BOOK BASH

Hormones, cognition and dementia

Hogervorst E, Henderson VW, Gibbs RB, Brinton RD (Eds) Cambridge, UK: Cambridge University Press; 2009. Hardback, 280 pages, US $99.00. ISBN: 9780521899376.

With our rapidly ageing population, interest in the potential for reproductive hormones to prevent or treat cognitive decline is increasing, despite a major setback from the much publicised results of the Women's Health Initiative. With over 15 million people worldwide affected by Alzheimer's disease (AD), this is a timely multi-author book reviewing, in 29 chapters, data regarding the role of the reproductive hormones in cognitive function and in particular, the potential contribution of hormone therapy (HT) to prevent cognitive decline and AD. However, it is not a book to read comfortably from cover to cover. It is an excellent reference book, bringing together re-analyses of major trial data with relevant animal and laboratory data.

There are interesting hypotheses explaining the data so far without, of course, definitive proof from adequate human trials. Although supportive evidence for benefit exists in non-randomised hormone trials and laboratory studies, a major negative result exists from the single large randomised controlled study (Women's Health Initiative) where conjugated equine oestrogen (CEE) and medroxyprogesterone (for those with uterus) were given, initiated over the age of 65 years. Valid argument persists regarding varied effects of timing, type and duration of HT and route of administration.

Section 1

Chapters 1 and 2 summarise the main randomised intervention study: Women's Health Initiative Memory Study-Magnetic Resonance Imaging study and Women's Health Initiative Study of Cognitive Aging highlighting its major shortcoming: that HT was instituted between ages 65 and 79 years. Late administration of HT (CEE) alone or combined with medroxyprogesterone did not prevent cognitive decline. There was no protective effect, and risk of dementia, minor cognitive impairment and stroke increased. Adverse effects of such HT administration (including breast cancer diagnosis) have been publicised extensively, reducing worldwide HT prescription.

Chapter 3 describes the observational Leisure World Cohort Study of 8000 women in a California retirement community who completed a postal survey of HT in 1981 with 22-year follow-up. Although there was lower mortality, after adjustment of other factors, the over 90-year-old cohort showed no relationship between HT and dementia, excepting an increase in those taking it between 5 and 9 years.

Chapter 4 provides an evidence of benefit from HT in a 'critical window' of time post-menopause from an observational prospective study called the Cache County Study. Whether absolute age or menopause is the basis of such a window is critical. Animal data are supportive of giving replacement close to cessation of ovarian function, for both vascular and neural effects, but the question remains open in humans.

Chapters 5–7 describe the effect in animal models (largely rodent) of oestrogen post-oophorectomy on specific cognitive functions. The influence of oestrogen on forebrain cholinergic neurones which then influence selected cognitive tasks is highlighted. Oestrogen effects on hippocampal structure are also reduced by cholinergic denervation. Oestradiol also decreases β-amyloid production in the brain and protects from Aβ-mediated toxicity. The use of a cholinesterase inhibitor to restore oestrogen responsiveness to aged mice is suggestive but preliminary.

The 'window of opportunity' concept is discussed in relation to the concept of 'healthy cell bias' i.e. a metabolically impaired cell may be unable to benefit, whereas the healthy cell may be receptive to HT benefits. Importantly, HT patch therapy releases oestradiol predominantly into blood, more similar to the pre-menopausal pattern than oral therapy (releasing mostly oestriol and other equine oestrogens). Notably, most laboratory studies with beneficial actions of oestrogen on brain function used 17β-oestradiol. The Kronos Early Oestrogen Prevention Study is a randomised patch study with follow-up planned for 25 years.

Chapter 8 underlines the importance of the type and route of therapy. The transdermal 17β-oestradiol patch showed benefit in uncontrolled observational studies (contrasted to the large CEE trials) and in controlled trials of AD treatment, where there was rapid memory improvement, correlating with oestradiol levels. They emphasise the more physiological balance of oestradiol to oestrone.

HT alternatives are explored in Chapter 9 (pulsatile intranasal oestrogen therapy) and Chapter 10 (SERMs: selective oestrogen receptor modulators like Raloxifene). Evidence is given for benefits of oestrogen in the male brain. They discuss phyto-oestrogens (plant-derived non-steroidal analogues of mammalian oestrogens), but note variable data from the use of unstandardised over-the-counter soy extracts. Chapter 13 reports the observational Indonesian data with higher tofu consumption relating to lower cognitive function in older women.

Chapter 11 reiterates beneficial oestrogen data, suggesting progesterone and HT combination is understudied, and the effects are adverse when not administered in pre-menopausal pattern. Chapters 12 and 14 deal with emotional

and neuroendocrine stress effects on cognition in ageing, emphasising marked gender differences and as yet inconclusive data on the benefits of HT. Importantly, the adverse effects of glucocorticoids on neuronal integrity are described and more work is needed to clarify possible benefits of oestrogen in stress in women.

Chapters 15 and 16 provide as yet unconvincing evidence to support elaborate hypotheses designed to explain how some gene polymorphisms might be responsible for the transience of the benefit of HT after surgical oophorectomy and could moderate response to HT.

Chapter 17 discusses how oestrogen benefit may be due to its effect on increasing ApoE expression as ApoE and oestrogen both improve brain recovery from various injuries. I find their suggestion stimulating, that it is because both ApoE and oestrogen suppress cytokine production and reactive oxygen species release by reactive microglia.

Chapters 18–25 deal with the role of androgens in the brain and their metabolism in both sexes. Much of the data is inconclusive due to the nature of the human studies so far, with very few long studies. There are data showing that the decrease of testosterone with ageing in men (in both circulation and brain) contributes to cognitive decline and AD. Testosterone therapy can apparently reduce Aβ levels partly through reduction to dihydrotestosterone and partly through aromatisation to oestrogen. The concept that gonadotrophins themselves [and Luteinizing Hormone (LH) in particular] are involved in AD is raised and discussed in the final Chapters 26 and 27. It is suggested that testosterone HT and LH suppression may both benefit cognition by reduction in β-amyloid accumulation. Finally, the possibility that a combination of suppression/replacement therapy may be most efficacious is raised.

However, the immediate take-home clinical message is that in older women (and men) HT is not likely to reverse AD and very high levels may be adverse. However, as yet incomplete evidence exists in an early window for benefit to symptoms and lack of harm from physiological HT replacement with possible later benefits. As always, better studies are needed with possible confounders measured accurately. Reading the concise but well-referenced chapters will stimulate thought in researchers and clinicians alike.

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