Anti-Depressants and Suicide Immediately after Commencing SSRIs
Why Not Pay Attention to Astrocytes' Glutamate Uptake Regulation in the PFC?

What happens when you hand out drugs without any understanding how they really work: Glutamate effects of SSRI Anti-Depressants

http://www.medicaldaily.com/antidepressant-drugs-affect-neurotransmitters-differently-sometimes-increasing-314710

The role of glutamate in the neuron-glia communication induced by antidepressants is still an area of unresolved mystery which has remained shrouded while the nature of glial neuronal interaction has been ignored.

The finding above with which this post began, was one which begins...only now...to understand why SSRI anti depressants frequently provoke worse depression and suicide in the first weeks of their use.

The answer they give is "glutamate" suppression. The actual answer beyond that for those who follow the epic sage of glial cells is astrocyte dysregulation (see below) and the impact of astrocyte regulation of glutamate in the synapses within the Pre-Frontoal Cortex.

The specific mechanisms through which a paucity of glia could contribute to the depressed phenotype are unknown. However, data suggest that glutamate dysregulation, and elevated glutamate, in particular, as would be expected with reduced numbers or function of astrocytes, play a role in the expression of symptoms of anxiety and depression, including anhedonia

The medications that currently treat MDD specifically target the serotonergic and noradrenergic systems and produce eventual therapeutic effects via mechanisms that are not fully understood and although these medications provide symptom relief for some, up to 60% of patients with unipolar depression suffer from treatment-resistant depression (

Furthermore, with over 50% of suicide victims having a previous diagnosis of treatment-resistant depression the need for improved therapeutics to better treat depression has become a global health concern

While SSRIs are among the most widely studied and prescribed form of antidepressants worldwide, it's still not entirely clear how they work. The drugs are believed to change brain connectivity in important ways, but those effects had generally been thought to take place over a period of weeks, not hours.

Their whole-brain network analysis shows that one dose of the SSRI reduces the level of intrinsic connectivity in most parts of the brain. However, Sacher and her colleagues

observed an increase in connectivity within two brain regions, specifically the cerebellum and thalamus.

http://medicalxpress.com/news/2014-09-dose-antidepressant-brain.html#inlRlv

Glutamate is the brain's main excitatory neurotransmitter, and it's important for neural communication, memory formation, learning and regulation.

There has been much interest in glutamate mechanisms in major depressive disorder (MDD) as a promising target for the development of new antidepressants.

A single intravenous infusion of ketamine, a N-methyl-d-aspartate (NMDA) receptor antagonist anaesthetic agent, can alleviate depressive symptoms in patients within hours of administration. The mechanism of action appears to be in part through glutamate release onto non-NMDA receptors including α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic receptors.

Here in this reserach it is clear that the effects of SSRI (Selective Serotonin Reuptake Inhibitor) antidepressants may also involve alterations in NMDA function as well as AMPA function.

http://www.ncbi.nlm.nih.gov/pubmed/25467702

Researchers culled data from existing studies and found when taking an SSRI, serotonin is immediately amplified while glutamate is suppressed. This balance is only restored after several days of drug treatment,

Adrian Fischer, lead study author, said in a press release. Fischer added the serotonin component has been linked to motivation, while the glutamate component has been linked to pleasure and learning.

Put it another way: An SSRI immediately boosts motivation in depressed patients, while at the same time it's hampering hedonic components (pleasure) of the reward system. The answer isn't a higher dose of SSRIs either.

Instead, researchers found this combination, whatever the dose, "could lead to the facilitation of suicidal thoughts or behavior in the early weeks of SSRI administration," especially in young adults.

Just what's going on here. Astrocytes, of course.

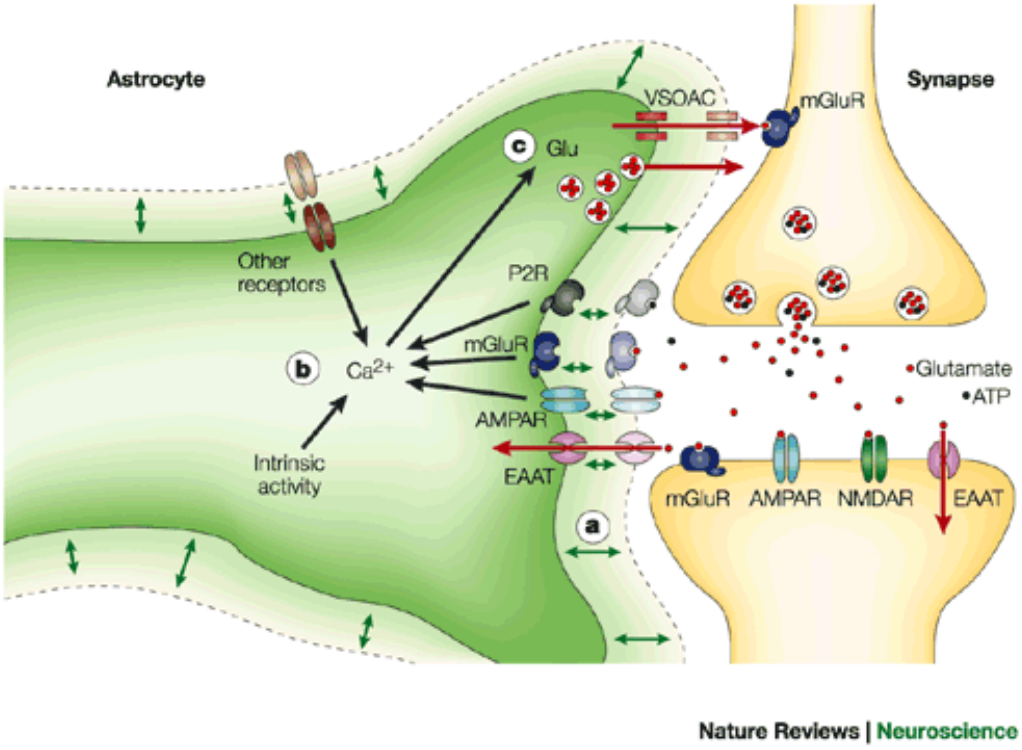
Major depression is associated with both dysregulated glutamatergic neurotransmission and fewer astrocytes in limbic areas including the prefrontal cortex (PFC).

Notably, astrocytes regulate glutamate levels by removing glutamate from the synapse via the glutamate transporter (GLT-1).

In this later study on Astrocytes and the PFC, they have shown that decreasing astrocytic glutamate uptake in the PFC can induce some of the symptoms observed in depressed patients, including anhedonia and irregular EEG patterns.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442341/ FULL TEXT

This dysfunction was achieved by direct infusion of the GLT-1 inhibitor DHK into PFC, which pharmacologically mimics the dysfunction of astrocytic glutamate uptake observed in patients with depression.



It has been demonstrated that central blockade of GLT-1 induces anhedonia and c-Fos expression in the PFC. Given the role of the PFC in regulating mood,

At lower doses, intra-PFC DHK (a GLT-1 Inhibitor) produced modest increases in ICSS thresholds, reflecting a depressive-like effect.

At higher doses, intra-PFC DHK resulted in cessation of responding.

A decrease in reward value followed by complete cessation of ICSS responding suggests an anhedonic-like effect of intra-PFC DHK; a conclusion that was substantiated by an increased latency to begin sucrose drinking.

These data suggest that the lack of astrocytes observed in MDD patients may have a causal role in producing or mediating some of the symptoms of depression. These data add to the growing body of literature suggesting that the ability to detect alterations in astrocytic function in vivo might serve as a diagnostic criterion for MDD, and that restoration or enhancement of astrocytic function might represent a novel treatment target for some symptoms of depressive disorders.

Overall, these results suggest that blockade of astrocytic glutamate uptake in the PFC is sufficient to produce anhedonia, a core symptom of depression.

The newly discovered "reasons" for suicidal episodes in the immediate aftermath of SSR! Antidepressants have actually been hidden beyond our collective lack of interest in the importance of these under-respected glia cells in all the brain's functions.