

Hormones, stress and your aging brain: cortisol, estrogen, DHEA

Hormones are major determinants of how fast we age. We'll look at three hormones with major roles in aging, and their effects on the brain:

- Cortisol, a stress hormone
- Estrogen, a sex hormone
- DHEA, a widely-used supplement

Stress, cortisol, and your hippocampus

A small amount of stress, say from exercise or a novel situation, can be stimulating and good for your brain.

Too much stress can be very bad for your brain. Unfortunately, most of us have too much stress.

How does stress make your brain age faster, and what can you do to reverse it?

When our ancestors were living on the plains of Africa, stress would be going down to the water hole and being surprised by a lion.



Our body reacts:

- Rapidly release the stress hormones cortisol and adrenaline. These help:
- Rapidly move glucose (sugar) from storage sites into the blood stream

- Increase heart rate, blood pressure and breathing rate to get sugar and oxygen to muscles
- Shut off digestion. If the stress is sufficiently great, empty the bowels to enable faster running.
- Shut off the immune system
- Shut off reproductive system

Our brain reacts:

- Vision and hearing become more sensitive
- Memory recall improves (did this happen before? how did I escape?)
- Learning improves (remember where this happened so I'm ready next time)

Everything essential to escape speeds up. Everything not essential gets shut down.

This is all fine, if the stress response gets shut off after we escape. Unfortunately, humans have the ability to stress ourselves continuously. We stress ourselves by worrying about the boss, the mortgage, relationships, status, being late, our kids, our parents, the guy who cut in front of us.

Staying in a constant, stress-induced state of "red alert" does all sorts of damage to our bodies. It also does damage to our brains.

- Short-term, a small dose of cortisol improves our memory by increasing levels of the neurotransmitter glutamate. Glutamate activates neurons in our hippocampus.
- Long-term, high levels of glutamate kill neurons. It over-excites them and burns them out. Excess glutamate is responsible for brain damage from stroke.

Robert Sapolsky, my colleague at Stanford University, wrote "Why Zebras Don't Get Ulcers", an outstanding book on stress and stress-related diseases (Sapolsky 1994). Sapolsky did his graduate work with Bruce McEwen at Rockefeller University (McEwen 2002). Together, their work has made major contributions to our understanding of how stress affects our brains.

In the 1960's McEwen and Weiss showed that cortisol gets into the brain through specialized cortisol receptors in the hippocampus. The hippocampus has a rich supply of these cortisol receptors to activate it at times of stress.

Beginning in the 1980's, Sapolsky contributed to a series of critical discoveries:

- Treating young rats with high levels of corticosterone accelerated aging of the hippocampus. High levels of corticosterone increased the damage that resulted from cerebral ischemia, the loss of blood flow and oxygen to the brain caused by strokes.
- The hippocampus is part of a feed-back system that regulates and shuts off the stress response. Rats and monkeys with poorly-functioning hippocampus are less able to shut off the stress response, and have high levels of cortisol in the blood.
- Older animals are more likely to have poorly-functioning hippocampus. Older animals suffer a vicious circle:
 - Aging hippocampus loses the ability to regulate cortisol
 - Cortisol levels increase, further damaging the hippocampus

Aging rats, baboons, and humans all have trouble turning off the stress response. They also have higher levels of stress hormones in their blood, even when nothing stressful is happening. Humans in their 70's and 80's show a big increase in circulating stress hormones. These probably contribute to higher blood pressure.

Many studies have shown that increasing cortisol levels (to levels seen in stress) or stress itself cause faster degeneration of the hippocampus in aging animals. Studies in older rats show that their increased resting corticosteroid levels inhibit neuron branching after injury. Lowering cortisol levels or lowering stress slows the damage to the hippocampus.

The hippocampus is one of the primary brain areas damaged by

- ischemia (lack of blood supply) due to stroke or cardiac arrest
- hypoglycemic coma
- epilepsy

Experiments in rats by Sapolsky and others have shown that high levels of corticoids increase the damage. Treat a rat with corticoids after ischemia and more neurons in the hippocampus die. Lower the circulating corticoids and more neurons survive.

The same thing happens in the test tube. Grow neurons on a plate and reduce the level of oxygen to simulate a stroke. The more corticoids in the tube, the more neurons die.

What's the common theme? As Sapolsky describes, it all relates to the mitochondria and energy in the neurons.

- Hypoglycemia cuts off the sugar that mitochondria need to produce energy.
- Stroke and cardiac arrest cut off the sugar and oxygen that mitochondria need to produce energy.
- Epilepsy causes uncontrolled firing of the neurons, which burns up the available sugar that mitochondria need to produce energy.

Corticoids divert glucose away from fat cells and non-working muscle cells into those muscle cells that are working (those in our legs that help us escape the lion). Unfortunately, corticoids also inhibit glucose transport into hippocampal neurons, which makes damage due to stroke or cardiac arrest even worse.

So a life full of stress kills off your hippocampal neurons by

- over-producing toxic glutamate
- inhibiting glucose uptake needed by mitochondria to produce energy

As a final note, Alzheimer's disease often first appears as damage to the hippocampus. Alzheimer's may occur sooner or be made worse by a life of stress.

In their books, Sapolsky and McEwen suggest several ways to reduce stress, as do many other books, TV shows, and popular articles. I'll limit myself to a couple of observations.

The stress response evolved to support intense physical activity: fight or flight.

It makes sense that a good way to relieve stress is intense physical activity: beat up a pillow, hit a punching bag, go for a run. This is what the stress response is intended to do, so why not do it?

Exercise protects your aging brain in many ways, including producing nerve growth factors (neurotrophins) like nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF). Exercise, NGF, and BDNF all increase neuron survival and neurogenesis in the hippocampus. Even going for a walk induces these changes. So when you feel stressed, do some physical activity and save your brain.

DHEA

Cortisol and DHEA are both hormones produced by the adrenal gland. They have opposite effects: DHEA increases immune function, cortisol suppresses it.

DHEA (dehydroepiandrosterone) is

- a steroid hormone pre-cursor to testosterone and estrogen
- a biomarker of aging that declines rapidly with age
- a widely-used supplement

There is considerable controversy about whether or not DHEA should be taken as a supplement. For example, Grimley (2006) reviewed the small number of controlled clinical trials of DHEA and concluded:

"What little evidence there is from controlled trials does not support a beneficial effect of DHEA supplementation on cognitive function of non demented middle aged or elderly people. There is no consistent evidence from the controlled trials that DHEA produces any adverse effects. In view of growing public enthusiasm for DHEA supplementation, particularly in the USA, and the theoretical possibility of long-term neuroprotective effects of DHEA/S, there is a need for further high quality trials in which the duration of DHEA treatment is longer than one year, and the number of participants is large enough to provide adequate statistical power."

In the absence of large, long-term placebo-controlled trials, let's see what's known about DHEA. DHEA production declines with age (Phillips 2007), beginning shortly after puberty, and can reach 5% of its original levels in the elderly (Migeon 1957) due to a progressive atrophy of the zona reticularis of the adrenal glands (Ferrari 2001).

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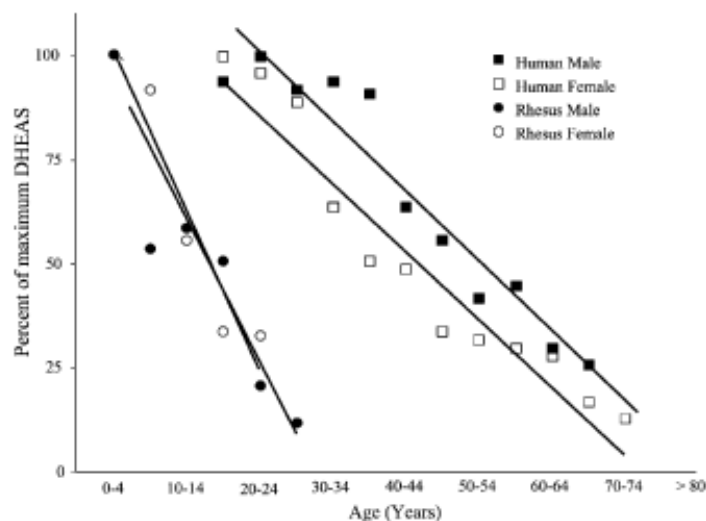


Fig. 7. Rate of serum DHEAS decline in humans (adapted from Orentreich et al., 1984) and rhesus monkeys. Each point represents the percentage reduction from maximal DHEAS levels in a given age group. Reprinted from Lane et al. (1997b).

In contrast, cortisol levels remain high and increase with age. This causes an imbalance between the two stress hormones.

So if high cortisol levels are bad for your brain, DHEA counteracts cortisol (at least in the immune system), and DHEA declines with age, should you take a DHEA supplement? Unfortunately, there are very limited studies of DHEA in humans, in particular long-term, randomized, placebo-controlled, double-blind studies.

If you don't want to take DHEA as a supplement, but want to maintain levels, there are alternatives.

- Exercise increases DHEAS levels (Filaire 2000, Riechman 2004).
- Caloric restriction dramatically slows the rate of decline of serum DHEA in aging monkeys and humans.

In the Okinawa study of the longest-lived people, both men and women had higher levels of DHEA, testosterone, and estrogen than Americans of the same age. As Willcox (2002) puts it, "Measuring DHEA levels in people may be akin to counting tree rings for trees". Tell me your DHEA level, and I can tell how old you are.

Because DHEA is a precursor of estrogen, there is concern that supplementation might increase the risk of breast cancer. We'll look more at estrogen shortly.

Thomas Buford and Darryn Willoughby from Baylor University recently reviewed the interactions between cortisol and DHEA and their effects on immune function in aging, as well as potential methods to combat the endocrine-related contribution to immunosenescence, including DHEA supplementation and exercise (Buford 2008).

Buford and Willoughby conclude:

"Supplementation with DHEA in the elderly may be beneficial to immune function, although in vivo human studies are needed to confirm this. Stress management and acute exercise appear to be the most effective way of improving the cortisol:DHEA ratio and thereby slowing immunosenescence."

Maninger (2008) and colleagues in the Department of Psychiatry, University of California San Francisco School of Medicine, recently reviewed the neurobiological and neuropsychiatric effects of DHEA. They conclude:

"The preclinical and clinical data we have reviewed here can, perhaps, be best summarized by the conclusion drawn by two of the original investigators of DHEA(S)' neuropsychiatric effects in 1955:

'Whether diandrone [dehydroepiandrosterone] turns out to be of therapeutic value in psychiatric practice remains to be seen. . .

However, we appear to have at our disposal a chemical agent that can exert a direct and prolonged action on the mental state” (Strauss 1955).

More research is needed, and the NIH is sponsoring studies of DHEA.

Meditation, mindfulness and depression

Meditation and mindfulness-based cognitive therapy (MBCT) are frequently recommended as methods to reduce stress, but their benefits extend to depression, which is particularly prevalent in aging and stressed individuals.

Teasdale (2000) report results of clinical trials on MBCT for depression:

"This study evaluated mindfulness-based cognitive therapy (MBCT), a group intervention designed to train recovered recurrently depressed patients to disengage from dysphoria-activated depressogenic thinking that may mediate relapse/recurrence. Recovered recurrently depressed patients (n = 145) were randomized to continue with treatment as usual or, in addition, to receive MBCT. Relapse/recurrence to major depression was assessed over a 60-week study period.

For patients with 3 or more previous episodes of depression (77% of the sample), MBCT significantly reduced risk of relapse/recurrence. For patients with only 2 previous episodes, MBCT did not reduce relapse/recurrence. MBCT offers a promising cost-efficient psychological approach to preventing relapse/recurrence in recovered recurrently depressed patients."

Ma (2004) replicated these results, as have other researchers (Kingston 2007, Barnhofer 2007):

"Recovered recurrently depressed patients were randomized to treatment as usual (TAU) or TAU plus mindfulness-based cognitive therapy (MBCT). Replicating previous findings, MBCT reduced relapse from 78% to 36% in 55 patients with 3 or more previous episodes"

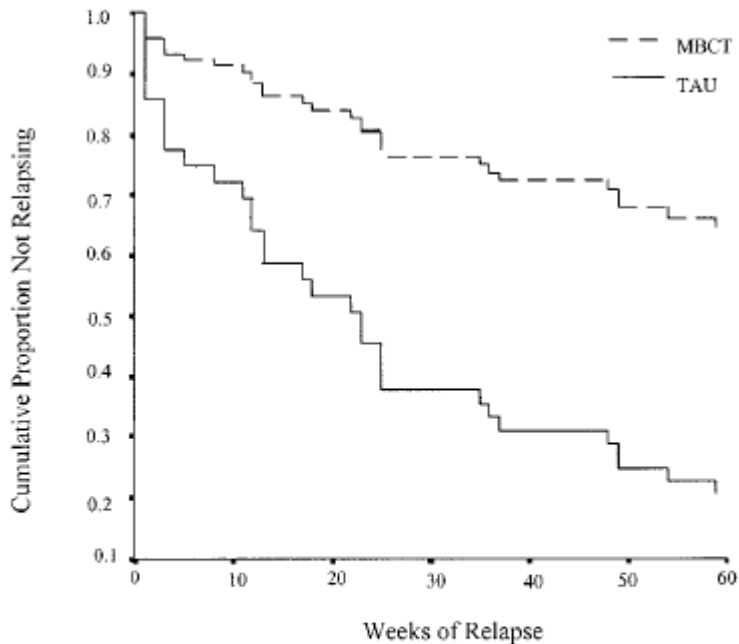


Figure 1. Survival (nonrelapse/nonrecurrence) curves comparing relapse/recurrence to *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) major depression for treatment-as-usual (TAU) and mindfulness-based cognitive therapy (MBCT) in patients with three or more previous episodes of major depression (intent-to-treat sample).

Source: Ma 2004

What is mindfulness-based cognitive therapy and why was it developed?

"The previous account suggests that risk of relapse and recurrence in recurrent major depression will be reduced if patients can learn to be aware of negative thinking patterns reactivated during dysphoria and disengage from those ruminative depressive cycles.

"MBCT was designed to achieve these aims. MBCT is an 8-week group program involving up to 12 recovered recurrently depressed patients. It is based on an integration of elements of CBT with components of the mindfulness-based stress reduction (MBSR) program, which provides training in voluntary deployment of attention, based on mindfulness meditation. MBCT aims at developing participants' awareness of, and changing their relationship to, unwanted thoughts, feelings, and body sensations, so that participants no longer avoid them or react to them in an automatic way but rather respond to them in an intentional and skillful manner." (Ma 2004)

"Aspects of CBT included in MBCT are primarily those designed to facilitate 'decentered' views, such as 'Thoughts are not facts' and 'I am not my thoughts'... The focus of MBCT is to teach individuals to become more aware of thoughts and feelings and to related to them in a wider, decentered perspective as 'mental

events' rather than as aspects of the self or as necessarily accurate reflections of reality." (Teasdale 2000)

"The Mindful Way through Depression: Freeing Yourself from Chronic Unhappiness" by Mark Williams, John Teasdale, Zindel Segal, Jon Kabat-Zinn is an introduction to MBCT for individuals who wish to learn the method.

How does Estrogen Hormone Replacement Therapy (ERT/HRT) affect brain aging?

There is abundant evidence from animal and clinical studies that estrogen protects the brain and promotes neurogenesis (Garcia-Segura 2001, Resnick 2001, Suzuki 2009, Wise 2009)

Clinical trials have shown that estrogen

- decreases the risk and delays the onset and progression of Alzheimer's disease
- decreases the risk and delays the onset and progression of schizophrenia
- may enhance recovery from traumatic neurological injury such as stroke.

Animal studies show that estrogen improves

- neurogenesis
- synaptic transmission
- axonal sprouting
- cell survival after stroke
- regeneration after injury

However, both animal studies and clinical trials have shown opposite effects of estrogen. Some clinical trials and epidemiological studies have shown that estrogen:

- increased risk of dementia
- increased risk of cognitive decline

So how does estrogen and Estrogen Hormone Replacement Therapy (ERT/HRT) affect brain aging?

Susan Resnick and Pauline Maki at the National Institute on Aging described their studies on the effects of hormone replacement therapy on cognitive and brain aging as of 2001:

"In a series of investigations in the BLSA [Baltimore Longitudinal Study of Aging], we have shown that ERT/HRT reduces the risk for Alzheimer's disease and offers some protection against cognitive aging in nondemented postmenopausal women. Our behavioral findings in nondemented women indicate

that ERT/HRT offers a selective benefit to specific memory processes. ERT/HRT protects against age-associated decline in figural memory and is associated with better encoding, retrieval, and recognition of verbal material.

Our results are consistent with other cross-sectional observational studies indicating an association between hormone therapy and enhanced memory on tests of verbal recall and recall of proper names from visual face cues. In the only other prospective study of longitudinal memory change, past use of hormone therapy was associated with less longitudinal decline in verbal memory over 2.5 years...

These observational findings from our studies in the BLSA have led to the development of a large-scale randomized clinical trial of hormone therapy and cognitive aging, the ancillary Women's Health Initiative Study of Cognitive Aging (WHISCA), and have important implications for studies of the effects of SERM's on cognitive and brain functioning." (Resnick 2001)

Resnick (2009) reported results for the Women's Health Initiative Study of Cognitive Aging (WHISCA):

OBJECTIVE: The objective of the study was to determine the effects of unopposed CEE [conjugated equine estrogens] on changes in domain-specific cognitive function and affect in older postmenopausal women with prior hysterectomy.

DESIGN: This was a randomized, double blind, placebo-controlled clinical trial.

SETTING: The study was conducted at 14 of 40 Women's Health Initiative (WHI) clinical centers.

PARTICIPANTS: Participants were 886 postmenopausal women with prior hysterectomy, aged 65 yr and older (mean 74 yr), free of probable dementia, and enrolled in the WHI and WHI Memory Study (WHIMS) CEE-Alone trial for a mean of 3 yr and followed up for a mean of 2.70 yr.

INTERVENTION: Intervention was 0.625 mg of CEE daily or placebo.

MAIN OUTCOME MEASURES: Annual rates of change in specific cognitive functions and affect, adjusted for time since randomization, were measured.

RESULTS: Compared with placebo, unopposed CEE was associated with lower spatial rotational ability ($P < 0.01$) at initial assessment (after 3 yr of treatment), a difference that diminished over 2.7 yr of continued treatment. CEE did not significantly influence change in other cognitive functions and affect.

CONCLUSIONS: CEE did not improve cognitive functioning in postmenopausal women with prior hysterectomy. CEE was associated with lower spatial rotational performance after an average of 3 yr of treatment. Overall, CEE does not appear to have enduring effects on rates of domain-specific cognitive change in older postmenopausal women."

The WHISCA study participants were a subset of women who had participated in the larger Women's Health Initiative Memory Study (WHIMS). The WHIMS trial was terminated early in 2004, and the results were reported in 2005:

"WHIMS was a multicentre, randomised, double-blind, placebo-controlled clinical trial in which a subgroup of women who participated in the Women's Health Initiative study were assessed for the effects of HT on dementia and mild cognitive impairment.

There were two study arms, one involving 4532 postmenopausal women who received continuous combined oestrogen (conjugated equine oestrogens [CEE] plus medroxyprogesterone acetate) or placebo, and the other involving 2947 hysterectomised women randomised to continuous unopposed CEE or placebo. All participants were age 65 years or older.

CEE with or without medroxyprogesterone acetate, given to women age 65 years and older, does not protect against dementia or cognitive decline, but substantially increases the risk of dementia of any cause and cognitive decline.

... WHIMS answered critically important questions about whether HT can protect against dementia in elderly women who start HT some years after menopause. However, several clinically important questions are unanswered, including questions about the generalisability of WHIMS to groups of women for whom HT is an indication -- perimenopausal women and those soon after menopause who have menopausal symptoms -- and other methods of treatment delivery and treatment regimens." (Craig 2005)

Case closed for HRT and the aging brain? Not yet. Suzuki (2009) described a re-analysis of the WHIMS data, addressing the issue pointed out by Craig (2005) of whether or not the WHIMS results applied to perimenopausal women:

"Contrary to numerous studies that demonstrate beneficial actions of estrogen, the WHI reported that ET under certain circumstances increases the risk for stroke, and it does not exhibit any beneficial effects on long-term stroke outcomes. The WHI consisted of a randomized, placebo-controlled clinical trial primarily designed to test whether ET is protective against coronary heart disease in postmenopausal women. In 2004, the WHI was terminated due to an increased risk of stroke in women receiving treatment.

It is important to remember that, in the WHI, the mean age of the subjects was 63 years, and the vast majority of subjects were on average 12 years postmenopause prior to the initiation of any hormone treatment. In striking contrast, observational studies that previously reported cardio- and cerebrovascular benefits of ET examined women averaging 51 years of age, many of whom initiated hormone therapy in their menopausal transition. ...

The secondary analysis of the WHI also suggests that the discrepancies between previous observational studies and recent clinical trials over the efficacy of ET may have resulted from the differences in the timing of hormone administration relative to the perimenopausal transition. This recent re-evaluation of the WHI reported differential effects of ET on the risk of cardiovascular diseases based on the age and years since menopause. In this report, the use of postmenopausal conjugated equine estrogens (CEE) was associated with a reduced risk for coronary heart disease (a hazard ratio of 0.63 [95% confidence interval], 0.36–1.09) in a group of women aged 50–59 years.

In addition, the study reported a hazard ratio of 0.89 ([95% CI], 0.47–1.69) for stroke incidence in the CEE trial within the same age group, further supporting the concept that the timing of initiation of hormone therapy influences its efficacy against stroke injury.

Together, our findings, in combination with the results of the WHI and its recent re-evaluation, emphasize the tremendous importance of strengthening the collaboration between basic science and clinical researchers to take the maximum advantage of empirical and mechanism-based information and approaches to gain deeper understanding of the diverse mechanisms of E2's protective actions." (Suzuki 2009)

We'll close with this perspective (Wise 2009).

"The concept that estrogens exert important neuroprotective actions has gained considerable attention during the past decade. Numerous studies have provided a deep understanding of the seemingly contradictory actions of estrogens. We realize more than ever that the effects of estrogens (with and without simultaneous or sequential progestins) are diverse and sometimes opposite, depending on the use of different estrogenic and progestinic compounds, on different delivery routes, on different concentrations, on treatment sequence, and on the age and health status of the women who receive hormone therapy.

During the past few years, we have gained an increasing appreciation of the impact of estrogens on the immune system and on inflammation. In addition, we have learned that estrogens cannot only protect against cell death, but can also stimulate the birth of new neurons. Here we posit the concept that estrogen's modulation of the immune status may be the basic mechanism that underlies its

ability to protect against neurodegeneration and its powerful neuroregenerative actions.

We hope that this update will encourage even richer dialogues between basic and clinical scientists to ensure that future clinical studies fully consider the information that can be derived from basic science studies. Only then will we have a better understanding of the impact of hormones on the menopausal and postmenopausal period in a woman's life." Wise 2009

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