Isopregnanolone is a potential treatment to preserve fertility in alcohol-dependent women

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Acute alcohol consumption causes fertility issues

Around **30%** of infertility cases in women are linked to alcohol consumption[8]

As few as **1 to 5** drinks per week is associated with reduced fertility in women[11]

Allopregnanolone (allo) regulates stress responses including alcohol triggers

- **Allopregnanolone (allo)** is a **neurosteroid** that helps in regulating stress and enhances the calming effects of **GABA receptors**[5,13]
- **GABA receptors** are key to **inhibiting** brain activity, acting as a "**brake**" to calm down neural function[3]
- **Luteinizing Hormone (LH)** triggers **ovulation** (the release of a female egg cell) and is involved with many supporting functions leading up to ovulation[10,16]

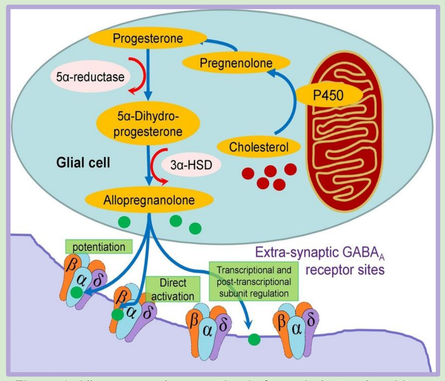

Figure 1. Allopregnanolone synthesis from cholesterol and its modulation of extrasynaptic GABA $_A$ A receptors to enhance inhibitory signaling and neuroprotection[6].

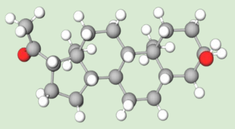

Figure 2. 3-D Ball-Stick model of Allopregnanolone[4].

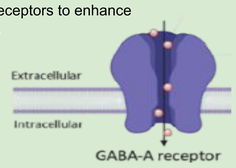

Figure 3. The regulated flow of chloride ions through GABA-A receptors[6].

The Physiology of Alcohol Consumption

Alcohol consumption increases allo, reducing luteinizing hormone (LH)

Alcohol intake in female rats decreases LH[19]

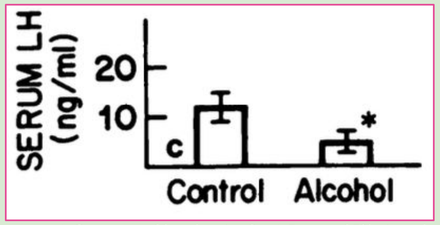

Figure 4. Serum LH of female rats after 4-5 days of 5% ethanol diet compared to control diet, asterisk indicates a significant decrease of LH in the alcohol group ($p<0.01$)[19].

Stress level Allo (6μM) decreases LH[17]

- **Allo** is **important** in regulating the reproductive function of female rats, a **main factor** affecting **allo** is **stress**[17]

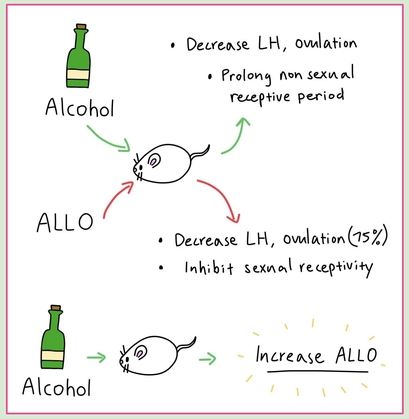

Figure 5. The effects alcohol and allo on reproduction and their relationship[3,17,19].

Alcohol (1g/kg) increases brain and plasma allo in male rats[3]

- Higher increase in alcohol preferring vs non-preferring rats[3]
- **Increase of allo** is interpreted to **restore** GABAergic transmission **decreased** by stress like **alcohol**[3]

The Effects on Reproduction

An increase in allo and decrease in LH has negative effects on fertility

Follicle development occurs in the ovaries before ovulation [15,17,18]

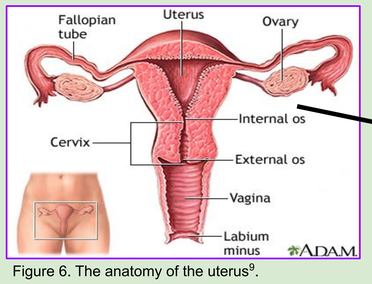

Figure 6. The anatomy of the uterus[9].

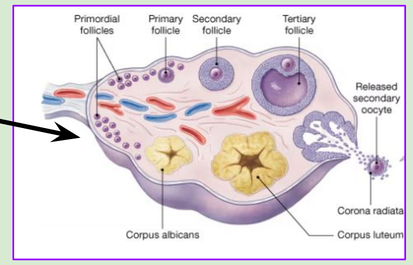

Figure 7. Stages of follicular development from primary to tertiary follicles, leading up to the release of an oocyte[14].

- A **follicle** is a small sac filled with fluid which encases the **oocyte** (female egg cell) [15,17,18]

Allo prevents follicle maturation in the ovaries and decreased LH produces luteinized unruptured follicles (LUFs)[15, 17]

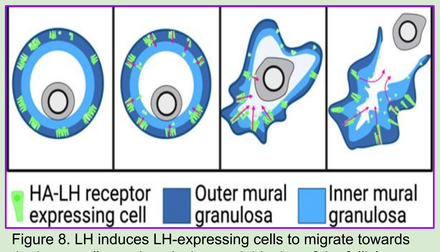

Figure 8. LH induces LH-expressing cells to migrate towards the inner wall, causing pinches and thinning of the follicle wall[15,17]. This results in the release of the egg cell.

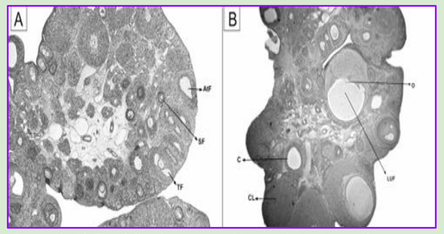

Figure 9. A) The follicular composition and structure of a regular ovary. B) The effects of allo decreases tertiary follicles and affects the overall ovary structure[17].

- **Pinching** of the follicle and **thinning** of the wall are key to **releasing the egg cell**[15]
- A decrease in LH causes LUFs, which can lead to **LUFs Syndrome**, which is a common **precursor for infertility**[17]

The Biochemistry of Isopregnanolone

Isopregnanolone (iso) blocks the effects of elevated allopregnanolone levels

- **Isopregnanolone** is a **neurosteroid** that modulates **GABA-A receptors**, helping balance **brain activity** and support **reproductive health**[7]

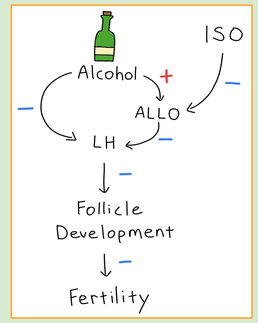

Figure 10. Flowchart summary of the effect of alcohol on fertility and the role of Isopregnanolone (iso).

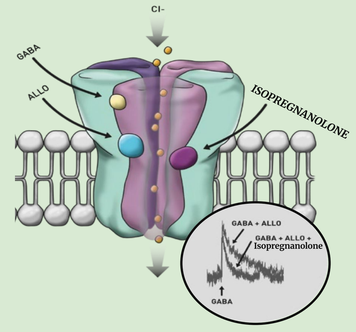

Figure 11. The neurosteroid isopregnanolone regulates and modulates the negative effects of allopregnanolone on GABA-A receptors[1].

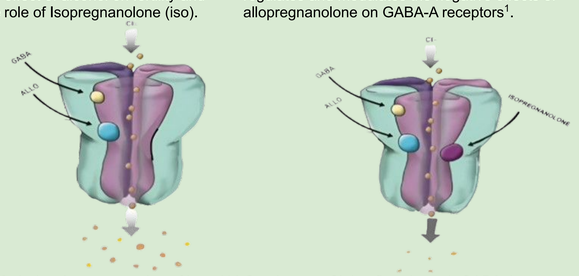

Figure 12: A visual representation of how ALLO enhances Cl^- ion flow through GABA-A receptors, while ISO modulates this effect, bringing Cl^- ion flow closer to baseline. This diagram is for illustrative purposes only and is not a scientifically accurate representation of chloride ion movement[1].

Potential Medicinal Use

This medication targets women with alcohol dependence, aiming to preserve fertility until sobriety is attained.

- Recommended time of use: **before or up to 30 mins after** acute alcohol consumption[3,5]
- This is a **potential treatment**, more research is needed on the actual application of this drug

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QR Code for References