Hormones and Behavior 76 (2015) 63–80

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review article

The endocrine dyscrasia that accompanies menopause and andropause induces aberrant cell cycle signaling that triggers re-entry of post-mitotic neurons into the cell cycle, neurodysfunction, neurodegeneration and cognitive disease

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ARTICLE INFO

Article history:
Received 22 December 2014
Revised 23 June 2015
Accepted 23 June 2015
Available online 16 July 2015

Keywords:
Endocrine dyscrasia
Luteinizing hormone
Gonadotropin-releasing hormone
Sex steroids
Dyotic signaling
Alzheimer's disease
Stroke
Blood–brain barrier
Parkinson's disease
Cognition
Amyloid-beta precursor protein
Tau
Cdk-5
Cell cycle re-entry
Hypothalamic–pituitary–gonadal axis
Menopause
Andropause
Senescence
Hormone replacement therapy

ABSTRACT

This article is part of a Special Issue "SBN 2014".

Sex hormones are physiological factors that promote neurogenesis during embryonic and fetal development. During childhood and adulthood these hormones support the maintenance of brain structure and function via neurogenesis and the formation of dendritic spines, axons and synapses required for the capture, processing and retrieval of information (memories). Not surprisingly, changes in these reproductive hormones that occur with menopause and during andropause are strongly correlated with neurodegeneration and cognitive decline. In this connection, much evidence now indicates that Alzheimer's disease (AD) involves aberrant re-entry of post-mitotic neurons into the cell cycle. Cell cycle abnormalities appear very early in the disease, prior to the appearance of plaques and tangles, and explain the biochemical, neuropathological and cognitive changes observed with disease progression. Intriguingly, a recent animal study has demonstrated that induction of adult neurogenesis results in the loss of previously encoded memories while decreasing neurogenesis after memory formation during infancy mitigated forgetting. Here we review the biochemical, epidemiological and clinical evidence that alterations in sex hormone signaling associated with menopause and andropause drive the aberrant re-entry of post-mitotic neurons into an abortive cell cycle that leads to neurite retraction, neuron dysfunction and neuron death. When the reproductive axis is in balance, gonadotropins such as luteinizing hormone (LH), and its fetal homolog, human chorionic gonadotropin (hCG), promote pluripotent human and totipotent murine embryonic stem cell and neuron proliferation. However, strong evidence supports menopausal/andropausal elevations in the LH:sex steroid ratio as driving aberrant mitotic events. These include the upregulation of tumor necrosis factor; amyloid-β precursor protein processing towards the production of mitogenic Aβ; and the activation of Cdk5, a key regulator of cell cycle progression and tau phosphorylation (a cardinal feature of both neurogenesis and neurodegeneration). Cognitive and biochemical studies confirm the negative consequences of a high LH:sex steroid ratio on dendritic spine density and human cognitive performance. Prospective epidemiological and clinical evidence in humans supports the premise that rebalancing the ratio of circulating gonadotropins:sex steroids reduces the incidence of AD. Together, these data support endocrine dyscrasia and the subsequent loss of cell cycle control as an important etiological event in the development of neurodegenerative diseases including AD, stroke and Parkinson's disease.

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Contents

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http://dx.doi.org/10.1016/j.yhbeh.2015.06.021
0018-506X/Published by Elsevier Inc.

Introduction

This review summarizes data collected over the last 15 years supporting age-related endocrine dyscrasia as the etiological event driving age-related neurodegeneration. Endocrine dyscrasia associated with menopause and andropause, i.e. including, but limited to decreased sex steroid and inhibin signaling, and elevated gonadotropin-releasing hormone 1 (GnRH1), luteinizing hormone (LH), follicle-stimulating hormone and activin signaling — has been postulated to lead to aberrant mitogenic/differentiative (dyotic) signaling that drives the re-entry of post-mitotic neurons into an abortive cell cycle that leads to cell death (Atwood et al., 2005). This concept developed from our original studies demonstrating that 1) circulating LH is elevated in male AD patients compared to age-matched controls (Bowen et al., 2000; Butchart et al., 2013), 2) that intraneuronal levels of LH are elevated in pyramidal neurons of the AD brain (Bowen et al., 2002), 3) that LH drives the processing of AβPP towards the amyloidogenic pathway in vitro and in vivo (Bowen et al., 2004b), and 4) that elevated LH decreases cognitive performance (Casadesus et al., 2006b; Bowen et al., 2015).

New data supports endocrine dyscrasia and the subsequent alterations in downstream cell cycle signaling as an etiological factor in Alzheimer's disease (AD) as well as vascular dementia, stroke, Parkinson's disease (PD) and other age-related neurological diseases. While all HPG hormones whose concentrations become dysregulated with aging contribute to neurodysfunction and neurodegeneration, in the brain most evidence has been obtained for the gonadotropin LH, and changes in the ratio of LH to sex steroids as mediators of senescent dyotic signaling. Indeed, the elucidation of the non-gonadal functions of LH/hCG in the brain has revealed the importance of these hormones in regulating not only the early development and adult maintenance of brain structure and function, but also the senescent decline of brain structure and function upon dysregulation of the LH:sex steroid ratio with menopause and andropause (reviewed in Vadakkadath Meethal et al., 2010). This review therefore focuses primarily on the role of LH in regulating brain structure and function, but also provides evidence for the role of other hormones that become dysregulated around the time of menopause and during andropause in promoting neurodegeneration.

Endocrine dyscrasia

The decline in gonadal production of sex steroids and inhibins following menopause and during andropause leads to a loss of hypothalamic feedback inhibition that stimulates GnRH1 and gonadotropin production (Larson et al., 2003; Rannevik et al., 1995; Wiacek et al., 2011; Morley et al., 1997; Tenover et al., 1987; Sartorius et al., 2012). In addition, the decrease in gonadal inhibin production at this time (Reichlin, 1998) results in decreased activin receptor inhibition, and together with the increase in bioavailable activin (Gray et al., 2002) leads to a further increase in the secretion of GnRH1 and gonadotropins (MacConell et al., 1999; Schwall et al., 1988; Weiss et al., 1993). Thus, the lack of negative feedback from the ovary/testis (progesterone (P_4), 17β-estradiol (E_2), testosterone and inhibins) is responsible for the unopposed and marked elevations in the secretion of GnRH1 and gonadotropins that is associated with ovarian and testicular senescence (Atwood et al., 2005; Chakravarti et al., 1976; Neaves et al., 1984; Reame et al., 1996; Schmidt et al., 1996). Although post-reproductive changes in reproductive hormones have been recognized for decades (Furuhashi et al., 1976; Greenblatt et al., 1976; Furuhashi et al., 1977; Chakravarti et al., 1976; Couzinet and Schaison, 1993; Neaves et al., 1984), their implications to the health of the brain only began to be elucidated at the molecular level in the 1990s (Bowen et al., 2000, 2002a, 2004b; Jaffe et al., 1994; Xu et al., 1998b). These discoveries led to the development of a new theory of aging in 2004 (The Reproductive-Cell Cycle Theory of Aging) that proposed reproductive hormones in balance promote brain growth and development but that the endocrine dyscrasia following menopause and during andropause induces the brain senescent phenotype via alterations in cell cycle signaling (Atwood and Bowen, 2011; Bowen and Atwood, 2004). This mechanism is relevant to all reproductive species. An important basis for the development of this theory was that receptors for hypothalamic–pituitary–gonadal (HPG) axis hormones are present not only in the brain, but in other tissues of the body (reviewed in Bowen and Atwood, 2004; Vadakkadath Meethal and Atwood, 2005). Moreover, the elevations in circulating hCG early in life required for embryogenesis (Gallego et al., 2008; Vadakkadath Meethal et al., 2010), and of the elevation in LH, a hCG homolog, postmenopause and during andropause (Chakravarti et al., 1976; Couzinet