Hormones, Cognition and Dementia

State of the Art and Emergent Therapeutic Strategies
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In the 1980s and 1990s, laboratory and clinical research suggested that estrogens were promising candidates in women for the treatment of dementia due to Alzheimer’s disease and for age-related cognitive decline. However, soon after the turn of the century, there was a remarkable change in attitude, which was almost comparable to a paradigm shift. As stated by Professor David Purdie (Edinburgh) in a 2003 BBC interview, “The only thing hormone replacement therapy has not yet been accused of is global warming and aggravating the national debt.” To a major extent, this change was the result of the Women’s Health Initiative, a large placebo-controlled clinical trial of conjugated equine estrogens with or without a progestogen, in which a number of health outcomes were examined. Beginning in 2002, Women’s Health Initiative publications reported important adverse health effects of hormone treatment, including the heretofore unappreciated risk of coronary heart disease. An ancillary study of women aged 65 years and older, the Women’s Health Initiative Memory Study (WHIMS), was an important milestone in scientific research on steroid hormones and cognition, and it is the logical starting point for work presented in this volume.

The WHIMS is the only clinical trial to have examined effects of estrogens on dementia risk, and it is one of the largest trials to have considered estrogenic effects on cognitive outcomes in older women without dementia. The primary finding of increased risk of dementia in women who were randomized to receive hormone therapy came at a time when several clinical trials failed to show clinical benefit of estrogens in women with Alzheimer’s disease. Further, results from the WHIMS, as well as from other clinical trials in older postmenopausal women, were unable to document cognitive benefit of estrogens in women without dementia.

These largely unexpected findings constitute a clarion call to reassess where the field is today and to re-examine some of the basic and clinical underpinnings of our current knowledge in areas related to sex steroid hormones, cognitive aging, and dementia. This book brings together contributions from many of the most prominent researchers in areas of women’s health, cognition, and steroid clinical endocrinology. These investigators have applied techniques from cell culture, animal models, human populations, clinical trials, and brain imaging in an attempt to understand effects of estrogens, androgens, progestogens, and the gonadotropins on human cognition and aging. Contributors to this volume summarize our current state of knowledge on selected topics and highlight areas where new research is needed. Through this means, we hope to promote collaborative, interdisciplinary research with translational goals: what can we learn from basic and clinical studies that we can apply to future therapies in older men and women?

This book is loosely divided into six sections. The first summarizes the most recent data from the WHIMS, including new brain imaging data, and it describes novel analytical techniques that attempt to find subgroups for whom cognitive outcomes might be improved by hormone therapy. Novel data from a study of nonagenarians and centurians substantiate increased risks for dementia among very old women using hormone treatment for long periods of time. One important question raised by the WHIMS is that of a critical window close to the time of natural menopause. During this so-called window, might estrogens reduce the risk of harmful outcomes, such as Alzheimer’s disease, even if later therapy does not? If so, what factors might account for such a window of opportunity? The role of the basal forebrain cholinergic system could be of paramount importance. Another potential mechanism is described by the “healthy cell bias” theory.

In the laboratory, different estrogens can have different effects, depending on the model system under consideration. Are some estrogens, some hormonal...
formulations, or some routes of estrogenic administration more conducive to cognitive benefit? The second section of the book describes some of these options. Effects of transdermal estradiol on cognition in women with and without dementia are reviewed, and nasal administration of estradiol is discussed as an alternative to the oral administration. In this section also, effects of selective estrogen receptor modulators (SERM) on cognitive function are discussed. Phytoestrogens, whose impact can also be tissue selective, are considered as well.

It is difficult to consider estrogen actions in the brain without at the same time considering progestogen actions. The third section discusses potential modulators of estrogenic effects by progesterone, as well as other modifiers of estrogen actions, such as cortisol and folate. Some researchers suggest that estrogens can affect cognitive function indirectly, working to improve mood, sleep, or vasomotor symptoms. Estrogen effects on mood disorders are reviewed in this section. In Section 4, the focus is on genetic variation related to steroid hormone metabolism, Alzheimer’s disease, and apolipoprotein E. This exciting research area may lead to new screening tools for assessment of risks and benefits of hormone treatment.

The relevance of testosterone to brain action in women and for men is being increasingly recognized. This steroid not only affects the nervous system directly, but it may also modulate brain effects of estradiol. Androgen research has received less attention than estrogen research, and substantial portions of Sections 5 and 6 are devoted to new insights on testosterone, cognition, and Alzheimer’s disease. The role of gonadotropins is discussed here in relation to dementia, as is the role of sex hormone binding globulin, whose levels determine those of free sex hormones. Lowering levels of this globulin would increase free levels of both estradiol and testosterone, which could be of value in some clinical settings. Reducing gonadotropins will increase sex steroid levels, but in some models these peptides are also neurotoxic. Data from trials in women with Alzheimer’s disease are presented, together with supportive results from animal and cell-culture experiments. The volume concludes with a perspective from Professor Wulf H. Utian, an expert in women’s health and Executive Director of the North American Menopause Society.