Research on novel and nonreproductive actions of steroid hormones has expanded in recent years. The neuroprotective actions of sex hormones in humans and in animal models have been known for some time. For example, women appear to recover better from head injuries than do men, and these and other observations have led to studies on the neuroprotective effects of estrogen. In animal models of brain trauma and stroke treatment with steroids (estrogen and progesterone) protected against brain swelling and neuronal death. The results of these studies suggested that hormone replacement therapy (HRT) in postmenopausal women, in addition to relieving symptoms of menopause, might also decrease the risk of neurodegenerative diseases and injury, such as Alzheimer’s disease and stroke. On the other hand, clinical and experimental evidence also indicate that excessive and prolonged steroid hormone treatment may, in fact, promote neuronal damage. Elevated doses of estrogen may attenuate the effects of this hormone, and it is well-established that prolonged increases in adrenal glucocorticoids, which occur during stress, aging, and other conditions, have been associated with memory impairment.

Estrogen therapy had been widely prescribed as a strategy for protection against heart disease, osteoporosis, vasomotor symptoms (hot flashes), and dementia, primarily Alzheimer’s disease (AD). There is strong biological evidence in support of the beneficial effects of estrogen on the brain including enhancement of neurotransmitter release and action, protection against neuronal damage, neurotrophic effects, and reductions in beta-amyloid accumulation. The enzymes involved in sex steroid biosynthesis have been identified in the hippocampus and amygdala, areas of the brain associated with learning and memory. These parts of the brain possess estrogen receptors and are therefore sensitive to estrogen. In addition, studies have shown that women who took estrogen had up to 50% lower risk of developing AD.

Estrogen and memory: In a seminal study in 1988, psychologist Barbara Sherwin at McGill University followed women who had undergone surgery to remove the ovaries and uterus, a procedure that caused a drop in blood estrogen levels. She found that women who received estrogen replacement therapy after surgery performed better on tests of verbal memory and other cognitive functions than did women who did not receive estrogen. That study has since been repeated many times. Other studies indicated that estrogen lowers the risk of developing Alzheimer’s disease (AD), although it did not appear to slow or reverse the course of the disease once symptoms had set in. Those women who received estrogen during or shortly after menopause were less likely to develop AD than women who had not been on estrogen therapy.
Others have been more cautious about these interpretations, since much of the evidence that estrogen deters memory loss in healthy postmenopausal women has come from observational studies. Such studies could be deceiving, because women who have more education and who tend to be healthier overall are also more likely to use estrogen, making it difficult to interpret the association between estrogen and cognition. Furthermore, other studies have shown no overall benefit of estrogen on cognition. Sherwin argues that tests for cognitive function showing no effect of estrogen have been too blunt to differentiate different aspects of cognitive function and that estrogen cannot be expected to affect all tests of cognition. Neuropsychologist Susan Resnick, at the National Institute of Aging, suggested that differences between the results of studies that showed an effect and those that did not may be explained by differences in the ages of women studied. Most women who use hormone therapy take estrogens around the time of the menopause, and even short-term exposure seems to result in some decrease in the risk of AD. Thus, there may be a critical period during which estrogen is most effective in reducing cognitive decline.

The Women’s Health Initiative (WHI) was begun in 1991 and headed by Wake Forest University psychologist Sally Shumaker, a 15 year, and multicenter study examining several aspects of women’s health. A companion study initiated by Susan Resnick and developed and performed in collaboration with Shumaker and colleagues was to examine the effects of estrogen on long-term cognitive changes among a smaller sample of women without dementia. The Women’s Health Initiative Memory Study (WHIMS) was an ancillary study to the two larger hormone therapy trials. It examined whether postmenopausal estrogen supplementation (estrogen alone and estrogen plus progestin) reduced the risk of dementia and mild cognitive impairment (MCI) in healthy women aged 65-79 years.

The WHI estrogen and progestin study was prematurely stopped in July 2002 because the overall risks of the intervention outweighed the benefits. There were significantly more noncognitive adverse events associated with conjugated equine estrogens plus medroxyprogesterone compared with placebo. Women in the study were at increased risk for heart disease, stroke, pulmonary embolism, and breast cancer compared with women receiving the placebo. The risks outweighed the beneficial effects of estrogen plus progestin on colon cancer and osteoporosis.

The WHIMS (memory) study included 4532 women in the WHI trial at 39 of the 40 participating clinical sites. The memory study was terminated in February, 2004, because the NIH (National Institutes of Health) considered the increased risk of stroke in the hormone group to be unacceptable in healthy women in the absence of benefit for coronary heart disease. The results of the study indicated that estrogen therapy alone did not reduce dementia or MCI incidence and increased the risk for both end points combined. Pooling data for estrogen alone and estrogen plus progestin resulted in increased risks for both end points. Therefore, use of hormone therapy to prevent dementia or cognitive decline in women 65 years of age or older was not recommended.
Critique of WHI findings: The results fly in the face of hundreds of studies indicating that estrogen could protect brain cells from damage and improve cognition in people and laboratory animals. Researchers are fighting back! They fear that volunteers for clinical trials will decline, and funding for some basic research may be in jeopardy. Several prominent scientists have formed a group: Consortium for the Assessment of Research on Progestin and Estrogens. They feel that the results of the memory study have been overinterpreted, and they claim that the increase in dementia risk cannot be extended to all forms of HRT (hormone replacement therapy) or even to women most likely to start HRT.

These scientists are critical of the formulation mixture used to test HRT. Estrogen + Progesterone (dubbed Prempro) is the most widely used HRT combination in the US, but its dose and the type of progestin (medroxyprogesterone acetate) work against estrogen’s ability to protect neurons. Prempro delivers a constant dose of hormones throughout the month. Before menopause, the female body gets only intermittent pulses of the hormone, and therefore the constant supply of estrogen may dull the sensitivity of estrogen receptors.

Medroxyprogesterone acetate (MPA) may be a poor choice for the natural progesterone, at least in the brain. Roberta Brinton and her colleagues at the University of Southern California found that MPA counteracts estrogen’s ability to protect neurons against toxic insults such as exposure to the peptide culprit in Alzheimer’s disease. In contrast, natural human progesterone enhanced estrogen’s protective effect.

There has also been criticism of the age range studied, 65-79, when the onset of menopause averages age 50. As noted above, results may differ depending upon whether hormones are taken at the time of menopause or shortly thereafter or whether they are taken than 15 or more years later when irreversible changes may already have taken occurred.

Other techniques may need to be developed, such as brain imaging, which would reflect the biological effects of estrogen, and thereby supplement the psychological evidence of memory performance.

Adrenal Steroids (glucocorticoids) and Memory: Adrenal steroids typically have adaptive effects in the short run, but promote impairment (structural and functional) under conditions of repeated stress or dysregulation of the hypothalamic-pituitary-axis (HPA). Neuroscientist Bruce McEwen at The Rockefeller University has emphasized the importance of the hippocampus and its adaptation to stress and the biphasic nature of glucocorticoid action. Acute stress enhances the memory of events that are potentially threatening to the organism. Chronic stress causes adaptive plasticity in the brain, in which local neurotransmitters and systemic hormones interact to produce structural and functional changes in the brain. Adrenal steroids modulate the excitability of the hippocampus neurons and have both protective and damaging effects in the hippocampus. High glucocorticoid levels and severe stress impair declarative memory. However, the hippocampus displays structural plasticity, which involves ongoing neurogenesis of the
dentate gyrus, synaptogenesis regulation by estrogens, and dendritic remodeling resulting from repeated stress or elevated levels of glucocorticoids. Excitatory amino acids participate in this plasticity along with the steroids. Glucocorticoids also suppress neurogenesis in the dentate gyrus and potentiate the damage resulting from ischemia and seizures.

James McGaugh at the University of California-Irvine, has investigated the critical involvement of the amygdala in memory consolidation. Memory is enhanced by hormones that are released during stress. This explains why emotional arousal has such a powerful influence on how well we remember things. When the brain senses danger, the instant fight-or-flight response involves the hypothalamus sending signals via the autonomic nervous system to the adrenal glands, specifically to the adrenal medulla, which secrete the hormones epinephrine (aka adrenaline) and norepinephrine into the blood stream. Adrenaline raises the heart rate, and norepinephrine, the blood pressure.

If the threat continues for more than a few seconds, the HPA axis is activated. The hypothalamus releases a hormone called CRH (corticotrophin releasing hormone), which stimulates the pituitary gland to secrete ACTH (adrenocorticotropic hormone), which in turn stimulates the adrenal cortex to produce cortisol (in humans) or corticosterone (in rats). Cortisol, among other things, increases the supply of blood glucose to make more energy available, enabling the fight and/or the flight. Both epinephrine and cortisol play a powerful role in regulating memory by regulating the release of norepinephrine in the amygdala. Although the amygdala is crucial for the consolidation of memories, it is not the site for long term storage of the memories. Animal studies show that when rats are trained with mild foot shocks and then have the amygdala inactivated by drugs, they can still perform the training task, the memory is not affected.

However, there is accumulating evidence that prolonged elevations of glucocorticoids may have detrimental effects on the brain, especially for specific neurons of the hippocampus that may lead to memory disorders. The circumstances that lead to elevated levels of glucocorticoids are numerous and include genetic factors, environment, aging, and the nature of the stressful events, including post-traumatic stress disorders, Cushing’s disease, depression, childhood abuse, etc. In some individuals the activation of the HPA axis is maintained in response to a modest stressful situation, whereas in others, the response is short-lived. It is not known why such differences occur between individuals, but these differences contribute to their degree of stress and the ultimate hormonal output. Prolonged glucocorticoid elevation leads to a wide range of degenerative conditions affecting most systems of the body. While these steroids seem to have short-term benefits in the brain, they also increase neural vulnerability with prolonged exposure resulting in atrophy of the hippocampus and memory impairment.

Critique of the literature on glucocorticoids, memory and stress: Although there is a strong association between stress, glucocorticoids, and memory impairment, the relationship between memory and stress is not always straightforward. It is not a simple relationship. The literature on human and animal models is difficult to compare because
of the variability in stress conditions, populations studied, and methodologies. Moreover, there are differential effects on specific components of the memory process, such as recall, consolidation and learning. The literature is also controversial regarding the effects of laboratory-induced stress. There have been questions regarding the validities of laboratory stressors as well as response stability. It is important to ascertain whether the effects of laboratory stress are significant and if the effects are comparable to prolonged exposure to life stress and rising glucocorticoid levels. Sex differences need further study, since in some studies, men report being under greater stress than women, whereas in other studies, women appear to experience greater stress. Some studies report greater cortisol secretion in response to stress in men, whereas other studies report greater cortisol responsiveness in women. Many studies fail to report the nature of the stressors. It is clear that further investigation is required, and among them, the role of other hormones and neuro-transmitters in the stress-memory relationship.

References:


