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Alzheimer's disease: the impact of age-related changes in reproductive hormones

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Over the last 2 decades, research into the role that hormones play in regulating brain structure and function during health and disease has increased exponentially. Research into the influence of hypothalamic-pituitary-gonadal (HPG) axis hormones on brain function during this time has been largely driven by epidemiological studies that have demonstrated a gender dependence in the prevalence, symptomatology and prognosis of neurodegenerative diseases such as Alzheimer's disease (AD; 2:1 female to male) [1, 2], Parkinson's disease (1:1.5 female to male) [3], multiple sclerosis (2:1 female to male) [4] and amyotrophic lateral sclerosis (1:1.3 female to male) [5]. Even taking into account the fact that women live longer than men, women appear to have consistently higher age-specific AD death rates [1]. These findings suggest gender-specific changes in serum hormones during aging as a common mechanism promoting neurodegeneration. Along this age-related hormonally driven continuum of neurological change, both genetic and environmental factors will influence who will experience 'normal' age-related changes in brain function versus those who will develop a central nervous system disease. This multi-author review is intended to provide an overview of our current knowledge on the role of reproductive hormones (i.e. hormones of the HPG axis) in regulating brain structure and function in health and in disease. The first review (Vadakkadath Meethal and Atwood) provides an overview of the HPG axis, the changes in serum concentration of HPG hormones during growth and development, adult reproductive life and senescence, HPG hormone receptor localization throughout the brain and how HPG hormones signal via receptor- and non-receptor-mediated mechanisms to affect the normal structure (neurogenesis, synaptogenesis and plasticity) and functioning (cognitive – memory, behavior) of the brain. Lastly, changes in signaling to the brain with the dysregulation of the HPG axis following menopause and andropause are discussed. The reviews that follow examine age-related neurodegeneration in light of these post-reproductive alterations in HPG axis hormones.

Epidemiological studies have provided support for sex steroids in driving neurodegenerative changes with aging since it has been found that there is (i) a positive relationship between AD and decreased estrogen/androgen levels after menopause/andropause; (ii) an abrupt earlier loss of gonadal function in females compared with males, correlating with the increased prevalence rate of AD in women; and (iii) a generally decreased incidence and delay in the onset of AD among women on hormone replacement therapies (HRT) after menopause. The basic and clinical literature indicating the potential of acute estrogen and progestin administration as a neuroprotective therapy for ischemia and chronic estrogen and/or progestin therapy as a potential preventative of AD is reviewed by Simpkins and colleagues. As these authors indicate it is becoming clear that the acute use of sex steroids may be a therapeutic adjunct for stroke. More recently, the role of androgens in neurodegenerative processes has gained increasing attention, and Bates, Martins and colleagues review the effects of testosterone, dehydroepiandrosterone, and related sex steroids on cognitive function in the male brain, together with the various mechanisms by which androgens may modulate cognitive function. Increasing evidence indicates that the loss of androgens leads to AD and cerebrovascular diseases such as stroke. These authors include an intriguing section on androgens and cognition in transsexuals that highlights the developmental and functional roles of HPG hormones.

As pointed out in the first review, epidemiological evidence presented for sex steroids applies equally to other hormones of the HPG axis since the feedback loops

involved in the axis result in changes to all HPG hormones, i.e. the decrease in sex steroid and inhibin production with the loss of reproductive function during menopause/andropause leads to alterations in the serum concentration of all HPG axis hormones [6]. For example, the loss of negative feedback by the sex steroids on the pituitary and hypothalamus following menopause/andropause results in large increases in hypothalamic GnRH and pituitary gonadotropin production, while the loss of inhibins leads to increased activin signaling. These findings illustrate that changes in serum sex steroids are accompanied by changes in other HPG axis hormones, and that it is therefore important to control for these other hormonal changes when ascribing biochemical or functional changes to particular hormones. In this context, Casadesus, Smith and colleagues review the early basic research regarding dysregulation of the HPG axis as it relates to neurodegenerative processes. They first review sex steroid-induced changes in biochemical processes related to the modulation of amyloid precursor processing and the deposition of amyloid-β, the major component of amyloid deposits in the AD brain. Following this, they address the possibility that changes in other hormones of the HPG axis, in particular luteinizing hormone, may modulate these biochemical and neuropathological (and cognitive changes) associated with dementia and AD.

To complete the series, the final two reviews discuss current and future hormone therapies that are aimed at restoring (partially) the HPG axis to that of a normal reproductive adult. Gleason, Asthana and colleagues review the neuroprotective effects of sex steroid replacement therapies in human clinical studies, and discuss the shortcoming of the Women's Health Initiative studies with regard to its interpretation for the use of human sex steroids in neurodegenerative disease. It is interesting to speculate whether the 'unnatural' conjugated equine estrogens and medroxyprogesterone used in Prempro® and Premarin® actually block signaling via the estrogen and progesterone receptors. Differential blockage of sex steroid signaling via the estrogen receptors (albeit low following menopause) by estrone sulfate, the major component of conjugated equine estrogens, and/or the lack of medroxyprogesterone, would explain the increased neurodegeneration but decreased incidence of breast cancer in studies using Premarin. These authors also review new strategies for the use of human sex steroids, selective estrogen receptor modulators and phytoestrogens in the treatment of AD. The concluding review by Gregory and Bowen discusses new therapies based on modulation of other HPG axis hormones, in particular the suppression of menopausal and andropausal increases in serum gonadotropins. Such new therapies that target other areas of the HPG axis will provide new therapeutic alternatives in our efforts to combat neurodegeneration.

It is clear from this series of reviews that HPG axis hormones play crucial roles in the development and maintenance of brain structure and function, and that alterations in HPG axis hormones are central to the neurodegenerative processes observed during aging and that manifest as diseases. It also is clear that hormones besides the sex steroids play important roles in maintaining cognitive function, and that other members of the axis such as gonadatropins are involved in degenerative processes. Still, other members of the axis (e.g. gonadotropin-releasing hormone and activins) have not been examined in this context.

This is a rapidly developing area of research, but much work lies ahead to differentiate the effects of various hormones of the HPG axis with regard their specific role(s) in the development and maintenance of structure and functioning in the brain. The next 10 years will see a better characterization of these functions for all the hormones of the axis, and this basic understanding should allow for the development of new therapies for the treatment of neurodegenerative diseases.

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