

Testosterone's

Effects on

Anxiety:

Androgens and Mood

EMAA 2006 Conference

Paris: October 13-15th

Generalised Anxiety Disorder

Definition (DSM 4) is descriptive:

Generalised persistent anxiety for one month or more (excluding phobias, panic attacks, obsessional/compulsive disorders).

The following signs are present to a variable extent:

- Motor Tension
- Autonomic hyperactivity
- Apprehensive expectation
- Vigilance and screening

Testosterone's Effects on Anxiety

Generalised Anxiety Disorder:

- Motor Tension:
Tremor, muscle aches and tension, and inability to relax. Easy startle, motor restlessness and sighing.
- Autonomic hyperactivity:
Sweating, palpitations, cold clammy hands, dry mouth, dizziness, polyuria and frequent motions; aching substernally, a lump in the throat, flushing, fast breathing and pulse.

Testosterone's Effects on Anxiety

Generalised Anxiety Disorder:

- Apprehensive expectation:
fearful, worries, ruminates something bad will happen to self or others.
- Vigilance and scanning:
Hypervigilant, 'edgy', distracted, irritable, difficulty concentrating, insomnia, difficulty going to sleep or interrupted sleep, fatigue on waking.

Generalised Anxiety Disorder

Hamilton Anxiety Scale (HAS) attempts to give accurate measurement of anxiety

13 items are rated on a 5 point scale.

Hamilton 1959

Generalised Anxiety Disorder

In practice we may use a less specific description:

Anxiety is intense nervousness or worrying that interferes with the ability to function.

Mood changes associated with a low Testosterone

In Clinical practice symptoms of hypogonadism (low testosterone) in older men often include:

- Loss of well-being
- Depression (sometimes referred to as ‘minor symptoms of..’)
- Anxiety
- Irritability
- Nervousness
- Mood swings

These are observationally based studies only.

Delhez M 2003

Mental symptoms of hypogonadism at Andropause:

Similar symptoms were described 60 years ago:

- nervousness 90 %
- irritability 80 %
- unease 56 %
- excitability 49 %
- fear 40 %
- unnecessary worrying 34 %

Werner 1946

Who also noted that the symptoms decrease or disappear with androgen therapy.

Androgen Deficiency in women

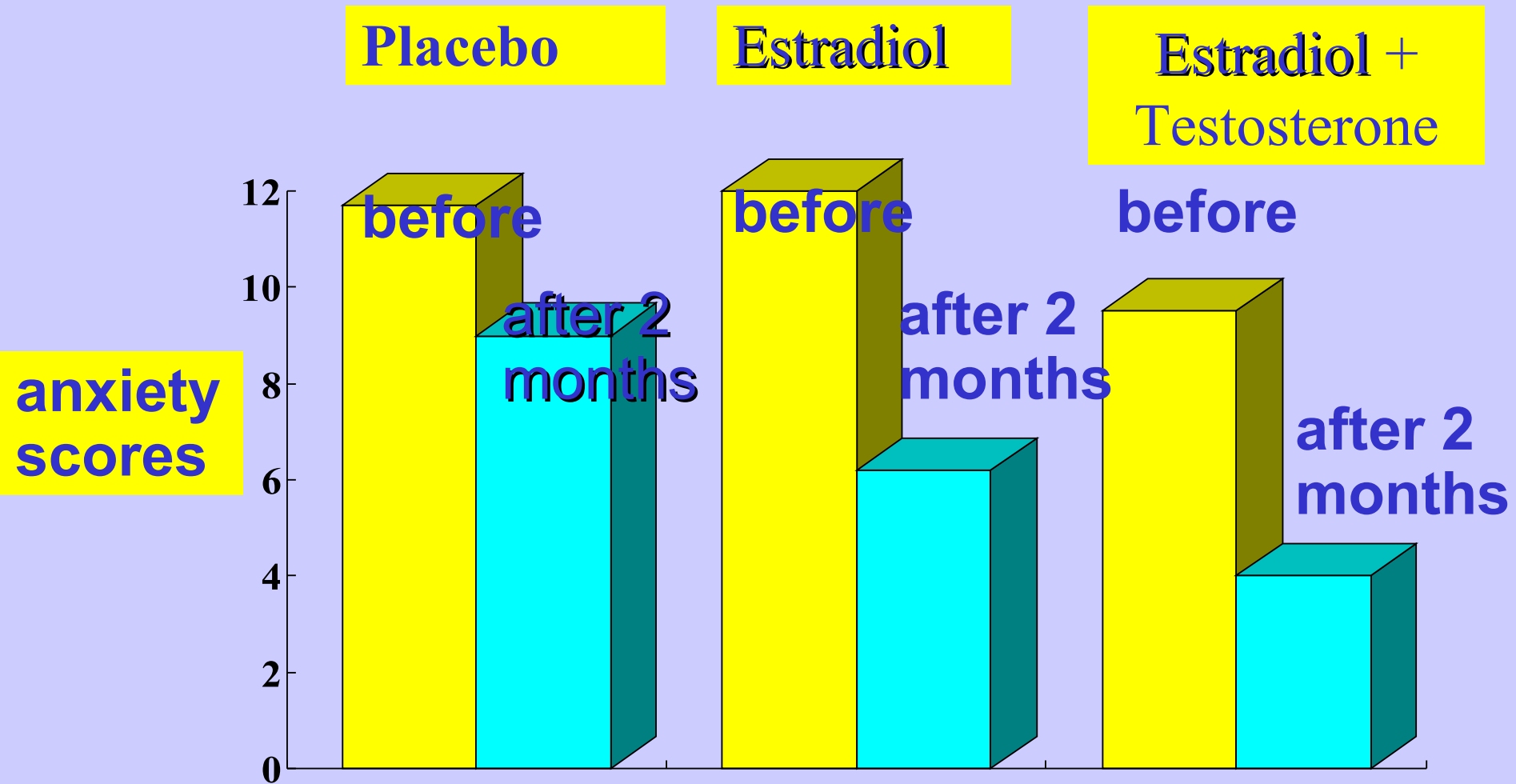
It was also described 60 years ago that:

‘Women treated with testosterone have significantly less anxiety than placebo after 2 months of therapy ...but are not significantly improved after 4 months’.

An anticonvulsant action with Testosterone was noted.

Montgomery JC 1987; Wyers HT 1945; Spiegel E 1946

Effect of estradiol and testosterone implants on anxiety in postmenopausal women



Montgomery: Lancet, 1987; 297-299

Testosterone's Effects on Anxiety

Animal Studies (in male rats) showing site of action in CNS:

Evidence of Testosterone's (T) action on hippocampus:

Gonadectomized male rats given T, DHT or metabolite 3alpha-diol as intrahippocampal implant exhibited reduced anxiety and improved learning.

Edinger 2005

Testosterone's Effects on Anxiety

Animal Studies (in male rats) showing androgen receptor (AR) involvement in T's action on hippocampus:

- Gonadectomized (GDX) rats showed increased anxiety
- DHT replacement to GDX rats showed decreased anxiety
- AR blockade of intact or DHT-replaced male rats with AR antagonist (Flutamide) ↑ anxiety.
- Flutamide alone did not further ↑ GDX rat's anxiety

Conclusion: androgens ↓ anxiety-like behaviour in male rats by action on AR's in hippocampus

Edinger 2006

Testosterone's Effects on Unconscious Anxiety

Animal studies show the effects of T on emotion are sub-cortical (Hippocampal) and therefore are not conscious.

Most human studies of T are with questionnaires which measure conscious fear.

In humans a 5 mg dose of T to 16 healthy female volunteers + placebo group. In a masked Stroop Task (showing unconscious responses to fearful faces) placebo group showed unconscious anxiety, while in group given T there was reduced unconscious anxiety. In both groups self-reported (conscious) responses remained unchanged.

Conclusion: T reduces unconscious fear but not consciously experienced anxiety in humans.

CNS Modification to Testosterone

Action of Enzymes in the CNS (especially the hypothalamus):

- 5alpha-reductase amplifies T's actions by conversion to DHT (a more potent form of T).
- Aromatase differentiates T by conversion to oestrogen.

These enzymes account for gender related differences in adult life (eg sexual and aggressive behaviour) which are the result of morphological changes in brain nuclei initiated in early foetal development.

Testosterone's Effects on Anxiety

Animal Studies:

In the CNS (eg prefrontal cortex):

- 5alpha-reductase has two isoforms: type 1 and type 2
- Type 1 has catabolic functions; type 2 is associated with sexual dimorphism in the male (rat).
- DHT powerfully effects type 1 and is responsible for sexual dimorphism of the CNS in the female (rat)
- DHT and T mildly effect type 2

Conclusion: The importanc of DHT in the sexual dimorphism of the female CNS

Depression

Definition (descriptive):

Dysphoric mood plus 4 or more of the following:

- Wt loss or ↓ appetite, insomnia or hypersomnia
- Agitation or retardation
- Fatigue
- Worthlessness, guilt
- Poor thinking, concentration, indecisiveness
- ↓ Pleasure or libido
- Thoughts of death, suicide.

DSM 3

Depression

Hamilton Rating Scale attempts to give accurate measurement of depression.

Ham-D score >18 is major depressive illness.

Hamilton 1967

... in practice clinical depression is often accompanied by anxiety.

Testosterone's Effects on Depression

A review of the clinical literature shows:

- Depression associated with ↓ T in some, but not all, older men.
- Depression associated with ↓ T is independent of age of men
- Some studies showed T improved mood in hypogonadism.
- Mood was not improved if men were eugonadal.

Conclusion: altered mood is multifactorial in hypogonadism: confounding factors include mental illness, obesity, smoking, alcohol use, diet and stress.

Testosterone's Effects on Depression

Intervention Study:

The efficacy of T therapy in treating depressed hypogonadal males is inconclusive.

But..

T Cypionate 100mg weekly for 6 weeks improved mood in late-onset (aged 45+) depressive illness with Ham-D >18 (15 patients).

Perry 2002

DHEA's Effects on Mood

Mechanism of action:

- DHEA is converted to sex steroids: Estrogen and Testosterone in women and men respectively.
- DHEA is a neurosteroid ie it is manufactured in the brain. It modulates GABA (gamma amino butyric acid) levels to act as an antidepressant.
- DHEA does not cross the blood-brain barrier
- DHEA reduces brain levels of neuroexcitatory PREGNENOLONE sulfate levels

Young J 1991

DHEA's Effects on Mood

Human Studies:

‘In double-blind crossover study DHEA 50mg showed ↑ physical and psychological well-being* in men (67%) and women (84%). Duration of study 6 month; Mean age 53.

Morales 1994

*Wellbeing = ↑ energy, deeper sleep, improved mood, more relaxed feeling, better ability to handle stressful events

DHEA's Effects on Mood

- In female patients with adrenal insufficiency: DHEA 20 to 50 mg improved mood, quality of life and libido. Studies only lasted < 6 months so benefits of long term treatment (or effectiveness in males) is not known.
- Depression: Improvement in mood in some studies only.
Dose: DHEA 50-100mg

Also 'limited benefits' to cognitive function in elderly people and immunomodulatory effect eg SLE in autoimmune disease

Arlt 2004

DHEA's Effects on Mood

‘DHEA may be a suitable option for androgen replacement in women with established androgen deficiency, for example, bilateral oophorectomy and premature menopause.’

Arlt 2004

DHEA's Effects on Mood

Animal Studies :

- DHEA reduces anxiety in the plus Nage test

Melchior 1994

- DHEA reduces sensitivity of mice to excessive noise

- DHEA attenuates the elevation in corticosterone produced by subjecting rats to cold stress

Ben Nathan 1992

note :

- DHEA may be involved in the termination of a stress response (Melchior et al., 1994)

DHEA & anxiety

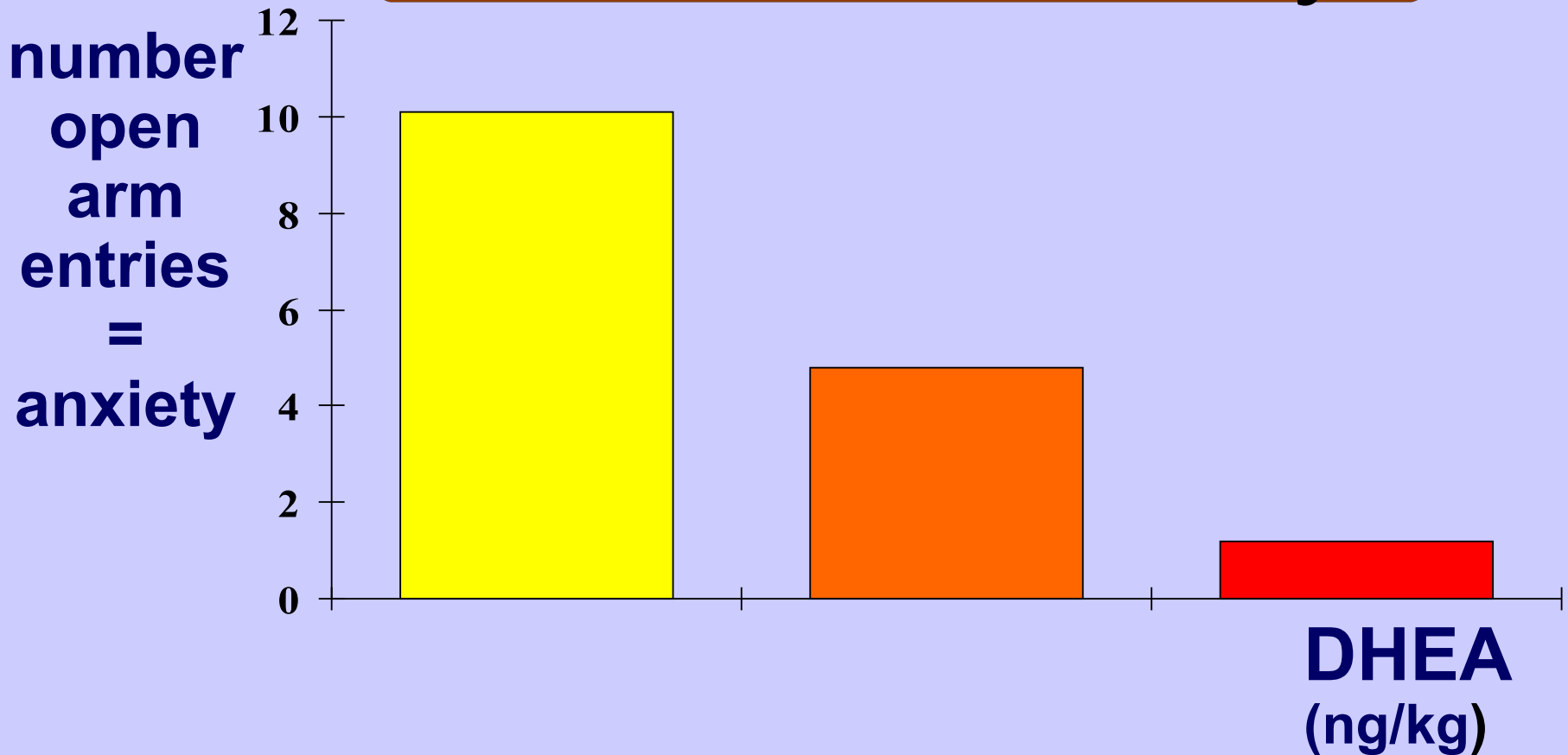


Figure : DHEA reduces anxiety and the number of open arm entries in the plus maze
(Melchior CL and Ritzmann RF, *Pharm Biochem & Behav.*, 1994; 47(3): 437-441)

Use of Estrogens in Depression

Estrogen has been used effectively as a treatment in some women with refractory depression, PPD, and perimenopausal mood disturbance. Estrogen has also been shown to be effective in some women in the treatment of acute depression, augmentation of partial antidepressant response, and prophylaxis against recurrence.

Use of Estrogens in Depression

Estrogen appears to have multiple neuromodulating effects in CNS:

- Serotonergic system: ? antidepressant action in certain groups of women.

But..

- In some women, with heightened sensitivity to normal hormonal changes, may increase risk of depression.

Androgens and Mood

References:

- Delhez M et al. | Testosterone and depression in men aged over 50. Andropause and psychopathology. *Ann Endocrinol (Paris)* 2003;64(2):162-9
- Edinger KL, Frye CA Testosterone's anti-anxiety and analgesic effects may be due in part to actions of its 5alpha-reductase metabolites in the hippocampus, *Psychoneuropharmacology*, 2005 Jun;30(5):418-30
- Edinger KL, Frye CA Intra-hippocampal admin of AR antagonist, flutamide, can increase anxiety-like behaviour in intact and DHT-replaced male rats. *Horm Behav.* 2006 Aug;50(2):216-22.
- Negri-Cesi P et al Sexual differentiation of the brain: role of testosterone and its active metabolites. *J Endocrinol Invest* 2004;27(6 Suppl):120-7
- Perry PJ et al Testosterone therapy in late-life major depressive in males. *J Clin Psychiatry.* 2002;63(12):1096-101
- Torres J; Ortega E. Steroid 5alpha-reductase isoenzymes in the adult female rat brain: central role of DHT. *J Mol Endocrinol and Molecular Biology*, Faculty of Medicine, Uni of Granada, Avda de Madrid s/n, 18012 Granada, Spain



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