

# Neuro-endocrinology

## BRIEFINGS

# 21

### SUMMARY

Estrogens act throughout the body and are important 'shapers' of development, including of brain sexual differentiation. This has raised concern that environmental estrogens could affect such processes. However, experience with studies of the male reproductive tract suggests that most environmental estrogens are too weak to pose such a threat. Conversely, as emerging data suggest that estrogens have health-beneficial effects on the brain, could environmental estrogens actually be good for us?

*The sources of estrogen in our environment.*

Modified from: Miller WR, Sharpe RM (1998). Review: Environmental oestrogens and human reproductive cancers. *Endocrine Related Cancer* 5: 69-96

## ENVIRONMENTAL ESTROGENS – FOE OR FRIEND?

### Horizons in a snowstorm

The possibility that environmental estrogens can exert adverse effects on a wide variety of reproductive developmental processes, with permanent consequences, has been around for a decade or more. During this period, opinion, derived from studies in animals and in isolated cells, has polarised as to whether human exposure to such compounds poses a genuine risk. What is beyond question is that the environmental estrogen saga has been a major force in pushing estrogen physiology up the medical interest ladder. The coincidence of concern about environmental estrogens with the discovery of a second estrogen receptor (ER $\beta$ ) and the development of ER $\alpha$ -, ER $\beta$ - and other gene-knock-

out mice, has resulted in a veritable snowstorm of new insights that are redefining horizons in estrogen biology and medicine. Understandably, gonadal and reproductive tract studies have led the way, but it is the new horizons that are now moving to centre stage, and amongst the most exciting are estrogen effects on the brain. This excitement is probably highest amongst those of us who find great humour in the stark differences in innate male and female attitudes, aptitudes and behaviour. The flurry of new data showing effects of estrogens on survival, proliferation and growth of specific neurons is matched by evidence for effects on female behaviour, depression and cognitive thinking, which have serious medical and therapeutic implications.



### Neuronal development – crossed wires?

In view of this new information, should we not be more concerned about environmental estrogens? If they could affect brain development and behaviour, they could literally reshape a person. 'Sexual differentiation of the brain' is a process that underlies most of the non-physical contrasts between male and female, ranging from the differences in sexual behaviour to those in communication and visuo-spatial skills; it also includes differences in neuronal wiring that determine a male or female pattern of gonadotrophin hormone secretion. In the human these processes occur in fetal life whereas in rodents many of them occur postnatally. Disruption of androgen or estrogen production or action or their 'over-action', during these programming periods, can result in altered brain sexual differentiation. So could exposure to environmental estrogens alter brain sexual differentiation? This is not an easy question to answer – we are all aware of how varied normal human male and female behaviour can be! There are two areas of (indirect) reassurance, stemming from studies of effects on the developing male reproductive system and our growing understanding of how androgens and estrogens may affect brain development.

First, it is evident that, with few exceptions, only very high doses of environmental or even synthetic, potent estrogens can induce 'reprogramming' of male reproductive tract development. When this occurs it involves suppression of androgen action, primarily by increasing degradation of the androgen receptor protein, and this only happens after exposure to high levels of

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*"...it appears that the developing brain is safe from environmental estrogens..."*

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potent (non-environmental) estrogens. Second, androgen- and estrogen-modulation of brain/neuronal development appears to stem largely from local production of estradiol or dihydrotestosterone at sites of their action within the brain through conversion of circulating testosterone produced by the gonads; disruption of such local processes by systemically delivered hormones invariably requires very high hormone levels or potency. Based on these twin pieces of information, it appears that the developing brain is safe from environmental estrogens unless they are present in huge, unlikely, amounts. There are of course caveats – are some areas of the brain extraordinarily more sensitive to estrogens than the male reproductive tract? What about chemicals that affect activity of the enzymes that regulate local sex steroid production within the brain?

### Soy protein diet

There is also an important exception to the arguments above, namely exposure of humans to very high levels of isoflavonoids, such as genistein, via consumption of a soy protein-rich diet (as is traditional in many Oriental countries) or the consumption in Western countries of soy/isoflavone supplements. Genistein is a moderately potent estrogen that may preferentially interact with ER $\beta$ , which is expressed in various brain regions. However, laboratory animal experiments with genistein, and close scrutiny of our Oriental neighbours, suggests that no obvious harm is done to brain sexual development.

### Takeaway message?

But let's finish on a positive note. The debate about environmental estrogens has all been negative – but could they have positive effects? There is growing evidence that estrogens have important 'neuro-protective' effects, and these may involve stoking up of antioxidant defences. There is abundant evidence that genistein and/or other soy constituents can activate the same mechanisms in various tissues in the body at dietary levels of exposure. Estrogens activate these pathways at quite low levels, certainly at far lower levels than those that cause aberrant development of the reproductive system. So, could this mean that exposure to environmental estrogens might actually be good for us?

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Editor's note: it is fitting that Briefings 21, in a new design, updates the environmental estrogens 'story' described in the first Briefings article in 1998.

**For further reading references, additional copies and general information, please contact the editor**

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