

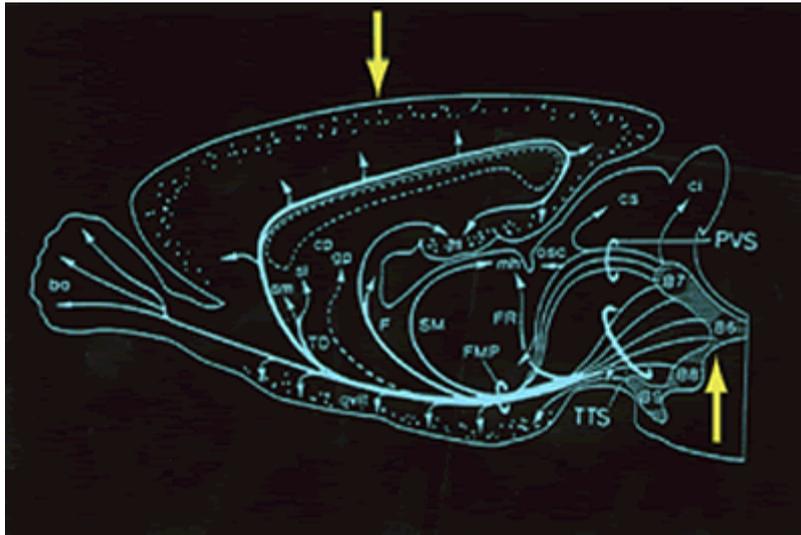
## 6. Sex hormones, mood, mental state and memory.

Professor George Fink,

MRC Brain Metabolism, Unit Department of Neuroscience, University of Edinburgh.

Oestrogen and testosterone, the main sex steroid hormones, have long been known to affect behaviour. They also affect mood, mental state and cognition. Recent experimental findings suggest that these effects of sex hormones may be mediated by serotonin, an important neurotransmitter, dysfunction of which has been implicated in mood disorders and schizophrenia. The oestrogen-serotonin link has relevance for the rational design of novel anti-oestrogens and of hormone replacement therapy.

### Sexual behaviour



*Sagittal diagram showing the massive projections of serotonin fibres (pale green) from nerve-cells located in the raphe nuclei of the rat brain (bottom arrow). These serotonin projections are also present in the human, innervate most regions of the forebrain, especially the cerebral cortex (top arrow), and play a key role in the control of mood and mental state. Modified after Dahlstrom, A. and Fuxe, K. (1964) Acta Physiol. Scand. (Suppl. 62), 232: 1-55*

The forests of France and the highlands of Scotland resound, each autumn, with the clash of antlers, fully grown, and the roar of stags locked in combat. Testosterone, the key male sex hormone (androgen) secreted by the testes, has orchestrated all the changes necessary for rutting - antler growth, attraction to the scent of the doe and aggression. In turn, oestradiol, the most potent of the female sex hormones secreted by the ovaries, stimulates mating behaviour in the does. Similarly dramatic effects of sex steroid hormones are seen in all vertebrates. Sexual behaviour in the human is more complicated in that it is affected by gender assignment and cultural and ritual determinants; nonetheless, the importance of sex hormones is exemplified by the intense sexual interactions at puberty triggered by the gonads as they become activated.

### Mood and mental state

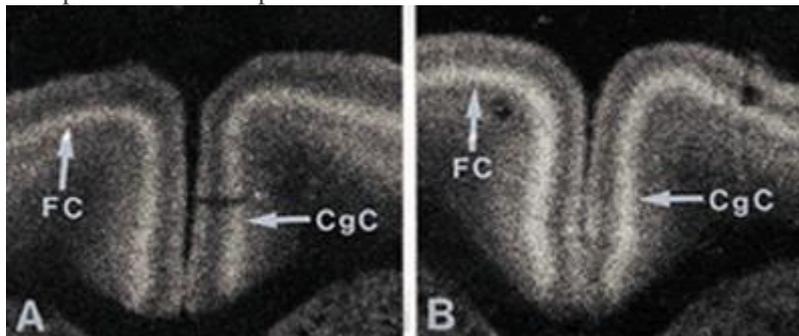
Sex steroid hormones also affect mood as suggested by the increased incidence of mood disorders in women around the time of menstruation (premenstrual syndrome or PMS), child-birth (puerperal depression) and the menopause (perimenopause) when oestradiol levels drop precipitously. The incidence of mood disorders is also increased in women after removal of the gonads and at the start of treatment with anti-oestrogens. In turn, oestrogen administered as 'hormone replacement therapy' (HRT) is often effective in improving depressed mood associated with PMS, the perimenopause or the puerperium. Although not as well defined as the menopause, an andropause, characterised by a fall in the concentrations of 'free' testosterone in the circulation, occurs in some men and is also associated with an increased incidence of mood disorders.

Oestrogen is also implicated in schizophrenia in that the average age of first onset is later in women than in men, there are qualitative sex differences in schizophrenic symptoms and a second peak of schizophrenia onset occurs in women after the age of 40 years.

Finally, recent epidemiological studies suggest that oestrogen HRT reduces the risk or delays the onset of Alzheimer's Dementia in post-menopausal women.

## The oestrogen-serotonin link

Although the potent effect of sex hormones on mood and behaviour has been accepted through the ages from Aristotle to Charcot, Steinach and Freud, mechanisms by which oestrogen could affect mood and mental state have only recently been established. Studies designed to identify the chemical messengers in the central nervous system that mediate oestrogen control of the secretion of pituitary gonadotrophins led to the discovery that oestrogen increases the density in forebrain of the serotonin 2A receptor. This receptor has been implicated in mood disorders as well as in schizophrenia.



*Increased density of serotonin 2A receptors in anterior frontal (FC) and cingulate (CgC) cortex in the brain of a rat treated with oestrogen (B) compared with that of an untreated rat (A). These brain areas play a major role in cognition, mood and mental state.*

Oestrogen also increases the density of serotonin transporter sites in the forebrain. The significance of this action of oestrogen is that dysfunction of the serotonin transporter, which plays a key role in serotonin signalling, has been implicated in mood disorders. The transporter is the target of potent antidepressants, the serotonin-reuptake inhibitors of which "Prozac" is probably the most widely known. Testosterone has the same effect as oestradiol on these serotonin mechanisms - but, the action of testosterone depends upon its conversion to oestradiol by a brain enzyme.

## Memory and cognition

The potent effects of oestrogen on the growth of nerve fibres and density of nerve connections ('synapses') in the brain offer possible mechanisms by which oestrogen could exert positive effects on memory and cognition. Furthermore, activation of the serotonin 2A receptor is known to reduce the production in cells of beta-amyloid protein, thought to cause the brain lesions in Alzheimer's Dementia. If the oestrogen-induced increase in the density of the serotonin 2A receptors in forebrain also results in increased activity of the receptor, then this may explain the apparent protective effect of oestrogen with respect to the onset of Alzheimer's Dementia.

## Hormone replacement therapy for mental disorders

More research is required in order to establish the precise mechanism of oestrogen's actions on the brain. However, the discovery that oestrogen affects serotonin mechanisms in brain regions that in the human are concerned with the control of mood, mental state and memory has important implications for the correct use of HRT, either alone or in conjunction with conventional psychotropic drugs, for the prevention and treatment of mental disorders and dementia. Hormone replacement therapy, when fully understood and rationally applied, may offer an important new strategy with which to tackle the awesome increase in the incidence of age-related mental disorders.