Reproductive Hormones and Dementia

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Dementia is an entity that has been thought of as a disease but is now understood as the outcome of a number of diseases:

> Dementia is a broad category of brain diseases that cause a long term and often gradual decrease in the ability to think and remember that is great enough to affect a person's daily functioning…A dementia diagnosis requires a change from a person's usual mental functioning and a greater decline than one would expect (to be) due to aging….The most common type of dementia is Alzheimer's disease (AD), which makes up 50–70% of cases. Other common types include vascular dementia (VD) (25%), Lewy body dementia (15%), and frontotemporal dementia…. A small proportion of cases run in families. In the DSM 5, dementia was reclassified as a neurocognitive disorder, with various degrees of severity. Diagnosis is usually based on history of the illness and cognitive testing with medical imaging and blood work used to rule out other possible causes. The mini mental state examination is one commonly used cognitive test. (Wikipedia, 2017)

Dementia is increasingly common as the population ages. In the past, the two most common causes of dementia, AD and VD, were treated as occurring independently; however, it has become increasingly clear that inflammatory changes associated with AD and vascular changes associated with VD are commonly found in the same individual [1]. Often, both are found in aging individuals who show signs of diminished cognitive function, emotional disruption, failure of memory, and dysautonomia, which make evaluation of cause and effect difficult. These signs and symptoms may accompany dementia, and it may not be possible clinically to clearly

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Fig. 16.1 Dementia has many causes; it is a final common clinical pathway that, itself, may not reveal the underlying cause

separate AD from VD. Therefore, without specific testing [2], it may not be possible to separate the effects of various agents on the genesis, prevention, or rate of AD- vs. VD-related dementia. Since they are caused by different processes and can have unrelated pathological and clinical progress, research to distinguish the genesis, prevention, progress, and treatment of multi-causal dementia has been slow.

Despite their availability, until recently the use of the imaging techniques that could reveal the onset and course of their underlying processes was either not applied or only performed to confirm a diagnosis rather than to reveal contributing factors to the clinical diagnosis, dementia; see Fig. 16.1. This has seriously hindered the understanding of dementia and its contributing factors and attempts at unraveling its antecedents. For example, the diagnosis and treatment of patients may be delayed by failure to separate organic from functional causes of dementia. Recently, the role of inflammation has been established in the development of organic dementias, such as AD and VD [5, 6]. The lack of determination of the underlying cause of dementia is a particular problem for interpreting published studies that are retrospective and depend solely upon clinical diagnoses made to facilitate medical care.

Fortunately, contemporary techniques of imaging and biomarker accumulation that are specific to lesions that lead to dementia have become available [3]. AD markers usually are concentrated in the limbic brain of the temporal lobe and diencephalon, while imaging studies identifying VD show that it can occur throughout the entire brain [3]. Widespread use of these techniques will allow specific diagnoses in clinical care and research situations.

Most cases of dementia are noticed because they involve cognitive dysfunction, dementia being most often associated with cortical disease, especially the temporal lobe (memory, planning, and emotion) and the prefrontal lobe (judgment, planning, higher functions). Brain shrinkage is a common accompaniment to both conditions; but, since nine out of ten brain cells are not neurons [4], the clinical outcomes of shrinkage do not have a linear relationship with the features of dementia (Fig. 16.2).

Degenerative dementia is often presaged by minimal cognitive impairment (MCI); but, both atherogenesis and neurodegeneration may be silent during their development, only being shown by diagnostic testing. With progression of dementia, connections eventually involve vegetative function (diencephalon) that contributes to the patient's demise [7].

The underlying lesions are well defined. Vascular insufficiency/VD is due to atherosclerosis and narrowing of cerebral small vessels, some of which actually may be due to accumulation of amyloid plaque. AD includes the extracellular accumulation of inflammatory insoluble amyloid (ironically, the result of precipitation of the soluble anti-inflammatory protein) and the intracellular

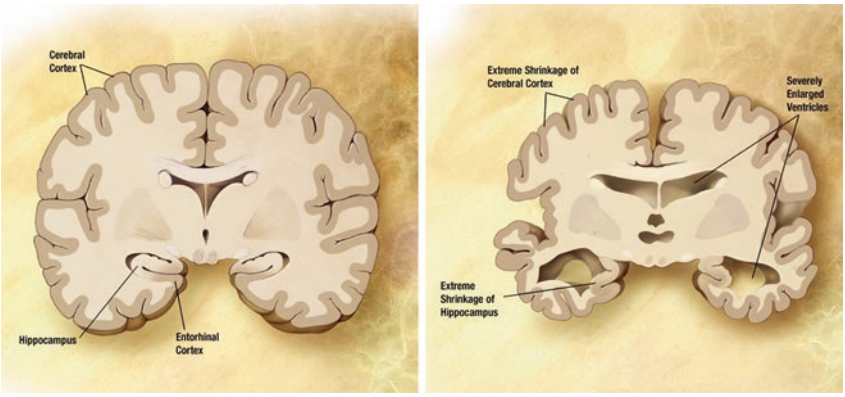

Fig. 16.2 Comparing a mid-frontal section of the normal brain (left) with one of the brain of a subject with AD (right). Imagine the meninges wrapped around the brain on the left, and loosely covering the brain on the right, brain shrinkage. Note that the cortex (gray matter) is formed about smaller gyri, implying that the chief shrinkage is in the non-neuronal white matter, lighter color. In AD, pictured, there is widespread shrinkage, but the most obvious is in the areas of the temporal lobe (lower structures on each image). Shrinkage associated with VD is more uniformly distributed, explaining why significant generalized shrinkage after ischemia and small infarcts may not result in dementia, while a single, strategically placed infarct (stroke) may result in dementia. As discussed in the text, AD and VD can coexist in cases of dementia (Image from Wikipedia, 2005)

accumulation of hyperphosphorylated tau (an activated microtubule assembly protein) [8]. While AD and atherosclerosis may manifest themselves early, and as the result of familial/genetic propensity [6], these are the minority of cases. They may be solitary or combined in the same individual. There is no literature on combined early VD and AD.

There are many practical reasons for healthcare professionals to develop a single descriptor for "dementia." But, the tendency to declare a single diagnosis of the type of dementia rather than "mixed dementia" becomes problematic when one considers the common coexistence of the two underlying diseases in the aging brain. It takes on added significance when considering possibly different effects of estrogen/MHT on the underlying diseases in dementia. For example, treatment of aging women with estrogen/MHT could provoke dementia because of intravascular clotting, as may have been the case in the WHIMS study that could obscure effects on AD [9].

Because of the difficulty in separating the two forms of dementia, especially in the absence of objective signs such as those seen on imaging or on biopsies, unless there are the requisite imaging studies, we address clinical research reports on "dementia" rather than attempting to separate effects of/on AD vs. VD. This practical approach is dictated by the difficulty in separating the underlying mechanisms of "AD" and/or "VD." Since the available literature is mainly comprised of retrospective studies based on clinical impressions rather than specific techniques, the possibility of mixed dementia remains a major obstacle.

Finally, although this chapter focuses on reproductive hormones and dementia, there are many other influences on brain function that may contribute to acute or

chronic dementia; for example, heavy smoking increases the risk of both AD and VD [10]. Other factors, such as reproductive history, metabolic syndrome, medications, trauma, associated neurodegenerative processes, and nonreproductive hormones such as thyroxin are associated with dementia (Fig. 16.1) [11–13]. While other risk factors will not be further addressed, they must be considered as possible co-variables in the development of AD/VD (Fig. 16.2).

16.1 Hormones and Dementia

16.1.1 Sex Steroids/Receptors and Dementia

Many, if not all, "steroid hormone actions" are due to liganding (binding) of a molecule by receptors that then dimerize. The paired, liganded receptors then address a second set of molecular binding sites or DNA configurations that affect either transcription or posttranscriptional modification of the product. In the case of estrogen receptor ligands, there is competition for binding between the putative ligands and other receptor binders. Once the receptor is liganded, receptor dimerization occurs, and the dimer is presented to the estrogen response element (ERE) of genes that are "estrogen responsive." Most human genes contain EREs or portions of EREs and are therefore estrogen responsive. We have elsewhere discussed these actions in detail [14]. Although there are exceptions, for the sake of brevity, we will use the terms "estrogen" and "estradiol" as being equivalent to activation of the above chain of events that lead to estrogen receptor-mediated gene regulation. The same generalities apply to other sex steroids/receptors and will not be repeated [15].

16.1.2 Estrogen(s)/Estrogen Receptors and Dementia

Estrogen receptors are widely expressed throughout the brain, including areas commonly affected in dementia (Fig. 16.3).

The hippocampus is a feed-forward system that acts to capture, process, and distribute information to the rest of the brain. Estradiol regulates hippocampal neurons [16] (Fig. 16.4).

In conjunction with the role of estrogen in dementia, postmortem brain sex steroid levels in both women and men have been shown to be inversely related to the degree of dementia at the time of death [17].

16.2 Estrogen and Cognition

Estrogen and memory—There is evidence of memory sparing if estrogen is administered immediately after oophorectomy. However, despite numerous attempts to show memory-sparing effects of estrogen/MHT on naturally postmenopausal women, evidence has not been adduced of this action [18].

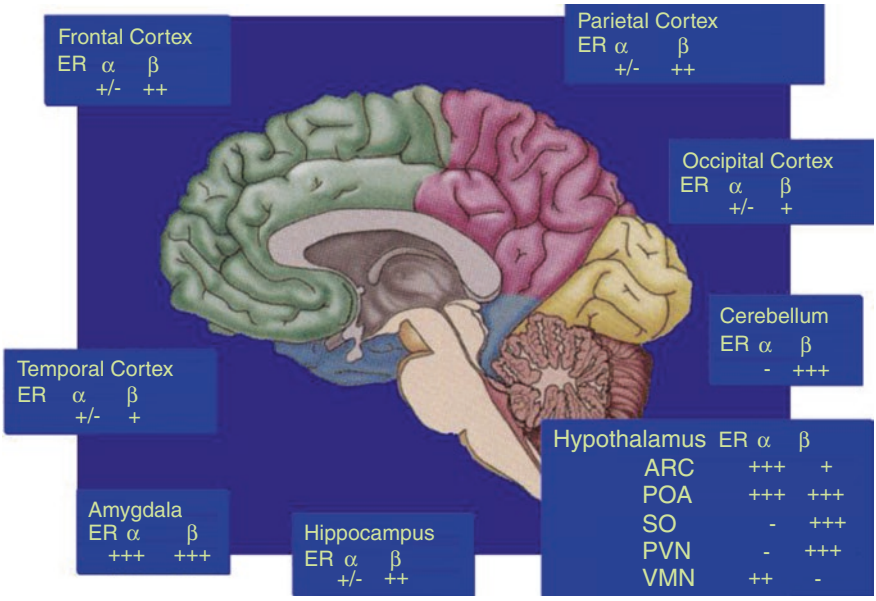

Fig. 16.3 Both estrogen receptor α (ERα) and β (ERβ) are widely represented in the brain. This makes estradiol a target for studies on both AD and VD as causes of dementia

Estrogen and minimal cognitive impairment—Minimal cognitive impairment (MCI) has long been mooted as a forerunner of dementia, particularly AD. However, effects of estrogen on cognition after menopause have not been proven. Recently, a prospective study of estrogen treatment on cognition was reported, again, and definitively shows little or no effect; but, this is not sufficient to assess whether the lack of effect relates to the occurrence of dementia, especially non-AD dementia [19, 20].

16.3 Estrogen and Dementia

Epidemiologic evidence—Although age is the most powerful factor in the occurrence of dementia, there is strong evidence that genetic sex and sex steroids/receptors are somehow associated with dementia [15]. Mainly, this stems from the relationship of the genetic sex to the incidence of age-related dementia, women having more dementia at a given age than men, unless the women took MHT. This has been defined further, to show that the MHT must have started within the first 10 years of menopause, to show the protective effect of MHT [21]. As well, retrospective studies have indicated, but not proven, that hormone treatment of post-reproductive women is associated with age-corrected lower rates of dementia [22, 23].

Drug-use registries—An important recent retrospective analysis of "AD" supports the protective effect of estrogen, although it suffers from the difficulties of being retrospective and depends upon clinical diagnoses [24].

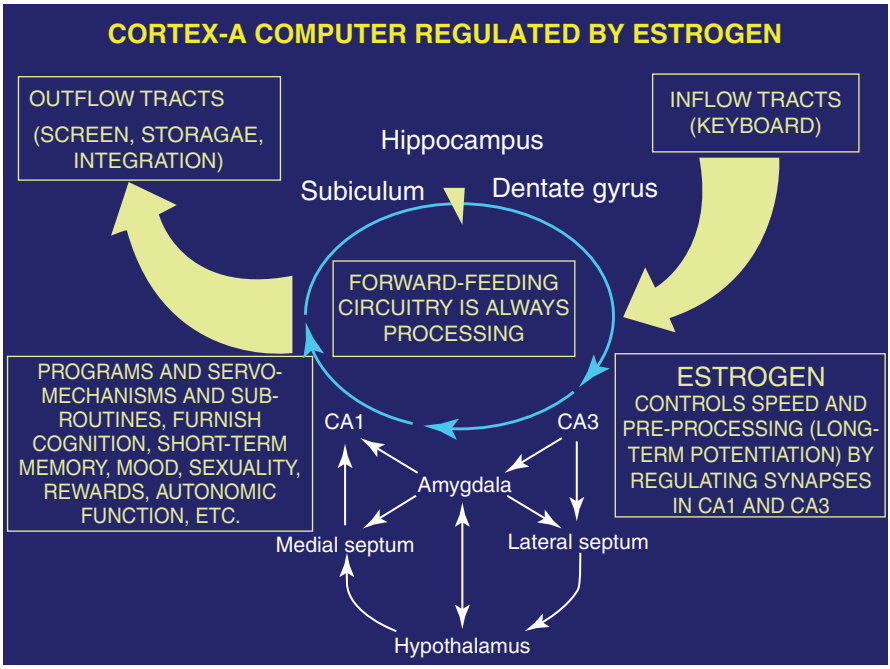

Fig. 16.4 The paired computer chips in the brain. The feed-forward three neuron loop (light blue) in the hippocampus receives information in a manner analogous to a computer chip, and both processes and distributes the information to other areas of the brain that are responsible for mood/emotion (amygdala), memory (cortex), autonomic function (hypothalamus), perception (specialized cortex), etc. Estrogen regulates many functions of the hippocampus, especially the transfer of information from the axons of the inflow tracts to the dendrites of the feed-forward neurons [16]

Prospective studies on estrogen treatment and dementia—During the Women's Health Initiative, a sub-study was undertaken to test for the effects of estrogen (conjugated equine estrogen, CEE) and/or the synthetic progestin medroxyprogesterone acetate (MPA) on the prevalence of dementia. Termed the WHIMS [25], it followed the occurrence of dementia in women who at the age of 65 years began daily CEE + MPA or CEE alone for 6 years. WHIMS' conclusions were that this hormone treatment was the cause of a slight excess of AD in the subjects [26, 27]. Some of the WHIMS survivors were studied with MRI to assess VD vs. AD; however, this remains conjectural [28, 29]. Overall, this study has many problems for interpretation. The primary one is the use of hormones in women who were decades past the menopause, which is fraught with an increase in intravascular clotting, the lack of determination of the status of vascular disease prior to starting MHT, and the use of medroxyprogesterone acetate, an androgen-derived synthetic progestin. There was no testing for minimal cognitive dysfunction at the outset of the study, which might have pointed to whether the dementia was AD, and the diagnoses were by consensus by individuals who had not examined the women. At this time, it is not possible to rule out VD as the underlying lesion [2].

In another prospective cohort study, women who started MHT during the first years of menopause appear to have a lower incidence of dementia than "comparable" subjects who did not use MHT [30]. Unfortunately, there were no pretreatment evaluations, and the contributions of AD and VD to the dementia burden were not determined.

Additional relevant experimental findings—Human arterial vascular endothelium expresses ER and is, therefore, responsive to estrogen [53].

AD—Estrogen has been shown to hinder tau hyperphosphorylation [8] and improve amyloid clearance [5]. Estrogen is anti-inflammatory and antioxidant and promotes apoptosis of immunocytes [23]. Preclinical studies in AD-mutated mice support prevention of AD by estrogen and some progestins [31, 32]. A recent systems biology evaluation concluded that androgen and estrogen receptors are involved in the development of AD [33].

VD—There is considerable evidence of estrogen protection against atherogenesis and arteriosclerosis. This is especially well-demonstrated in the recently published prospective estrogen treatment of menopausal women [34].

Interactions of VD and AD—Considerable attention has been played to the possibility that AD and VD could be mechanistically related. Capture of leucocytes that may penetrate brain parenchyma has been shown [35]. As well, impaired clearance of amyloidβ by the cerebral capillaries has been shown in animal models of AD [36]. The possibility of intravascular pressure changes affecting amyloidβ accumulation in cerebral capillaries has been posited [37]. The accumulation of amyloidβ in the capillaries of the eye is under active study [38].

Studies on capillary and blood-brain barrier aspects of the cerebral vasculature system is of especial interest. Estrogen/ER has been shown to block the binding of monocytes to arterial endothelium [39] to affect the passage of monocytes across the blood-brain barrier [40] and to affect the response to inflammatory signals in the nervous system [41, 42].The possibility that AD and VD are intertwined and that estrogen may be a key factor cannot be dismissed.

Antihormone effects on dementia—While evidence has been accumulating of increased rates of dementia in men taking androgen-blocking treatments, prospective trials are just becoming available [43–45]. On the contrary, and despite tantalizing animal studies indicating an association between antiestrogen treatment and dementia, data indicating a relationship between antiandrogen treatment and dementia has not appeared [46]. However, the apparent increase of cardiovascular complications in long-term aromatase inhibitor treatment may indicate that it will only be with large sample, long-term prospective studies that a role for AIs in dementia will be resolved [47].

Estrogen treatment and dementia—Logical extension of the possible role of estrogen in dementia resulted in a burst of reports that estrogen treatment appeared to improve the dementia of identified subjects; however, prospective clinical trials have not shown either delay or reversal of dementia by sex steroid treatment. [23, 29, 48]. The same result of no effect on dementia was found in a prospective trial of the selective estrogen receptor modulator, raloxifene, on established dementia [49].

Summary—There are many reasons that could explain the apparent lack of experimental effectiveness of sex steroid treatments against dementia. Until these have been ruled out as confounders, and definitive clinical trials performed, it remains prudent to consider sex steroids as possible factors in protection against dementia and to keep in mind possible protective effects of estrogen treatment/replacement. Data is accumulating that this could apply in the cases of mixed dementias.

Androgens and dementia—Although long a subject of interest, the relationship of dementia to testosterone remains unclear [6, 50].

Neurosteroids and dementia—In vitro and animal studies have indicated that allopregnanolone is neuroprotective. However, the results of clinical studies on dementia and neurosteroids are not yet available [31].

Gonadotrophins and dementia—It has recently been reported that gonadotropin-releasing hormone (GnRH) may increase the effect of acetylcholinesterase inhibitor (AChEI) in slowing the decline of patients with dementia. This finding is exciting but requires repetition and further exploration [51].

Human chorionic gonadotrophin also has been raised as having a positive role in the management of dementia [52]. Both hCG and its hyperglycosylated counterpart are active on steroidogenic and TGFβ systems; therefore, this is an interesting suggestion, and further results are awaited.

16.4 General Conclusions

Dementia, regardless of its cause, remains the scourge of aging. As the population of developed countries continues to age, the personal tragedy and cost of dementia rises. One of the most important deficits is the lack of reliable data on the cause(s) of dementia in subjects included in population studies or undergoing clinical trials. This also hinders development of treatment plans and management. Part of the problem is that the structure of our reimbursement systems requires a single diagnosis, which works against precise assessment of the roles of the individual causes of dementia. These requirements were imposed before specific methods were available to diagnose AD vs. VD and to deal with mixed dementias. This is changing, and we can look forward to cause-related datasets from which to plan research and treatment of the underlying condition, rather than the outcome, dementia.

Nowhere is the problem of undiagnosed partitioning of causes of dementia more evident than in determining the role of reproductive hormones in dementia. There are many indications that reproductive hormones, especially estrogen/estrogen receptors, may be protective against dementia. Thus far, preclinical experimental evidence supports prevention of both AD and VD. However, clinical studies have not revealed evidence that reproductive hormones, particularly estrogen, prevent or treat AD. On the other hand, there is evidence of prevention of the most common cause of VD, atherogenesis, and arteriosclerosis and data indicating that estrogen could be protective against vascular-related parenchymal (AD) dementia. This raises the possibility that it is VD, either singly or in mixed dementia cases, that is being prevented/treated by estrogen. We have made a case for this hypothesis in this manuscript.

It is expected that wide use of specific, quantitative imaging and other techniques will define the contributions of AD and VD in individual cases, thereby allowing testing of this hypothesis. Clinical research leading to improved, specific diagnosis and appropriate prevention and interventions is of the highest priority.

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