a compromise between cognitive talent and lower oncogenic potential.

4.1.3 Estrogens delivered intranasally

Direct brain targeting has been realized with intranasal estrogen formulations such as mucoadhesive nanoparticles, and effectively bypasses the BBB [58]. This is way limits the side effects of the system and strengthens neuroprotection.

4. 2. Anti-Inflammatory and Antioxidants Formulations

Since oxidative stress and neuroinflammation play a role in OIVD, different formulations of antioxidants and anti-inflammatories are being studied.

4.2.1. Mitochondrial-Targeted Antioxidants

Mito Q, coenzyme Q10 and N-acetylcysteine are highly effective antioxidants in the mitochondrion that improves energy metabolism in the neurons and lowers oxidative damage [59]. Nonetheless, it is still difficult to target the CNS in an efficient manner.

4.2.2. Polyphenol-Based Nanocarriers

Curcumin, resveratrol and quercetin are polyphenolic compounds and they are synthesized in the form of liposomes, nanoparticles to enhance drug release and increase bioavailability [60]. These solutions possess high anti-inflammatory and neuroprotective effects.

4.2.3. NSAID-Loaded Nanocarriers

The effect of nanocarriers in encapsulating ibuprofen and celecoxib can be useful to increase their penetration into the brain and avoid side effects on the periphery. The treatment can be used on microglial activation and minimizes neuroinflammation in OIVD [61].

4.3. Formulations of Regenerative and Neurotrophic Factor

Therapies with stem-cells and neurotrophic factors are exciting options towards synaptic repairing and neurogenesis in OIVD.

4.3.1Exosome Therapy of Stem Cells

Neurotrophic factors present in neural stem cell and mesenchymal stem cell-based exosome drug formulations enhance repair of the neurons and decrease neurodegeneration [62]. Nonetheless, the scalability and standardization are the main issues.

4.3.2. Neurotrophic factor biodegradable Hydrogels

BDNF and NGF embedded hydrogels provide a sustained release- a localized neuroprotection [63]. The formulations can participate in the restoration of the synaptic and cognitive resistance to OIVD models.

4.4. Advanced Drug Delivery Systems and Nanotechnology

The use of nanotechnology drug delivery systems enhances specific drug brain penetration as well as specific sustained response.

4.4.1. Liposomal Nanoparticles, Polymeric Nanoparticles

Neuroprotective substances like estrogen, curcumin and resveratrol have increased stability and half-life when administered in PEGylated liposomes and by polymeric nanoparticles (e.g., PLGA) [64].

4.4.2. Nanocarriers administered by intranasal and Transdermal methods

Non-invasive administration can be offered by nasal formulations based on mucoadhesive nanoparticle formulations and transdermal microneedle patches, which have not only led to enhanced brain bioavailability but also reduced the occurring side effects [65].

4.4.3. Hydrogel Scaffolds which are Biodegradable

The use of injectable biopolymer scaffold enables the neuroprotective agents to be released over an extended period and thus eliminates the necessity of frequent administrations as well as allows therapeutic effects to take place.

5. Future directions in formulation based approach to Ovariectomy induced Vascular Dementia (OIVD)

As scientific developments in the area of pharmacotherapy against OIVD progress, the emergence of formulation-based methods is combining the most innovative drug delivery technologies with precise medicine strategies. Such novel developments focus on increasing the bioavailability of drugs, prominent delivery, and controlled release and optimizing therapeutic effects of drugs minimizing systemic side effects. Some of the major advancements in this aspect are AI-enabling smart drug delivery devices, gene therapeutic nanoparticles, and 3-dimensional printed biodegradable brain implants.

5. 1. Smart Drug Delivery Systems as AI Driven

This shift is very clear in the phenomenon of smart drug delivery systems that use responsive nanocarriers to sense neural activity in real-time and deliver therapeutic agents selectively as required in the neuropharmacological effect of artificial intelligence (AI). Such nanocarriers are commonly containing biodegradable polymer or lipid-based vesicles; they can be designed to read a shift in pH, temperature, or even specific biomolecular cues in the brain [66]. As an example, neuroprotective agents (e.g., estrogen analogues, antioxidants, or neurotrophic factors) can be loaded into smart nanocarriers, which will be activated in the presence of an oxidative stress or inflammation ensuring local and time-confined drug release [67]. Smart pharmaceuticals in implanted microchips have been demonstrated by AI algorithms that transparently control the release of a drug and change release patterns according to individual biomarker feeds taken of cerebrospinal fluid or blood samples [68]. These smart systems improve precision in therapy, lower the chances of overdose and avoid unnecessary exposure to drugs.

5.2. Gene Therapy-Packed Nanoparticles

Gene therapy is very promising in treatment of OIVD since they affect genes related to neuroprotection, mitochondrial processes, synaptic remodeling, and plasticity. Nevertheless, the traditional methods of gene delivery lack transfection efficiency and are associated with immunogenicity. To address these, recent works have looked into nanoparticle delivery to CRISPR/Cas9 and RNA interference (RNAi) therapies [69]. To treat pro-inflammatory dysregulation (e.g., TNF-alpha, IL-6), oxidative stress (e.g., SIRT1, NRF2), and other conditions, lipid nanoparticles (LNPs) and polymeric nanocarriers have been designed to convey CRISPR-Cas 9 elements or little interfering RNA (siRNA) targeting pro-inflammatory genes (e.g., TNF-alpha, IL-6) or regulators of oxidative stress (e.g., Such nanoparticles can cause specific genetic modulation without causing reproducible risk of delivery across BBB in a safe, effective, and less invasive manner [71]. New preclinical studies have shown that in diseases like OIVD, the intravenous injection of gene therapy-loaded nanoparticles can be used to greatly diminish neuronal inflammation, recover synaptic activity, and enhance cognitive refinements [72]. Such an approach has the potential of personalizing treatment therapy depending on the genetic makeup of an individual hence enhancing treatment efficiency.

5.3. Biodegradable brain Implants

D-Printed The 3D-printing technology has given birth to the potential of fabricating long-term neuroprotective agent-delivering biodegradable brain implants. These implants are biodegradable and can be implanted into or onto the body where there is local release of the drug but sustained release over an extended period, thus eschewing the necessity of frequent dose administration and drug delivery to the body [73]. To treat OIVD, the implants are made with the supplement of estrogen analogues, neurotrophic factors (e.g., BDNF, NGF) or antioxidant compounds where slow release incorporation of therapy agents would provide maximum neuroprotection and support mitochondrial functions [74]. Implants made out of 3D printing can be adapted to an individual according to his or her brain structure and the severity of the disease which can enhance treatment precision and patient adherence [75]. In animals the transplantation of stem cell-derived exosomes using implantable scaffolds has been demonstrated to induce neuronal regeneration, restore synaptic activity and support the structural integrity and function of cerebral vascular structure.. In the future, patient-specific implants incorporating nanodrug formulations and bioactive materials may revolutionize the long-term management of OIVD and related neurodegenerative disorders.

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