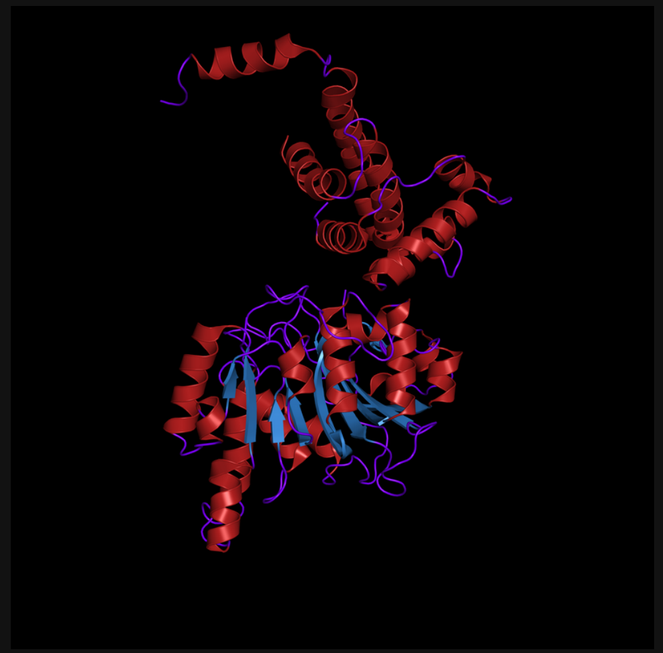
POST SSRI SYNDROME HYPOTHESIS

INTRODUCTION

October 2022

Selective Serotonin Reuptake Inhibitors (SSRIs) have a secondary effect beeing DNMT inhibitiors

DNMT (DNA Methyltransferase)



DNA methyltransferases catalyze the transfer of a methyl group to DNA (Deoxyribonucleic acid).

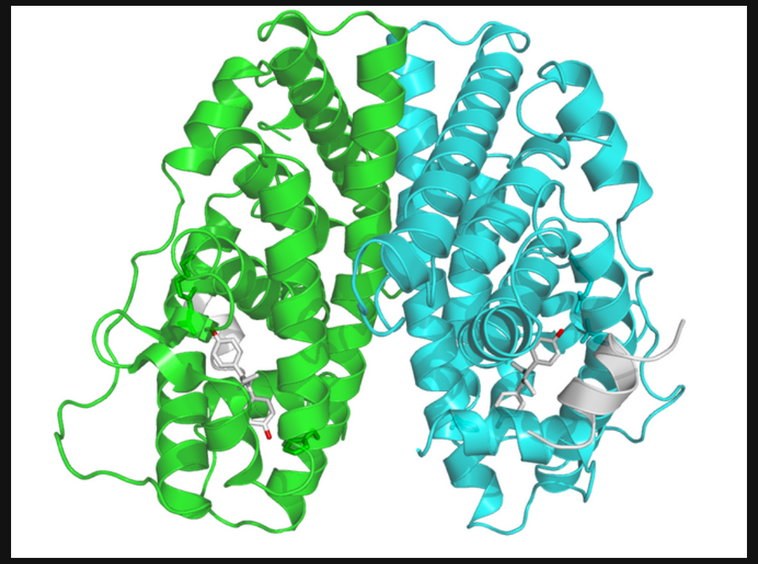
Normally, a patient might end up withdrawing from a SSRI and end up returning to pre-SSRI baseline.

Hypothesis: In very rare cases, Post SSRI Syndrome develops due to failure to getting back to baseline on a epigenomic level. This might be due to a malfunction in within the methylatory mechanisms responsible for altering the epigenome.

Targets

I hypothetisize that patients end up with abnormal densities of the estrogen, androgen and serotonin receptors in the central nervous system. This can have many down-stream consequences, affecting the body and cognitive functions.

Estrogen Receptor



Two classes of Estrogen Receptors exist: ERa and ERb

Estrogen receptors control the release of several neurotransmitters in different brain areas

Estrogen Receptors are coupled to Metabotropic glutamate receptors

Androgen Receptors depend on Estrogen signalling for upregulation in the brain

Cognitive Symptoms

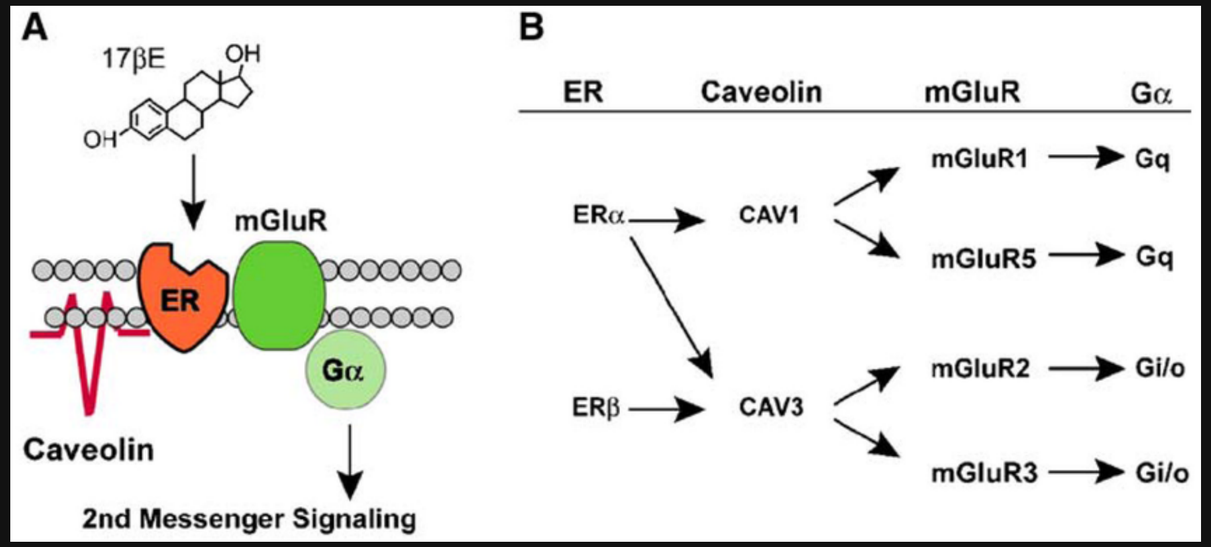
Post SSRI Syndrome sufferers often report similiarities to negative schizophrenia symptoms. These are hypothesized to be caused by hypoactivation of the prefrontal cortex

Table 18.1. Positive and Negative Symptoms of Schizophrenia

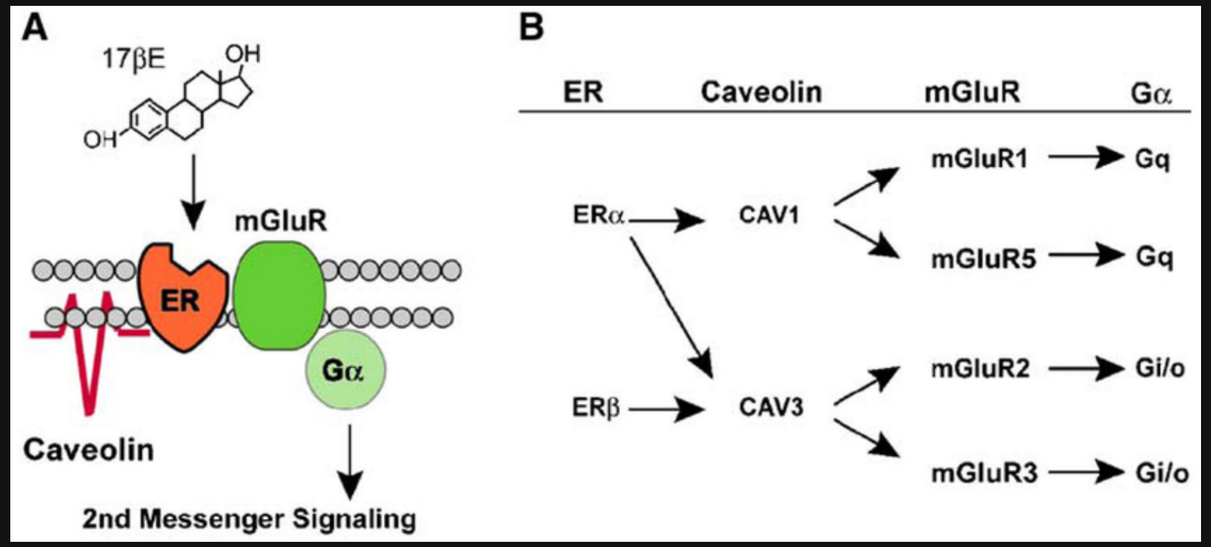
POSITIVE SYMPTOMS	NEGATIVE SYMPTOMS	COGNITIVE SYMPTOMS
Hallucinations	Flat affect	Disorganized thinking
Delusions (e.g., paranoia)	Lack of pleasure	Poor concentration
Thought disorders	Social withdrawal	Poor memory
Movement disorders	Alogia (poverty of speech)	Difficulty expressing ideas
Depersonalization	Loss of interest and motivation	Difficulty integrating thoughts and feelings

Hypofrontality in Post SSRI Syndrome

But what causes the hypoactivation of the prefrontal cortex and the cognitive symptoms seen in Post SSRI Syndrome? The theoretical answer is a shifted ER-a to ER-b ratio



Hypofrontality in Post SSRI Syndrome

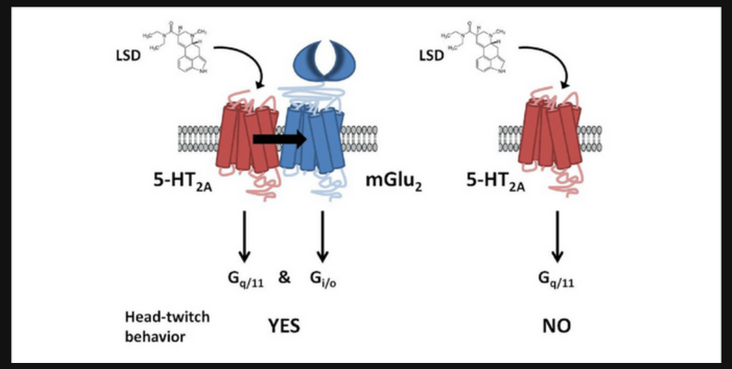


A shifted ratio from ERa to ERb would mean less mGluR5 signalling - mGluR5 knockout mice are associated with negative schizophrenia symptoms - mGluR5 upregulation is associated with OCD

Psychedelics

Post SSRI Syndrome sufferers report loss of response to psychedelics and other drugs. Hypo-activation of ER-a inactivates mGluR1-5 - leading to a blunted psychedelic reaction.

mGluR1-mGluR5 are major targets of psychedelics (indirectly through mGluR2 autoreceptor inactivation) - 5ht2a receptors form a heterodimer with mGluR2



Unrefreshing sleep

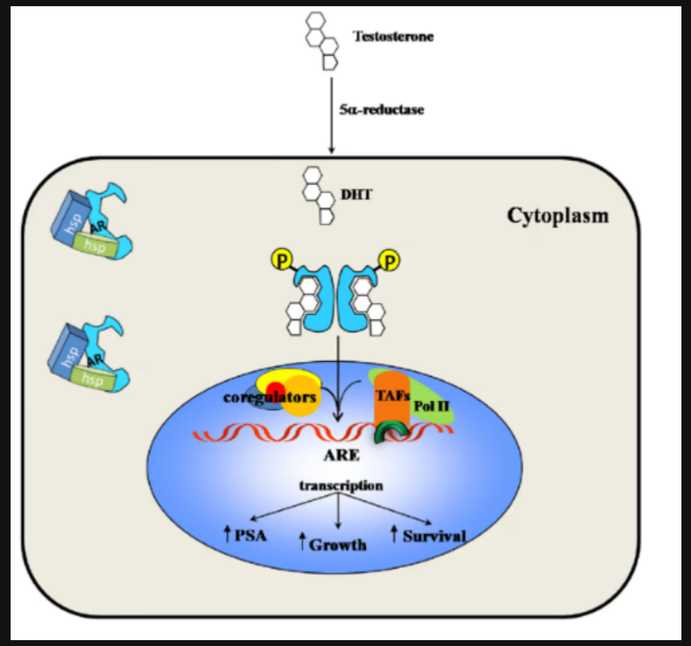
Many Post SSRI sufferers report sleeping for 8 hours and still not feeling refreshed. This could be because of downregulated AQP4 expression in the central nervous system.

Aquaporin-4 clears toxic waste from the brain and is responsible of removal of beta-amyloid. AQP4 is mainly regulated by Estrogen Receptors and Melatonin.

A lower density of Estrogen Receptors, or a decreased Estrogen Signal would mean loss of AQP4 expression and decreased sleep quality.

Loss of muscle

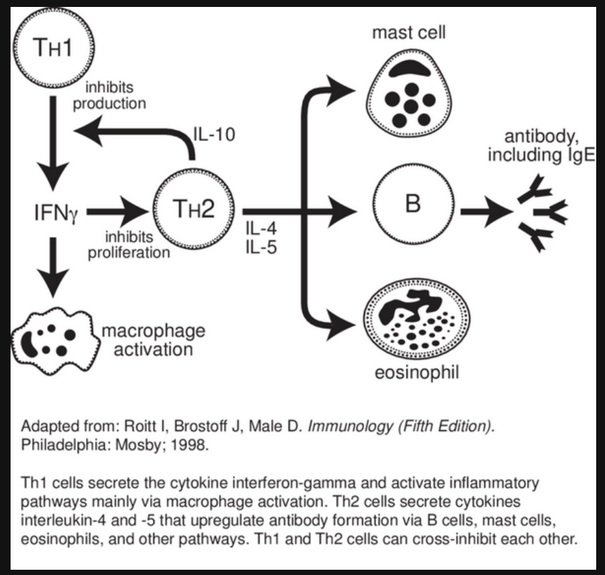
Post SSRI Syndrome sufferers complain from sudden loss of muscle mass or inability to gain muscle. This could be directly caused by the altered density of estrogen and androgen receptors and subsequent loss of androgen/estrogen signalling in the CNS.



Gut dysbiosis, immune system

Abnormal serotonin signalling can change the gut microbiome through the gut-brain axis. Consequences of this can be a shift in the immune system from Th1 to Th2 dominant - inflammatory cytokines in the CNS.

Many Post SSRI Syndrome sufferers report gut dysbiosis and never getting sick which is a sign of Th2 dominance



Adapted from: Roitt I, Brostoff J, Male D. *Immunology (Fifth Edition).* Philadelphia: Mosby; 1998.

Th1 cells secrete the cytokine interferon-gamma and activate inflammatory pathways mainly via macrophage activation. Th2 cells secrete cytokines interleukin-4 and -5 that upregulate antibody formation via B cells, mast cells, eosinophils, and other pathways. Th1 and Th2 cells can cross-inhibit each other.

Therapeutic approaches

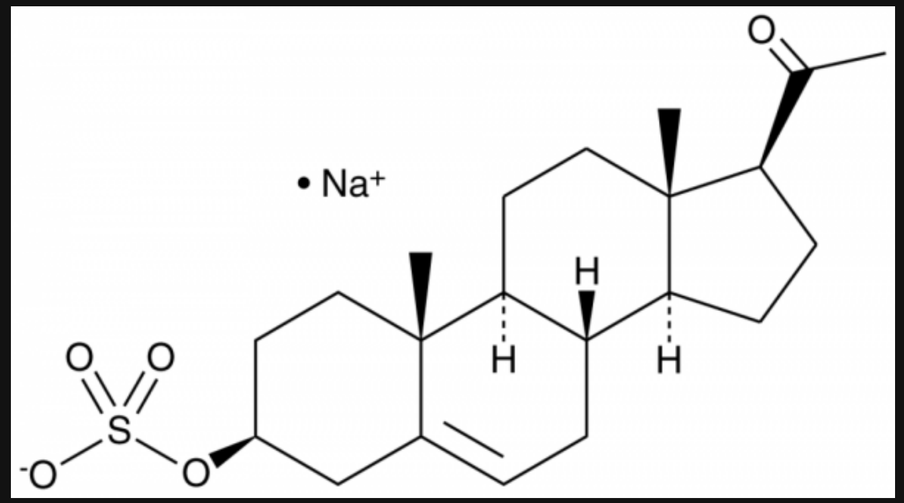
Since epigenetic changes are at the core of this disease, the main goal should be to restore the altered epigenome. For this, HDAC inhibitors come to mind. (Lithium, Vorinostat, ..)

For symptomatic relief of cognitive symptoms, psychostimulants, d2 agonists, or atypical antipsychotics seem to work. PregS also seems promising

Exogeneous hormones may be helpful to restore downregulated androgen and estrogen receptors.

Pregnenolone Sulfate

PregS is a endogenous neurosteroid, below are the noteworthy targets, it also acts at other receptors though



Primary Target	Pharmacology	**Potency**
GABA-A receptor	Negative Allosteric Modulator	7.2 μM [IC50]
Glutamate (NMDA) Receptor	Positive Allosteric Modulator	33.0 μM [EC50]

May improve NMDAR Signalling and improve Hypofrontality / low PFC activation

Lithium

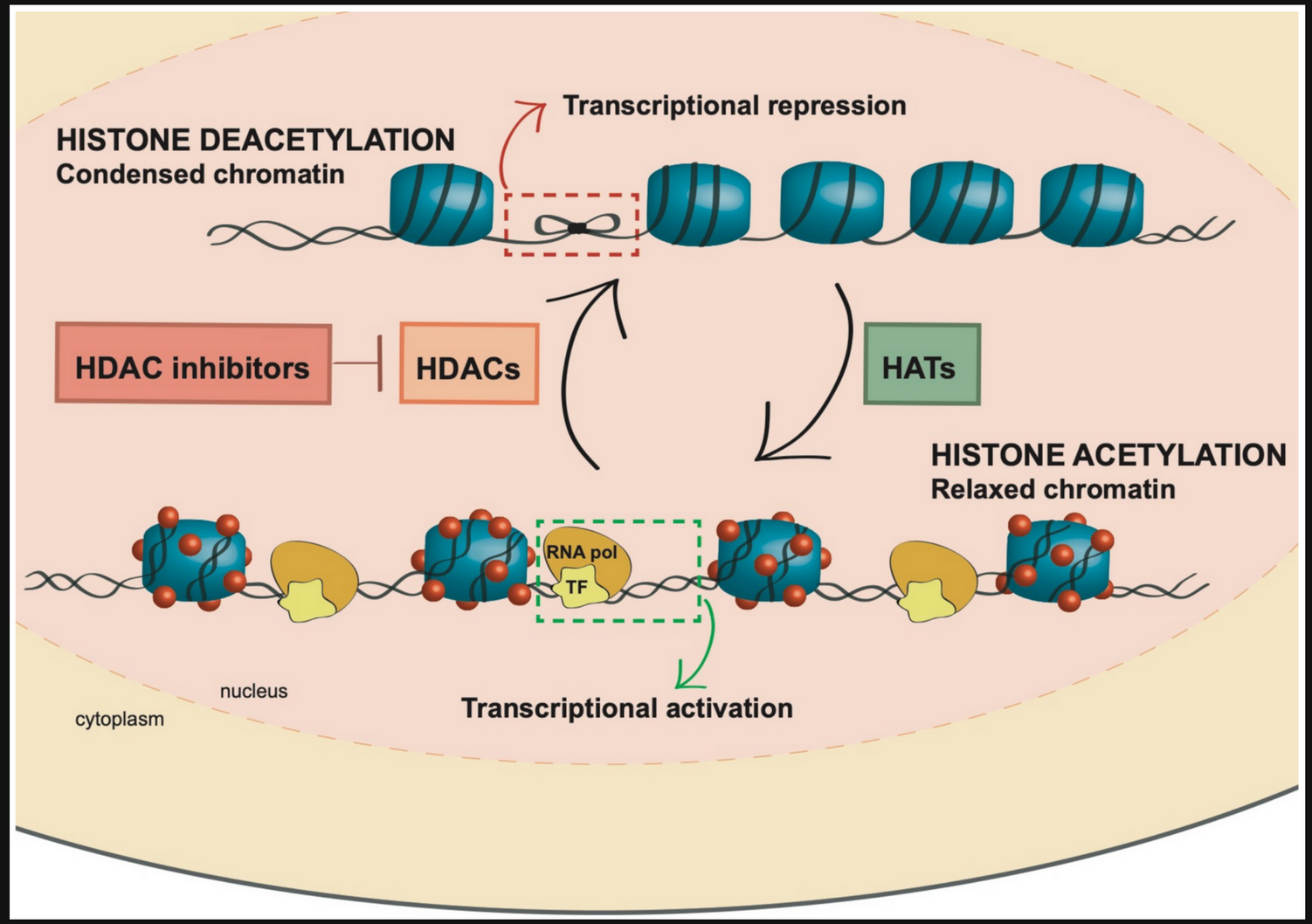
Lithium is a HDAC(1) inhibitor -theoretically Lithium should increase the sensitivity of the Estrogen Receptor in the CNS

Since Androgen Receptors require ER signalling for upregulation, ER signalling must be restored first

Progestins upregulate the Estrogen Receptor and may be useful in addition

A protocol may look like this: Lithium + Testosterone + Progesterone

Lithium


Transcriptional repression
HISTONE DEACETYLATION
Condensed chromatin
HDAC inhibitors
HDACs
HATs
HISTONE ACETYLATION
Relaxed chromatin
RNA pol
TF
nucleus
cytoplasm
Transcriptional activation