

SEX PLAYING WITH THE MIND

EFFECTS OF OESTROGEN AND TESTOSTERONE ON MOOD AND COGNITION

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ABSTRACT - Women now spend more than 1/3 of their lives in a state of oestrogen deprivation as a result of increased life expectancy. A similar, but milder, hypogonadal state has been described for elderly men. This paper aims to review the available literature on the effects of both oestrogen and testosterone on mood and cognition. Oestrogen replacement therapy of postmenopausal women is associated with improvements in measures of well being and decline in depression scores. In addition, oestrogen seems to augment the response of postmenopausal women with major depression to antidepressant treatment. Most studies designed to investigate the impact of oestrogen on cognition indicate that replacement therapy is associated with better performance on neuropsychological tests, particularly in measures of verbal memory and fluency. The data also supports claims that oestrogen replacement therapy reduces the risk of Alzheimer's disease in later life and improves response of patients to anticholinesterase treatment. Data on the effects of testosterone is sparser. Preliminary findings suggest that testosterone therapy may improve mood when used in isolation or in association with oestrogen. The effects of testosterone on cognitive functioning are less clear — some studies indicate that the administration of testosterone to non-demented subjects is associated with better visuospatial functioning and deterioration of verbal skills. In summary, gonadal hormones seem to modulate various aspects of mental functioning. If future studies prove this to be true, hormone replacement therapy should have a major impact on the physical and mental health of older people in the years to come.

KEY WORDS: estrogen, oestrogen, testosterone, gonadal hormones, depression, depressive disorder, memory, cognition, dementia, Alzheimer's disease, old age, aged, elderly, postmenopause

Sexo mexendo com a mente: efeitos do estrógeno e testosterona sobre humor e cognição

RESUMO - O aumento na expectativa de vida fez com que as mulheres de hoje passassem a viver 1/3 de suas vidas em hipoestrogenismo. Um estado hipogonadal semelhante, porém mais leve, vem sendo descrito para homens idosos. Este artigo tem o objetivo de rever os efeitos do estrógeno e testosterona sobre o humor e funcionamento intelectual. A reposição estrogênica em mulheres na pós-menopausa está associada a melhora em medidas de bem-estar e a declínio nos escores de depressão. Além disso, o estrógeno parece aumentar a taxa de resposta ao tratamento antidepressivo de mulheres com depressão maior no climatério. Em sua maioria os estudos desenhados para investigar o impacto do estrógeno sobre a cognição indicam que a reposição hormonal está associada a melhor desempenho nos testes neuropsicológicos, particularmente em tarefas de memória e fluência verbal. Os dados também sugerem que a reposição estrogênica reduz o risco de doença de Alzheimer e aumenta a resposta dessas pacientes ao tratamento com anticolinesterásicos. Dados sobre os efeitos da testosterona são mais escassos. Achados preliminares sugerem que a testosterona melhora o humor quando utilizada de forma isolada ou em associação com estrógeno. Os efeitos do hormônio sobre o funcionamento cognitivo são menos claros — alguns estudos indicam que a administração de testosterona a indivíduos não demenciados está associada a melhora do desempenho cognitivo em testes visuoespaciais e deterioração em testes medindo habilidades verbais. Em resumo, os hormônios sexuais parecem modular vários aspectos do funcionamento mental. Se esses

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achados vierem a ser confirmados por novos estudos, a terapia de reposição hormonal passará a ter um papel central para a manutenção da saúde física e mental de pessoas idosas nos próximos anos.

PALAVRAS-CHAVE: estrógeno, testosterona, hormônios gonadais, hormônios sexuais, depressão, transtorno depressivo, memória, cognição, demência, doença de Alzheimer, climatério, idoso, envelhecimento

Gonadal hormones have a number of physiological functions that extend well beyond the regulation of prolactin and gonadotrophin secretion and the modulation of sexual behaviour. Recent reports have highlighted the beneficial role of oestrogen in coronary heart disease, hypertension, lipid metabolism, osteoporosis, and the incidence of strokes^{1,2}. There is evidence that androgens too regulate many of these health parameters, although in some instances their action may oppose that of oestrogen^{2,3}. In addition, the existence of clinical conditions such as premenstrual dysphoria and puerperal psychosis indicate that sex hormones may interfere with some aspects of mental functioning. This paper aims to summarise the results of studies looking into the association between behaviour and oestrogen and testosterone, emphasising their effects on mood and cognition in later life.

OESTROGEN

Oestrogen increases serotonergic (5-HT) postsynaptic response, the number of receptors, and 5-HT synthesis and uptake^{4,5}. It also upregulates 5-HT₁ receptors and downregulates 5-HT₂ receptors^{4,5}. In addition, oestrogen selectively increases norepinephrine (NE) activity in the brain by increasing the turnover of NE and inhibiting monoamine oxidase activity⁴. These findings suggest that oestrogen may influence mental state. Schmidt and colleagues⁶ have recently shown that women who experience symptoms of premenstrual dysphoria are more sensitive to fluctuations on oestrogen levels. Similarly, postpartum mood disorders have been associated with the sudden and dramatic decline of oestrogen levels that take place during the puerperium⁷. There is also evidence suggesting that low levels of oestrogen are associated with depressive symptoms in postmenopausal women. Ditkoff and colleagues⁸, for example, reported that conjugated oestrogen in doses of 0.625 and 1.25 were superior to placebo in decreasing the depression scale scores of postmenopausal women. Klaiber and associates⁹ compared the effect of high doses of oestrogen and placebo on the depressive scores of 40 women with treatment-resistant depression. Depression ratings were significantly reduced in the oestrogen-treated group, but not in the placebo control group. A more recent study¹⁰ reported the impact of oestrogen replacement therapy (ERT) on the clinical response to fluoxetine in a 6-week randomised, placebo-controlled, double-blind trial. Seventy-two women received ERT and 286 did not. There was a significant interaction between ERT status and treatment effect. Patients on ERT who received fluoxetine showed greater reduction on depression scores than the fluoxetine treated group not on ERT, suggesting that oestrogen may augment response to antidepressant treatment.

Oestrogen also increases blood flow and glucose utilisation in the brain, displays anti-inflammatory and antioxidant properties, lowers lipoproteins and apolipoprotein E levels in the blood, induces choline acetyltransferase and acetylcholinesterase according to a sexually dimorphic pattern, and regulates synaptogenesis in the CA1 region of the hippocampus¹¹. These effects of oestrogen in the central nervous system are thought to modulate various aspects of cognitive functioning, and a number of clinical reports support this hypothesis¹². Sherwin and Tulandi¹³ investigated the association between oestrogen replacement therapy and memory. They assessed nineteen women receiving a GnRH agonist (leuprolide acetate depot) every four weeks for twelve weeks for the treatment of uterine myomas. They were then randomly allocated to receive conjugated oestrogen (0.625 mg/day) or placebo. Scores on tests of verbal memory decreased from pretreatment to twelve weeks posttreatment amongst women treated with leuprolide and placebo, but were reversed in those treated with leuprolide and oestrogen. The authors concluded that oestrogen replacement might be important in maintaining appropriate levels of memory functioning in hypoestrogenic women. Recent reports have confirmed and extended those findings for women in the climacteric.

Resnick and colleagues¹⁴ evaluated the performance of 288 women after the menopause on the Benton Visual Retention Memory Test. Women on ERT (n=116) performed significantly better than women who were not receiving replacement therapy. A comprehensive review of this subject¹⁵ described five observational studies and eight controlled clinical trials of ERT in postmenopausal women. Most, but not all, studies indicated that oestrogen use is associated with better cognitive functioning. There are also a number of case-control studies that have evaluated the risk of dementia amongst oestrogen users¹⁵. Their results were inconclusive. However, two large cohort studies indicate that oestrogen may indeed reduce the risk of dementia. Tang and colleagues¹⁶ followed-up a sample of 1124 elderly women for up to five years. During this period, 167 of them became clinically demented. Only 9 (5.8%) of the 156 women who received ERT developed dementia, compared to 158 (16.3%) of the 968 women that did not use ERT. The odds ratio for the development of Alzheimer's disease (AD) amongst oestrogen users was 0.40 (CI=0.3-0.9). Similarly, Kawas and colleagues¹⁷ reported the results of a 16-year follow-up study of 472 women living in the community. Thirty-eight of them became demented during this period. The odds ratio for the development of AD was 0.5 (CI=0.2-1.0) amongst oestrogen users.

Further support for the beneficial effects of oestrogen on cognition comes from four small-scale clinical trials of oestrogen for patients with AD. Two of the trials were not controlled and had only 7 participants^{18,19}. Severity of dementia was assessed at baseline and after 6 weeks of oestrogen therapy. Both studies described improvement on cognitive measures such as the Mini Mental State Examination (MMSE), the Randt Memory Test, and the Hasegawa Dementia Scale. One other trial²⁰ compared 15 women with AD treated with oestrogen with 15 untreated women with AD in a non-blind, non-randomised design. Compared with baseline, there was improvement on MMSE and Hasegawa scores for the oestrogen treated group, but not for the control group. Honjo and colleagues²¹ reported the results of a six-week placebo-control clinical trial of 14 women with AD. Women receiving oestrogen showed significant improvement on the scores of the Hasegawa scale. Finally, there is also evidence that oestrogen may augment the response of AD patients to anticholinesterase therapy. Schneider and colleagues²² evaluated retrospectively the effects of oestrogen on the response of AD patients to tacrine in a controlled, randomised, double-blind clinical trial. Thirty-seven (11.8%) of the 314 women in the trial received ERT. The response of these patients to treatment was significantly better than those who had received placebo or tacrine alone.

ANDROGENS

In contrast to the increasing amount of data on oestrogen, there is only sparse information about the effects of androgens on brain function and behaviour. Androgen binding sites can be found in the hypothalamus, diencephalic nuclei, and the amygdala of nonhuman primates and rodents^{23,24}. In addition, testosterone is aromatised to oestrogen and acts through oestrogen receptors in some parts of the brain²³. Janowsky and colleagues²⁵ have remarked that the exogenous manipulation of testosterone levels can affect the endogenous production of other hormones such as oestrogen. It is possible, therefore, that the effects of androgens in the central nervous system are at least partly mediated by oestrogen.

The few studies that set out to investigate the effects of androgens on mood have produced inconsistent results²⁶⁻³¹. Sternbach³² has argued that discrepancies in these studies could be accounted for by differences in patient groups (e.g., age), method for measuring testosterone (e.g., total versus free, serum versus salivary), cortisol levels (which interfere with testosterone levels), degree of weight loss (loss of weight is associated with lower testosterone levels), and concomitant use of medication. A more recent and larger study, however, showed that testosterone administration may improve some aspects of mood. Wang and colleagues³³ investigated the effects of testosterone replacement therapy on the affective state of 51 hypogonadal men. Treatment was associated with decline in the Likert rating scale scores associated with anger, irritability, sadness, tiredness, and

nervousness. There were also significant improvements in energy level, friendliness, and sense of well being. Similarly, the administration of dehydroepiandrosterone (30 to 90 mg/day) to 3 men and 3 women for 4 weeks produced a significant reduction on the scores of the Beck Depression Inventory, Hamilton Rating Scale, Global Depression Scale, and the Symptom Checklist-90³⁴.

Seidman and Rabkin³⁵ reported last year the results of testosterone replacement (400 mg) for 8 weeks in five men who were refractory to antidepressant treatment with selective serotonin reuptake inhibitors (SSRI). Four patients later underwent single-blind placebo discontinuation. The introduction of testosterone was associated with prompt recovery from major depression, whereas 3 of the 4 subjects who underwent discontinuation of testosterone relapsed after 12 weeks.

There are also studies that have evaluated the ability of testosterone to improve mood when used in association with oestrogen or oestrogen and progesterone. Brincat and colleagues³⁶ studied 55 postmenopausal women who were receiving standard hormone replacement therapy treatment. Treatment with testosterone+oestrogen+progesterone for 8 months was associated with improvement of climacteric symptoms (including mood and well-being). Relapse of climacteric symptoms was observed amongst placebo users. Three years later the same group reported the results of a double-blind trial of oestrogen, testosterone+oestrogen, or placebo implants on symptoms of anxiety and depression³⁷. Women receiving active treatment performed better than the placebo group on self-rating scales of distress, anxiety, and depression. Similarly, Sherwin and Gelfand³⁸ investigated the effect of oestrogen and/or androgen on the mood of surgically menopausal women in a prospective, double-blind, cross-over trial. Women who received oestrogen, androgen, or a combined oestrogen-androgen preparation attained lower depression scores during both treatment phases compared to the placebo-control group.

There are also claims that androgens may modulate certain aspects of cognitive functioning^{32,39}. Janowsky and colleagues²⁵ evaluated 27 healthy elderly subjects who used 15 mg testosterone patches for 3 months and compared their cognitive performance with that of 29 healthy controls who used a placebo patch for the same period of time. Neuropsychological assessment included tasks of delayed recall, visual reproduction, block design, and trail making. Testosterone treatment enhanced spatial cognition, as measured by the block design test, but had no other obvious effect on cognitive functioning. Other studies have also shown that there is a curvilinear relationship between testosterone levels and visuospatial abilities in humans — low and high levels are associated with poor performance⁴⁰.

An interesting study reported by van Goozen and colleagues⁴¹ suggests that androgens may indeed affect cognition. They investigated 22 female-to-male transsexuals with a battery of visuospatial and verbal cognitive tasks. Subjects were tested immediately before and 3 months after the introduction of testosterone therapy. Treatment was associated with improved visuospatial performance, but deterioration on the scores of verbal tasks such as verbal fluency, sentence production, and verbal reasoning. These results indicate that visuospatial and verbal abilities are influenced by the actions of androgens in the brain. Unfortunately, the scarcity of data on this subject precludes further insights into the role of androgens on cognition at this point.

CONCLUSION

The potential health benefits of oestrogen replacement therapy for postmenopausal women have attracted a great deal of attention from both the general public and medical community. There is currently great excitement with the prospect of oestrogen improving mood and reducing the risk of Alzheimer's disease in later life. But there are also problems. The sample size of most studies reported to date are rather small and the exposure to hormonal replacement was often assessed retrospectively. The concomitant use of progesterone during treatment is hardly ever taken into account, and there is evidence suggesting that progesterone may have detrimental effects on mood

and cognition^{42,43}. Other problems include the use of multiple assessment instruments with no clearly stated primary outcome measure and limited time of follow-up. In other words, the data on oestrogen is promising, but not yet conclusive. Data on the effects of testosterone on mood and cognition is even more sparse and flawed.

More than one hundred years ago Sigmund Freud proposed that 'sex' was one of the driving forces of human behaviour. The initial results of clinical research looking at the effects of oestrogen and testosterone on behaviour seem to indicate that he was not totally wrong after all.

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