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IS OESTROGEN NEUROPROTECTIVE?

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SUMMARY

Neuro-protection in this context is an important concept in the treatment of patients in the early, prodromal phase of psychosis, otherwise known as the 'At Ultra High Risk Mental State'. Neuro-protection as described here refers to the use of agents to control the process of apoptosis, which occurs more rapidly in the earliest phases of schizophrenia. There is a need to identify medications with fewer side effects than anti-psychotics in order to treat at risk mental states, or prodromal psychosis. Studies have shown that schizophrenia occurs in males at an earlier age than females. Later, at about the time of the menopause, there is a second peak in the incidence of psychosis (schizophrenia) in women. Hence it has been suggested that Oestrogen may be neuroprotective. Studies have shown that the addition of oestradiol to anti-psychotics in the treatment of schizophrenia in females increased the efficacy of the treatment, which suggests that oestrogen does indeed have a neuroprotective action. However oestrogen has never been used in 'at ultra high risk mental states', perhaps because of concern regarding side effects.

Key words: *schizophrenia - neuro-protection – prodrome - at risk mental state - oestrogen*

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Aim

To establish whether there is evidence that oestrogen is neuroprotective and can be used in treating early (prodromal) schizophrenia, or as an adjunct in treating schizophrenia itself.

Method

Literature search using Google Scholar. It is fully acknowledged that this article is a review in order to answer the question posed to us in this meeting and as such is entirely dependent on the work of the original authors, particularly Riecher-Rössler, Hafner, Kulkarni, and others, all of whom are fully referenced and acknowledged in the text.

Results

The concept of Neuroprotection is new to psychiatry. So far it has been applied to Neurological conditions. Neuroprotection refers to modulation of the regulatory processes of growth, regeneration and survival of brain cells that might be at risk of damage or even death. Berger (2007) provided histological evidence that neurodegeneration in neurological disorders is mediated by cell necrosis, with subsequent gliosis (Berger 2007). This is not so in the early phase of psychotic illness, in which apoptosis is an important process which regulates brain development and synaptic plasticity. In conditions such as schizophrenia or bipolar affective disorders, there is no sign of gliotic changes at post mortem even after years of illness (Berger 2007).

Neuro-protection is an important concept in the treatment of patients in the early, prodromal phase of psychosis, otherwise known as the 'At Ultra High Risk Mental State'. Neuro-protection as described here refers to the use of agents to control the process of apoptosis, which occurs more rapidly in the earliest phases of schizophrenia. There is a need to identify medications with fewer side effects than anti-psychotics in order to treat at risk mental states, or prodromal psychosis if safe treatments for this stage of the illness state are to be produced (Berger 2007).

Berger et al have conducted a A systematic literature search in order to identify neuroprotective agents with a more favourable side effect

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profile than Atypical Antipsychotics. This list would then provide a basis for further research (Berger 2007).

The substances identified include antidepressants, low dose lithium, omega-3 fatty acids, modulators of glutamateric neurotransmission (e.g. ampakines, glycine, memantine), erythropoietin, *N*-acetylcysteine, COX-2 inhibitors and antioxidants, as well as oestrogen (Berger 2007).

It is important that all of these substances be studied as possible neuroprotective agents at each stage of psychotic illness. Those substances which have shown limited efficacy as augmentation treatments in chronic illness, may in fact be sufficient to counteract the underlying biological processes in at-risk mental states which eventually lead to full-blown psychotic disorders. Thus, Berger postulates that, early in psychotic illness, milder treatments may be adequate to prevent further deterioration in the mental state (Berger 2007).

Oestrogen is an example of a substance which has been proposed to have neuroprotective action because of the observed epidemiology of schizophrenia. A number of epidemiological studies have shown that schizophrenic psychoses begin on average 4–5 years later in women than in men (Hafner 1991).

This was most impressively by the ABC study of Hafner (Hafner 2002, Hafner 2003). This study has shown that schizophrenia occurs in Males at an earlier age than females. Later, at about the time of the menopause, there is a second peak in the incidence of onset of psychosis (schizophrenia) in women. Based on these facts, it has been suggested that Oestrogen may be neuroprotective.

Hafner's ABC study made male-female comparisons about the age and type of onset, symptomatology, course and outcome of psychotic illness in a sample of 232 first episodes of psychotic illness (Hafner 2002). The patients were assessed using the IRAOS interview (Hafner 1992) retrospectively at first admission and then prospectively for six times over five years after the first presentation. A sub-sample of 130 first admissions for first psychotic episodes were compared with 130 controls, matched by age, sex and area of residence (Hafner 2002).

On average, women were 3 to 4 years older than men at the onset of psychotic illness, and continued to show this 3 to 4 year delay in development of first negative, then first positive symptoms, first full episode of psychosis, and first hospitalisation. Women showed a second peak of onsets in the 45 to 50 year age group (Hafner 2002, Hafner 2003). After animal experiments (Gattaz 1992) this finding was explained by a protective effect of oestrogen which persisted until the menopause. The underlying neurobiological mechanism appears to be a reduction in sensitivity in D2 receptors in the brain through the effect of oestrogen. At the a cellular level, the biological actions of oestrogens occur only in cells expressing oestrogen receptors (McDowall 2003).

The nature and extent of the oestrogenic response depends upon the interactions of these receptors with several different proteins which are involved in various processes. Oestrogen receptors (ERs) are transcription factors, and activate or inhibit expression of many genes (McDowall 2003).

Cells will respond to oestrogen in different, often opposing ways, because there are two functionally distinct oestrogen receptors which may interact with several different cofactors or signalling proteins (McDowall 2003).

These two receptors are called the oestrogen receptor alpha (ERa) and the oestrogen receptor beta (ERb). They are functionally distinct, and activate genes in different ways. Both ERa and ERb interact with the same oestrogen ligand, oestradiol-17b, but they behave differently, sometimes having opposing effects (McDowall 2003).

In the absence of the oestrogen ligand, the ERs are found in the nucleus within a heat shock protein complex which inhibits their action. Once bound to the hormone, the ligand-binding domain changes shape, the heat shock protein is displaced, and the binding of cofactors is facilitated (McDowall 2003). The cofactors act to promote (coactivators) or inhibit (corepressors) the interaction of the receptor with its target genes. The ERs affect gene expression by binding directly to DNA target genes through specific oestrogen response elements (ERE), or by binding to other DNA-bound transcription factors such as AP1, SP1, or NF-kappaB. ERs, since they occur in the cell nucleus, are part of a large family of nuclear receptors. The nuclear receptor family include, among others, receptors for ligands such as steroid hormones, vitamin D, retinoids and thyroid hormones (McDowall 2003).

The effect of oestrogen, also includes genomic and nongenomic effects and interactions with free-radical detoxifying systems and the inhibition of the cellular liquid peroxidation (McEwen 1981,

Woolley 1994, Sumner 1995, Shughrue 1997, Fink 1998, Sumner 1999, Behl 2002), thus demonstrating the neuroprotective potential of oestrogen. Many studies have shown that oestrogen has potent neuromodulatory effects which are neuroprotective in terms of modulating apoptosis as described above. Oestrogen thus has many benefits in both health and disease (Kulkarni 2000).

From a genetic point of view, two genotypes associated with a preschizophrenic condition, neuroregulin 1 (Ma 1999) and COMT1 (Huber 2002), are closely related to the metabolism of oestrogens. Psychotic disorders are usually treated with antipsychotic drugs, which help to normalise neurotransmitter activity. Oestrogen appears to reverse some neurotransmitter activities which are abnormal in both depression and schizophrenia (Archer 1999).

Various studies have demonstrated that oestrogens may have a protective effect in schizophrenia (Riecher-Rössler 2003, Riecher-Rössler 2005, Riecher-Rössler 1993).

The protective effect in schizophrenia, as shown in Hafner's study, is based not only on a reduction in sensitivity of central D2 receptors but also on the induction of an increase in 5HT3A receptors and a serotonine transporter (SERT). Animal studies (Behrens 1992, Di Paolo 1982, Clopton 1986) have shown that estradiol downregulates dopamine neurotransmission. Other studies (Fink 1998, Fink 1999, Fink 2001) show that estrogen induces a significant increase in serotonin receptors.

Thus, the actions of estrogen on the serotonin receptor (5-HT2A) and the dopamine receptor (D2) mimic the actions of the new atypical antipsychotic drugs, such as risperidone and olanzapine.

The reduction of D2 sensitivity is likely to be responsible for attenuating positive symptoms, and the increase in 5HT2A receptors might be protective against depressive and negative symptoms (Fink 1995).

Oestrogen acts independently of receptors as a potent neuroprotective factor at various sites of the brain, especially the basal forebrain, the hypothalamus, and the spinal cord. Oestrogen appears to improve synaptic connectivity, neurotrophic signalling, dendritic plasticity and cholinergic activity (Fink 1995). Oestrogen improves cognitive functioning and memory not only in the early stages of Alzheimer.s disease, but also throughout life. It is not yet known whether this neuroprotective property of oestrogen can be used for preventive or restitutive purposes in schizophrenia (Hafner 2002).

That the results of Hafner's animal experiments can be applied to human schizophrenia was demonstrated by Riecher-Rössler et al. (Riecher-Rössler 1994, 1994).

They showed that there was an excess of onsets and relapses of schizophrenia during the perimenstrual low oestrogenic phase of the menstrual cycle. They also showed that the intensity of psychotic symptoms correlated inversely with serum oestradiol levels during the menstrual cycle (Riecher-Rössler 2005).

Riecher-Rössler et al studied 61 women, comparing 32 women with schizophrenia and 29 women with depression, both with normal menstrual cycles, they showed that women with higher plasma levels of oestrogen scored lower on rating scales of psychosis. Thus oestrogen behaves as a weak neuroleptic agent (Riecher-Rössler 1994). A similar variation in symptom severity over the menstrual cycle was also reported by Hallonquist et al. (Hallonquist 1993), and similar clinical observations had been published by Dalton (Dalton 1959) and Endo et al. (Endo 1978). It has also been shown that schizophrenic women with intact menstrual cycles require less antipsychotic medication than postmenopausal women or men (Seeman 1983).

Seeman and Cohen (Seeman 1999), tested the proposition that an earlier onset of functional oestrogen secretion with puberty might be associated with a later onset of schizophrenia in women. They found a significant negative correlation between age at puberty and age at schizophrenia onset in women, but no correlation in men.

Women exhibit an additional smaller peak of onset of schizophrenia after age 45, described as "late onset schizophrenia" (Hafner 1991, Riecher-Rössler 1997, Riecher-Rössler 1994, Hafner 1998). It has been suggested that this peak of late onset schizophrenia is caused by the loss of the protective effect of oestrogens. Women are believed to be protected to some extent against schizophrenia during their reproductive life span by the relatively high gonadal oestrogen levels which exist during this period. Then, around age 45, when oestrogen production begins to fall, vulnerable women without the protective action of oestrogens may develop schizophrenia. The incidence of schizophrenia after the age of 40 was found to be twice as high in women as in men.

While the onset of illness was after age 40 in only 10% of all men with schizophrenia, this was true of 20% of all women (Riecher-Rössler 1997). Illness course, was more unfavourable in postmenopausal women than in men of the same age (Hafner 2002). The severity of the disease was greater among these late onset women as compared with men at a similar age (Riecher-Rössler 1997). Furthermore, chronic psychoses may deteriorate after the menopause (Riecher-Rössler 1997).

Postmenopausal schizophrenia is more frequent and more severe in women (Hafner 2002). The reduction in oestrogen levels during the menopause may contribute to the outbreak of schizophrenic psychotic reactions, since oestrogens may modulate many, and especially the dopaminergic, neurotransmitter functions (Riecher-Rössler 2005).

Men fell ill more frequently and more severely at a young age and less frequently and more mildly later in life.

The protective effect of oestrogen in women depends upon the degree of predisposition to the illness: the higher the familial load for schizophrenia, the weaker the protection by oestrogen (Hafner 2002). Hafner has also demonstrated that the more favourable illness course in premenopausal women resulted from their higher degree of social development at illness onset, because of their higher age at onset and their socially more adaptive behaviour. The illness behaviour of young men demonstrated significantly more socially negative behaviours which unfavourably impact on their early illness course. In contrast, older men were socially better adjusted. The distribution of subtypes of schizophrenia was equal across the sexes.

Early trials of exogenous oestrogen in women with schizophrenia have been performed with conflicting, but promising, results. Kulkarni et al. (Kulkarni 1996, Kulkarni 2001) showed that schizophrenic women treated with oestradiol as an adjunct to neuroleptic treatment show more rapid improvement of psychotic symptoms than women receiving neuroleptics only.

In the study, twelve women with acute schizophrenia received 100 micrograms (mcg) of transdermal estrogen together with a standardized dose of antipsychotic drug for 28 days. They made a more rapid and better recovery compared with 12 women who received 50 mcg of transdermal estrogen plus the antipsychotic drug. Both groups, but especially the 100-mcg transdermal estrogen-treated group, did make a much better and faster recovery than a matched group of 12 women who received a placebo patch plus the antipsychotic drug.

This study suggests that oestrogen may play a useful role in the treatment of women with schizophrenia.

However, in a recent Cochrane review on the use of oestrogens for schizophrenia, the authors concluded that at present there are too few studies which support the evidence for clinical use of oestrogens in schizophrenia (Chua 2005).

Since this study was reported, and while this paper was in preparation, a further study was published by Kulkarni (Kulkarni 2008). It was a randomized, double-blind study, comparing the efficacy of adjunctive transdermal estradiol with that of adjunctive placebo in the treatment of acute psychotic illness.

Patients were recruited from inpatient acute wards and outpatient clinics in 2 general hospitals in Melbourne. One hundred and two women of childbearing age with schizophrenia were studied. Participants were in an acute or chronic phase of their illness; 73 participants were outpatients and the rest were inpatients. Patients were randomized to receive 100 μg of transdermal estradiol (n = 56) or transdermal placebo (n = 46) for 28 days. Psychotic symptoms were assessed weekly with the Positive and Negative Syndrome Scale. The addition of 100 μg of transdermal estradiol significantly reduced positive ($P < 0.05$) and general psychopathological ($P < 0.05$) symptoms over the 28-day trial period compared with women who received antipsychotic medication alone.

Thus Kulkarni's work suggested that Estradiol appears to be a useful treatment for women with schizophrenia and may provide a new adjunctive therapeutic option for severe mental illness.

However, no studies at present focus on peri or postmenopausal women. There is only a single case report of a single postmenopausal woman with schizophrenia who benefited mentally from oestrogen replacement therapy (Lindamer 1997). Lindamer and co-workers (Lindamer 2001) also reported interesting results on a community sample of postmenopausal women with schizophrenia who received hormone replacement therapy from their gynaecologist for reasons other than psychosis. The users of HRT appeared to need a relatively lower average dose of antipsychotic medication and reported less severe negative symptoms than the control group without HRT. Furthermore, in

postpartum psychosis, oestrogen substitution has been reported to bring about a significant improvement (Ahokas 2000).

Discussion

All the above data suggest that there are a number of differences in the manifestations of schizophrenia between men and women, and that these differences may be explained by the neuroprotective effect of oestrogen during the reproductive years of a woman's life. These effects disappear in the peri and post menopausal periods when the effects of oestrogen are no longer present.

Oestrogen has been described as a mild antipsychotic, and has been compared to the atypical anti-psychotics. It has been shown to exert a neuromodulatory effect by downgrading dopamine neurotransmission, and causing an increase in serotonin receptors.

Oestrogen has also been postulated to have a positive effect on short- and long-term verbal memory in postmenopausal women, as well as increasing the capacity for new learning. Since cognitive deficits are a major problem for women with schizophrenia, oestrogen replacement therapy may have an added benefit for postmenopausal women with schizophrenia (Sherwin 2001).

In addition to direct clinical differences between the sexes, there are also other differences as shown by neuro-imaging;In first-episode patients with schizophrenia, magnetic resonance imaging show that compared with women, males had more "immature" amygdala structures suggesting the possibility of a neurodevelopmental delay in young men with schizophrenia. There were no gender differences in the hippocampal volumes in this patient group (McGorry 2001).

It has been reported that women experiencing a first episode of psychosis had a longer duration of untreated psychosis compared with men. As with the more established schizophrenia group, young women with schizophrenia had fewer negative symptoms and a better quality of life compared with young men. However, There were no gender differences in the positive psychotic symptoms (hallucinations, delusions, thought disorder) experienced by this early-onset-schizophrenia group, and both men and women received similar doses and types of antipsychotic medication (McGorry 2001).

Recent studies on the gender differences in the quality of life of people with schizophrenia, reported in a major conference, the First World Congress on Women's Mental Health, in 2001 in Berlin, have demonstrated that women are more likely to present with affective symptoms as part of their psychosis presentation (Maurer 2001, Kulkarni 2001). Other differences include the finding that women have fewer negative symptoms (ie, anhedonia, apathy, alogia, and amotivational states) compared with men. This finding was also replicated in studies of first-episode psychosis patients (McGorry 2001).

Kulkarni reports a study on the Global Assessment of Function in 350 patients with established schizophrenia. These scores were significantly better in women, although overall they were only in the mild to moderate range of function (Kulkarni 2001). The difference in GAF scores between the genders may reflect a difference in the premorbid functioning of patients, which may be a product of the age difference at the onset of the illness.

Kulkarni reported on the quality of life (Kulkarni 2001) in the same group of 350 patients with schizophrenia using the Quality of Life Scale (QLS). Women were found to have a higher quality of life, according to this scale, than men.

Women with schizophrenia scored better than men in the areas of interpersonal relations, instrumental role, and activities. There were no significant gender differences in life satisfaction, social needs, and basic needs.

After 12 months, data on the quality of life of the same patients showed no significant difference between men or women with schizophrenia. None of the QLS subsections on interpersonal relations, instrumental role, activities, and intrapersonal activities such as motivation, empathy, or curiosity had improved, despite the fact that the actual psychotic symptoms had improved.

It must be assumed that oestrogen, through its neuroprotective action in women, is responsible for some of the reported differences and similarities in both global functioning and quality of life. Thus far, the data has not determined a causal role for oestrogen, because there could be other factors involved, for example male/female personality traits and gender roles.

As has been shown, some studies have demonstrated that the addition of oestradiol to anti-psychotics in the treatment of schizophrenia in females increased the efficacy of the treatment, which suggests that oestrogen may have a role in future therapy, and does indeed have a

neuroprotective action, however the use of exogenous oestrogen has been restricted to date because of concern regarding side effects. Exogenous oestrogen therapy carries risks of thromboembolism, endometrial cancer, breast cancer and stroke.

Nor have any trials been reported of oestrogen for use in 'at ultra high risk mental states', perhaps because of concern regarding side effects.

Conclusion.

Much has been said about the neuro-protective effects of oestrogen. Decisions about whether oestrogen therapy should be used routinely in the management of schizophrenia need to be guided by further research, in particular, it will be necessary to carefully evaluate the risk -benefit ratio and cost-effectiveness of this treatment. However the study of the 'Oestrogen Hypothesis' has given us a deeper insight into the mechanisms of the development of psychotic illness.

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