Neuroendocrine
BRIEFING
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Neurosteroids – fine tuning of brain function

SUMMARY
Neurosteroids are steroids produced in the brain that bind to neurotransmitter receptors via an allosteric site, to rapidly influence brain function. They play an important role in modulating the response to stress, maintaining an optimal pregnancy, and have recently been developed as a drug to treat postpartum depression. Studies are starting to reveal their role in mediating sex differences in mood and stress-related disorders.

Steroids produced by the brain, for the brain

In 1941, Hans Selye first discovered that administration of a high dose of steroids (i.e. progesterone) could induce deep anesthesia in rats within minutes. This indicates steroids can also exert fast actions on the brain, beyond their conventional role in reproduction. In the 1980s, the rapid effects of steroids on the brain were shown to be mediated via their modulation of membrane-bound neurotransmitter receptors, rather than through traditional nuclear steroid receptors. These steroids are termed "neurosteroids" and can be produced locally within the brain by neurons and glia, independent of the adrenal glands or gonads.

Neurosteroids influence neurotransmission in the brain by enhancing the activation of excitatory (e.g. NMDA) or inhibitory (e.g. GABA) receptors. Different neurosteroids bind different receptors depending on their structure, thus having wide-ranging effects on various brain functions. For instance, allopregnanolone, one of the most well-studied progesterone metabolites, binds to GABA receptors to enhance inhibitory signaling, which generally has anxiety-reducing and sedative effects. Whereas, pregnenolone, a cholesterol metabolite, positively modulates NMDA receptors, which enhances synaptic plasticity and has beneficial effects on cognition.

Due to their key roles in fine-tuning brain function, the production of neurosteroids is tightly regulated. Concentrations in the brain increase dramatically under certain physiological conditions, notably after stress and during pregnancy.

Stress is the spice of life

Whilst the term "stress" often comes with negative connotations, experiencing some level of stress and adversity is a normal part of life. The body has an adaptive mechanism to deal with stress - hypothalamic-pituitary-adrenal (HPA) axis activation and the production of cortisol. Cortisol is a glucocorticoid that enables the mobilisation of glucose to cope with the stressor in the short-term, but excessive levels are harmful to cellular processes. An accompanying increase in allopregnanolone production in the brain following acute stress therefore acts as an additional endogenous protective mechanism to terminate HPA axis activation and prevent harmful overproduction of cortisol.

"Neurosteroid therapy is an exciting new development in the treatment of mood disorders."

Although this adaptive response enables the body to respond well to acute stress, this mechanism may be dysregulated when stress becomes chronic or extreme. Detrimental changes may occur in HPA axis regulation and allopregnanolone production, which can develop over time into stress-related mood disorders. In rodents, prolonged stress downregulates allopregnanolone synthesis in the brain and results in anxiety-like and depression-like behaviours. In humans, levels of neurosteroids in the plasma and cerebrospinal fluid are also reported to be lower in patients with stress-related mood disorders.

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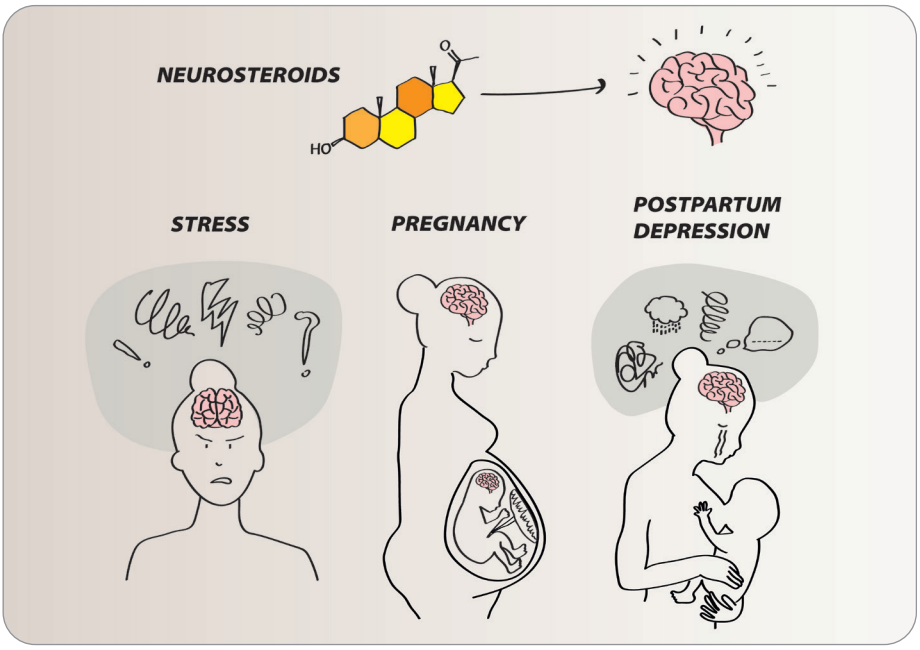


Figure. Neurosteroids fine tune brain function, especially in stressful situations and during pregnancy. They have also become an important new tool in the treatment of postpartum depression.

Ensuring a successful pregnancy

The second physiological state in which neurosteroids are elevated is during pregnancy. The placenta produces large amounts of progesterone, an allopregnanolone precursor. The increase in allopregnanolone in the pregnant mother contributes to the increase in inhibitory signaling and the dampening of the HPA axis, so that the fetuses are less susceptible to the damaging effects of stressors. In the fetus, higher allopregnanolone levels help maintain a quiescent state that is imperative for proper brain growth and development.

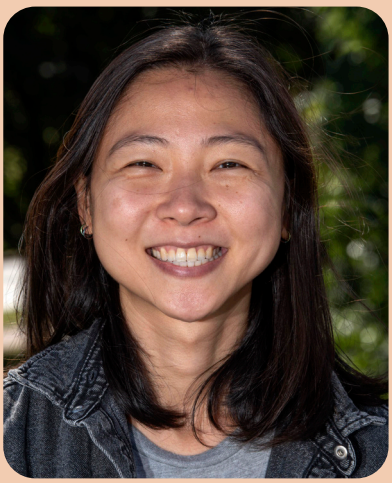
After childbirth, allopregnanolone levels drop dramatically in both the mother and the fetus. This has implications for the health of the fetus, especially in cases of preterm birth. In guinea pigs, the premature loss of allopregnanolone associated with preterm birth exposes the developing brain to increased stimulation and excitotoxic damage. However, the detrimental effects of preterm birth can be reversed by treating the newborn guinea pigs with ganaxolone, a synthetic allopregnanolone analogue.

In the mother, the rapid drop in allopregnanolone after childbirth can lead to imbalances in GABA signaling. For up to one in five women, this may lead to postpartum depression, which is a type of major depression that occurs in the first year postpartum. After decades of research in neurosteroid replacement therapy, a formulation of allopregnanolone, Brexanalone, was approved by the United States Food and Drug Administration in 2019 as the first drug available for the treatment of postpartum depression via intravenous infusion. Further improvements in the design of the drug resulted in the approval of Zuranolone in 2023, an oral formulation that is more easily administered than Brexanalone.

The Gender Gap

The discovery that allopregnanolone can successfully treat postpartum depression represents one of the most groundbreaking advancements in the field of maternal health. The recognition that there is a unique hormonal milieu involved in postpartum depression, which differs from other forms of major depression, highlights the need for further sex-specific research to improve women's health, which has previously been overlooked.

Women are at greater risk of developing mood disorders. However, until recently most neuroscience research was performed using male subjects and animal models. Neurosteroid levels differ significantly between males and females, but the downstream effects of neurosteroid action have yet to be fully characterised. Neurosteroid therapy has meaningful effects in improving brain function and is an exciting new development in the treatment of mood disorders, but is likely to affect males and females in different ways. Ongoing efforts are being made to narrow the gender gap in the field, and digging deeper into neurosteroid research is a step in the right direction.



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