

Bowen RL, Verdile G, Liu T, Parlow AF, Perry G, Smith MA, Martins RN, Atwood CS. Luteinizing hormone, a reproductive regulator that modulates the processing of amyloid-beta precursor protein and amyloid-beta deposition. *J Biol Chem.* 2004 May 7;279(19):20539-45. Epub 2004 Feb 9.

Hormonal changes associated with the dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis following menopause/andropause have been implicated in the pathogenesis of Alzheimer's disease (AD). Experimental support for this has come from studies demonstrating an increase in amyloid-beta (Abeta) deposition following ovariectomy/castration. Because sex steroids and gonadotropins are both part of the HPG feedback loop, any loss in sex steroids results in a proportionate increase in gonadotropins. To assess whether Abeta generation was due to the loss of serum 17beta-estradiol or to the up-regulation of serum gonadotropins, we treated C57Bl/6J mice with the anti-gonadotropin leuprolide acetate, which suppresses both sex steroids and gonadotropins. Leuprolide acetate treatment resulted in a 3.5-fold ($p < 0.0001$) and a 1.5-fold ($p < 0.024$) reduction in total brain Abeta1-42 and Abeta1-40 concentrations, respectively, after 8 weeks of treatment. To further explore the role of gonadotropins in promoting amyloidogenesis, M17 neuroblastoma cells were treated with the gonadotropin luteinizing hormone (LH) at concentrations equivalent to early adulthood (10 mIU/ml) or post-menopause/andropause (30 mIU/ml). LH did not alter amyloid-beta precursor protein (AbetaPP) expression but did alter AbetaPP processing toward the amyloidogenic pathway as evidenced by increased secretion and insolubility of Abeta, decreased alphaAbetaPP secretion, and increased AbetaPP-C99 levels. These results suggest the marked increases in serum LH following menopause/andropause as a physiologically relevant signal that could promote Abeta secretion and deposition in the aging brain. Suppression of the age-related increase in serum gonadotropins using anti-gonadotropin agents may represent a novel therapeutic strategy for AD.

Genazzani AR, Pluchino N, Luisi S, Luisi M. Estrogen, cognition and female ageing. *Hum Reprod Update.* 2007 Mar-Apr;13(2):175-87.

Starting from fetal life, estrogens are crucial in determining central gender dimorphism, and an estrogen-induced synaptic plasticity is well evident during puberty and seasonal changes as well as during the ovarian cycle. Estrogens act on the central nervous system (CNS) both through genomic mechanisms, modulating synthesis, release and metabolism of neurotransmitters, neuropeptides and neurosteroids, and through non-genomic mechanisms, influencing electrical excitability, synaptic function and morphological features. Therefore, estrogen's neuroactive effects are multifaceted and encompass a system that ranges from the chemical to the biochemical to the genomic mechanisms, protecting against a wide range of neurotoxic insults. Clinical evidences show that, during the climacteric

period, estrogen withdrawal in the limbic system gives rise to modifications in mood, behaviour and cognition and that estrogen administration is able to improve mood and cognitive efficiency in post-menopause. Many biological mechanisms support the hypothesis that estrogens might protect against Alzheimer's disease (AD) by influencing neurotransmission, increasing cerebral blood flow, modulating growth proteins associated with axonal elongation and blunting the neurotoxic effects of beta-amyloid. On the contrary, clinical studies of estrogen replacement therapy (ERT) and cognitive function have reported controversial results, indicating a lack of efficacy of estrogens on cognition in post-menopausal women aged ≥ 65 years. These findings suggest the presence of a critical period for HRT-related neuroprotection and underlie the potential importance of early initiation of therapy for cognitive benefit. In this review, we shall first describe the multiple effects of steroids in the nervous system, which may be significant in the ageing process. A critical update of HRT use in women and a discussion of possible prospectives for steroid use are subsequently proposed.

[Kenny AM, Bellantonio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2002 May;57\(5\):M321-5.](#)

BACKGROUND: Many men older than 50 years have bioavailable testosterone levels below the reference range for young adult men. The impact of the decreased androgen levels on cognition and health perception has received little attention. **METHODS:** Sixty-seven men (mean age 76 \pm 4 years, range 65-87) with bioavailable testosterone levels below 128 ng/dl (lower limit for adult normal range) were randomized to receive transdermal testosterone (2-2.5 mg patches/d) or placebo patches for 1 year. All men received 500 mg supplemental calcium and 400 IU vitamin D. Outcome measures included sex hormones [testosterone, bioavailable testosterone, sex hormone binding globulin (SHBG), estradiol, and estrone], cognitive tests (Digit Symbol, Digit Span, Trailmaking A and B), health perception (Medical Outcome Survey Short-form 36 or SF-36), lower extremity muscle strength and power, and calcium intake. **RESULTS:** Twenty-three men (34%) withdrew from the study; 44 men completed the trial. Bioavailable testosterone levels increased from 93 \pm 34 (SD) to 162 \pm 100 ng/dl ($p < .002$) at 12 months in the testosterone group ($n = 24$) while no change occurred in the control group ($n = 20$). (NOTICE—levels increased on average to just above lower limit of “normal”. Better target would have been youthful level of 250ng/dl for all exp. patients -HHL.) While there was no change in estradiol levels in either group, estrone levels increased in the testosterone group (28 \pm 7 to 32 \pm 9 pg/dl, $p = .017$). Scores on the Digit Symbol test improved in both the testosterone and placebo groups. Scores on Trailmaking B improved in men treated with testosterone ($p < .005$), although the changes were not statistically different from the changes seen in the placebo group.

Twelve-month scores on Trailmaking B for the entire group were correlated with 12-month testosterone levels ($p = .016$). Scores for health perception measured by SF-36 did not change significantly, though scores of mental and general health declined in both groups during the 12-month intervention. Twelve-month bioavailable testosterone scores were directly correlated with scores for physical role ($p = .022$), vitality ($p = .036$), and the physical composite score ($p = .010$). CONCLUSIONS: Transdermal testosterone treatment in men with low bioavailable testosterone levels does not impair and may improve cognitive function. Treatment did not improve health perception but this may have been due to the side effects of skin irritation suggested by similar reactions in both the testosterone and placebo groups.

[McEwen B. Estrogen actions throughout the brain. *Recent Prog Horm Res.* 2002;57:357-84.](#)

Besides affecting the hypothalamus and other brain areas related to reproduction, ovarian steroids have widespread effects throughout the brain, on serotonin pathways, catecholaminergic neurons, and the basal forebrain cholinergic system as well as the hippocampal formation, a brain region involved in spatial and declarative memory. Thus, ovarian steroids have measurable effects on affective state as well as cognition, with implications for dementia. Two actions are discussed in this review; both appear to involve a combination of genomic and nongenomic actions of ovarian hormones. First, regulation of the serotonergic system appears to be linked to the presence of estrogen- and progestin-sensitive neurons in the midbrain raphe as well as possibly nongenomic actions in brain areas to which serotonin neurons project their axons. Second, ovarian hormones regulate synapse turnover in the CA1 region of the hippocampus during the 4- to 5-day estrous cycle of the female rat. Formation of new excitatory synapses is induced by estradiol and involves N-methyl-D-aspartate (NMDA) receptors, whereas downregulation of these synapses involves intracellular progestin receptors. A new, rapid method of radioimmunocytochemistry has made possible the demonstration of synapse formation by labeling and quantifying the specific synaptic and dendritic molecules involved. Although NMDA receptor activation is required for synapse formation, inhibitory interneurons may play a pivotal role as they express nuclear estrogen receptor-alpha (ER α). It is also likely that estrogens may locally regulate events at the sites of synaptic contact in the excitatory pyramidal neurons where the synapses form. Indeed, recent ultrastructural data reveal extranuclear ER α immunoreactivity within select dendritic spines on hippocampal principal cells, axons, axon terminals, and glial processes. In particular, the presence of ER in dendrites is consistent with a model for synapse formation in which filopodia from dendrites grow out to find new synaptic contacts and estrogens regulate local, post-transcriptional events via second messenger systems.

Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM. Free testosterone and risk for Alzheimer disease in older men. *Neurology*. 2004 Jan 27;62(2):188-93.

OBJECTIVE: To investigate the relationships between age-associated decreases in endogenous serum total testosterone (T) and a free T index (FTI) in men and the subsequent development of Alzheimer disease (AD). **METHOD:** The authors used a prospective, longitudinal design with follow-up in men since 1958. Participants were from the Baltimore Longitudinal Study of Aging, a community-dwelling volunteer sample with baseline ages of 32 to 87 years. All subjects were free of AD at baseline T assessment. Five hundred seventy-four men assessed at multiple time points were followed for a mean of 19.1 years (range, 4 to 37 years). Diagnoses of AD were based on biennial physical, neurologic, and neuropsychological evaluations. **RESULTS:** Diagnosis of AD was associated inversely with FTI by itself and after adjustments for age, education, smoking status, body mass index, diabetes, any cancer diagnoses, and hormone supplements. In separate analyses, total T and sex hormone binding globulin were not significant predictors after adjustment with covariates. Increases in the FTI were associated with decreased risk of AD (hazard ratio = 0.74; 95% CI = 0.57 to 0.96), a 26% decrease for each 10-nmol/nmol FTI increase. **CONCLUSIONS:** Calculated free testosterone concentrations were lower in men who developed Alzheimer disease, and this difference occurred before diagnosis. Future research may determine whether higher endogenous free testosterone levels offer protection against a diagnosis of Alzheimer disease in older men.

Monks DA, Arciszewska G, Watson NV. Estrogen-inducible progesterone receptors in the rat lumbar spinal cord: regulation by ovarian steroids and fluctuation across the estrous cycle. *Horm Behav*. 2001 Dec;40(4):490-6.

Ovarian hormones influence the physiology of the spinal cord through incompletely understood cellular mechanisms. To date, there has been little compelling evidence for progesterone receptors in spinal cord neurons. Using two antibodies specific for progesterone receptors in an immunohistochemical investigation, we now report the presence of estrogen-inducible progesterone receptors in the spinal cord. Estrogen-inducible progesterone receptors were observed in the neurons of lamina X and the interomedialateral cell column, which are also known to express estrogen receptors. Estrogen-inducible progesterone receptors similar to those observed in females were also apparent in lamina X and interomedialateral cell column neurons in the spinal cords of males treated with estradiol. Furthermore, the density of progesterone receptors in lamina X was observed to fluctuate across the estrous cycle in female rats, with the highest progesterone receptor expression levels occurring late in proestrus, following the estradiol surge and coincident with high circulating progesterone levels. The lowest progesterone receptor expression levels were observed late in estrus following the progesterone surge. Together, these

results demonstrate that estrogen-sensitive progestin targets exist in the spinal cord, and their possible role in the nervous control of reproduction and ovarian steroid modulation of nociception is discussed.(Quoted by T.S. Wiley as proof that women must cycle, yet nothing here indicates there is no benefit with a constant estrogen and progesterone level—HHL)

[Perez J, Luquin S, Naftolin F, Garcia-Segura LM. The role of estradiol and progesterone in phased synaptic remodelling of the rat arcuate nucleus. Brain Res. 1993 Apr 9;608\(1\):38-44.](#)

During the estrous cycle there is a phasic synaptic remodelling in the hypothalamic arcuate nucleus, consisting in a loss and regain of axo-somatic synapses during the 48 h period between the morning of proestrus and the morning of metestrus. Synaptic changes are accompanied by cyclic modifications in the number of intramembrane particles in the plasma membrane of arcuate neuronal somas. To test the effect of the ovarian steroids on arcuate axo-somatic synapses we treated castrated females either with oil vehicle, 17 beta-estradiol, progesterone, or a combination of estradiol and progesterone, and observed them for 48 h. The number of axo-somatic synaptic profiles showed a 33% fall by 24 h after estradiol treatment and returned to control levels by 48 h. The effect of estradiol on axo-somatic synapses was accompanied by a marked and reversible modification of the number of intramembrane particles in the plasma membrane of arcuate neuronal somas. Progesterone alone did not affect the number of axo-somatic synaptic profiles nor the number of intramembrane particles, but when administered together with estradiol, blocked the effects of estradiol on neuronal membrane and synapses.(also quoted by Wiley to justify cycling, however it's not clear that the estrogen/progesterone cycle is more beneficial than the static estrogen/progesterone of pregnancy or breastfeeding—HHL)

[Prinz PN; Scanlan JM; Vitaliano PP; Moe KE; Borson S; Toivola B; Merriam GR; Larsen LH; Reed HL Thyroid hormones: positive relationships with cognition in healthy, euthyroid older men. J Gerontol A Biol Sci Med Sci. 1999 Mar;54\(3\):M111-6.](#)

BACKGROUND: Although the association of clinical hypothyroidism with cognitive deficits is well known, the cognitive effects of thyroid hormones in euthyroid subjects are less studied and understood. The purpose of this study was to examine thyroid-cognition relationships in healthy, euthyroid older men. **METHODS:** We examined healthy men (N = 44, mean age = 72), excluding clinically hypothyroid/hyperthyroid or diabetic/hyperglycemic subjects and those with dementia, depression, CNS medications, or recent illness. Plasma samples obtained across a 24-hour period were pooled, then assayed for total thyroxine (TT4), total triiodothyronine (TT3), and T3 resin uptake. Free thyroxine index (FT4I) was calculated. A broad cognitive battery (including the Wechsler Adult Intelligence Scale-Revised [WAIS-R], the Dementia Rating Scale [DRS], and the Rivermead Behavioral Profile [PROFILE]) was administered to all subjects. **RESULTS:** Regression analyses controlling age and education showed TT4 and FT4I to have

significant positive relationships with measures of overall cognition; TT4 accounted for 8% to 12% of the variance in omnibus cognitive measures such as WAIS Performance, WAIS Verbal score, and GLOBAL cognitive scores. CONCLUSIONS: Our findings suggest that within "normal" range of variation in plasma thyroid hormones, TT4 but not T3 positively associates with general cognition in healthy elderly men.

[Rosario ER, Carroll JC, Oddo S, LaFerla FM, Pike CJ. Androgens regulate the development of neuropathology in a triple transgenic mouse model of Alzheimer's disease. J Neurosci. 2006 Dec 20;26\(51\):13384-9.](#)

Normal age-related testosterone depletion in men is a recently identified risk factor for Alzheimer's disease (AD), but how androgen loss affects the development of AD is unclear. To investigate the relationship between androgen depletion and AD, we compared how androgen status affects the progression of neuropathology in the triple transgenic mouse model of AD (3xTg-AD). Adult male 3xTg-AD mice were sham gonadectomized (GDX) or GDX to deplete endogenous androgens and then exposed for 4 months to either the androgen dihydrotestosterone (DHT) or to placebo. In comparison to gonadally intact 3xTg-AD mice, GDX mice exhibited robust increases in the accumulation of beta-amyloid (Abeta), the protein implicated as the primary causal factor in AD pathogenesis, in both hippocampus and amygdala. In parallel to elevated levels of Abeta, GDX mice exhibited significantly impaired spontaneous alternation behavior, indicating deficits in hippocampal function. Importantly, DHT treatment of GDX 3xTg-AD mice attenuated both Abeta accumulation and behavioral deficits. These data demonstrate that androgen 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, our finding that DHT protects 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.

[Stern RA; Davis JD; Rogers BL; Smith KE; Harrington CJ; Ott BR; Jackson IM; Prange AJ Jr. Preliminary study of the relationship between thyroid status and cognitive and neuropsychiatric functioning in euthyroid patients with Alzheimer dementia. Cogn Behav Neurol. 2004 Dec;17\(4\):219-23.](#)

OBJECTIVE: To investigate whether variations within normal ranges of thyroid functioning are related to cognitive and neuropsychiatric functioning in Alzheimer disease (AD). BACKGROUND: Mild alterations of thyroid hormone levels, even in the normal range, are associated with changes in mood and cognitive functioning in older, nondemented adults, and lower concentrations of thyroid hormones have been shown to be associated with an increased risk for cognitive decline. Less is known about the relationship between thyroid hormone levels and cognitive and neuropsychiatric dysfunction in AD. METHOD: Twenty-eight euthyroid patients with AD on donepezil underwent evaluation of thyroid status, including measures of

thyroid-stimulating hormone (TSH) and free thyroxine (FT4), and cognitive and neuropsychiatric assessment with the Alzheimer's Disease Assessment Scale, Neuropsychiatric Inventory, and Visual Analog Mood Scales. RESULTS: Correlational analyses indicated statistically significant associations between FT4 concentrations and self-reported feelings of fear and fatigue. Fear and fatigue were negatively correlated with FT4. There were no significant relationships between thyroid hormones and cognition and other depressive and anxiety symptoms. CONCLUSIONS: Results of this preliminary study support a relationship between thyroid status and neuropsychiatric symptoms in euthyroid individuals with AD, with lower concentrations of FT4 associated with fear and fatigue.

[Volpato S; Guralnik JM; Fried LP; Remaley AT; Cappola AR; Launer LJ. Serum thyroxine level and cognitive decline in euthyroid older women. Neurology 2002 Apr 9;58\(7\):1055-61.](#)

BACKGROUND: Clinical and subclinical hypothyroidism is associated with cognitive impairment. OBJECTIVE: This study investigated the association between thyroxine (T(4)) and thyroid-stimulating hormone (TSH) level and change over time in cognitive performance in a sample of older women with normal thyroid gland function. METHODS: T(4) and TSH were measured at baseline in 628 women (> or = 65 years) enrolled in the Women's Health and Aging Study, a community-based study of physically impaired women. Cognitive function was assessed at baseline and after 1, 2, and 3 years, using the Mini-Mental State Examination (MMSE). Incident cognitive decline was defined as a decrease of more than one point/year in MMSE score between baseline and the end of the follow-up. The analysis included 464 subjects with normal thyroid gland function with a baseline and at least one follow-up MMSE. RESULTS: At baseline there was no association between T(4) and TSH level and cognitive function. In longitudinal analysis, adjusting for age, race, level of education, and other covariates, compared with women in the highest T(4) tertile (8.1 to 12.5 microg/dL), those in the lowest tertile (4.5 to 6.5 microg/dL) had a greater decline in MMSE score (-0.25 point/year vs -0.12 point/year; $p = 0.04$). A total of 95 women (20.5%) had cognitive decline during the study period (mean MMSE decline, 5.5 points). Compared with women in the highest T(4) tertile, those in the lowest tertile had a twofold risk of cognitive decline (adjusted relative risk, 1.97; 95% CI, 1.10 to 3.50). The results were not modified by baseline cognitive and physical function. There was no association between baseline TSH level and change in cognitive function. CONCLUSIONS: In older women, low T(4) levels, within the normal range, were associated with a greater risk of cognitive decline over a 3-year period. Thyroid hormone levels may contribute to cognitive impairment in physically impaired women.

Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, Breitner JC; Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. *JAMA*. 2002 Nov 6;288(17):2123-9.

CONTEXT: Previous studies have shown a sex-specific increased risk of Alzheimer disease (AD) in women older than 80 years. Basic neuroscience findings suggest that hormone replacement therapy (HRT) could reduce a woman's risk of AD. Epidemiologic findings on AD and HRT are mixed. **OBJECTIVE:** To examine the relationship between use of HRT and risk of AD among elderly women. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective study of incident dementia among 1357 men (mean age, 73.2 years) and 1889 women (mean age, 74.5 years) residing in a single county in Utah. Participants were first assessed in 1995-1997, with follow-up conducted in 1998-2000. History of women's current and former use of HRT, as well as of calcium and multivitamin supplements, was ascertained at the initial contact. **MAIN OUTCOME MEASURE:** Diagnosis of incident AD. **RESULTS:** Thirty-five men (2.6%) and 88 women (4.7%) developed AD between the initial interview and time of the follow-up (3 years). Incidence among women increased after age 80 years and exceeded the risk among men of similar age (adjusted hazard ratio [HR], 2.11; 95% confidence interval [CI], 1.22-3.86). Women who used HRT had a reduced risk of AD (26 cases among 1066 women) compared with non-HRT users (58 cases among 800 women) (adjusted HR, 0.59; 95% CI, 0.36-0.96). Risk varied with duration of HRT use, so that a woman's sex-specific increase in risk disappeared entirely with more than 10 years of treatment (7 cases among 427 women). Adjusted HRs were 0.41 (95% CI, 0.17-0.86) for HRT users compared with nonusers and 0.77 (95% CI, 0.31-1.67) compared with men. No similar effect was seen with calcium or multivitamin use. Almost all of the HRT-related reduction in incidence reflected former use of HRT (9 cases among 490 women; adjusted HR, 0.33 [95% CI, 0.15-0.65]). There was no effect with current HRT use (17 cases among 576 women; adjusted HR, 1.08 [95% CI, 0.59-1.91]) unless duration of treatment exceeded 10 years (6 cases among 344 women; adjusted HR, 0.55 [95% CI, 0.21-1.23]). **CONCLUSIONS:** Prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use unless such use has exceeded 10 years. (This study shows the long-term protective effects of estrogen if started early and used for at least 10 years. 72% used unopposed oral estrogen—Premarin—HHL)