Background

Naturally occurring neurosteroids, such as pregnenolone and allopregnanolone, have shown protection against alcohol use disorder, depression, multiple sclerosis, Alzheimer’s disease, traumatic brain injury, and other neuropsychiatric disorders in animal models, however the mechanism of this protection is not well characterized. These disorders affect a large portion of the population, with 16.2% of adults in the United States suffering from alcohol use disorder alone. It is thought that neurosteroid responses contribute to alcohol use disorder and therefore neurosteroid supplementation may have therapeutic effects for recovery and symptoms associated with alcohol withdrawal, craving and relapse. Neurosteroid levels have also been observed to fluctuate from their normal levels during certain physiological and disease states, such as in depression, stress conditions, chronic pain and psychiatric disorders.

Neurosteroids are synthesized in the brain, adrenal glands, ovaries and testes, and
are modulators of GABAA receptors, CRF expression and TLR signaling. It has been
demonstrated that neurosteroid activity is cell and region specific in the brain,
indicating a targeted effect from these compounds. The GABAergic activity of
neurosteroids informs the therapeutic effect seen in epileptic and traumatic brain
injury patients treated with neurosteroids. However, the therapeutic mechanism(s)
that has been observed for treating other diseases is not well understood. This
highlights the need for a better understanding of the therapeutic mechanism of action
from pregnenolone and allopregnanolone, which will inform novel methods of
treatment for treating several diseases.

Technology Overview
Researchers in the Departments of Psychiatry and Pharmacology at the University
of North Carolina at Chapel Hill have identified a novel mechanism of action for
the neurosteroids pregnenolone and allopregnanolone to inhibit proinflammatory
signaling in the brain. The inhibitory action is mediated through targeting of toll-like
receptors (TLRs), which are involved in the progression of a wide range of diseases
including, alcoholism, depression, traumatic brain injury, schizophrenia, multiple
sclerosis, and Alzheimer’s disease. The anti-inflammatory effect of pregnenolone and
allopregnanolone was observed \textit{in vivo} in rats selectively bred to prefer alcohol as
well as mouse and human macrophages. The novel mechanism for the therapeutic
effects of neurosteroids in CNS diseases provides a method of treatment that utilizes naturally occurring compounds, as well as a platform for developing novel therapeutic agents. Importantly, pregnenolone and allopregnanolone have already demonstrated safety and minimal off-target effects in patients. Given the roll of the TLR-mediated inflammatory response in other diseases, this therapeutic approach can also be applied to treating patients suffering from sepsis, gastrointestinal disease, asthma, and atherosclerosis.

**Benefits**

**Applications**
The neurosteroids pregnenolone and allopregnanolone can be used to treat TLR-mediated inflammatory diseases in humans and animals. Diseases that can be treated
include alcohol use disorder, multiple sclerosis, Alzheimer’s disease, depression, chronic pain, traumatic brain injury, sepsis, gastrointestinal disease, asthma, and atherosclerosis.

Related Publications:

• **Endogenous Neurosteroid (3a,5a)3-Hydroxypregn-20-one Inhibits Toll-like-4 Receptor Activation and Pro-inflammatory Signaling in Macrophages and Brain**

• **Recent developments in the significance and therapeutic relevance of neuroactive steroids–Introduction to the special issue.**

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