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Neurosteroid hope to end misery of PMS

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Neuroscientists are developing a new treatment for the symptoms of PMS

Neuroscientists at the University of Birmingham are working on a novel approach to ending the scourge of premenstrual syndrome (PMS) after identifying, for the first time, an organic cause for the condition.

Researchers led by Dr Thelma Lovick have shown that premenstrual-like symptoms can be triggered in female rats by a change in the level of secretion of one of the female sex hormones that normally occurs towards the end of the menstrual cycle in women.

In the Birmingham tests the PMS could be prevented by giving low doses of the commonly prescribed anti-anxiety drug fluoxetine (Prozac).

Dr Lovick and her team believe that if affected women were to take a very low dose of fluoxetine for just a few days during the premenstrual period, they should avoid developing the negative physical and emotional symptoms that characterise the syndrome.

‘All that would be needed for countless women to benefit from what could be a simple and accessible treatment, involving a drug that is already in widespread use, is clinical tests to refine it and identify the optimal dosing strategy,’ she says.

The team is now seeking a clinical partner to confirm their laboratory findings and fund a clinical trial.

PMS causes misery for millions of women worldwide every month. Developing in many women the week before their menstrual period, common symptoms include psychological changes such as anxiety, mood swings, tiredness, irritability, depression, a loss in confidence and clumsiness. Physical changes such as headaches, feeling bloated, altered appetite, joint pain and breast tenderness may also be experienced.

Not all women show all the symptoms, but it has been estimated that 75 per cent of women experience some and that, in 30-40 per cent of cases, they are sufficiently severe to impair daily activities, with knock on effects for family and friends. In the worst cases (three to four per cent of women), a psychiatric condition called Premenstrual Dysphoric Disorder (PMDD) can develop.

Dr Lovick and her team discovered that a steroid substance called allopregnanolone (ALLO) - which is one of the breakdown products of the female sex hormone progesterone - normally inhibits activity in the brain circuits involved in controlling emotions. When levels of ALLO drop– as during the premenstrual period - this inhibition is reduced and symptoms of PMS, such as anxiety, irritability and aggression, emerge.

‘ALLO can alter the activity of nerve cells, thus it is described as a neuroactive steroid,’ explains Dr Lovick. ‘It enhances the activity of GABA, one of the brain’s inhibitory neurotransmitter chemicals, and in those parts of the brain that process emotional responses ALLO normally produces calming effects. However, when brain levels of progesterone, and hence ALLO, fall sharply during the late premenstrual period the natural inhibition is effectively turned off.

‘As a consequence these brain circuits become more excitable, leaving the individual more responsive to stress, which is often manifested behaviourally as anxiety and aggressive behaviour.’

Dr Lovick hypothesised that if the sharp fall in ALLO levels is the factor that triggers these brain changes, then if you could make ALLO levels decrease gradually at the end of the cycle, the symptoms of PMS should not develop.

Using this premise, the Birmingham group has devised an approach termed ‘neuroactive steroid replacement treatment’, which has been shown to completely prevent the development of premenstrual symptoms in rats.

‘We knew that the widely used anti-anxiety drug fluoxetine (Prozac) could raise levels of ALLO when taken for short periods. This effect happened quickly and occurred in response to a very low dose of fluoxetine’ says Dr Lovick. ‘We thought that if dosing with fluoxetine was carefully timed to boost brain ALLO levels just when they were due to fall sharply at the end of the cycle, the normal trigger for the development of premenstrual syndrome would be absent.’

Most significantly, the dosage needed to achieve this was only about one tenth of the standard strength of the most commonly prescribed form of fluoxetine.

‘Excitingly, fluoxetine completely prevented the development of the signs of anxiety and increased pain and sensitivity normally shown by female rats in late dioestrus, their version of the premenstrual period. Moreover, it completely changed the way in which the brain circuits responded to anxiety-inducing stress.’

The team also went on to find they could successfully replicate the effects of fluoxetine using a synthetic version of ALLO. They are now seeking a clinical partner to test the results of the three-year Medical Research Council-funded research. They are due to report the results of their research later this autumn.

Dr Lovick concludes: ‘The time is right for a controlled clinical trial in women. The solution to PMS could be as simple as taking a pill for a few days towards the ends of your menstrual cycle.’

Notes to Editors

Dr Lovick is available for comment. Please see contact details.
Professor Femi Oyebode, Consultant Psychiatrist, University of Birmingham is also available for comment. Please contact the University Press Office for details.

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PMS research story (/research/our/news/items/PMS.aspx)

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