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A Unified Hypothesis of Early- and Late-Onset Alzheimer's Disease Pathogenesis

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Abstract

Early-onset familial Alzheimer's disease (EOFAD) and late-onset sporadic AD (LOSAD) both follow a similar pathological and biochemical course that includes: neuron and synapse loss and dysfunction, microvascular damage, microgliosis, extracellular amyloid- β deposition ($A\beta$), and the deposition of phosphorylated tau protein in the form of intracellular neurofibrillary tangles in affected brain regions. Any mechanistic explanation of AD must accommodate these biochemical and neuropathological features for both forms of the disease. Cell cycle abnormalities represent another major biochemical and neuropathological feature common to both EOFAD and LOSAD, and 1) appear very early in the disease process, prior to the appearance of plaques and tangles, and 2) explain the biochemical (e.g., tau phosphorylation), neuropathological (e.g., neuron hypertrophy) and cognitive changes observed in EOFAD and LOSAD. Since neurogenesis after the formation of a memory is sufficient to induce forgetting, any stimulus that promotes cell cycle re-entry will be a negative event for memory. In this insight paper, we propose that aberrant re-entry of terminally differentiated, post-mitotic neurons into the cell cycle is a common pathway that explains both early and late-onset forms of AD. In the case of EOFAD, mutations in *APP*, *PSEN1*, and *PSEN2* that alter $A\beta$ PP and Notch processing drive reactivation of the cell cycle, while in LOSAD, age-related reproductive endocrine dyscrasia that upregulates mitogenic TNF signaling, $A\beta$ PP processing toward the amyloidogenic pathway and tau phosphorylation drives reactivation of the cell cycle. Inhibition of cell cycle reentry of post-mitotic neurons may be a useful therapeutic strategy to prevent or halt disease progression.

Keywords

Alzheimer's disease; amyloid- β protein precursor; Cdk-5; cell cycle reentry; cognition; endocrine dyscrasia; hypothalamic-pituitary-gonadal axis; luteinizing hormone; presenilin; tau

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The neurodegenerative disorder of Alzheimer's disease (AD) accounts for ~70% of all dementia cases [1, 2] and is characterized neurologically by progressive memory loss, impairments in behavior, language, and visuo-spatial skills ultimately leading to death [3]. AD is usually divided into two forms: (1) familial cases with Mendelian inheritance of predominantly early-onset (<60 years, early-onset familial AD [EOFAD]), and (2) late-onset cases with undefined genetics (>60 years, late-onset AD [LOSAD]) [4]. The three clinically indistinguishable subtypes of EOFAD based on underlying genetics are: Alzheimer disease type 1 (AD1), caused by mutation of *APP* (10%–15% of EOFAD); Alzheimer disease type 3 (AD3), caused by mutation of *PSEN1*, (30%–70% of EOFAD); and Alzheimer disease type 4 (AD4), caused by mutation of *PSEN2* (<5% of EOFAD). EOFAD comprises ~1–5% of the total AD population [5] and follows a more aggressive course with shorter relative survival time [6]. Neuropathologically, both EOFAD and LOSAD are characterized by neuron and synapse loss and dysfunction, microvascular damage, microgliosis (inflammation), the deposition of amyloid- β (A β) in extracellular amyloid (neuritic) plaques, and the deposition of phosphorylated tau protein in the form of intracellular neurofibrillary tangles (NFTs) in affected brain regions. EOFAD may have a more variable presentation, including posterior cortical atrophy, frontal variants, and linguistic presentations [7]. Furthermore, the pathology in EOFAD may be more severe with prominent synaptic fallout and neuronal loss [8]. EOFAD is also characterized by more severe perfusion and metabolic defects [9]. Although amnesic presentation is observed, it is less common [7].

Research over the last decade has suggested that cell cycle abnormalities also represent a major neuropathological feature for both EOFAD [10, 11] and LOSAD (e.g., [12–15]). These abnormalities appear very early in the disease process, prior to the appearance of plaques and tangles and can explain many of the biochemical and neuropathological changes observed [16]. Thus, neuronal cell cycle regulatory failure may be a significant component of the pathogenesis of AD [17].

Although there are differences, EOFAD and LOSAD follow a similar pathological and biochemical disease course. Any mechanistic explanation of AD pathogenesis must therefore accommodate both forms of the disease. In this insight paper, we propose that aberrant reentry of post-mitotic neurons into the cell cycle explains both early and late-onset forms of AD; with aberrant cell cycle signaling being driven in EOFAD by mutations in *APP*, *PSEN1*, and *PSEN2* and in LOSAD by age-related endocrine dyscrasia (Fig. 1).

EVIDENCE FOR CELL CYCLE REENTRY OF POST-MITOTIC NEURONS IN THE ALZHEIMER'S DISEASE BRAIN

In this section we focus on the re-entry of *post-mitotic, terminally differentiated* neurons into a cell cycle. While neurogenesis is well known to proceed within the subventricular zone and dentate gyrus [18, 19] of the adult brain for the maintenance of brain structure and function, the evidence presented here is for terminally differentiated neurons resident in the hippocampus and cortical regions of the brain.

Aberrant cell cycle signaling in AD

Although numerous hypotheses have been postulated to explain AD, much evidence now exists that AD is a disease of aberrant, albeit unsuccessful, reentry of neurons into the cell cycle resulting in synapse and neurite contraction and neuron death ([14, 16, 20–41]; see [12–15] for reviews). The unscheduled initiation of a cell division cycle in a mature, normally post-mitotic neuron has been demonstrated to lead to an abortive re-activation of a variety of cell cycle components and ultimately the demise of the cell (Fig. 1). Neuronal changes supporting the involvement of cell cycle related events in the etiology of AD include:

Cell cycle markers—The ectopic expression of a number of cell cycle proteins have been reported in those regions of the brain affected by AD (e.g., cyclin B1, cdc2 kinase, PCNA, cdk4, p16, but not cyclins A and D), but not in areas unaffected by AD pathology or in control brains [20, 21, 42]. As might be expected of a process that is central to the etiology of neurodegeneration, changes in cell cycle markers have been found early in the disease process in those individuals with mild cognitive impairment (MCI) [42]. These researchers found markedly increased numbers of neurons immunopositive for cyclin D (5.2% and 6.3%) and PCNA (7.0% and 7.1%) in MCI and AD, respectively, compared with controls (0.4% and 0.4%, respectively). A number of the cell cycle regulators have been detected in vulnerable neurons before lesion formation [43, 44]. Progression into the cell cycle as assessed by the expression of different cell cycle markers appears to be dependent upon AD severity; neurons positive for NFTs stain strongly for cdc2 kinase (cdk1) and its associated cyclin B1 in hippocampal regions of the AD brain, suggesting that in some cases the G1/S checkpoint has been bypassed and that the cell cycle is arrested at G2. These findings led Herrup and colleagues [42] to suggest that both the mechanism of cell loss (a cell cycle-induced death) and the rate of cell loss (a slow atrophy over months) are identical at all stages of the disease process.

Chromosome replication (endoreduplication)—The most compelling evidence that differentiated neurons reenter the cell cycle comes from Yang, Herrup, and colleagues [22] who demonstrated that a significant number of neurons in affected regions of AD brain (hippocampal pyramidal and basal forebrain neurons) have undergone full or partial DNA replication, suggesting certain neurons have completed S phase. Cells in unaffected regions of the AD brain or in the hippocampus of nondemented age-matched controls show no such anomalies. Therefore, AD neurons appear to complete a nearly full S phase, but because mitosis is not initiated, the cells remain polyploid. This genetic imbalance seems to persist for many months before the neurons die [22, 42] and this genomic replication without cytokinesis (endoreduplication) will have dramatic implications for the overexpression of neuronal proteins such as amyloid- β protein precursor (A β PP), as is the case with Down syndrome [45] and AD (see below). Endoreduplication in plants is a well-described phenomenon that allows for sufficient protein synthesis [46]. However, such overexpression in a normally differentiated cell population appears to promote neuron death.

Neuronal hypertrophy—DNA content is almost invariably associated with the size of a cell [47]. In this respect, hypertrophy of neuronal cell bodies, nuclei, and nucleoli of CA1 of

hippocampus and anterior cingulate gyrus neurons has been reported in asymptomatic AD and MCI subjects [48–51].

Mitochondrial alterations—Changes suggestive of mitochondria replication have been reported in those neurons vulnerable to AD neuropathology [23]. Pyramidal neurons of the AD brain contain 3-fold elevated levels of cytoplasmic mitochondrial DNA and increased Cox-1 expression, indicative of *de novo* mitochondrion synthesis that would be expected during cell division to meet the energy demands of the newly created daughter cells [24]. Unlike division competent neurons, it remains to be determined if such alterations in mitochondrial metabolism in differentiated neurons are responsible for an imbalance in energy metabolism observed in the AD brain.

Tau phosphorylation and NFT formation—Phosphorylation of the microtubule-associated protein tau occurs during metaphase of neuronal division, and during differentiation [25, 26], hyperphosphorylated tau is observed in neurons of the fetal brain [25]. Disassembly of the rigid microtubule structure of neurons for neuronal division is accomplished by removing the microtubule stabilizing protein tau, by its phosphorylation. Therefore, it is interesting that hyperphosphorylation of the microtubule-associated protein tau, as detected in NFT, is one of the major pathological features of neuronal degeneration in AD [52], and indicates attempted division of pyramidal neurons in AD.

Mitotic signal transduction pathways—Signal transduction pathways, regulated by a variety of mitogens and growth factors, are upregulated in the AD brain [27]. Mitogen-activated protein kinases such as ERK and other signal transduction and transcription activators, such as Janus kinase and phosphoinositol 3-kinase/Akt [28], play a major role in the entry of cells into the cell cycle, as well as controlling their progression throughout the various stages [29]. These pathways are associated with AD neuropathology [30].

AD neurons proceed to metaphase and then arrest?—The above data suggest that most all the biochemical and pathological changes associated with AD can be explained by the aberrant reentry of terminally differentiated neurons into the cell cycle (e.g., chromosomal replication leading to polyploidy, upregulation of cell cycle markers, tau phosphorylation, A β PP metabolism and A β deposition, neuronal hypertrophy, oxidative stress, increased mitochondrial DNA and Cox-1 expression, upregulated growth factor signaling pathways, synapse loss, and death of differentiated neurons) [12, 53]. Two studies support this claim. Forced cell cycle activation in terminally differentiated neurons via conditional expression of the simian virus 40 large T antigen (oncogene) forms A β deposits and tau pathology in the mouse cortex [54]. Similarly, forced cell cycle activation in primary neurons is accompanied by tau phosphorylation [55]. Not surprisingly, the AD brain displays many of the neuropathological and biochemical changes observed in the rapidly growing and differentiating fetal brain, namely the presence of A β [56], hyperphosphorylated tau [25], and presenilin expression [57]. It is unclear whether neurons in the AD brain are proceeding via the normal cell cycle division pathway, or an aberrant, uncoordinated, pathway. In this connection, the failure of microtubules to form spindle fibers to attach to kinetochores [58, 59] has been shown to arrest the cell in metaphase (M

checkpoint). Likewise, improper alignment of the spindle will block cytokinesis; either of these processes if irreparable triggers neuron death.

EVIDENCE THAT CELL CYCLE REENTRY INDUCES MEMORY LOSS

It has been demonstrated that neurogenesis in the adult brain is linked to memory loss [60]. Increasing neurogenesis after the formation of a memory was sufficient to induce forgetting in adult mice. However, in contrast, during infancy, when hippocampal neurogenesis levels are high and freshly generated memories tend to be rapidly forgotten (infantile amnesia), decreasing neurogenesis after memory formation mitigated forgetting. This is supported by studies in precocial species, including guinea pigs and degus, where most granule cells are generated prenatally [60]. Consistent with reduced levels of postnatal hippocampal neurogenesis, infant guinea pigs and degus do not exhibit forgetting. However, increasing neurogenesis after memory formation induced infantile amnesia in these species [60].

EVIDENCE THAT THE DIFFERENTIAL REGULATION OF A β PP PROCESSING REGULATES CELL CYCLE REENTRY AND NEURODEGENERATION

Mutations associated with EOFAD drive A β PP processing and cell cycle reentry

A β PP, PS1, and PS2 are developmental proteins [57, 61–63]. It is therefore not surprising that mutations in these genes might impact cell cycle dynamics.

The overexpression of FAD mutant A β PP, which promotes A β generation [64], has been shown to promote the aberrant reentry of primary neurons into the cell cycle, as demonstrated by the initial induction of DNA synthesis and cell cycle marker expression, followed by apoptotic cell death [65]. Recently it has been shown that A β signaling through tau is necessary to drive ectopic neuronal cell cycle reentry in mouse primary neurons and in an A β PP-transgenic (hAPPJ20) mouse [66]. Overexpression of FAD mutants of A β PP [67–69] has been shown to induce apoptosis in both primary neurons and cell lines. The expression of the Swedish double mutations of A β PP or the A β PP intracellular domain, into nerve growth factor differentiated PC12 cells or rat primary cortical neurons reactivates the cell cycle by upregulating cyclins D1 and B1 [70]. Elevations in cyclins D1 and B1 expression are observed in the brains of Tg2576 mice harboring the Swe-A β PP (A β PP^{sw+}) mutations.

Like FAD mutant A β PP, presenilin-1 FAD mutations also increase A β production [71] and induce cell cycle abnormalities in mitotically competent cells [72–75]. Mice expressing the knock-in presenilin-1 mutation M146V (presenilin-1 KIM146V) display accelerated entry of cortical neurons into the cell cycle as determined by accumulation of cyclin D1 and phosphoretinoblastoma proteins, and by an increase in BrdU incorporation rates [76]. These neurons become arrested at S phase or underwent apoptosis, a response that was blocked by downregulating cyclin D1 or inhibiting the cell cycle with quercetin, but not by γ -secretase inhibition. The results of γ -secretase inhibition in this study are difficult to interpret given the non-specificity of action of such inhibitors. In this regard, presenilin-1 mutations have

been proposed to affect γ -secretase processing of Notch, accounting for impairments in self-renewal and altered differentiation toward neuronal lineages in subventricular zone neural progenitor cells expressing the FAD-linked presenilin-1 DeltaE9 variant [75]. Given that presenilin-1 is one component of the γ -secretase complex that processes A β PP and Notch, and that presenilin-1 mutations promote A β production [77], these results suggest that presenilin-1 mutations also may induce cell cycle abnormalities via alterations in the processing of A β PP or Notch.

Overexpression of PS1 and PS2, mutations of these proteins: PS1(P117L), PS1(P267S), PS1(E280A), PS2(N141I), and the carboxyl-terminally deleted PS2 construct PS2(166aa) in HeLa cells arrests the cells in the G1 phase of the cell cycle [78, 79]. The highly pathogenic AD PS1 (P117R) mutation, but not other PS1 mutations, causes a specific increase in key G1/S phase regulatory proteins, p53, and its effector p21, causing G1 phase prolongation with simultaneous S phase shortening, and lowering basal apoptosis in human lymphocytes [10]. Lymphocytes from AD patients have been demonstrated to show an enhanced rate of proliferation and increased phosphorylation of the retinoblastoma protein and other members of the family of pocket proteins compared with cell lines derived from normal age-matched controls [80]. Changes in these cell cycle proteins in lymphocytes have been proposed as a potential biomarker for the diagnosis of AD [10, 80–84].

That A β PP is directly involved in cell cycle signaling and neurogenesis has recently been reviewed (Atwood and Bowen, *Hormones and Behavior*, in submission). Briefly, it has been shown that the differential processing of A β PP regulates the proliferation and differentiation of human embryonic stem cells (hESC); A β promotes hESC proliferation while sA β PP α drives hESCs toward a neuronal precursor cell phenotype [85, 86]. In differentiated neurons, A β _{1–42} promotes neurogenesis of subventricular zone precursor cells derived from developing or young adult animals [26, 87–92]. *In vivo*, an increase in hippocampal neurogenesis and/or proliferation has been reported in younger transgenic mouse models overexpressing A β PP mutations [88, 93–97]. The impact of other A β PP mutations that lead to cerebral amyloid angiopathy and stroke (e.g., Dutch and Iowa mutations) on cell cycle reentry has not been explored.

Age-related endocrine dyscrasia drives A β PP processing and cell cycle reentry

We and others have demonstrated that the endocrine dyscrasia following menopause and during andropause (suppressed sex steroid and inhibin signaling, elevated gonadotropin-releasing hormone 1 (GnRH1), luteinizing hormone (LH), follicle-stimulating hormone, and activin signaling) regulates A β PP processing pathways *both in vivo* and *in vitro* [98]. LH/human chorionic gonadotropin (hCG), when in balance with other hormones of the HPG axis, is a well-known mitogenic signal that drives normal cell proliferation and differentiation (reviewed in [18, 85, 99, 100]). However, when the ratio of LH:sex steroids increases, the differentiation signal is lost as A β PP processing toward the amyloidogenic pathway drives cell cycle reentry without the requisite differentiation signal to allow for completion of the cell cycle [101–108]. The increase in circulating LH at menopause and during andropause corresponds to the time when increases in A β [109] and cell cycle reactivation are observed during MCI [110]. In human studies, multiple linear regression

analysis reveals that serum LH concentration, but not testosterone, significantly correlates with plasma A β levels in men [111, 112], suggesting that increased serum LH concentration is associated with the accumulation of A β in plasma.

Reproductive endocrine dyscrasia may act via the regulation of inflammatory cytokines. Gonadotropins likely regulate A β PP processing and A β generation and deposition via tumor necrosis factor (TNF) (see [113, 114] for reviews), a master inflammatory cytokine, and which is known to alter cell cycle dynamics [115]. LH, which is elevated in men with AD, is positively correlated with TNF [116].

LH also has been shown to regulate tau phosphorylation *in vitro* [117] and *in vivo* [108]. Genetic ablation of *LHCGR* in APP^{sw} mice decreased tau phosphorylation by ~50% that induced by A β PP overexpression in these mice [108]. The residue-specific phosphorylation of tau in mitotically active neurons is driven by cyclin-dependent kinases (Cdk; [25, 118–121]. Several Cdk5 are associated with phosphorylated tau in AD and *in vitro* phosphorylate tau in a manner similar to that found in AD [122–125]. A number of other kinases such as glycogen synthase kinase-3 β (GSK3 β) also are pivotal in tau phosphorylation (e.g., [126]). Compelling evidence that reactivation of the cell cycle induces tau phosphorylation is provided by two studies: McShea and colleagues [55] demonstrate that cell cycle induction *in vitro* induces tau phosphorylation, while Park and colleagues [54] demonstrate that cell cycle induction *in vivo* induces NFT and amyloid deposits. More recently, it has been demonstrated that specific phosphorylation of tau (Thr231) can promote MAPK activation in PC12 cells, which in turn could (further) activate the cell cycle reentry mechanisms in neurons [127, 128].

In reproductive tissues, LH has been shown to increase both the expression and kinase activity of Cdk5 in Leydig TM3 cells [129]. Supporting LH-induced Cdk5 metabolism, a significant decrease in Cdk5 expression and activity has been noted in rat testis after hypophysectomy [129]. These LH-mediated changes in Cdk5 metabolism are important in the context of reports that Cdk5 is a potent cell cycle suppressor [130, 131]. In particular, although Cdk5 is normally located in both nucleus and cytoplasm [131–135], the loss of nuclear Cdk5 leads to a failure of cell cycle suppression both *in vivo* and *in vitro*. Cell cycle activity detected in Cdk5^{–/–} neurons includes the abnormal expression of cell cycle proteins such as cyclin D, cyclin A, and PCNA (proliferating cell nuclear antigen) as well as 5-bromo-2-deoxyuridine incorporation [130]. Similar cell cycle events are found in neurons at risk for death in AD [43, 136]. In post-mitotic neurons in culture, Cdk5 nuclear export is required for cell cycle reentry [137]. Cell cycle suppression by Cdk5 requires its binding to the p35 activator protein and E2F1. Formation of this complex excludes the E2F1 cofactor, DP1, thus inhibiting E2F1 binding to the promoters of various cell cycle genes. In this way, the formation of the E2F1–Cdk5–p35 complex in the nucleus prevents the advance of the cell cycle and appears to be a neuroprotective function of Cdk5 [138]. The Cdk5 activator protein p25, however, preferentially binds GSK3 β which leads to enhanced phosphorylation of tau, but decreased phosphorylation of β -catenin. Coexpression of GSK3 β and p25 in cultured neurons results in a neurodegeneration phenotype [139]. LH/hCG also regulates the phosphorylation of microtubule-associated proteins and GSK3 β phosphorylation [140].

LH induced changes in both A β PP metabolism and Cdk5 metabolism (and concurrent tau phosphorylation) may be required for cell cycle reentry. While both A β and P301L tau expression independently affect the regulation of cell proliferation and synaptic elements, cell cycle reentry as assessed by DNA synthesis is only observed when SH-SY5Y cells overexpressing human wild-type or P301L tau were incubated with A β [141]. Similarly, studies using differentiated neurons exposed to A β exhibit Cdk5-mediated tau hyperphosphorylation, cell cycle reentry, and neuronal loss [66, 142, 143]. Inhibition of Cdk5 activity or tau phosphorylation (reviewed in [26]) prevents A β -mediated cell death. *In vivo*, icv-injection of mice with A β activates Cdk5, promoting tau phosphorylation, cell cycle induction, synaptotoxicity, and death of post-mitotic neurons [143–145]. The sex hormone-mediated changes in A β PP and Cdk5 metabolism (see above) may therefore be responsible for inducing cell cycle reactivation and apoptotic death of post-mitotic neurons. Similar cell cycle changes were not observed in the 3xTg-AD model [146], although the hormonal status of these young mice is different to the hormonal status of older mice.

Advanced glycation end-products also have been demonstrated to be mitogenic signals that trigger cell cycle reentry of neurons in a mouse model of neurodegeneration [147]. Sex hormones are known to regulate advanced glycation end-product levels [148, 149], although whether age-related endocrine dyscrasia alters advanced glycation end-product formation/degradation remains to be determined. Likewise, it is not known whether advanced glycation end-product-induced cell cycle reentry is mediated via A β and tau metabolism.

EVIDENCE THAT EOFAD MUTATIONS AND ENDOCRINE DYSCRASIA INDUCE COGNITIVE DECLINE

Mutations in *APP*, *PSEN1*, and *PSEN2* induce EOFAD (Fig. 1) [150–154]. Similarly, epidemiological and clinical evidence supports endocrine dyscrasia (particularly high LH:sex steroids) as regulating cognitive health and AD (Fig. 1), and includes: 1) the abrupt cognitive deficits observed in premenopausal women following chemical castration (with GnRH agonists), deficits that are reversible with simultaneous administration of 17 β -estradiol [155]; 2) the increased risk of dementia in premenopausal women who have had a bilateral oophorectomy [156]; 3) improvement in cognitive performance of cognitively healthy postmenopausal women taking 17 β -estradiol in 12 separate trials [157]; 4) the increased prevalence of cognitive disease in women, which correlates with the abrupt earlier loss of gonadal function [158–163]; 5) the negative correlation between serum 17 β -estradiol in women [164] and testosterone in men [165, 166] with AD, but positive correlation between serum gonadotropins in men and women with AD [116, 165–171]; 6) the 50% decrease in the prevalence of AD following treatment with GnRH agonists (gonadotropin-lowering drug Lupron Depot®) [172, 173] (Beaird, Bowen, Perry, Atwood et al., unpublished data); 7) the significant improvement in memory in men with prostate cancer treated with GnRH1 agonists after 6 to 12 months [174], and 8) the stabilization of cognitive performance in women with mild to moderate AD taking acetylcholine esterase inhibitors and a GnRH1 agonist over a 48-week period [175]. The loss of cell cycle control also has been demonstrated in another neurodegenerative condition, ataxia-telangiectasia, and likely

represents a common disease mechanism that underlies various (neurodegenerative) diseases and conditions in humans and animals [176–178].

Therapeutic strategies targeting the cell cycle

Therapeutics that target aberrant cell cycle reentry are therefore most likely to succeed in preventing or reversing the neurodegeneration associated with EOFD and LOSAD. One approach has involved the rebalancing of reproductive hormones after menopause and during andropause. Although hormone replacement therapy with either 17 β -estradiol or testosterone only elicits partial rebalancing of the HPG axis, these physiologically relevant sex steroids have been shown to decrease the incidence and delay the onset of cognitive decline among elderly women and men (reviewed in [157, 179, 180]). Indeed, an improvement in cognition has been reported in women with AD treated with 17 β -estradiol in three controlled [181–183] intervention studies, and in men with AD treated with testosterone in two controlled intervention studies [179, 180]. Moreover, 17 β -estradiol has been shown to improve the cognition of cognitively normal post-menopausal women in 12 of 15 studies (three studies indicated no difference) [157].

Another strategy to rebalancing the HPG axis to prevent aberrant cell cycle activation has involved the use of the GnRH superagonist leuprolide acetate (Lupron Depot). Leuprolide acetate acts to suppress gonadotropins and sex steroids, thereby rebalancing the ratios of these hormones, albeit at lower concentrations. Leuprolide acetate also only partially rebalances the axis as it does not greatly impact other hormones of the HPG axis. A Phase II dose ranging study performed in 2003/2004, although only recently published [175], demonstrated that the combination of leuprolide acetate and an acetylcholinesterase inhibitor (AChEI) was both safe and efficacious in the treatment of women with mild to moderate AD. Sub-group analysis of cognitive performance in women with mild to moderate AD taking AChEIs and implanted subcutaneously at 0, 12, 24, and 36 weeks with high-dose (22.5 mg) leuprolide acetate showed a stabilization in cognitive decline (ADAS-Cog, ADCS-CGIC) and activities of daily living (ADCS-ADL) over a 48 week period. A similar effect was not observed in the low dose Lupron group taking AChEIs, or in the placebo group taking AChEIs, or when patients were treated with Lupron alone. A possible mechanism of action for this combination therapy is that Lupron acts to halt any further cell cycle-related neurodegeneration and suppress neuroinflammation thereby allowing AChEIs to act on remaining neurons to maintain cholinergic function [175]. A small study has confirmed these results, demonstrating that suppression of androgens and gonadotropins with GnRH1 agonists in men with prostate cancer significantly improved visual-memory (Rey test) 6 and 12 months, and significantly improved inversed number-memory test (WAIS) after 6 months [174]. Thus, global cognitive performances were preserved after 12 months of androgen and gonadotropin suppression.

Preclinical studies have demonstrated the efficacy of increasing sex steroids and suppressing gonadotropins in reversing neurodegeneration and cognitive decline in animal models of AD (reviewed in [98, 184]). Preclinical studies in mouse models of AD also have demonstrated that specific inhibitors of the cell cycle, such as the oral administration of the synthetic retinoid X receptor-selective retinoid bexarotene, stimulates the rapid reversal of cognitive,

social, and olfactory deficits, improves neural circuit function and enhances the clearance of soluble A β within hours in an apolipoprotein E-dependent manner [185, 186].

Non-steroidal anti-inflammatory drugs (NSAIDs) also have been shown to prevent, but do not reverse, neuronal cell cycle reentry in a mouse model of AD [187]. Inflammation in AD is likely driven by the neurodegeneration induced by excessive A β deposition and cell cycle reentry in the case of EOFAD, and by the neurodegeneration induced by excessive A β deposition and cell cycle reentry driven by reproductive endocrine dyscrasia in the case of LOSAD [113, 114]. In the study of Herrup and colleagues, inflammation promoted by LPS at young ages in R1.40 mice induced the early appearance of cell cycle reactivation, whereas treatment with two different NSAIDs blocked neuronal cell cycle activation and alterations in brain microglia without altering A β PP processing and steady-state A β levels [187]. Since retrospective human epidemiological studies, but not prospective clinical trials, have identified long-term use of NSAIDs as protective against AD, these authors have suggested that NSAID use in human AD may need to be initiated as early as possible to prevent disease progression.

SUMMARY

Aberrant cell cycle reactivation in neurons is a common pathway that can explain familial AD, late-onset AD, Down syndrome, and other neurological diseases. In the case of EOFAD, mutations in *APP*, *PSEN1*, and *PSEN2* that alter A β PP and Notch processing drive reactivation of the cell cycle [11, 66], while in LOSAD, endocrine dyscrasia that drives A β PP processing towards the amyloidogenic pathway and tau phosphorylation (via TNF) [113, 114] drive reactivation of the cell cycle in mature post-mitotic neurons [101]. Since neurogenesis after the formation of a memory has been shown to be sufficient to induce forgetting [60], any stimulus that promotes cell cycle reentry of post-mitotic neurons appears to be a negative event for memory. In this connection, since hormones of the HPG axis regulate fetal and adult neurogenesis, any disruption in their signaling such as occurs following menopause and during andropause leads to dyotic signaling that drives aberrant reentry of neurons into the cell cycle would therefore result in the loss of previously encoded memories and prevent the retention of new information as memories. Similarly, EOFAD mutations that drive cell proliferation are going to limit the capacity of the brain to store memories. The relationship between these mutations and endocrine dyscrasia with aging between 30 and 60 warrants exploration.

It is hoped that this understanding of the mechanisms driving cell cycle reentry of neurons can be used to develop appropriate therapies for this devastating disease. Upstream targets are more likely to hold promise in preventing or halting the progression of AD. This is becoming evident from the failure of numerous clinical trials aimed at decreasing brain A β concentration and aggregation, since downstream targets such as A β have multiple functions [188] and the non-discrepant removal of all forms of A β results in serious side-effects. This is becoming more evident from our increased understanding of the roles of A β PP in cell cycle events, which indicates that the appropriate regulation of A β PP cleavage products is required for normal neuron survival. As a result, drugs that prevent cell cycle reentry of vulnerable post-mitotic neurons in the brain may not be effective unless they are specific.

The inhibition of cell cycle reentry of neurons is a therapeutic target that could be achieved by the rebalancing of the reproductive and stress hormone axes in the case of LOSAD, and by clustered, regularly interspaced, short palindromic repeat (CRISPR) genome editing in the case of EOFAD, particularly in conjunction with *in vitro* fertilization techniques, for those individuals carrying A β PP, PS1, or PS2 mutations.

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Figure 1.

Endocrine dyscrasia and AD-related genetic mutations intersect at the cell cycle to drive neurodegeneration and cognitive decline in AD. Model of aberrant cell cycle reentry initiated by 1) aging-related endocrine dyscrasia leading to LOSAD and 2) genetic mutations in *APP*, *PS1*, and *PS2* leading to EOFAD. Endocrine dyscrasia and genetic mutations of *APP*, *PS1*, and *PS2* alter TNF and AβPP metabolism to reactivate the cell cycle in a post-mitotic, terminally differentiated neuron. This abortive cell cycle reentry drives neuron hypertrophy, autophagy, synapse and neuron loss, neuron dysfunction, amyloid deposition, neurofibrillary tangle formation, and ultimately cell death.