Brain and steroids: a long history of love

ANDREA RICCARDO GENAZZANI, NICOLA PLUCHINO

Abstract
In the aftermath of the Women’s Health Initiative studies, both the clinical and basic science communities had to sort out divergent results among experimental findings, observational data and randomized controlled trials in order to establish a shared analysis. The scientific community formally debates the role of different HRT formulations, hormone doses, time of treatment initiation since the menopause and the age of treated women. Basic scientists demonstrated that the multiple neuroprotective effects of estrogen on brain cells may induce a differential biological response according to the time of treatment. Progesterone (but not all synthetic progestins) also has pivotal neuroactive functions in animal models of reproductive aging. Additionally, epidemiological surveys provide information regarding the detrimental role of hypogonadism on mental well-being. The present article briefly summarizes current evidence supporting the neuroactive role of estrogen, with reference to the clinical finding sustaining the intriguing hypothesis of the early female brain senescence as a highly responsive period to estrogen treatment.

Key words: brain, steroids, estrogen, progestins

Introduction
Sex steroids hormones play fundamental roles in the development and function of central nervous system (CNS). Estrogens, progestins and androgens are able to induce several effects in brain areas of the central nervous system (CNS), through the binding with specific receptors. The action of sex hormones is not limited to the regulation of endocrine functions and mating behavior; the identification of estrogen, progestin and androgen receptors outside the classical CNS regions, such as pituitary and hypothalamus, justifies their role in controlling different brain functions [1].

These findings highlight the importance of sex steroids in development and regulation of the CNS. Marked differences are found in the structure and in the function of brain of male and female animals and humans [2]. Indeed, in humans and in rats several areas of the brain show gender dimorphism, as indicated by differences in structure (such as different numbers of cells in specific areas). The different organization of brain areas in males and females appears to be largely dependent on the action of sex steroid hormones as demonstrated by the differential expression of steroid receptors in sexually dimorphic nuclei [3]. These “organizational/developmental” effects are permanent and are acting during development, mainly in the fetal-neonatal period when estrogens and aromatizable androgens modulate neural development and the formation of neuronal circuits.

As a result, several areas of the CNS become sexually differentiated. This is also suggested by the evidence that the levels of circulating and locally-produced steroids control the structure and activity of sexually dimorphic nuclei. Therefore, exogenous sex steroids could cause differences in the structure/function of specific brain areas with measurable clinical effects. Although abundant morphological and functional evidence exists for sex differences in brain development, much less is known regarding the underlying developmental mechanisms that direct these differences [4]. Since neurons are limited in their proliferative life and there is considerable programmed cell death after birth, the effect of steroids appears to involve regulation of neural cell kinetics and apoptosis. Sexual dimorphism is also present in other cellular compartments such as the glia, and the sex steroid-related developmental differences seen in both animals and humans are real and complex [5]. Gender differences show up, among others, in dendritic structure, organization of the neuronal membrane, neuronal connectivity patterns, as well as in opiate receptor numbers [6].

Gonadal steroids, brain through the lifespan
Brain plasticity is most apparent during early development as formation of the nervous system but it continues through puberty, reproduction and adult life [5, 7]. These “activational/neuroplasticity” effects are
transient and fluctuate considerably as the hormonal milieu changes then affecting almost potentially every aspect of brain physiology in different biological phase. Estrogen-induced synaptic plasticity is well seen during puberty and seasonal changes as well as during the ovarian cycles. Estrogen appears to be important for the regulation and maintenance of network integrity of several brain areas related to cognition [8]. In addition to changes in the cortex accompanying cognitive tasks estrogen regulates the anatomy and connectivity of the hippocampus and associated structures [9, 10]. In postmenopause, neurotransmitters, neuropeptides and neurosteroids undergo important changes as a consequence of the failure of gonadal hormone production, at a time when many CNS activities deteriorate, particularly those associated with hippocampal functions such as memory, attention, cognition and autonomic control [11]. This neuroendocrinological aging process represents a unique opportunity to investigate the actions of gonadal hormones on their specific receptors in the Nervous System.

One of the most exciting areas of research in women’s health over the past 10 yr involves our growing appreciation that estrogens play important neurotrophic and neuroprotective roles during adulthood. This brings new meaning to the potential impact of the prolonged postmenopausal hypoestrogenic state on learning and memory and the potential increased vulnerability of aging women to brain injury and neurodegenerative diseases. The increase in female life expectancy during the past century has meant that women now live one-third of their lives beyond cessation of their ovarian function. This evolution in demography has increased the need for the development of new therapeutical strategies to promote successful aging, defined as low probability of disease, high cognitive and physical capacity and active engagement in life. Because changes in the aging nervous system are subtle, it may be possible to reverse them and to improve cognitive performance by pharmacological treatments. The administration of steroids may be particularly promising in this regard: (a) they play an important role in the functioning of the central and peripheral nervous system (CNS and PNS); (b) some steroids have neuroprotective effects; (c) the levels of some neuroactive steroids markedly decrease with age; and (d) unconjugated steroids easily cross the blood-brain barrier and rapidly accumulate throughout the brain.

Estrogen receptors (ERs) are found in both the hippocampus and frontal lobes which subserve verbal memory, working memory and retrieval. It was reasonable to hypothesize that this hormone might play an important protective role against the deterioration in these cognitive functions that occur with normal aging. It is indeed now well recognized that the functions of gonadal and adrenal steroid hormones go far beyond reproduction and that they regulate vital neuronal and glial functions by a variety of mechanisms of action [12]. In addition, some steroids, named “neurosteroids,” can be synthesized within the nervous system by both neurons and glial cells that are produced in concentrations high enough to exert paracrine effects. Synthesis of brain neurosteroids declines with age, during stressful conditions (including major depression, chronic psychological stress), and in chronic inflammatory and neurodegenerative diseases. Recent reports associate the decrease of brain neurosteroids to neuronal dysfunction and degeneration. Stimulation of their synthesis offers new therapeutical possibilities to counteract brain-aging process.

Menopause as a model to understand the role of sex steroids in the brain

Epidemiologic data suggest an increased incidence and prevalence of depressive symptoms in women in their mid-40s and again between the ages of 55 and 64 years. Estrogen deficiency has been suggested as a cause of this increased prevalence of depressive disorders in women and the menopausal transition appears to be a period of vulnerability to depressive symptoms with or without a history of depression. It has demonstrated that psychological distress appears to increase in early perimenopause compared with premenopause and vasomotor symptoms further increase the risk of psychological distress. The Study of Women Across the Nation (SWAN), reported that more than 40% of participants had increased irritability, nervousness, mood changes and dysphoric mood in the previous 2 weeks in early perimenopause compared with premenopause [13-14]. Additionally, 14.3% reported feeling depressed 6 or greater days within the past 2 weeks. Considering that the perimenopause can last up some years, the risk of developing depression during the perimenopause can be as high as 14 times that of premenopausal women. Depression is the second leading cause of disability in developed countries and the potential burden of illness experienced by depressed perimenopausal women is significant. In particular, women experiencing long transitions to menopause were at greater risk of depression than those having short transitions. The association
between a long perimenopause and depression appeared to be explained by increased menopausal symptoms rather than by the menopause status: the presence of vasomotor symptoms appears to be associated with a higher prevalence of depressed mood, and anxiety is a significant predictor of hot flashes among women in the late reproductive years.

Additionally, Brown et al. in a population-based cross-sectional study of 639 women, found significant links between depressive symptoms and several menopausal symptoms including hot flashes, sleep disturbance, irritability (the Harvard Study of Moods and Cycles). In particular, Brown et al., found a two-fold increase in the risk of developing depressive symptoms during the perimenopause among women who nocturnal hot flashes without a history of depression [14] experience of hot flashes at baseline was marginally significantly more frequent among women who reported severe depressive symptoms during an 8-year follow up as compared to women who did not exhibit mood symptoms during the follow up period. Additionally, participants with severe mood symptoms during follow up were 2.16 times more likely to report hot flashes at the same visit.

The effect of the menopausal transition and sex hormones on anxiety disorders is much less studied than depression, despite the finding that nearly half women during the climacterium experience anxiety and stress symptoms. Data from the Penn Ovarian Aging Study (POA) strongly support that anxiety was associated with hot flashes in a community-based cohort of African American and white women. The most anxious women had the most severe and most frequent vasomotor symptoms. The relationship between hot flashes and anxiety persisted after adjusting for menopause transition stage, depressed mood symptoms, smoking, body mass index, estradiol, age, race, and time since the baseline measures in the study.

Interesting data on the relationship between sex steroids, menopause and mood disorders come from the Mayo Clinic Cohort Study of Oophorectomy and Aging by Rocca et al. [16]. The study involves a population-based cohort of women residing in Olmsted County, MN, who underwent oophorectomy before the onset of menopause for a non cancer indication from 1950 to 1987. For a median follow-up period of 24 years, the risk of anxiety symptoms increased significantly in women who underwent bilateral oophorectomy compared with referent women (adjusted HR, 2.29; 95% CI, 1.33-3.95). The increased risk of anxiety symptoms was particularly evident among women who underwent surgery before the age of 48 years (adjusted HR, 2.66; 95% CI, 1.39-5.09). Bilateral oophorectomy was also a risk factor for depression diagnosed by a physician (adjusted HR, 1.54; 95% CI, 1.04-2.26) [15-22].

Neurobiologically, both vasomotor symptoms and mood disorders are regulated by the monoamine neurotransmitters serotonin, norepinephrine and dopamine. Thus, dysregulation of these systems can lead to depression when that dysregulation occurs within brain areas deputed to mood control (prefontral cortex, limbic system) and can lead to vasomotor symptoms when the dysregulation involves the hyphotalamic centers deputed to thermoregulatory body mechanism.

In the previous paragraph we evaluate the positive neurobiological effect that estrogens have in the brain monoamine turnover; thus it is theoretically possible that treating vasomotor symptoms using estrogens could prevent depressive symptoms in vulnerable women. In addition, remission from symptoms of mood disorders such as anxiety, depression and sleep disturbance without a full reduction of vasomotor symptoms could be a signal that estrogen fluctuation in the brain continues to create vulnerability for mood disorders relapse [23].

A role of neurosteroids in central menopausal symptoms has been also recently hypothesized. Menopause transition is associated with decreased allopregnanolone levels, mainly due to reduced ovarian synthesis of progesterone, supporting its role in the mood disorder physiology during the climacterium. Indeed low circulating allopregnanolone levels are associated with the onset of depression and anxiety during the reproductive aging.

In postmenopausal women, HRT is able to modify circulating levels of neurosteroids, determining an increase in allopregnanolone levels and a decrease in DHEA. These data indicate a main role for these compounds as neuroendocrine mediators of the effects of estrogens on the CNS and the effect exerted by HRT on allopregnanolone levels might be related to the anxiolytic and sedative effects of HRT in menopausal women. However synthetic progestins available in the clinical setting have different effects on central neurosteroidogenesis supporting the concept that synthetic progestins may show differential activity on brain biology. This feature involves the synthesis of brain allopregnanolone and the specific activity on GABA-A receptor of progestins, rather than the activation of PRs [24].

Certainly, the study of neurosteroids in menopausal-related mood changes may offer several new perspectives to understand the brain pathophysiology of the climacterium and the hormonal strategies to cure it.
Fig. 1. Sex hormones are directly involved in the brain gender differentiation processes; gender cognitive and behavioural actions are due to the influences of estrogens and androgens on neuronal development during fetal-neonatal life and on circuits activation during adulthood.

Fig. 2. Neurosteroids levels fluctuate throughout the lifespan. During intrauterine life neurosteroids participate in the control of neuronal survival and apoptosis and on the neuronal stem cell differentiation. During childhood and adult brain neurosteroids reach elevated values to protect the CNS from endogenous and exogenous neurotoxic factors and to promote neurogenesis. During aging neurosteroids levels progressively decrease leaving brain unprotected from neurotoxic factors.

Fig. 3. Brain vulnerability throughout the lifespan

Menopause and cognitive decline: early symptoms for an early treatment

The detection of early neural markers of brain aging and cognitive dysfunction is one of the main challenges during the climacterium and the early postmenopause and the degree of cognitive vitality during the aging process could depend on early clinical interventions.

The evidence that estrogen has several neuroprotective effects brings new meaning to the potential impact of the prolonged post-menopausal hypoestrogenic state on learning and memory and the potential increased vulnerability of ageing women to brain injury and neurodegenerative diseases.

Although the apparent dichotomy between the beneficial actions of E2 on the brain of experimental animals (see previous paragraphs) and report from randomized controlled trials in women (mainly WHI) could be great conundrum, a critical analysis of clinical data robustly supports the neurotrophic effect of estrogen.

Results from the Mayo Clinic Cohort Study of Oophorectomy and Aging provide the degree of the long-term influence that sex steroid deprivation has on cognitive vitality. In particular women who underwent either unilateral or bilateral oophorectomy had an increased risk of cognitive impairment or dementia compared with women with natural menopause (adjusted HR, 1.46; 95% CI, 1.13-1.90). In another study, the risk of Parkinson disease was higher in women who underwent either unilateral or bilateral oophorectomy (adjusted HR, 1.68; 95% CI, 1.06-2.67) [19]. In both studies, a younger age at menopause was associated with increased risk of neurological impairment. In particular, Rocca et al. observed significant linear trends of increasing risk for either outcome with younger age at oophorectomy. Estrogen deficiency is the initial step in a chain of causality that determined the increased risk of cognitive impairment or dementia. In support of a neuroprotective effect of estrogen, women who underwent bilateral oophorectomy before age 49 years but were given estrogen treatment until at least age 50 years had no increased risk.

Epidemiological surveys prospectively monitoring women as they progress through the menopause transition have suggested that self reports of decreased concentration and poor memory are frequent accompaniments of this phase of life and the postmenopause. In the Study of Women’s Health Across the Nation (SWAN), more than 40% of perimenopausal and postmenopausal women endorsed forgetfulness on a symptom inventory compared with 31% of premenopausal women [20]. In the Seattle Midlife Women’s Health...
learning and cognition would normally start to become
delay in other brain areas years before deficits in
gonadism that could trigger menopause-related mental
axis senescence induces vasomotor symptoms and hypo-
gen users is particularly compelling because they avoid
from the menopause had improvement in verbal memo-
ory, vigilance, reasoning and motor speed when given
HRT. The same meta-analysis of observational studies
examining HRT and cognitive function also suggest a
significant reduction in the risk of AD among women
who have ever used HRT [23]. In particular, the strong-
est evidence for an association between HRT and Alzhei-
er disease comes from 2 cohort studies: the Manhat-
tan Study of Aging [24] and The Baltimore Longitudinal
Study of Aging [25]. The two prospective cohort studies
that reported a significantly reduced risk of AD in estro-
gen users is particularly compelling because they avoid
both recall and prescribing-practice bias. In the Italian
Longitudinal Study on Aging, ERT was associated with
a reduced prevalence of AD in 2816 women (OR, 0.24; 95% CI, 0.07-0.77) [26]. Analysis of observational data
from the Cache County Study suggested a reduction in
the risk of AD for past HRT users for 3-10 years. In the
same study, the "excess" risk of AD when compared
with age-equivalent men disappeared among women who
received HRT for more than 10 years [23-33].

In conclusion, the majority of studies and meta-ana-
lyses evidencing cognitive benefits during HRT analyze
young symptomatic postmenopausal women, supporting
the concept of the "window of opportunity" for estrogen
neurotrophic effects.

Conclusion and perspectives

In the aftermath of the WHI studies, both the clini-
cal and basic science communities were forced to try and
make sense of these divergent results and take a careful
look at the nature of HRT formulations and variables,
such as the time of initiation of treatment and the age of
the subjects.

Basic scientists demonstrated that multiple neuro-
protective effects of estrogen on brain cells may have
a time bias and that progesterone (but not all synthetic
progestins) has also pivotal neuroactive functions in ani-
mal models of reproductive aging.

Furthermore epidemiological surveys add informa-
tion on the detrimental role of hypogonadism on mental
well-being stratifying findings for patient characteristics
and symptoms and for time of steroid withdrawal and
subsequent exposition.

All these analysis could reconcile finding from basic
research and clinical data supporting the concept for
a positive role of sex steroids in mental well-being and as
powerful therapeutic tool for those women for whom
ovarian steroids are critically involved in the regulation
of affective, cognitive, and behavioral adaptation to aging.

Evidences sustain the intriguing hypothesis that
eye symptoms of hypothalamic and HPG axis senes-
ce (i.e. vasomotor symptoms) might indicate the vulne-
rability of other brain areas (i.e. amygdale, hippocampus
and prefrontal cortex) to develop future dysfunctions
during the aging process. The identification of the early
role for estrogen deficiency in the chain of causality that
determined the lifelong increased risk of mood disorders
and cognitive impairment in vulnerable women, supports
solidly the early temporal initiation of estrogen therapy.

References

Eds: Genazzani A.R., Petraglia F. and Purdy R.H. The
Parthenon Publishing Group 1996.
female transsexuals have female neuron numbers in a lim-
Sex differences in androgen receptors of the human ma-
millary bodies are related to endocrine status rather than
to sexual orientation or transsexuality. J. Clin. Endocrinol.
Metab. 86: 818-27.
S.M. (1998) Sexual differentiation of the vertebrate brain:
principles and mechanisms. Front. Neuroendocrinol. 19:
323-362.
er-Verlag, New York.