

Hormones, gender and **the aging brain**

The endocrine basis of geriatric psychiatry

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CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS

The Edinburgh Building, Cambridge CB2 2RU, UK <http://www.cup.cam.ac.uk>
40 West 24th Street, New York, NY 10011-4211, USA <http://www.cup.org>
10 Stamford Road, Oakleigh, Melbourne 3166, Australia
Ruiz de Alarcón 13, 28014 Madrid, Spain

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First published 2000

Printed in the United Kingdom at the University Press, Cambridge

Typeface Minion 10.5/14pt System QuarkXPress™ [SE]

A catalogue record for this book is available from the British Library

Library of Congress Cataloguing in Publication data

Hormones, gender, and the aging brain : the endocrine basis of geriatric psychiatry /
[written by Mary F. Morrison . . . et al.].

p. cm.

Includes index.

ISBN 0 521 65304 5

1. Geriatric psychiatry. 2. Aged-Diseases-Endocrine aspects. 3. Aging-Endocrine
aspects. 4. Aged-Mental Health. I. Morrison, Mary F. (Mary Frances), 1958-

RC451.4.A5 H67 2000

618.97'689-dc21 99-045853

ISBN 0 521 65304 5 hardback

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Summary chapter: The endocrine basis of geriatric psychiatry: an integrative approach

John E. Morley

Introduction

Life is becoming less like a short sprint and more like a marathon.

Kofi Anan, UN Secretary General, October 1, 1998

Man is born, grows up and dies according to laws which have never been properly investigated either as a whole or in the mode of their mutual reactions.

Quetelet, 1835

The world is rapidly aging. The concept of a few older persons aging successfully into old age was well established at the time of the ancient Greek philosophers, e.g. Socrates, 98 years; Sophocles, 91 years; and Plato, 81 years. In 1900 the average citizen of the United States lived less than 50 years, whereas at the end of the century life expectancy has reached the late seventies. By the year 2030, the percentage of older individuals in the population of most developed nations will be approaching 20%. However, it is not only in the developed nations that persons are living longer. By the year 2000 approximately two-thirds of older persons will live in developing nations, e.g. 300 million in China and 170 million in India.

It is against the backdrop of this age wave that there has been an increasing interest in understanding the scientific basis of the aging process, both physiological and pathological. In the area of mental disorders and aging there have been tremendous advances in our understanding of the pathophysiology of these disorders and an extraordinary development of new therapeutic agents.

Since the original work by Moos and Solomon (1965) recognizing the important mind–body connections with disease, there has been an explosion in our knowledge of how the mind communicates with the body and the body with the mind. It is now recognized that, in many cases, their communications involve the secretion of the ductless glands, i.e. hormones. It is also clear that many peptide hormones have a second role as neurotransmitters within the central nervous system.

In addition, the immune system releases a series of peptide hormones, better recognized as cytokines, that both modulate the endocrine system and a variety of behaviors. Behavior, in turn, through hormonal release and the autonomic nervous system, can modulate the immune system. These interactions have spawned the field of psychoneuroimmunology. The waning immune system seen with aging creates special challenges for the understanding of how behavior–endocrine interactions modulate the immune system of older persons.

This book is presented to the reader as an overview of the endocrine basis of geriatric psychiatry. It is hoped that, with the material provided in this book, the intrepid researcher will be able to revolutionize this field in the next millennium. This chapter will attempt to integrate some of the more exciting findings in the field of hormones, aging, and mental disorders and provide some signposts for where the future advances may lie.

Endocrine disorders as a cause of mental illness

The concept of endocrine disorders resulting in mental illness is well established. Early reports of hypothyroidism discussed ‘myxedema madness.’ This is especially important in older persons where atypical presentations are common. Thus, we see apathetic hyperthyroidism, with depression and weight loss being major symptoms. Older hypothyroid patients often present with cognitive abnormalities that are reversed with thyroid hormone replacement (Osterweil et al., 1992). Hypothyroidism can also present as depression. Both an excess and a deficiency of thyroid hormone can present as delirium or as a reversible cause of dementia. Addison’s disease (hypoadrenocortisolism) often presents insidiously in older persons with a mild delirium, abdominal pain, hypotension, hyperkalemia, weight loss, and hypoglycemia. Hypercalcemia is not rare in older persons and can present with either depression or cognitive impairment. Pheochromocytoma – the classical medical cause of a panic attack – occurs as commonly in persons over 60 years of age as in younger persons, but the diagnosis is rarely made.

Diabetes mellitus has been shown to be associated with cognitive impairment secondary to hyperglycemia and dementia secondary to vascular infarcts (Morley, 1998). This can lead to major problems with compliance leading to worsening glycemic control. Depression occurs more commonly in older persons with diabetes mellitus, and depression is a major cause of noncompliance leading to increased hospitalizations and mortality in older diabetics (Rosenthal et al., 1998). Both hypoglycemia and hyperglycemia can present with delirium.

Hypopituitarism can present with delirium. Elevated prolactin levels are associated with decreased libido and impotence. Adult growth hormone deficiency has been associated with fatigue.

Table 1.1. Behavioral effects of endocrine disorders

Delirium	Dementia	Depression	Anxiety/panic
Hypoglycemia	Hypothyroidism	Hypothyroid	Pheochromocytoma
Hyperglycemia	Vitamin B ₁₂ deficiency	Hyperthyroid	Hyperthyroidism
Hyponatremia (syndrome of inappropriate ADH)	Diabetes mellitus	Addison's disease	
Hypothyroidism	Hyperparathyroidism	Diabetes mellitus	
Hypopituitarism		Hypercalcemia	
Addison's Disease			
Vitamin B deficiency			
Hypercalcemia			

Older persons often have elevated levels of circulating cytokines due to chronic disorders. In addition, acute infections lead to a marked increase in cytokines. Tumor necrosis factor α and interleukin-1 both produce delirium. While this may, in part, be due to small amounts crossing the blood–brain barrier (Banks et al., 1994), the major effect appears to be on ascending vagal fibers through neuronal synapses from the nucleus tractus solitarius to the amygdala to the hippocampus, resulting in release of interleukin-1 from hippocampal microglial cells. This glial interleukin-1, in turn, results in decreased release of acetylcholine and cognitive impairment. Cytokines may also play a role in the pathogenesis of dysphoria associated with physical illness.

Table 1.1 summarizes the endocrine disorders responsible for some major psychiatric symptoms in older persons.

Hormones and aging

As shown in Table 1.2, the majority of hormones show a physiological decline with aging. This has led to an enthusiasm for hormone replacement as a modern-day fountain of youth. Unfortunately, with the exception of the data for estrogen and testosterone replacement, the controlled studies in humans have failed to match the promise of animal studies.

Dehydroepiandrosterone (DHEA) and its sulfate show the largest decline of any of the hormones with aging. The function of this adrenal cortical hormone remains elusive. Replacement studies in middle-aged persons suggested an improved mood (Morales et al., 1994) but this could not be replicated by another group (Wolf et al., 1998). As pointed out by Wolkowitz (Chapter 7), DHEA may have a role to play in

Table 1.2. Hormonal changes with aging

Decrease	No change	Increase
Insulin growth Factor I	Epinephrine	Insulin
Vitamin 25(OH)D	Thyroxine	Vasopressin (basal)
Testosterone (males)	Amylin	Cholecystokinin
Estradiol (females)	Glucagon	Atrial natriuretic peptide
DHEA and its sulfate	Glucagon like Peptide I	Norepinephrine
Triiodothyronine	Thyrotropin	Epinephrine (> 80 years)
1,25(OH) ₂ Vitamin D	Calcitonin	FSH
Inhibin	Activin (females)	LH (women)
Arginine vasopressin (nocturnal increase)	ACTH	Parathormone
Pregnenolone	Prolactin (females)	Cortisol
		Activin (males)
		Prolactin (males)

depression, but adequate control trials are not yet available. In men, but not in women, high doses of DHEA (100 mg daily) have increased muscle mass and strength (Morales et al., 1998). In mice, DHEA is a potent enhancer of memory, most probably by a nongenomic effect involving GABA (Flood et al., 1992). However, while some epidemiological studies have suggested that DHEA may be correlated with the decline in functional status with aging (Morrison et al., 1998; Rudman et al., 1990b), there is no clear evidence for DHEA improving cognition in humans (Horani & Morley, 1997).

Pregnenolone is the first steroid hormone formed from cholesterol on the adrenal cortex. It is the true 'mother hormone.' In mice it is the most potent memory enhancer yet to be discovered (Flood et al., 1995).

Unfortunately, our study in humans failed to demonstrate any clear cognitive effects of pregnenolone at a 50 mg dose. Previous studies have suggested that pregnenolone may enhance attention and improve function through this route (Horani & Morley, 1997). Pregnenolone may also have small effects on improving sleep.

Melatonin is produced by the pineal gland. Descartes originally suggested that the pineal was the seat of the soul. At present, the best data for melatonin is an effect on sleep in older persons (Dawson et al., 1998). Continued studies on the potential role of melatonin on mental function are warranted.

In the 1980s, Dan Rudman (1985) suggested that aging was due to a growth hormone 'menopause.' His early study suggested positive effects of growth hormone in older men (Rudman et al., 1990a; Cohn et al., 1993). However, subsequent studies have only been able to demonstrate an increase in muscle mass without an increase

in muscle strength and no positive behavioral effects (Papadakis et al., 1996). Overall, side-effects have been extremely rate limiting. This is in contradistinction to growth hormone replacement in growth hormone-deficient younger men where positive effects on mood have been demonstrated (Burman & Deijen, 1998). The recent availability of orally active growth hormone secretagogues may allow replacement with more physiological levels of growth hormone.

Arginine vasopressin (AVP) levels increase during the day but the nocturnal surge is attenuated with aging. This is responsible for the well-known nocturia that occurs with aging. In addition, AVP has been demonstrated in animals to enhance memory. In rodents the decline in AVP that occurs with aging is related to the decline in testosterone (see below) and can be restored with testosterone replacement.

Cortisol levels show no change or a small increase with aging. This is most probably predominantly due to the decrease in cortisol production rate that occurs with aging. Thyroxine levels remain stable throughout the lifespan as the decrease in thyroxine production rate is balanced by a decrease in thyroxine clearance. Triiodothyronine levels decline slightly in persons beyond 80 years of age.

25(OH) vitamin D levels decline with aging resulting in an increase in parathyroid hormone levels and an increased loss of calcium from bone, resulting in osteoporosis in the old-old (Type II osteoporosis). This can have an indirect effect on mental function as it can lead to lumbar spinal fractures with severe pain.

Norepinephrine increases in the young old and epinephrine in the old-old. This is due predominantly to a postreceptor defect. This postreceptor defect leads to a decreased catecholamine responsiveness with aging. This may result in altered stress responses in older individuals.

Estrogen and cognitive dysfunction

The rapid fall in estrogen in women at the time of the menopause is the most dramatic hormonal change that occurs with aging. This occurrence is marked by hot flashes. Chapters 8 and 9 discuss the putative effects of estrogen deficiency on cognitive dysfunction and dementia in older persons.

Estrogen has a number of effects on the brain that may improve cognition. These include an increase in choline acetyl transferase, an increase in cholinergic neuron survival and an increase in axonal sprouting and dendrite spine formation. Estrogen stimulates nerve growth factor. Estrogen may also protect against vascular dementia through its positive effects on lipids and vasodilation through the stimulation of endothelial nitric oxide.

A number, but not all, cross-sectional studies have suggested that estrogen use is associated with better cognitive function than non-estrogen use. Estrogen use may also delay the onset of Alzheimer's Disease.

One controlled study in nursing home residents suggested improved function in those residents receiving estrogen (Birge, 1996). Other small controlled trials have found some improvement in cognition with estrogen use in postmenopausal women. Progesterone, which is usually co-administered with estrogen, is amnesic (Farr et al., 1995), and this may make it difficult to interpret the effects of some studies on cognition.

Overall, the possible role of estrogen in enhancing cognitive function is extremely exciting, but final proof must await the results of ongoing controlled trials.

Testosterone and behavior

There are now multiple cross-sectional studies demonstrating that testosterone, free testosterone and bioavailable testosterone (albumin plus free testosterone) decline with aging (Morley et al., 1997d). This has been confirmed in a longitudinal study (Morley et al., 1997b). This decline is due primarily to a failure of the gonadotropin-releasing hormone-pituitary unit, and thus luteinizing hormone fails to rise as testosterone declines.

We have recently defined a testosterone deficiency syndrome called Androgen Deficiency in Aging Males (ADAM) that occurs when bioavailable testosterone levels fall below those seen in young males (Table 1.3). This syndrome identified dysphoria as one of the symptoms of testosterone deficiency, as discussed in Chapter 6.

In the SAMP8 mouse, a spontaneous model of cognitive dysfunction due to overproduction of β -amyloid, testosterone levels fall early in the lifespan (Flood & Morley, 1998). Testosterone replacement reverses the memory and learning defects seen in these mice. Testosterone appears to produce this effect by suppressing amyloid precursor protein production in the limbic system.

Cross-sectional studies have suggested that bioavailable testosterone is a major factor in age-related cognitive decline (Morley et al., 1997c). Two interventional studies in older males have shown that testosterone replacement results in enhanced visual-spatial cognitive function (Janowsky et al., 1994).

Testosterone has also been clearly demonstrated to increase libido (Hajjar et al., 1997). Testosterone replacement results in increased strength (Sih et al., 1997; Urban et al., 1995).

Since the time before Christ, when Areteaus the Cappadocian first demonstrated behavior effects in cocks when they were castrated, our knowledge of the effects of testosterone on behavior has come a long way (Chapter 6). However, it is important to realize that many of these effects are small – although small effects can have dramatic affects on quality of life.

Table 1.3. St Louis University. ADAM: Androgen deficiency in aging males

Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost weight?
5. Have you noticed a decreased 'enjoyment of life'?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Positive questionnaire is defined as 'yes' answers to questions 1 or 7 and/or 'yes' answers to any three other questions.

Depression and the hypothalamic–pituitary–adrenal axis

Some of the most important advances on the understanding of hormones and behavior in the last decade have come from the increased recognition of the role of the hypothalamic–pituitary–adrenal axis in depression (Chapter 3). Stress activates this axis through the actuation of hypothalamic corticotropin releasing factor (CRF). CRF levels are elevated in the majority, but not all, persons with depression.

CRF appears to play a particularly important role in the genesis of the vegetative signs of depression. These include sleep disturbance, decreased locomotion, anorexia, and weight loss. Older persons with depression are more likely to have anorexia and weight loss than young depressives (Fitten et al., 1989). In addition, the elevated glucocorticoid levels in depression lead to hippocampal neuronal loss and impaired cognition (the pseudodementia syndrome of depression in older persons). The elevated cortisol levels also increase the likelihood of older depressed women to develop osteoporosis (Michelson et al., 1996).

Alcoholism is associated with direct activation of the hypothalamic–pituitary–adrenal axis (Willenbring et al., 1984). This could, in turn, result in some of the depressive symptoms seen in older alcoholics.

An interesting therapeutic development in the treatment of late life depression has been the use of electromagnetic brain stimulation (EBS). Our unpublished studies have suggested that EBS has direct effects on the hypothalamic–pituitary–adrenal axis.

The potential of the treatment of vegetative symptoms, such as weight loss, in older depressives with CRF antagonists is enormously exciting.

Anorexia of aging and hormones

Food intake declines throughout the lifespan, and beyond the age of 70 years, there is a declining in body mass (Morley, 1997). A part of this decline in food intake is due to overproduction of the gastrointestinal hormone, cholecystokinin, and an enhancement of its satiating effect with aging (Silver et al., 1988; Morley et al., 1997a). In addition to this there is a decrease in the ability of the gastric fundus to relax to accept normal sized meals. This leads to early satiation in older persons and is due to a deficiency in nitric oxide (Morley & Flood, 1994).

Leptin is a peptide hormone produced by fat cells (Morley et al., 1999). It plays a role in decreasing intake through inhibiting neuropeptide Y in the central nervous system. Testosterone deficiency with aging leads to an increase in circulating leptin levels with aging and this is responsible for the greater decrease in food intake that occurs with aging in men. Estradiol has no effect on leptin.

A number of neurotransmitters within the hypothalamus drive food intake. Dynorphin (an opioid peptide) increases fat intake and neuropeptide Y increases carbohydrate intake. Both of these peptides decline with aging. Their effects appears to be mediated by activation of nitric oxide in the hypothalamus. Levels of the mRNA for nitric oxide synthase also decline with aging (Morley et al., 1996).

Depression is the most common cause of anorexia and weight loss in older persons (Wilson et al., 1998). Anorexia nervosa (or tardive) can reoccur in older women and appears for the first time in older men. The potential relationship of this condition to sex hormone changes in the elderly is in need of exploration. Late life paranoia can also be associated with refusal to eat because of fear that the food is poisoned.

Dementia is most often associated with failure to eat, apraxia of swallowing, and weight loss. In the midstages of dementia some patients develop hyperphagia. Ingestion of unpalatable objects, e.g. coprophagia, can also occur in demented persons. While it has been suggested that Alzheimer's disease may be associated with an increased metabolic rate, double labeled water studies have failed to confirm this (Poehlman et al., 1997).

The endocrinology of disturbances of food intake and metabolism associated with aging represents one of the cutting edge issues in geriatric psychiatry.

Conclusions

As illustrated in Fig. 1.1, the interaction of hormones and behavior is inordinately complex. In older persons hormonal alterations can lead to depression, delirium, dementia, and panic attacks. Depression or a decline in food intake can lead to

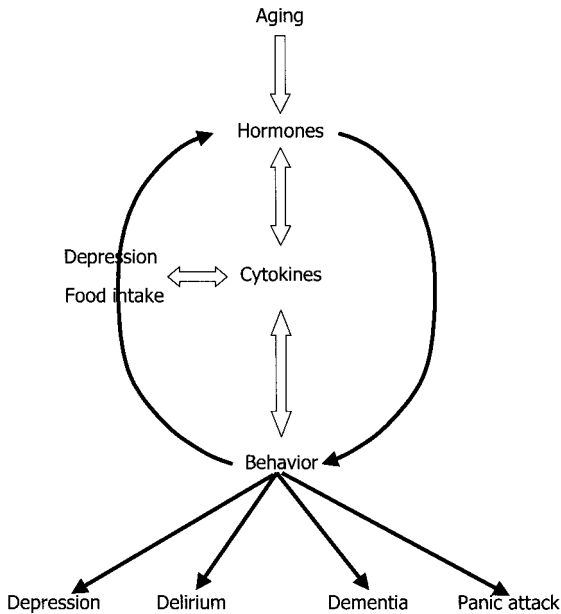


Figure 1.1. The interaction of hormones and behavior in the aging brain.

marked alterations in hormonal levels. Aging can result in a decline in hormonal levels making the aging brain more vulnerable to developing cognitive defects. Cytokines produced by the immune system can directly alter both hormones and behavior. With the increased computer power in the next millennium, together with full knowledge of the human genome, we should be much more capable of understanding these complex interactions and developing new approaches to the management of mental disorders in older persons. However, it is perhaps best to close with the comment of the English philosopher, Emerson Pugh: 'If the human brain were so simple that we could understand it, we would be so simple that we couldn't.'

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