The Role of Astrocytes in the Long-Term Action of Antidepressant Drugs

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❖INTRODUCTION

- According to the **tripartite synapse** model, the astrocyte is part of the functional unit of the synapse and is able to modify or disrupt it.
- When **synapse disruption** occurs in prefrontal cortex (PFC) and limbic regions that control emotions it causes the major depressive disorder (MDD).
- Perisynaptic astrocytes are therapeutic targets of **antidepressant drugs** (AD) participating in the therapeutic effect.
- The aim of this project to collect the last advances in the MDD research field, taking the astrocyte as a key element of the synapse and as a target of AD.

❖ METHODS

Extended reading of references related to MDD obtained from PubMed, SciElo and Scopus. The used references collect data from 2001 year up to now.

❖ PHYSIOPATHOLOGY OF MDD

Neurotrophic hypothesis of MDD

Stress decreases the levels of the neurotrophic/growth factors leading to **neuronal and glial atrophy** in PFC and limbic structures that control emotions, thus causing the MDD (Fig. 1).

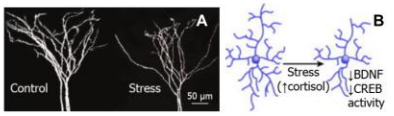

Figure 1. A. Confocal micrographs of prefrontal cortex neurons showing the atrophy caused by stress. Duman, R. S. *et al. Science* 68 (2012). B. Model of neuronal atrophy caused by stress.

Antidepressants (AD) re-establish the levels of neurotrophic/growth factors **VEFG**, **BDNF**, **IGF-1**, **FGF-2** and **GDNF** decreased by stress. The neurotrophic/growth factors activates RTKs which coupled to similar signal transduction pathways restore the neuronal atrophy, improve synaptic function and increase neurogenesis.

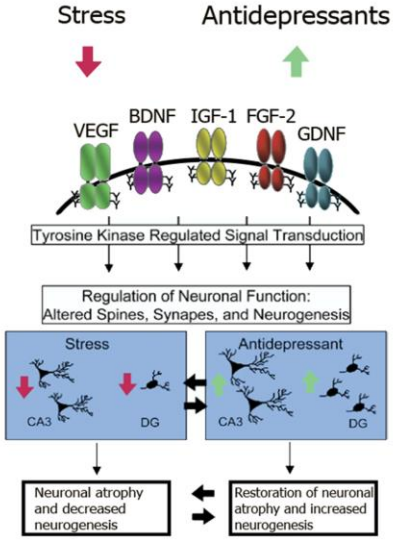

Figure 2. Involvement of neurotrophic/growth factors in the physiopathology and treatment of depression.

❖ANTIDEPRESSANTS ACT ON ASTROCYTES

Different classes of AD increase GDNF **release** in C6 cells (a model of astrocytes) in a dose dependent manner, but not non-AD which act in the CNS. This corroborates that release is a selective effect of AD (Fig. 3).

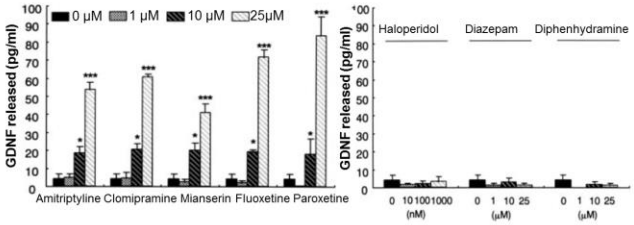

Figure 3. Different classes of AD induced the release of GDNF after treatment at different concentrations, but not non-AD (right). Hisaoka, K. *et al. J Neurochem,* 79, 25 (2001).

The different classes of AD not only increase the release of neurotrohpic/growth factors but also increase its **transcription**. After a treatment with a tryciclic AD (TCA) it is reported a significant raise in the astrocyte mRNA levels of FGF-2, BDNF, VEGF and GDNF (Fig. 4).

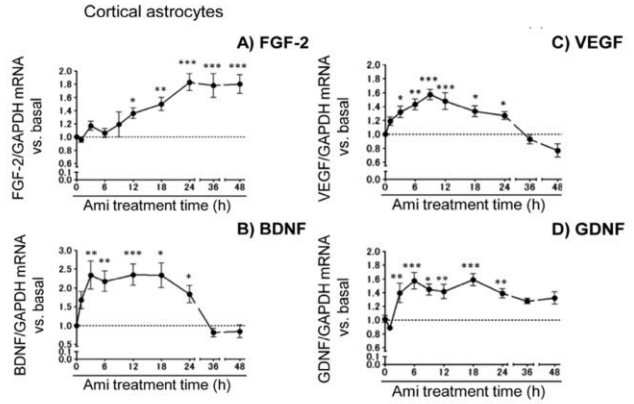

Figure 4. The effects of amitriptyline AD in the mRNA expression of neurotrophic/growth factors in astrocytes. Kajitani, N. *et al. PloS one,* 7 (12).

❖SIGNALING PATHWAYS IN ASTROCYTES

The current available classes of AD SNRI, SSRI, IMAOs and TCA increase the availability of monoamines noradrenalin (NA) and serotonin.

- **NA:** activates PKC and PKA through α1 and β adrenergic-R.
- **Serotonin:** activates PKC through 5-HT2R. New pathway elucidated is based on transactivation of FGFR2 through Src tyrosine-kinase and stabilized microtubules.
- **TCA** activate both FGFR1 and FGFR2 through an extracellular pathway consisting on the mobilization of FGFR ligands from a membrane store of heparan sulfate proteoglycans (HSPG) by matrix metalloproteinase (MMP).

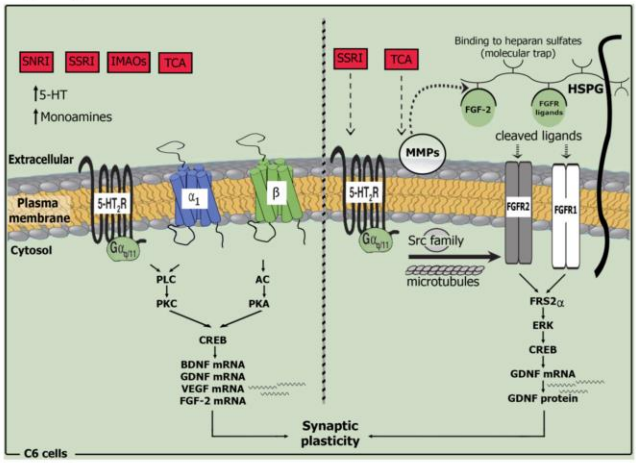

Figure 5. Implicated signaling pathways in the long term action of AD in C6 cells. Left side: the two main described pathways. Right side: new elucidated pathways.

❖SYNAPTIC PLASTICITY

In the **hippocampus** is expressed eprin-A3 and its receptor EphA4 (Fig. 6 A).

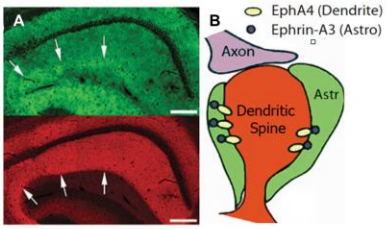

Figure 6. A. Immunofluorescence delineating the complementary expression of ephring-A3 (green) with EphA4 (red) in the adult mouse hippocampus. Murai, K. *et al. Nature neuroscience*, *6*(2), 153. B. Proposed ephrin-A3/EphA4 mechanism.

	Localization	Control
EphA4	Dendritic spines	The morphology of postsynaptic spines (Fig. 6B, 8)
Ephrin-A3	Astrocytes	The glial glutamate transporters expression (Fig. 7)

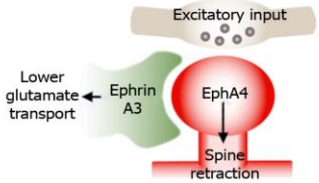

Figure 7. Interaction of dendritic EphA4 with glial ephrin-A3 activates astrocyte signaling resulting in lower glutamate transport.

Neuron-astrocyte interactions regulate spine morphology and glutamatergic transmission

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Long lasting synaptic changes

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Clinical outcome

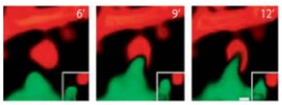

Figure 8. Dual time-lapse imaging showing neuron (red) – astrocyte (green) interactions regulating spine morphology

❖FUTURE CHALLENGES OF AD

- Rapid therapeutic action
- Rapid induce of the long lasting changes based on plasticity (not a chronic treatment)
- Reduce the risk of MDD recurrency
- Low rate of non-responding patients

❖ CONCLUSIONS

- AD act on astrocytes leading to an increase in the neurotrophic/growth factors transcription and release.
- AD re-establish the neuronal atrophy and neurogenesis induced by stress.
- AD induce the transcription of target genes in astrocytes resulting in synaptic plasticity.
- Astrocytes control the dendritic spines dynamics and glutamatergic transmission, thus stimulating long lasting synaptic changes leading to the clinical outcome.