Ansiedade, neuroplasticidade e efeito de fármacos

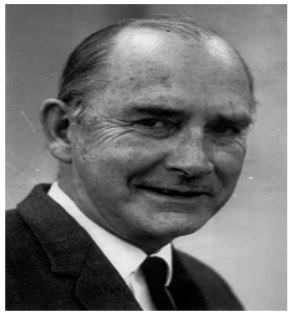
Neuroplasticidade: alterações estruturais e funcionais no sistema nervoso central que decorrem de novas experiências (incluindo fármacos, por exemplo)

Descoberta dos tratamentos farmacológicos utilizados nos transtornos de humor

LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

By John F. J. Cade, M.D.,
Senior Medical Officer, Victorian Department of Mental Hygiene.

✓ 1949 - John Cade



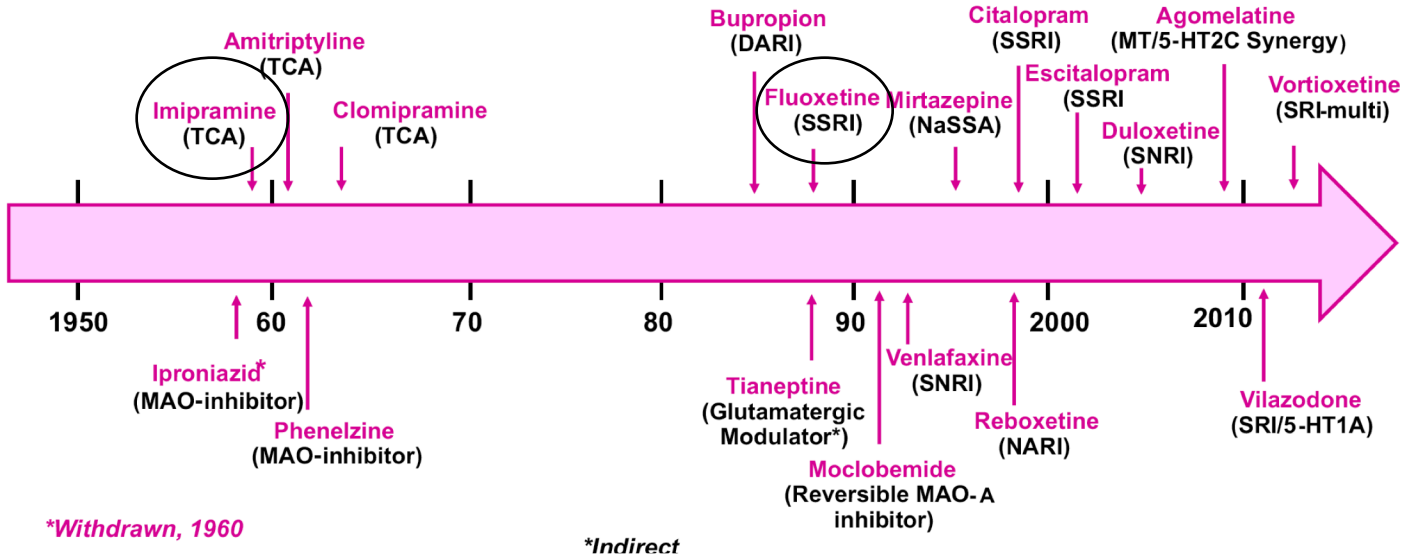
✓ 1952 - Selikoff et al.: iproniazida melhora o humor em pacientes tuberculosos

✓ 1952 - Zeller et al.: iproniazida inibe a MAO

✓ 1957 - R. Kuhn: imipramina: primeiro antidepressivo tricíclico
- N. Kline: IMAOs no tratamento da depressão

✓ 1950 - M. Schou: lítio efetivo clinicamente

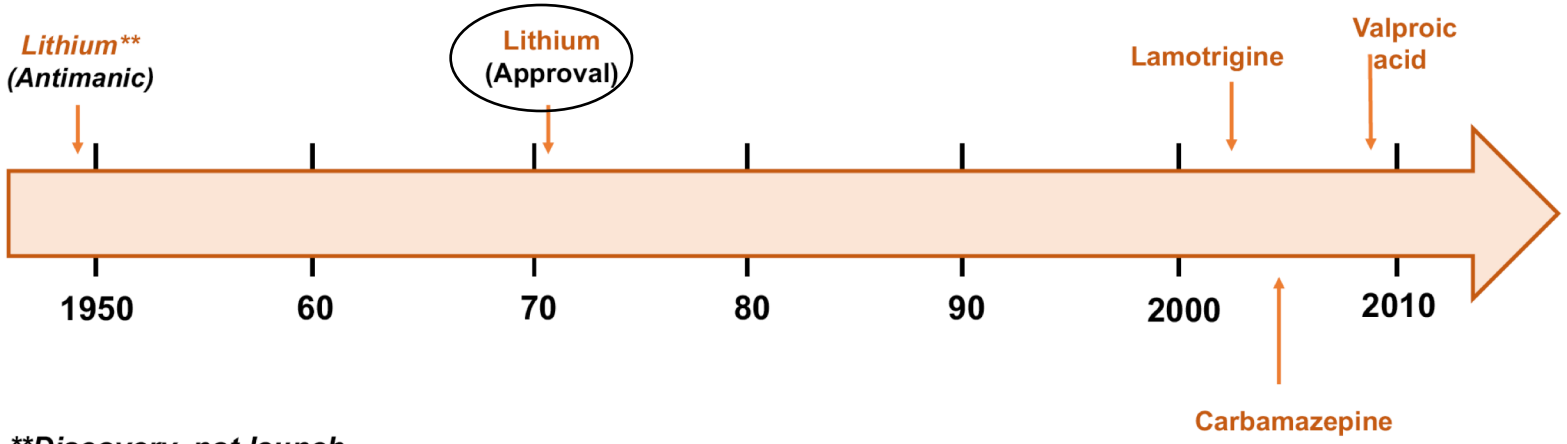
Major depression



*Withdrawn, 1960

*Indirect

Bipolar disorder*



**Discovery, not launch

Several antipsychotics shown in Figure 1 have been authorised for the treatment of bipolar disorder - see Table 1

Inhibition of Uptake of Tritiated-noradrenaline in the Intact Rat Brain by Imipramine and Structurally Related Compounds

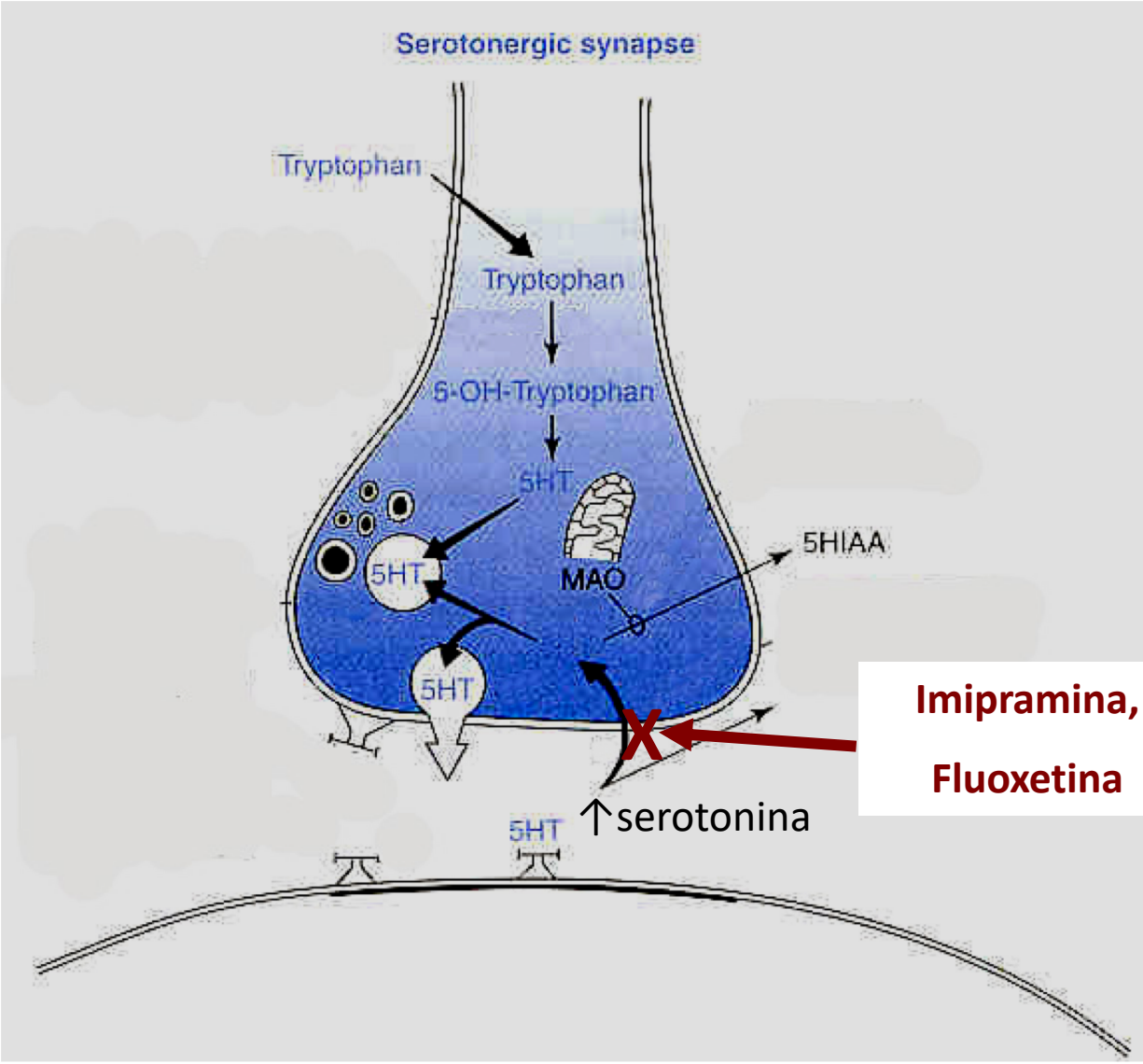
NATURE December 26, 1964 VOL. 204

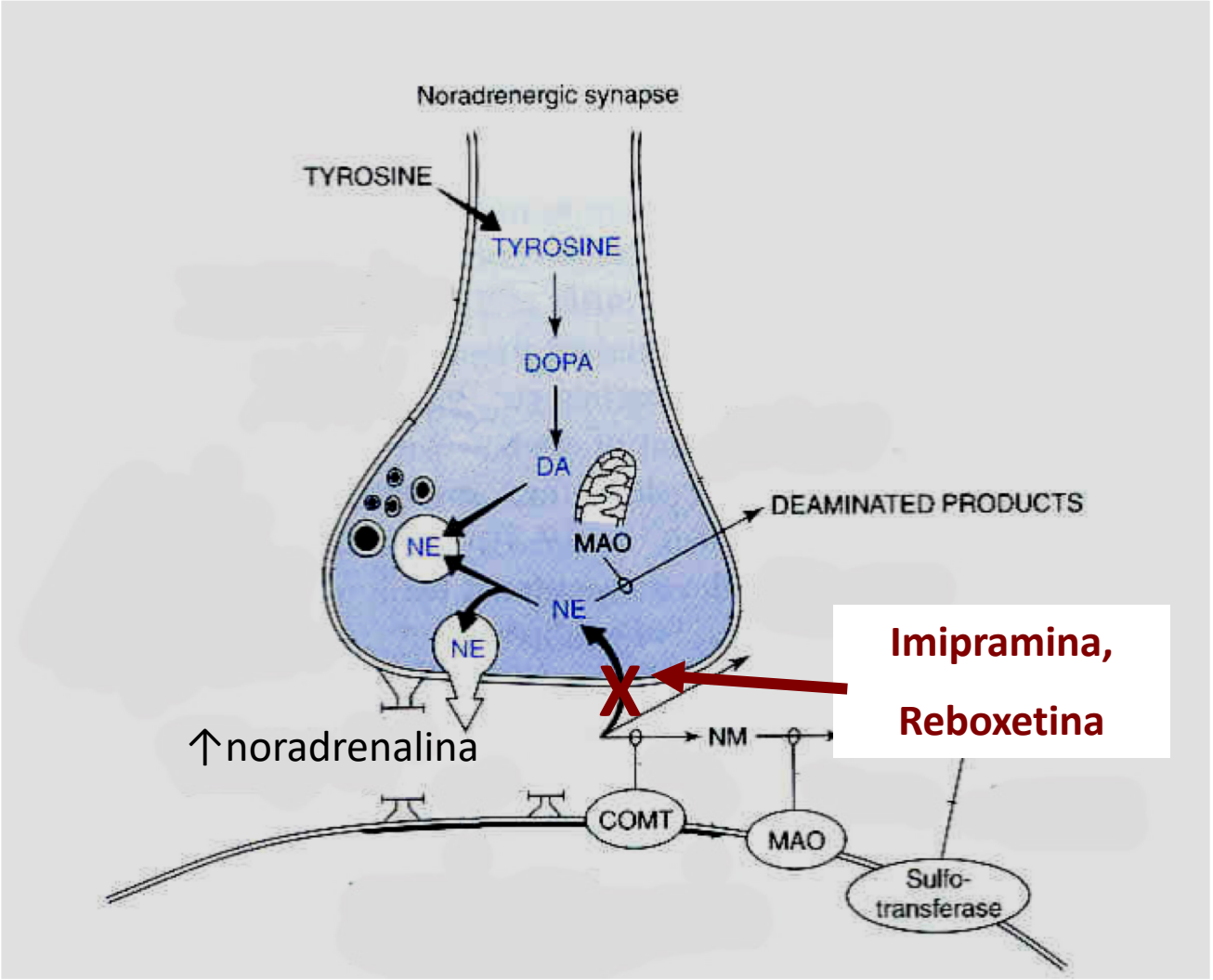
J. Glowinski, J. Axelrod

The ability of imipramine to prevent the rebinding of noradrenaline by cerebral tissues may be a mechanism for the antidepressant action of this drug. Such an action of the drug would allow more free physiologically active noradrenaline liberated from the central sympathetic neurones to react with the central adrenergic receptors.

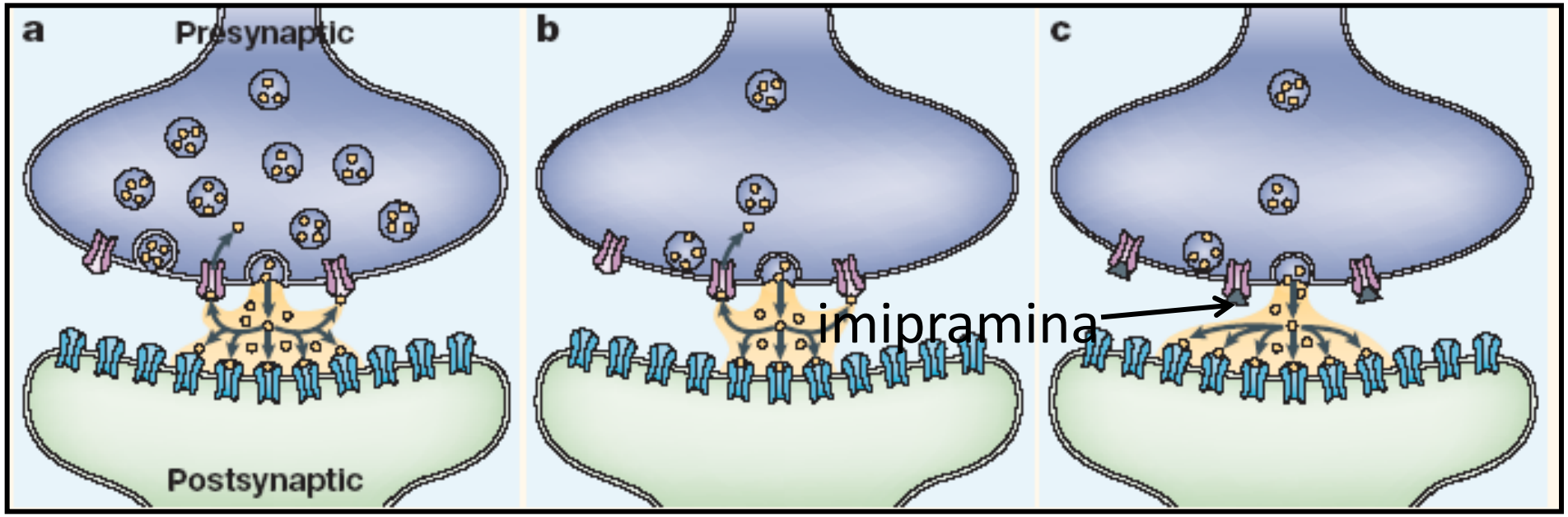
Boa parte dos antidepressivos inibem a recaptação neural de serotonina e/ou noradrenalina

Treatment (mg/kg)	Clinical Antidepressant action	% Control Value
Imipramine (20)	Yes	63*
Desmethyl-imipramine (20)	Yes	64*
Amitriptyline (10)	Yes	77*
Compound II (20)	No	99
Chlor-promazine (40)	No	91


Serotonergic synapse
Tryptophan
Tryptophan
5-OH-Tryptophan
5HT
5HT
MAO
5HIAA
5HT
X
Imipramina,
Fluoxetina
↑serotonina
5HT


Noradrenergic synapse
TYROSINE
TYROSINE
DOPA
DA
NE
MAO
DEAMINATED PRODUCTS
NE
NE
Imipramina,
Reboxetina
↑noradrenalina
NM
COMT
MAO
Sulfo-
transferase

Hipótese Monoaminérgica Clássica da Depressão

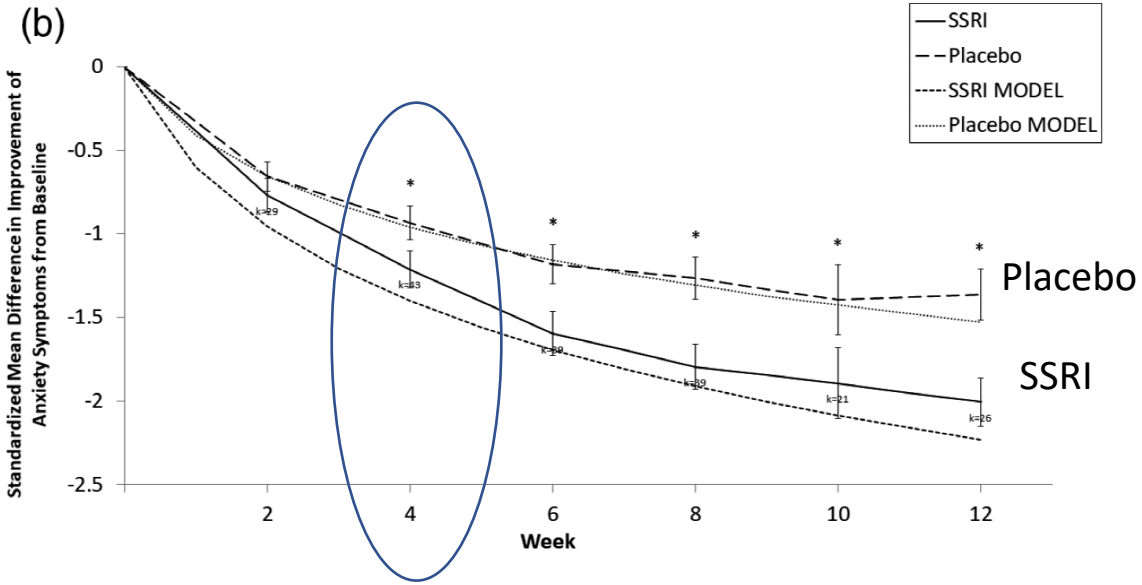


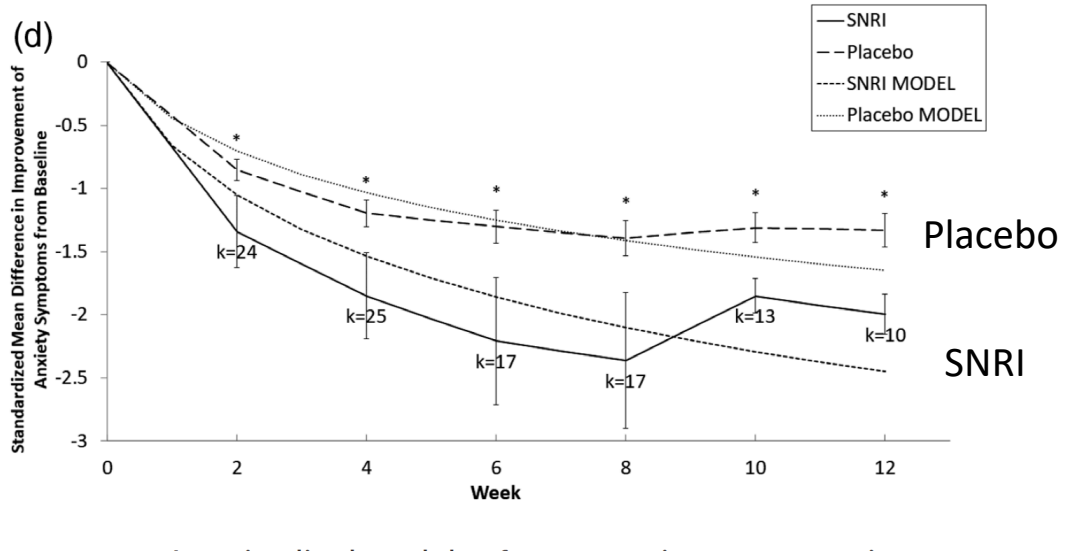
↓ Noradrenalina (Schildkraut e Kety, 1965) e ↓ Serotonina (Lapin e Oxenkrug, 1969)

no SNC

Castrén, 2005

Metanálise de estudos com inibidores de recaptação de serotonina (SSRI) ou de noradrenalina (SNRI) em transtornos de ansiedade (ansiedade generalizada, pânico e ansiedade social): **existe latência para o aparecimento dos efeitos clínicos**





Systematic review and meta-analysis: Dose–response curve of SSRIs and SNRIs in anxiety disorders *Depress Anxiety.* 2018;1–15.

Ewgeni Jakubovski[1] | Jessica A. Johnson[2] | Madeeha Nasir[2] | Kirsten Müller-Vahl[1] | Michael H. Bloch[2,3]

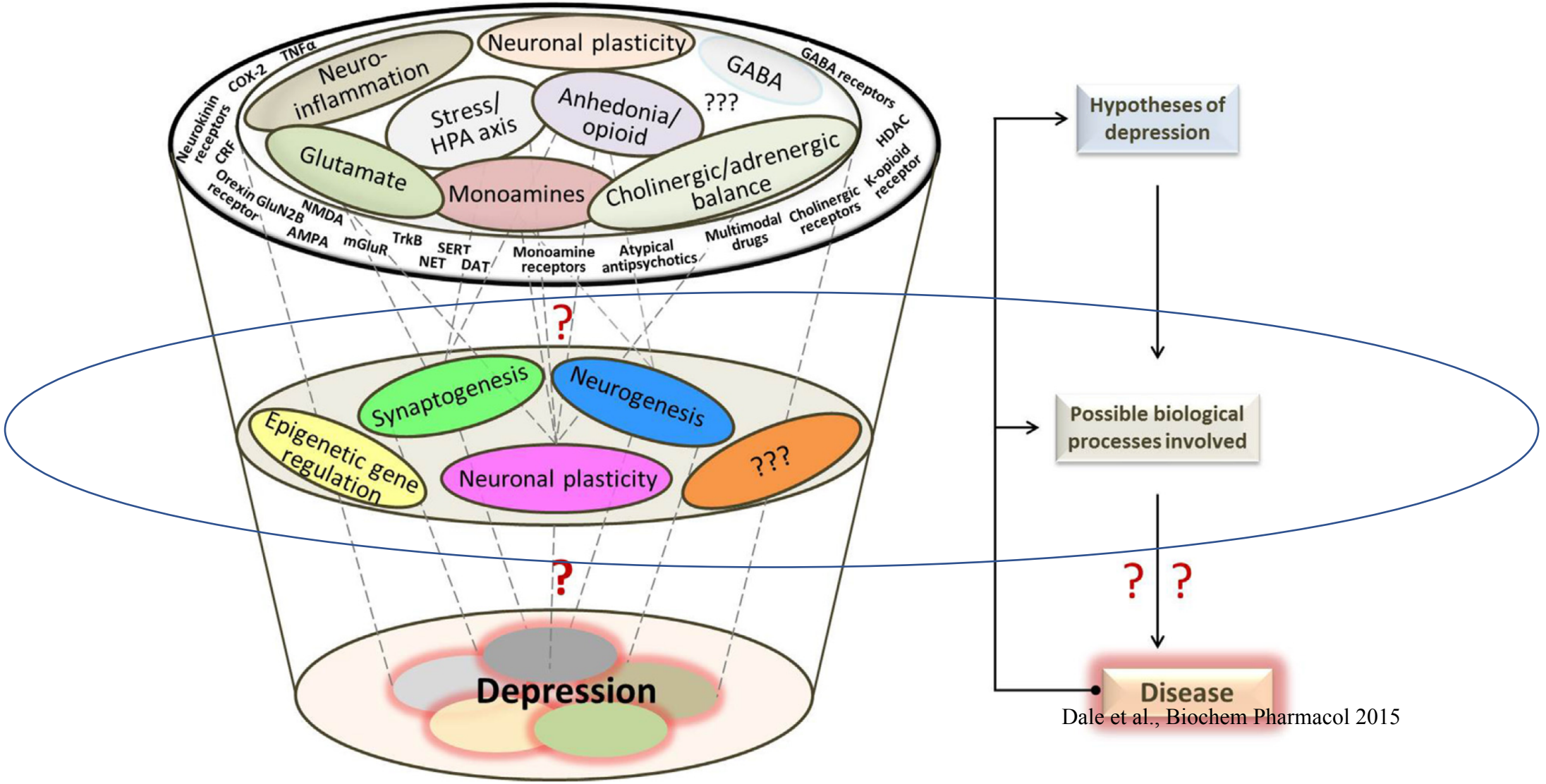
Obs. A resposta terapêutica em altas doses de SSRI parece um pouco melhor do que a dos SNRI)

Perguntas que não querem calar

Porque da “latência” para o aparecimento destes efeitos?

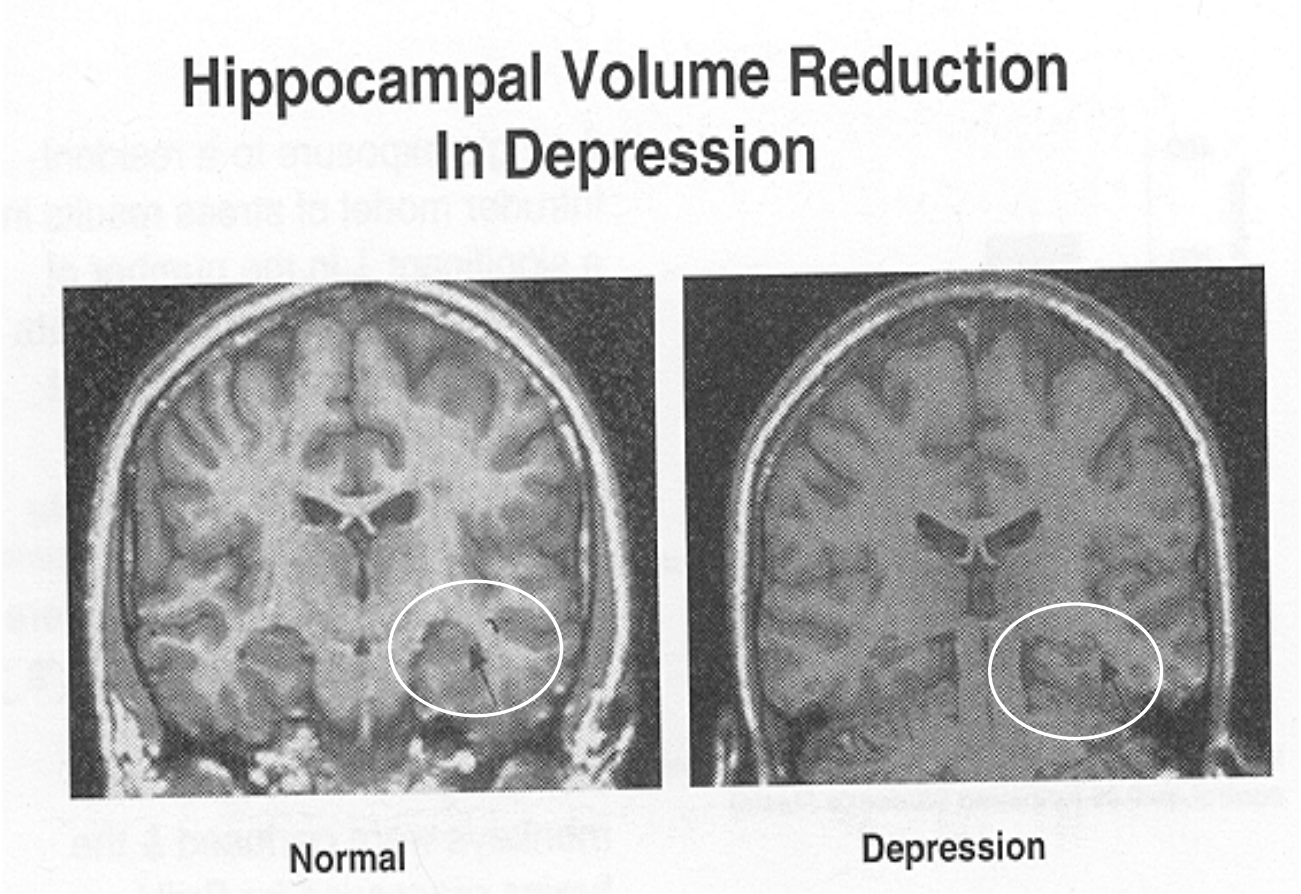
Como a facilitação da neurotransmissão mediada por monoaminas produziria efeitos antidepressivos e ansiolíticos?

Hipóteses atuais sobre a depressão (e ansiedade crônica): fatores neuroplásticos são cada vez mais importantes

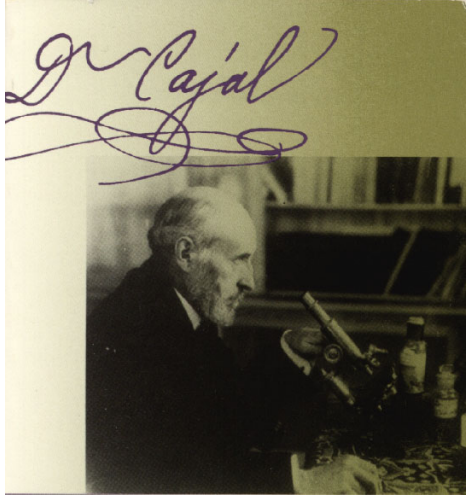


Dale et al., Biochem Pharmacol 2015

Pode existir **diminuição do volume do hipocampo** em pacientes com depressão e em transtorno de estresse pós-traumático: **efeito é revertido com tratamento crônico com antidepressivos**



Gurvits et al., Biol Psych 40:1091, 1996, Bremer et al., Am J Psychiatry 2004, Sheline et al., 1996



"In the adult centers the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated."

Santiago Ramon y Cajal (1913)

Autoradiographic and Histological Evidence of Postnatal Hippocampal Neurogenesis in Rats [1]

JOSEPH ALTMAN AND GOPAL D. DAS
Psychophysiological Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts

ABSTRACT In the autoradiograms of young rats injected with thymidine-H^3 many of the granule cells of the dentate gyrus were found labeled. The number of labeled cells declined rapidly with increased age at the time of injection. Histological studies showed the presence in young rats of a large germinal matrix of mitotic cells in the ependymal and subependymal layers of the third and lateral ventricles. The areal

J. Comp. Neurol., 124: 319-336 (1965)

A descoberta da neurogênese em cérebro de adultos

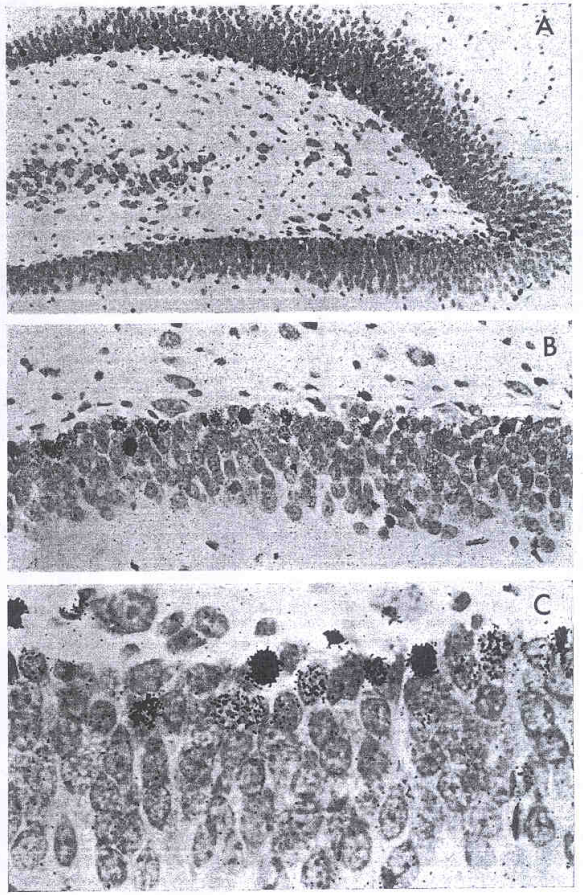


Fig. 1 Low and high power microphotographs of autoradiograms from the area of the dentate gyrus of the hippocampus in a rat injected with thymidine-H^3 at the age of ten days and killed two months after the injection. Note labeling of granule cells, predominantly in the internal border (basal surface) of the granular layer. A, 100 ×; B, 256 ×; C, 640 ×.

Neurogênese em humanos e roedores adultos (Borsini et al., 2015): regiões subventricular e subgranular do giro denteado

No rato ≅ 3. 000 novas células por dia no giro denteado

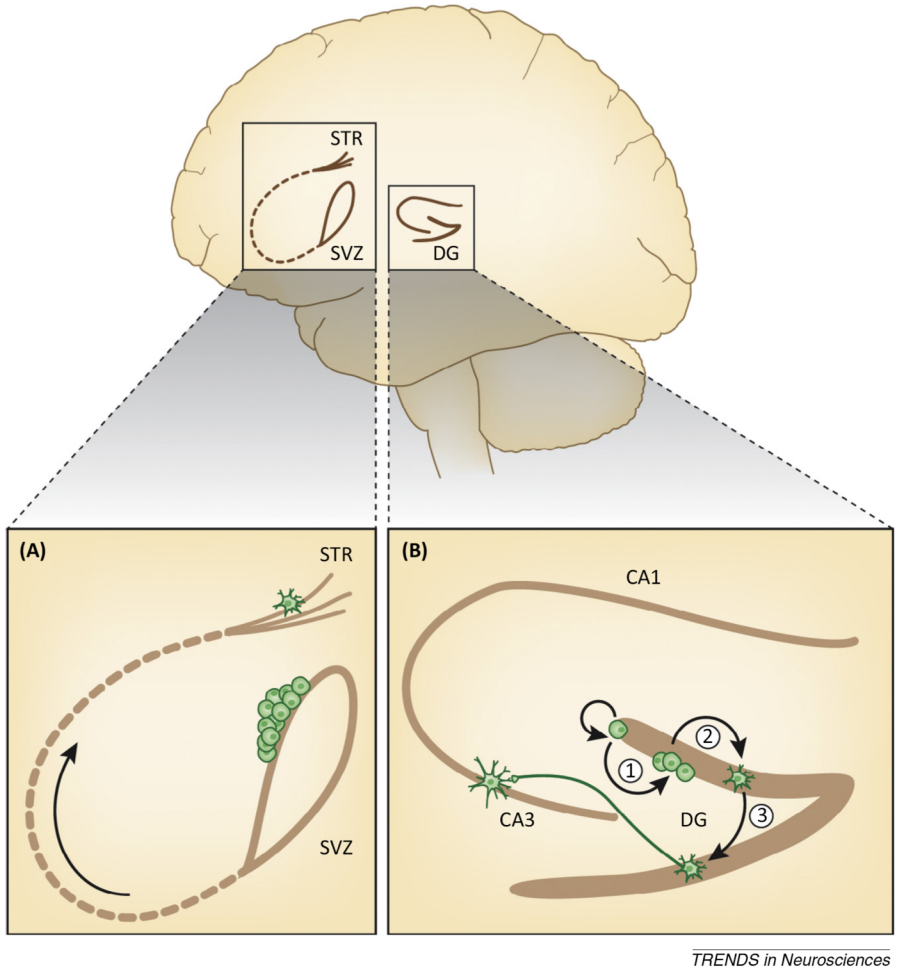
80% morrem no 1o. mês

20% sobrevivem

70% viram neurônios

30% viram astrócitos ou oligodendróglias

Em humanos ≅ 700 novos neurônios por dia no giro denteado



Vários estímulos (incluindo o estresse) podem alterar a neurogênese hipocampal em animais adultos

Adult neurogenesis: a substrate fo experience-dependent change

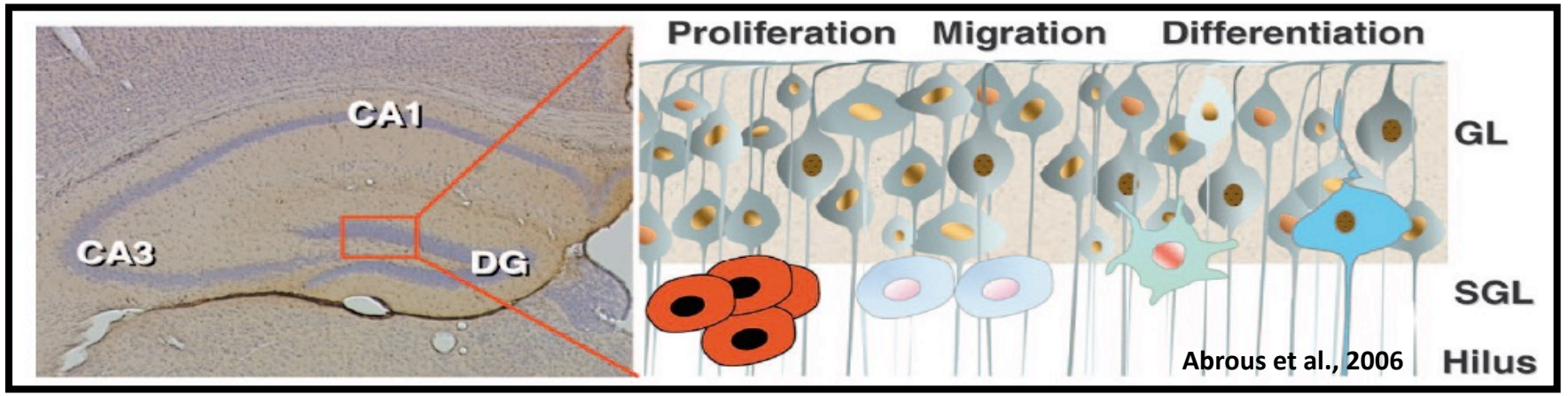
Maya Opendak and Elizabeth Gould

TICS 2015

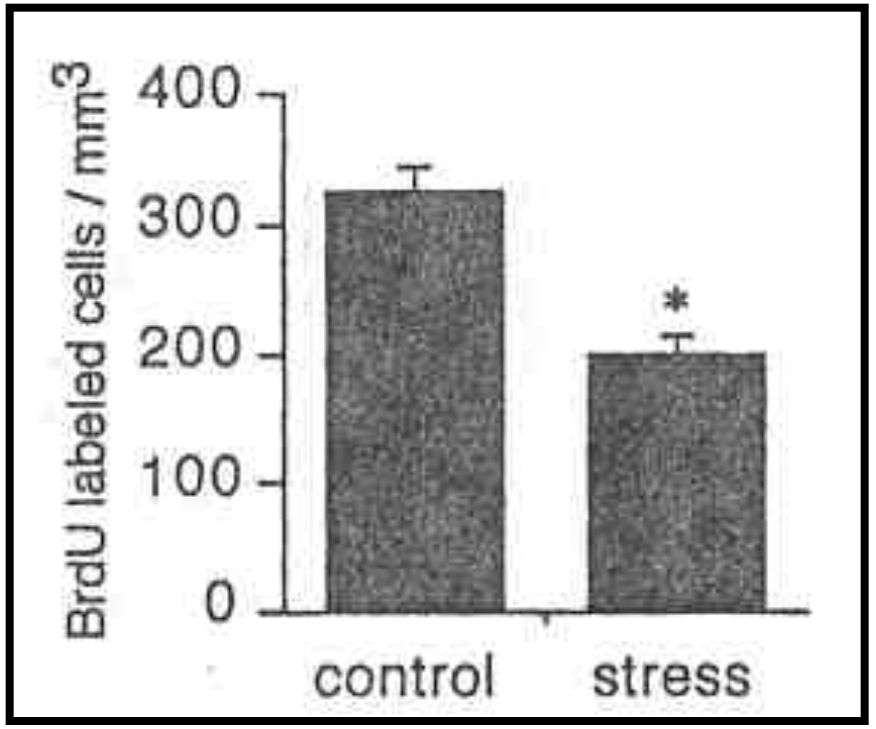
	Stimulus	Adult neurogenesis	Cognitive performance	Anxiety-like behavior	References
Negative	Stress	↓	↓	↑	5,8,82,83
Negative	High fat diet/obesity	↓	↓	↑	84,85
Positive	Physical exercise	↑	↑	↓	18,19,21,22,39
Positive	Sexual experience	↑	↑	↓	36,86,87
Positive	Enriched environment (EE)	↑	↑	↓	89,90
Positive	Intracranial self-stimulation	↑	↑	?	91,92
Mixed	Parenting	↓	↑ ↓	↓	34,35,88,93
Mixed	Stress + physical exercise	=	=	=	74,75,94
Mixed	Stress + sexual experience	=	=	?	76,95
Mixed	Stress + EE	=	=	=	96,97

TRENDS in Cognitive Sciences

Estresse psicossocial reduz a neurogênese no giro denteado do hipocampo



Participação de glicocorticóides e de glutamato (Cameron et al., 1998)

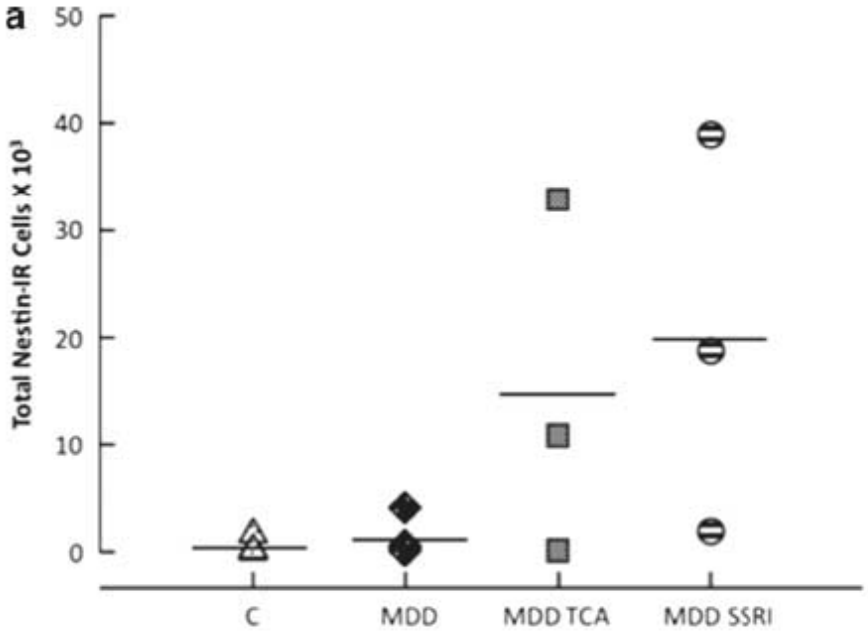


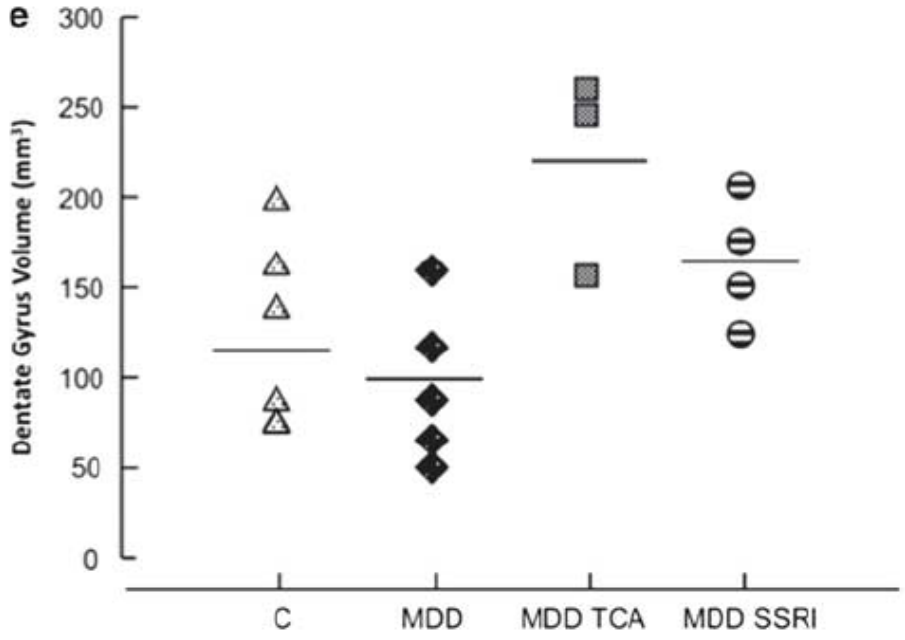
Gould et al., 1998

Antidepressivos aumentam a neurogênese hipocampal em pacientes com depressão

Antidepressants increase neural progenitor cells in the human hippocampus

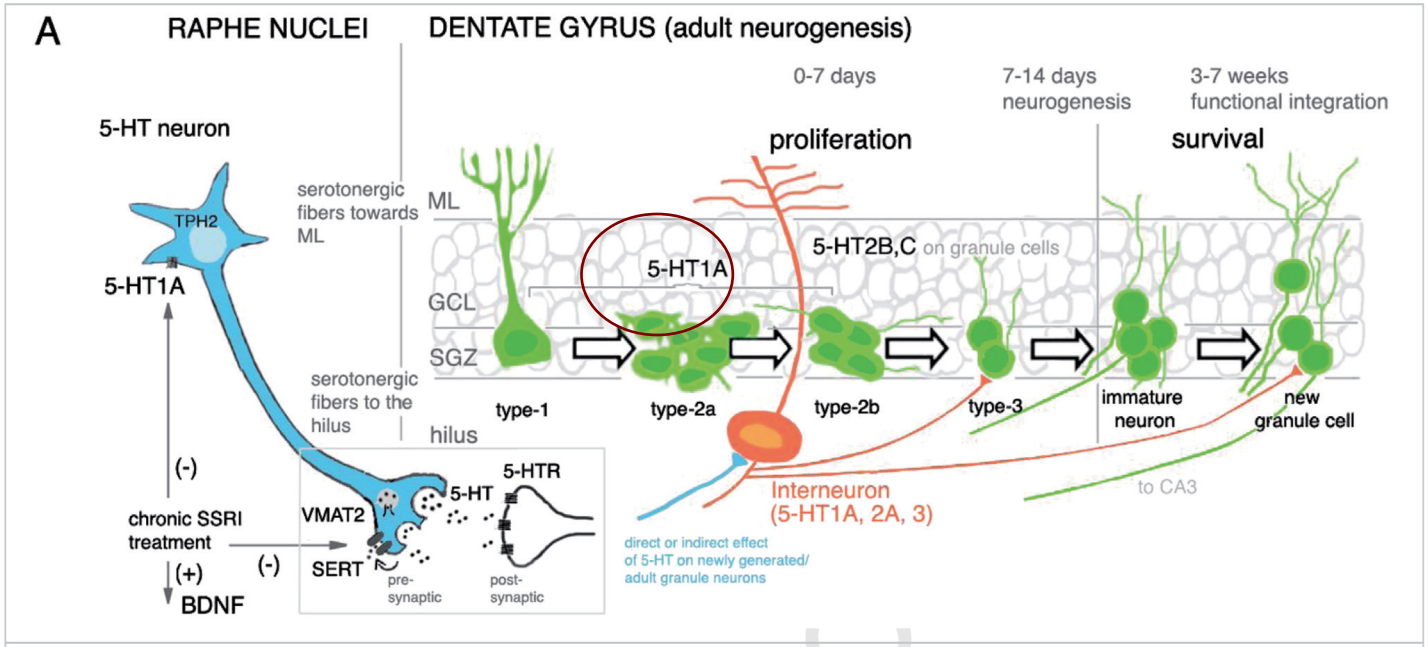
Boldrini et al., Neuropsychopharmacology 1-14, 2009





Isto envolveria serotonina?

Serotonina regula a neurogênese



B

Pharmacological manipulation	*Drug effect*	type-1	type-2a/2b	type-3	net neurogenesis	BDNF
5,7-DHT	Lesion of 5-HT neurons	n/a	–	– / 0	– / 0	
PCPA	Inhibition of 5-HT synthesis	–	–	–	– / +	
5-HT1A (postsynaptic)	Stimulation Blockage	n/a –	++ –	+ –	+ –	
5-HT1B	Stimulation	n/a	+	n/a	n/a	
5-HT2A	Stimulation Blockage	n/a	– +	n/a 0	– 0	↓
5-HT2B	Stimulation Blockage	Induces antidepressant-like response Decreases 5-HT levels				
5-HT2C	Stimulation Blockage	– n/a	– / 0 +	+ 0	++ 0	↓ ↑
5-HT4	Stimulation	n/a	n/a	+	+	
SSRI-Flx[1]	Increases extra-cellular 5-HT levels	No effect	++	+	++	↑
Animal models	*Phenotype*					
5-HT1A KO		0	0	n/a	n/a	
Tph2$^{-/-}$	No serotonin	0	Increased Sox2	0	0	↑
VMAT2$^{SERT\text{-}Cre}$	Reduced 5-HT levels	0	0	0	++	
Tph2KI	Reduced 5-HT levels	n/a	0	+	++	↑
Pet1$^{-/-}$	Reduced 5-HT levels	n/a	0	n/a	++	
SERT$^{-/-}$	Increased extra-cellular 5-HT levels	n/a	+	+	n/a	

[1]

The role of serotonin in adult hippocampal neurogenesis
Natalia Alenina, Friederike Klempin*

Behav Brain Res 2014

The Neuroscientist
1–20

DOI: 10.1177/1073858414561303
nro.sagepub.com
SAGE

Serotonin 1A and Serotonin 4 Receptors: Essential Mediators of the Neurogenic and Behavioral Actions of Antidepressants

Benjamin Adam Samuels[1], Indira Mendez-David[2], Charlène Faye[2], Sylvain André David, Kerri A. Pierz, Alain M. Gardier[2], René Hen[1], and Denis J. David[2]

Serotonina (via 5HT1A e 5HT4) facilitam a neurogênese na região subgranular do giro denteado da formação hipocampal

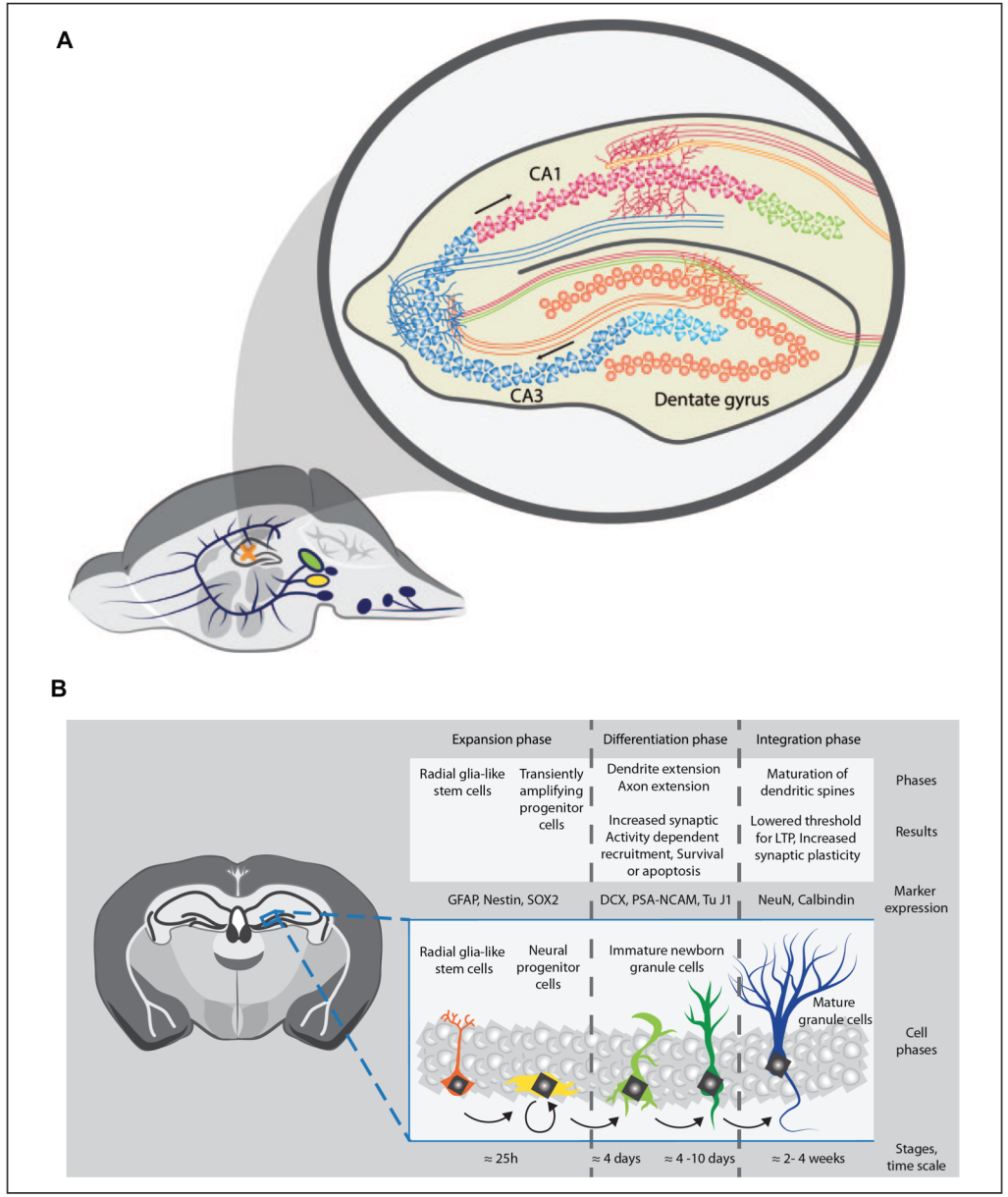


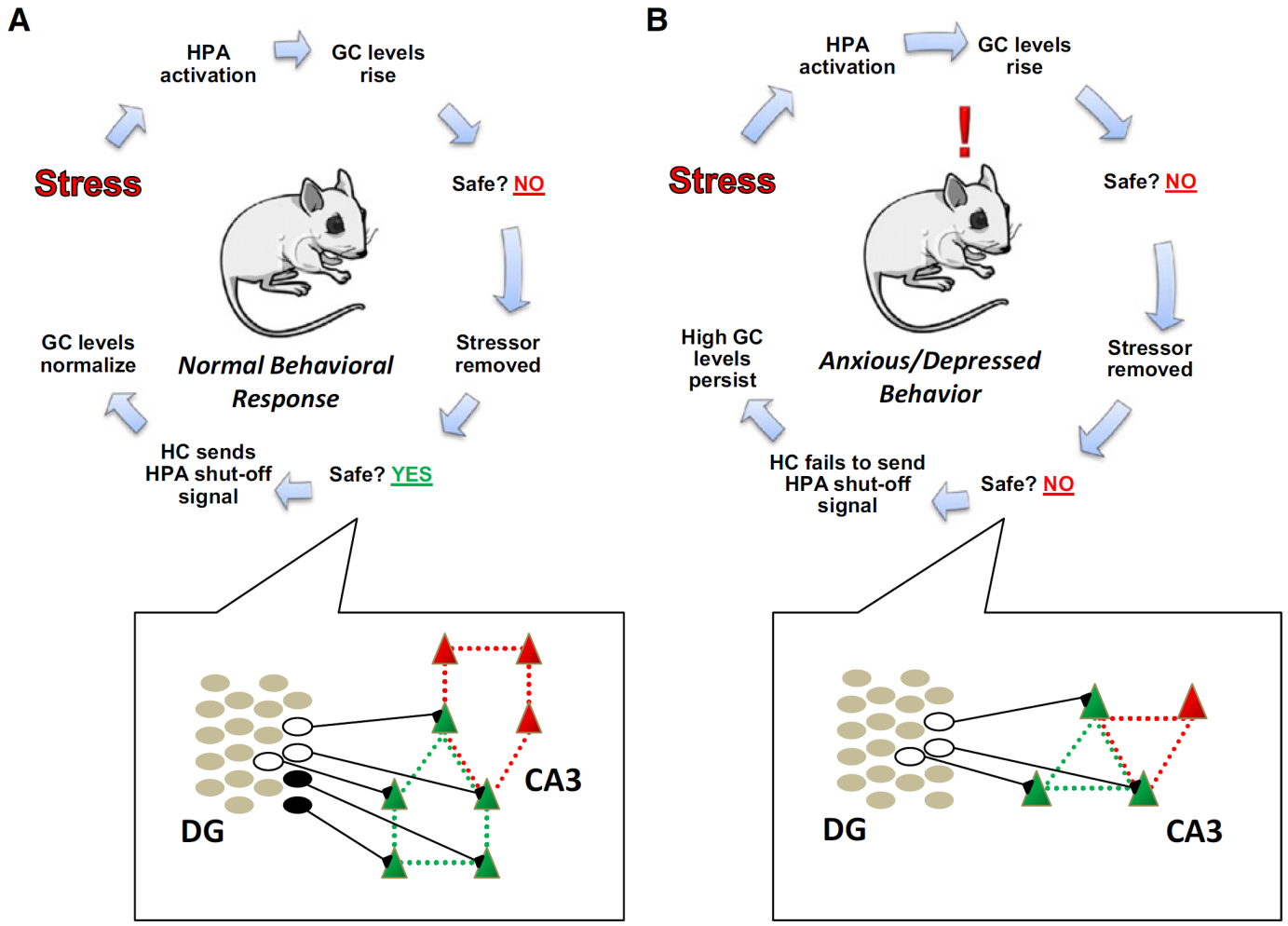
Figure 4. Production of new neurons in the adult dentate gyrus. (A) The hippocampal trisynaptic circuit in mouse brain. Neurons of the enthorinal cortex project to the dentate gyrus, with additional collaterals projecting to the CA3 subfield (perforant pathway). Granule cells in the dentate gyrus project to the CA3 field of the hippocampus via the mossy fiber pathway. The CA3 pyramidal cells project onto themselves and also to the CA1 through Schaffer collaterals. (B) Hippocampal neurogenesis is possible in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus because of the presence of stem cells. These stem cells evolve into neural progenitor cells that can produce multiple cell types in the central nervous system such as neurons, astrocytes, oligodendrocytes, or microglial cells. In rodents, the duration of the mitotic cycle of proliferating precursors is approximately 12 to 24 hours, leading to the production of about 8,000 to 10,000 new neurons per day.

Como relacionar neurogênese hipocampal com depressão e ansiedade?

Depression and Hippocampal Neurogenesis: A Road to Remission?

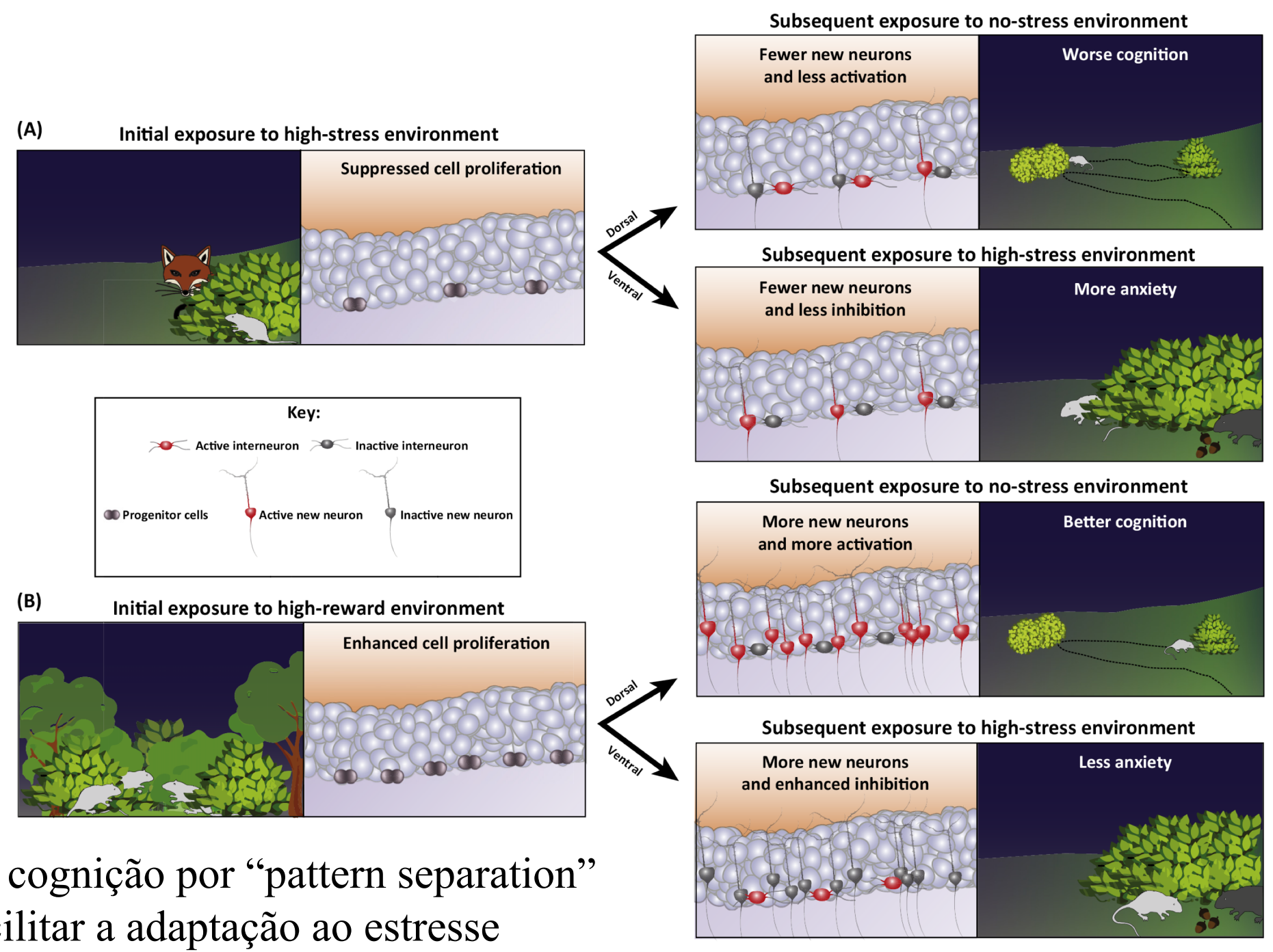
Amelia J. Eisch* and David Petrik

Science 2014



Key: Inactive DG cell | Active mature DG cell | Active immature DG cell | Green CA3 representation of "safe" | Red CA3 representation of "danger"

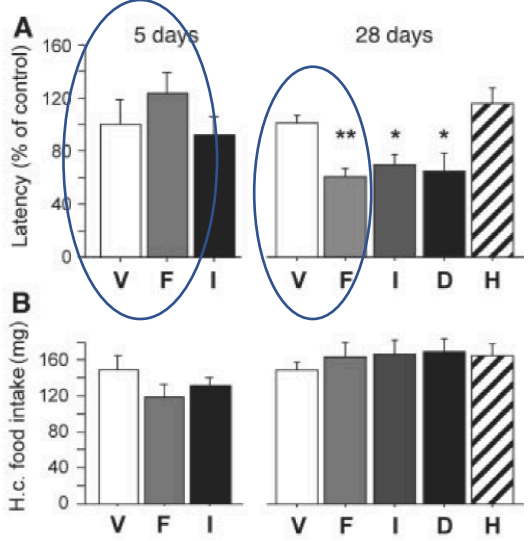
Neurogênese hipocampal parece ser importante para a "separação de padrões" (pattern separation), necessária para a discriminação de estímulos semelhantes, porém não iguais



Melhora da cognição por “pattern separation” poderia facilitar a adaptação ao estresse

TRENDS in Cognitive Sciences

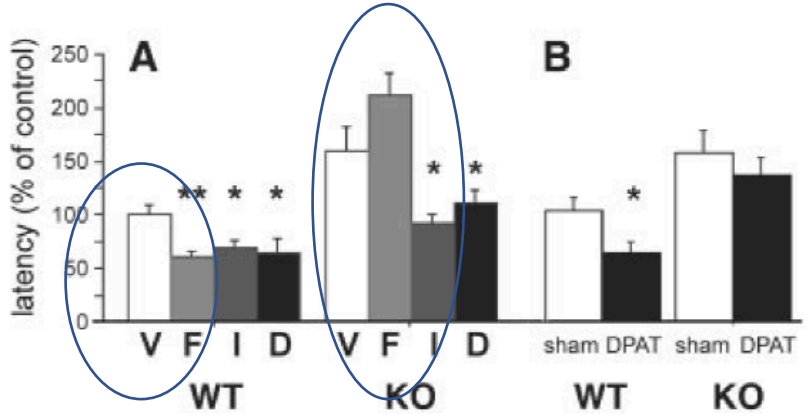
Poderia o aumento de neurogênese induzida por antidepressivos administrados cronicamente explicar a latência do seus efeitos sobre ansiedade e depressão?



Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants

Luca Santarelli,[1]* Michael Saxe,[1]* Cornelius Gross,[1]
Alexandre Surget,[2] Fortunato Battaglia,[3] Stephanie Dulawa,[1]
Noelia Weisstaub,[1] James Lee,[1] Ronald Duman,[4]
Ottavio Arancio,[3] Catherine Belzung,[2] René Hen[1]†

Science 2003



Evidências correlacionais!

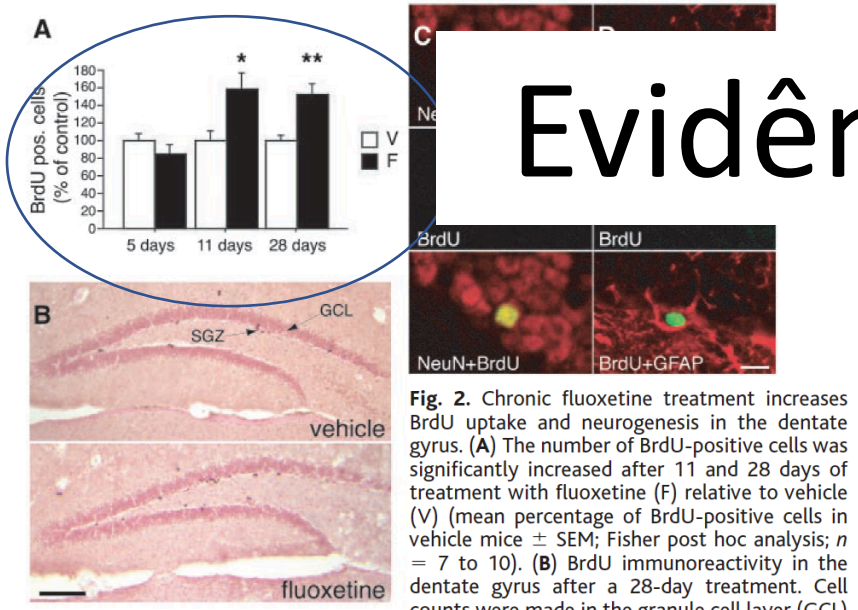
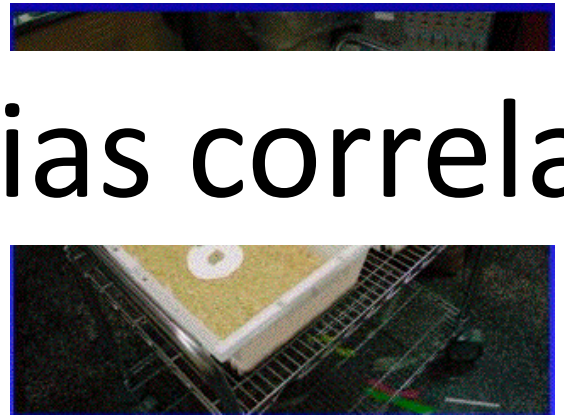
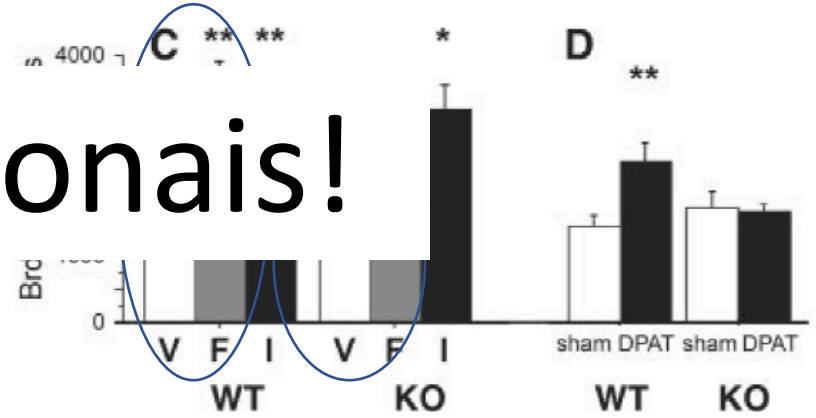


Fig. 2. Chronic fluoxetine treatment increases BrdU uptake and neurogenesis in the dentate gyrus. (**A**) The number of BrdU-positive cells was significantly increased after 11 and 28 days of treatment with fluoxetine (F) relative to vehicle (V) (mean percentage of BrdU-positive cells in vehicle mice ± SEM; Fisher post hoc analysis; n = 7 to 10). (**B**) BrdU immunoreactivity in the dentate gyrus after a 28-day treatment. Cell counts were made in the granule cell layer (GCL) and in the SGZ. Scale bar, 200 μm. (**C** and **D**) Confocal micrographs of cells double-labeled for BrdU (green) and NeuN or GFAP (red). Scale bar, 10 μm.

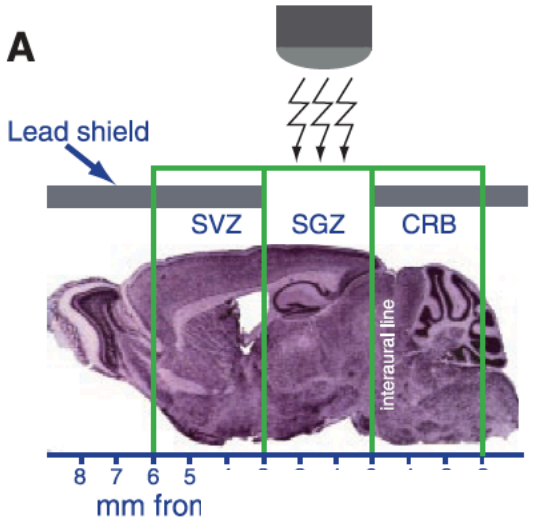


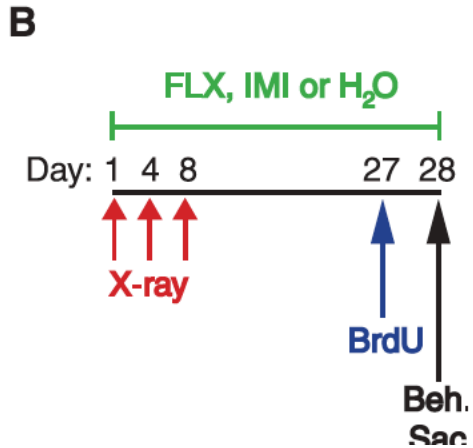
Teste da supressão da alimentação pela novidade



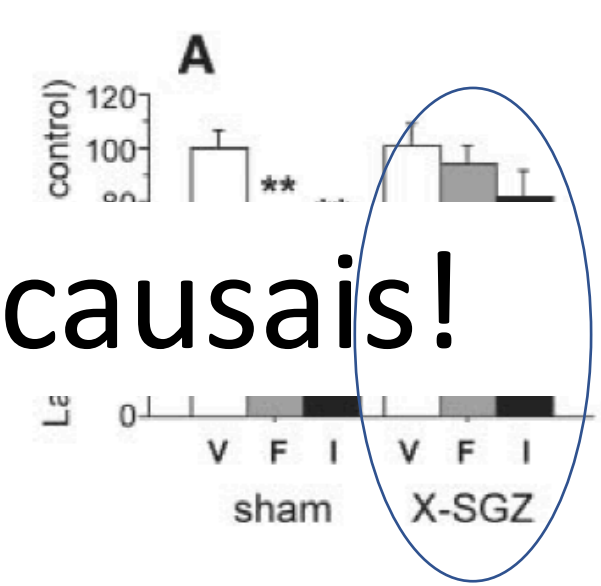
Fluoxetina **não apresentou** efeito ansiolítico ou aumentou a neurogênese em Knockout 5HT1A

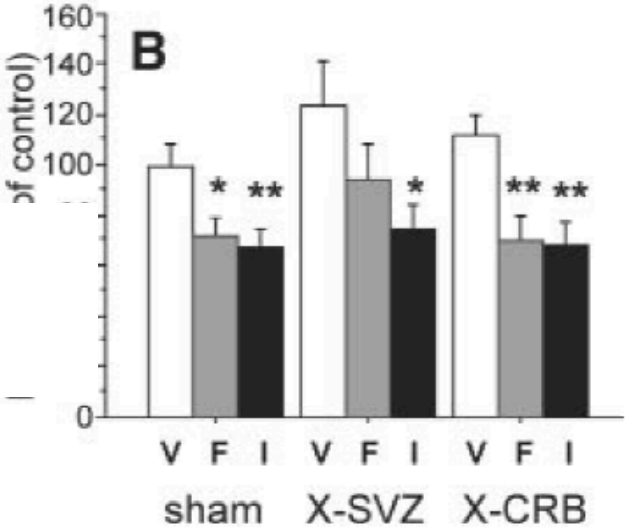
Fluoxetina crônica por 28 dias (mas não 5 dias) apresenta efeito ansiolítico e aumenta a neurogênese

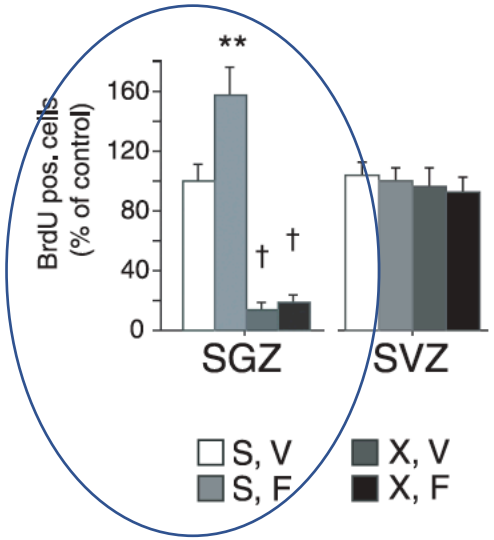


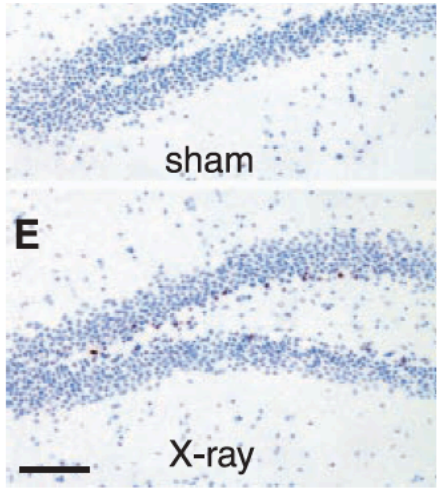


Evidências causais!



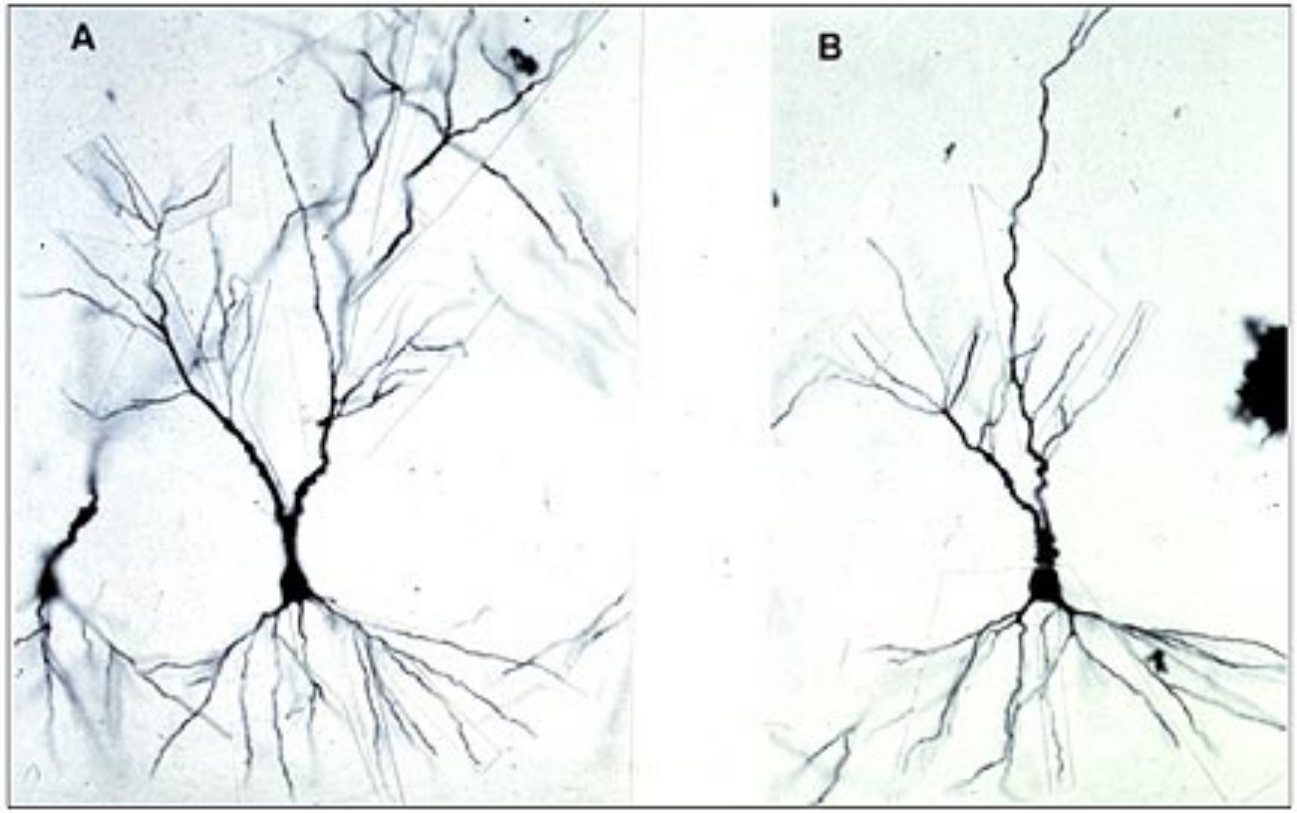






Inibição da neurogênese hipocampal adulta no giro denteado impediu o efeito ansiolítico/antidepressivo da fluoxetina

A interferência no remodelamento neuronial no hipocampo e córtex préfrontal também poderia ser outro fator importante



Controle

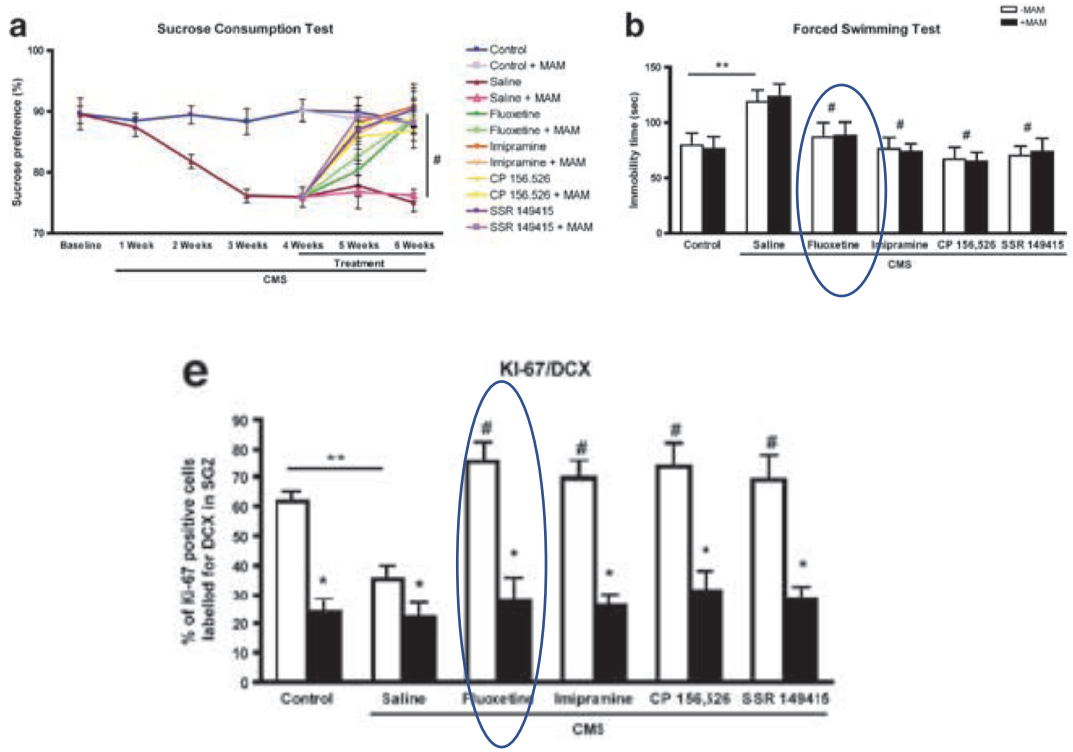
Estressado

McEwen BS et al

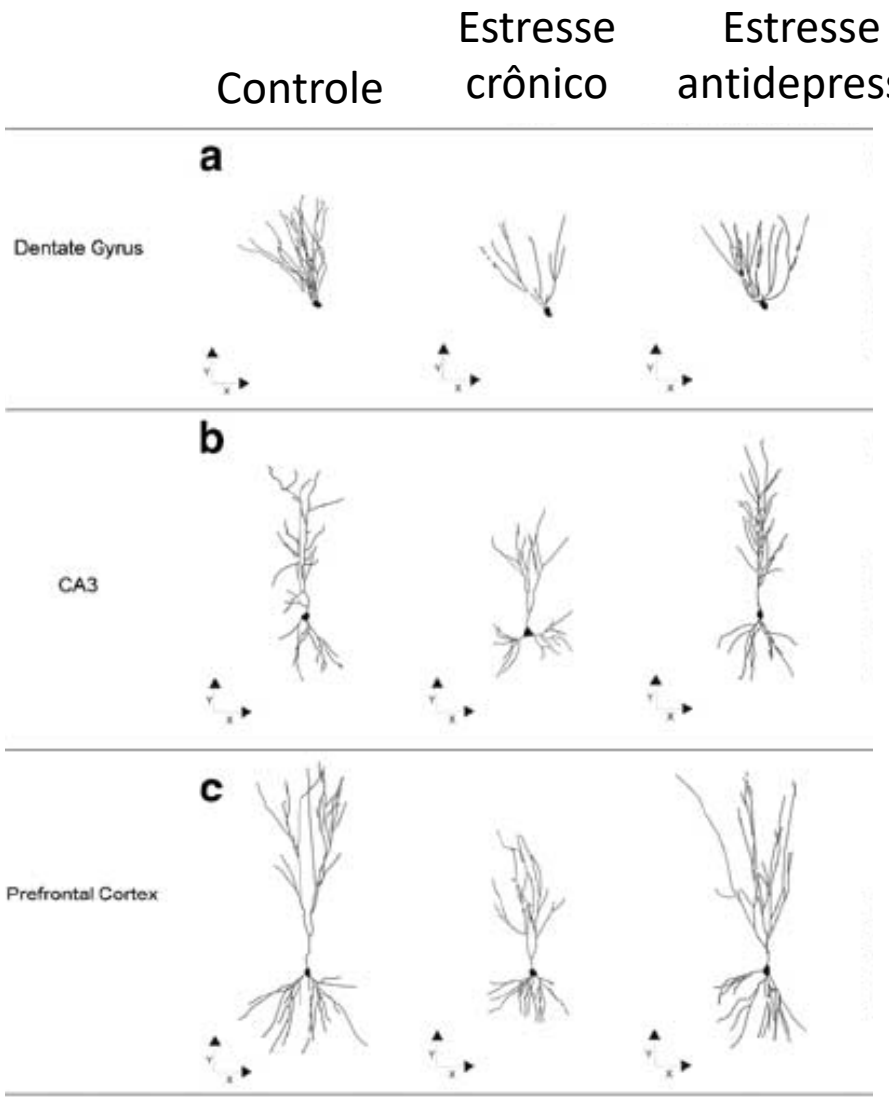
The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling

Molecular Psych 2009

JM Bessa[1], D Ferreira[1], I Melo[1], F Marques[1], JJ Cerqueira[1], JA Palha[1], OFX Almeida[2] and N Sousa[1]



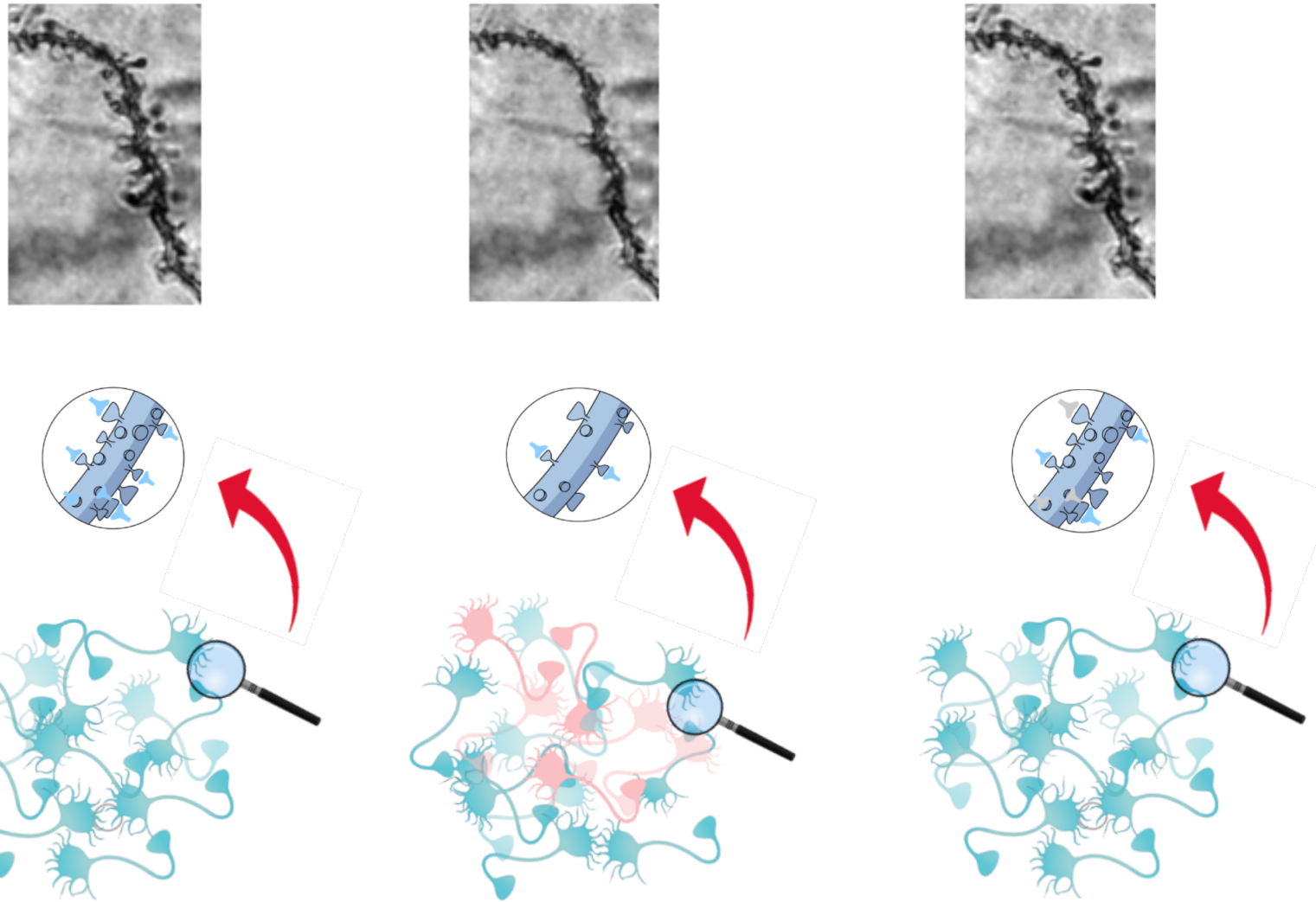
Inibição da neurogênese por metilazoximetanol (MAM) não impede efeito de antidepressivos no modelo de <u>estresse crônico (CMS)</u>



Antidepressivos revertem remodelamento neuronial no hipocampo e córtex préfrontal induzido por estresse crônico imprevisível

Estresse **diminui a arborização e o número de espinhas dendríticas** no hipocampo e córtex pré-frontal

Efeito é revertido por antidepressivos administrados cronicamente

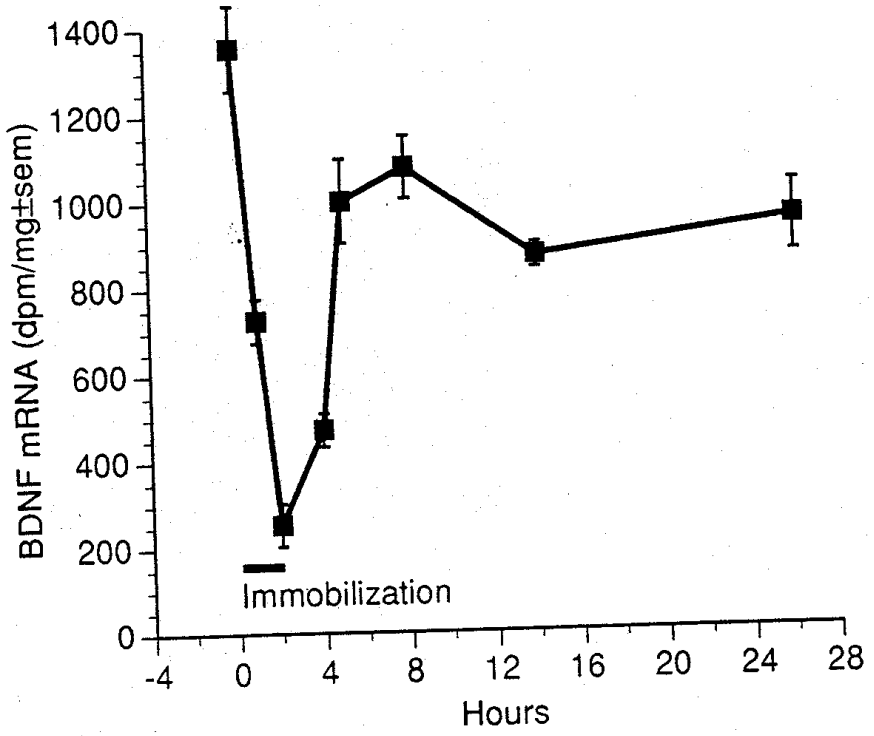


Normal

Estresse crônico/ Depressão

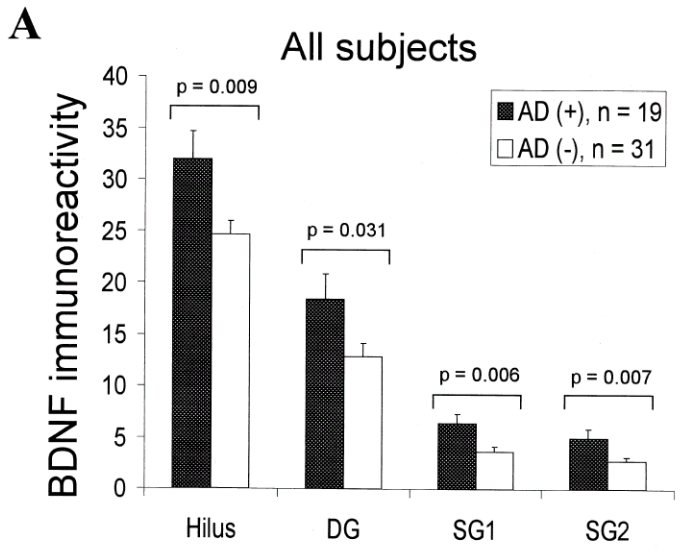
Após antidepressivo

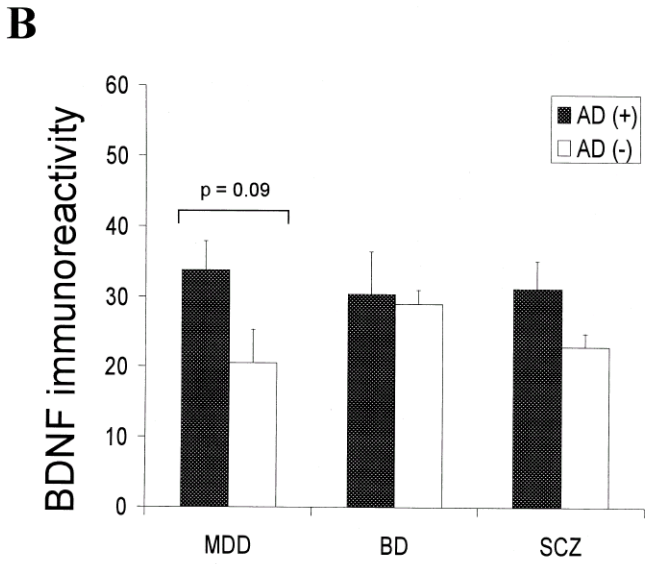
Como o estresse diminui neurogênese e arborização dendrítica?



Estresse diminui a expressão da neurotrofina BDNF no hipocampo

Smith et al., Ann NY Acad Sc, 1995; Chen et al., Biol Psychiatry 50:260-265, 2001





BDNF hipocampal aumenta com antidepressivos

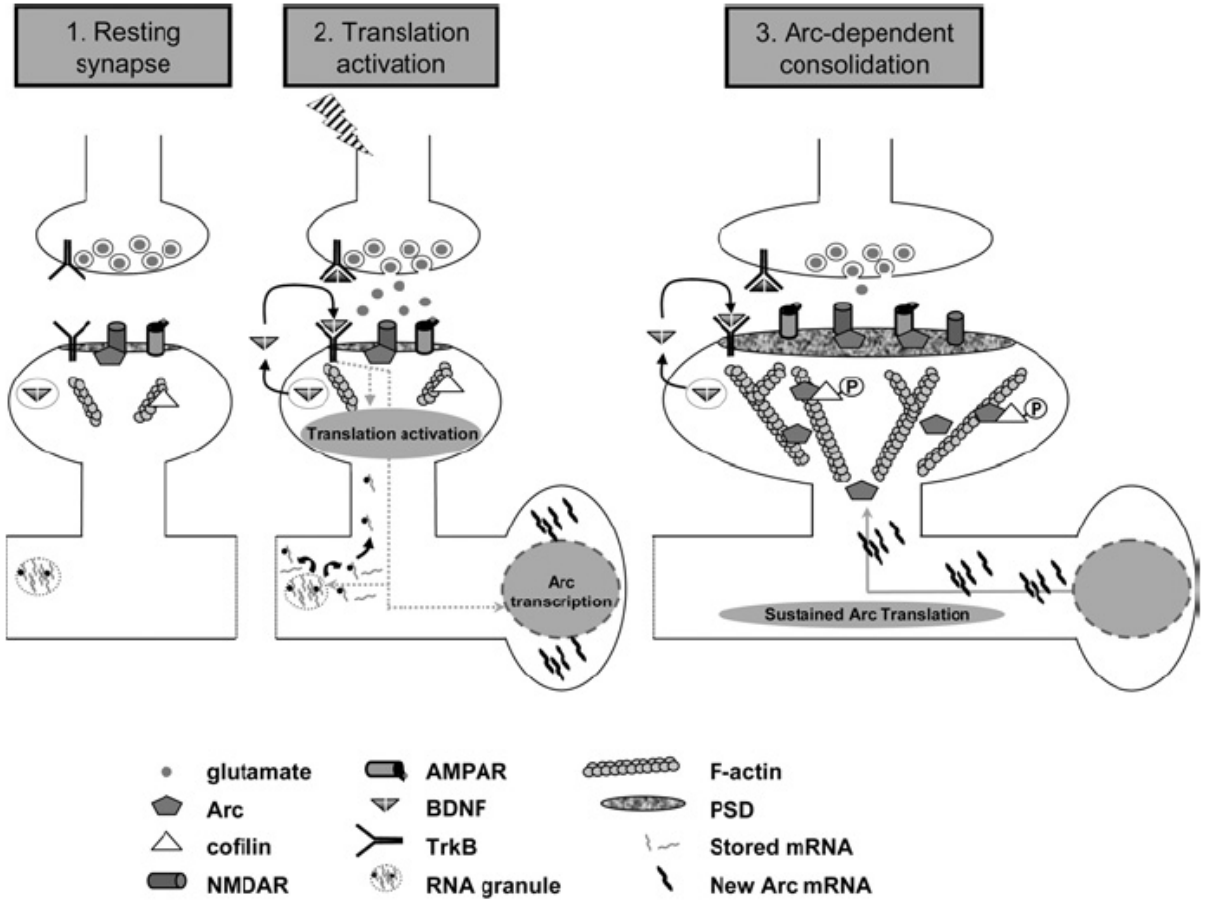
Para que servem as neurotrofinas?

Rita Levi-Montalcini
Descoberta do nerve growth fator (NGF), primeira neurotrofina

Brain-derived neurotrophic factor and control of synaptic consolidation in the adult brain

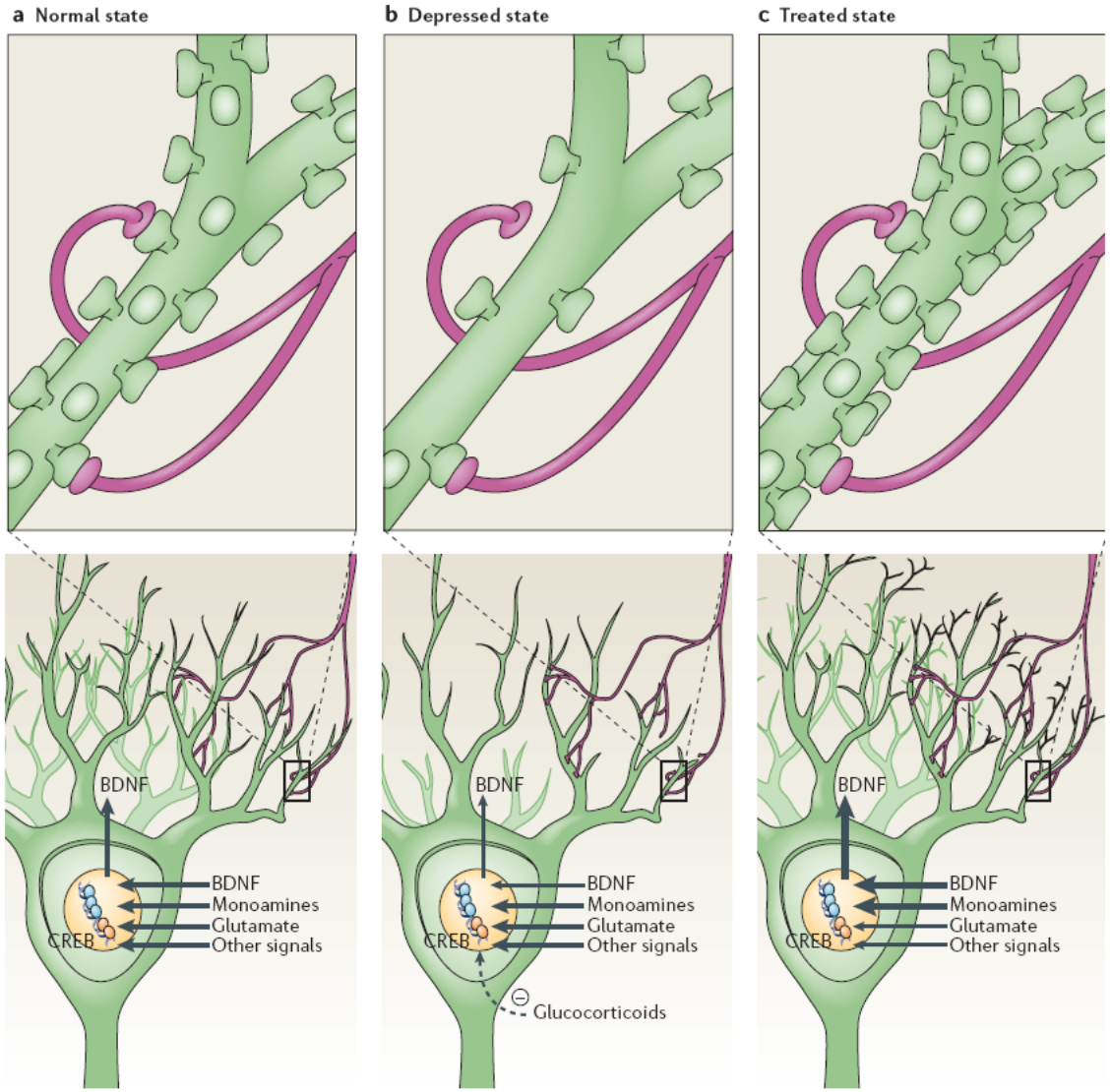
2006

J. Soulé, E. Messaoudi and C.R. Bramham[1]



Neurotrofinas servem para <u>otimização</u> de contatos sinápticos <u>dependente de atividade</u>

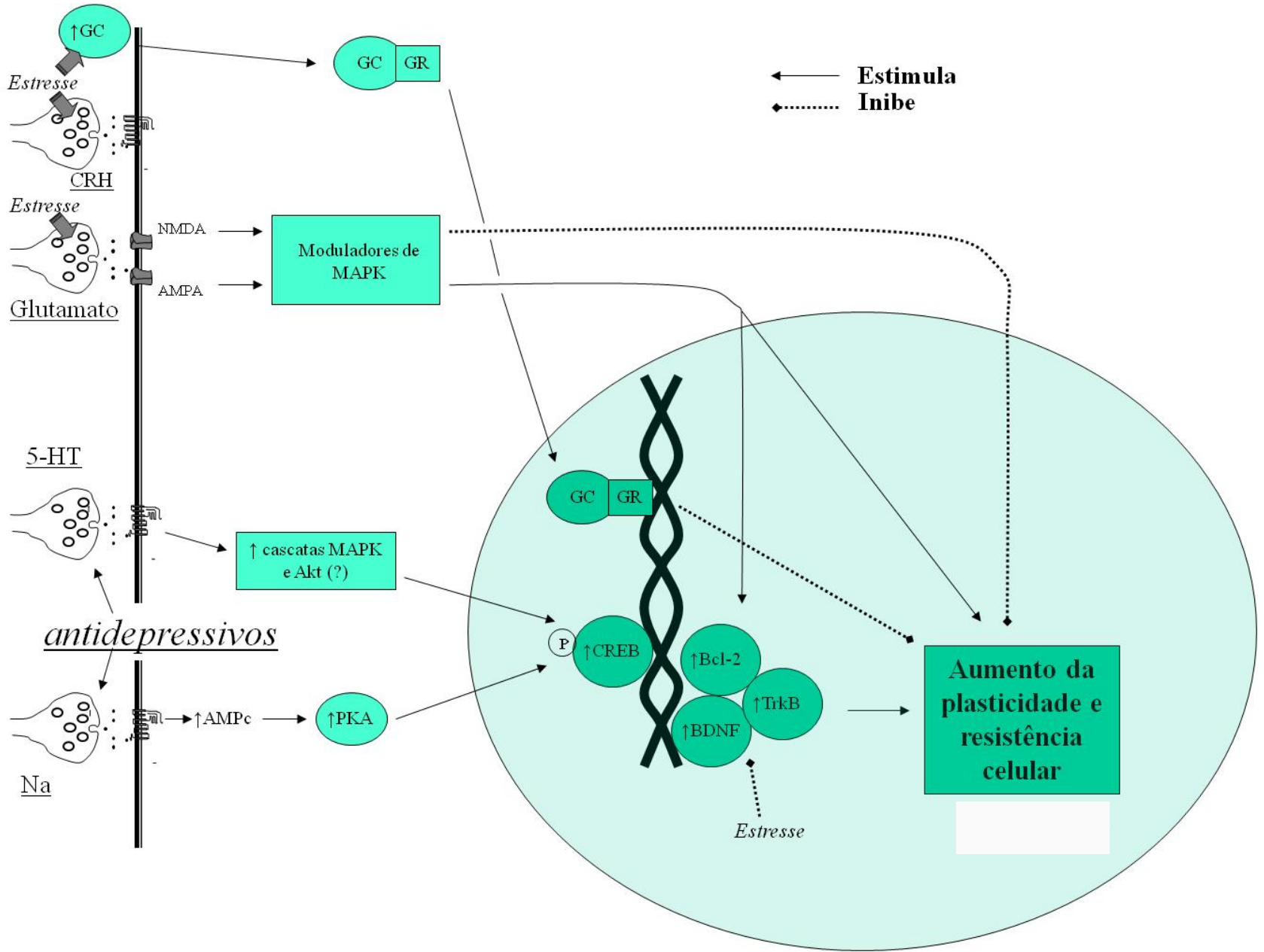
Exposição a estressores diminui fatores neurotróficos como o BDNF (fator neurotrófico derivado do cérebro) e causa remodelamento dendrítico (e facilita e neurogênese)



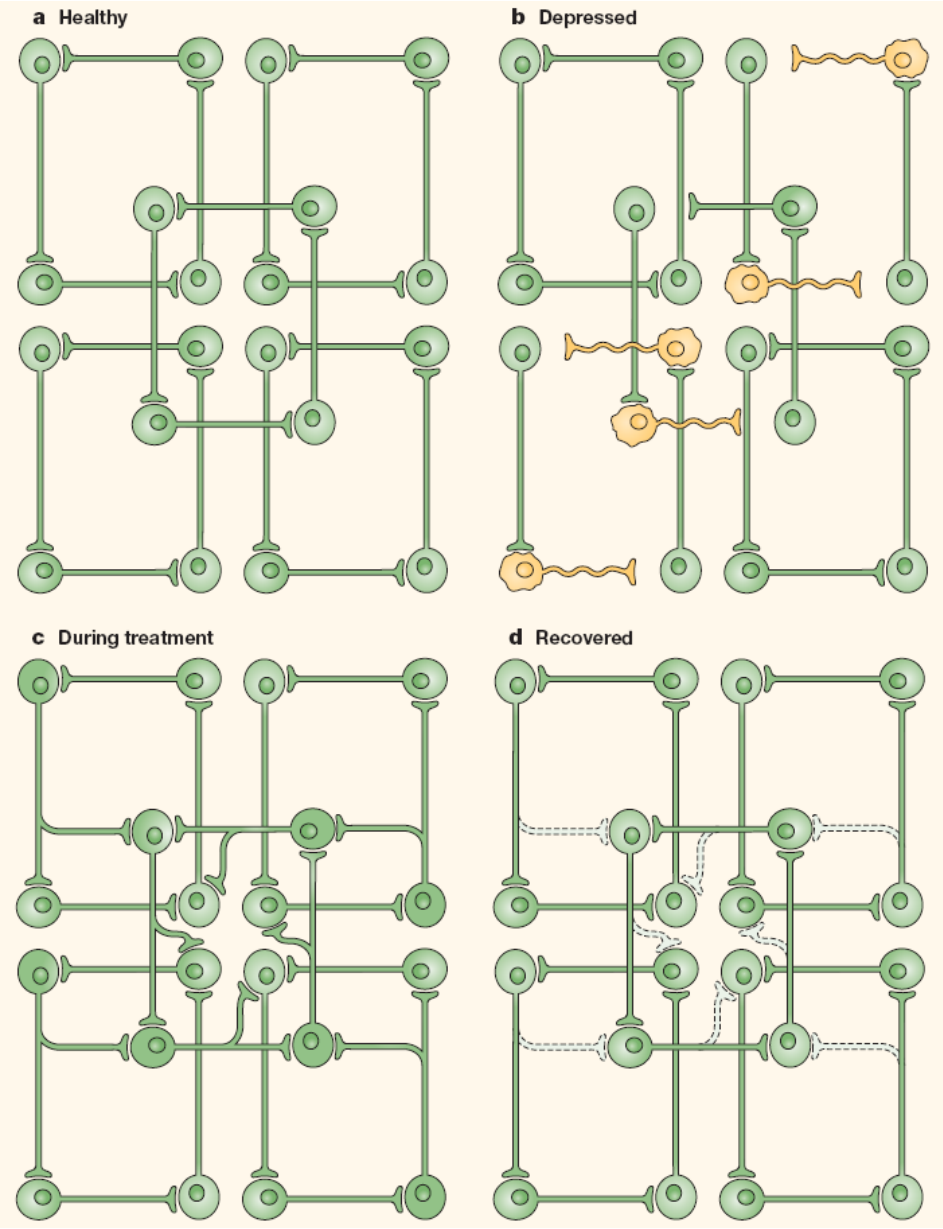
Berton e Nestler, Nature Rev 2006

Como o estresse influencia a plasticidade sináptica?

Envolvimento de glicocortiócides e glutamato (via receptores NMDA)



A hipótese neuroplástica ou de “redes neurais” da depressão



Antidepressivos não aumentariam o humor diretamente, mas teriam efeito permissivo

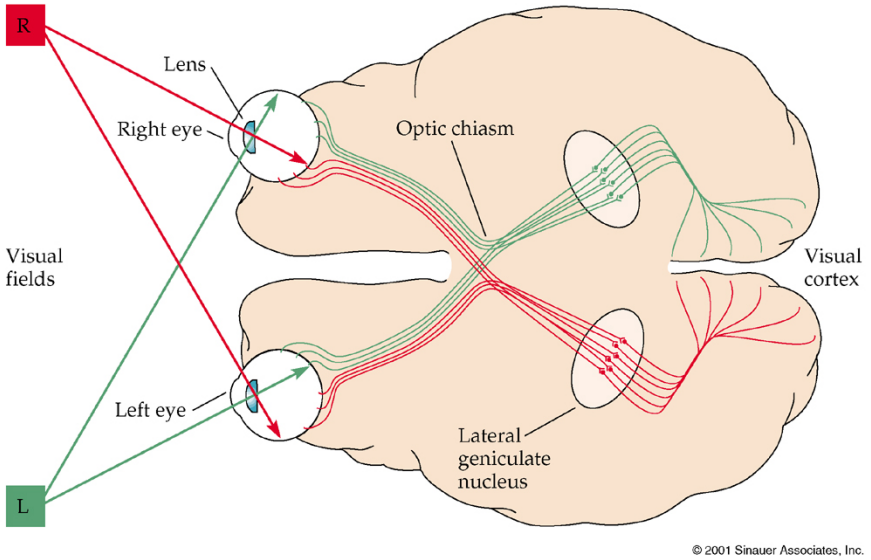
Castren 2007

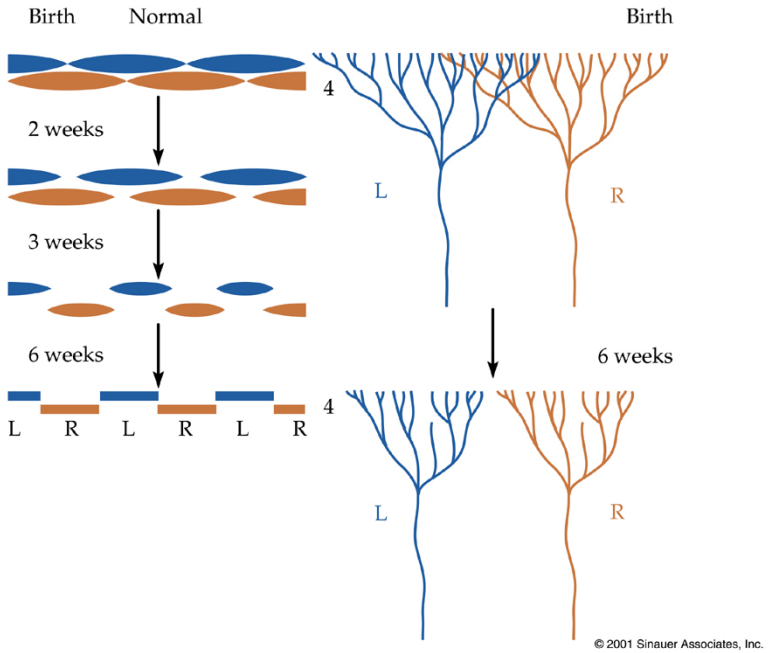
Teste desta hipótese no córtex visual

The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex

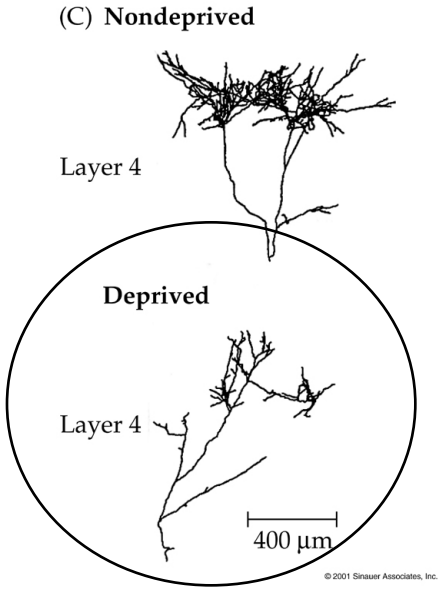
José Fernando Maya Vetencourt,[1]* Alessandro Sale,[1] Alessandro Viegi,[1] Laura Baroncelli,[1] Roberto De Pasquale,[1] Olivia F. O'Leary,[3] Eero Castrén,[3] Lamberto Maffei[1,2]

SCIENCE VOL 320 18 APRIL 2008

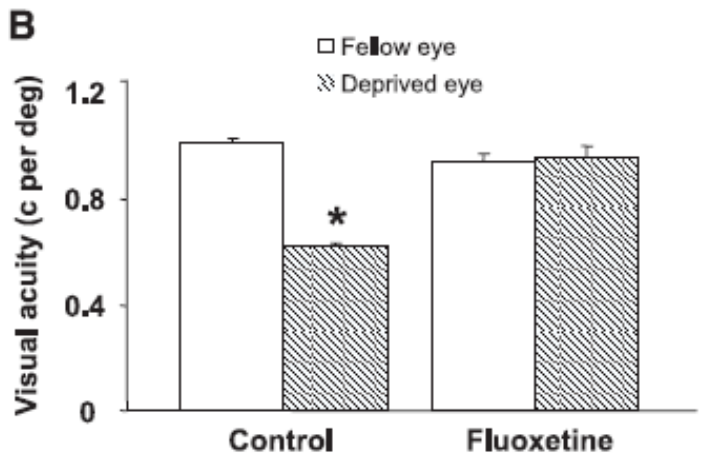


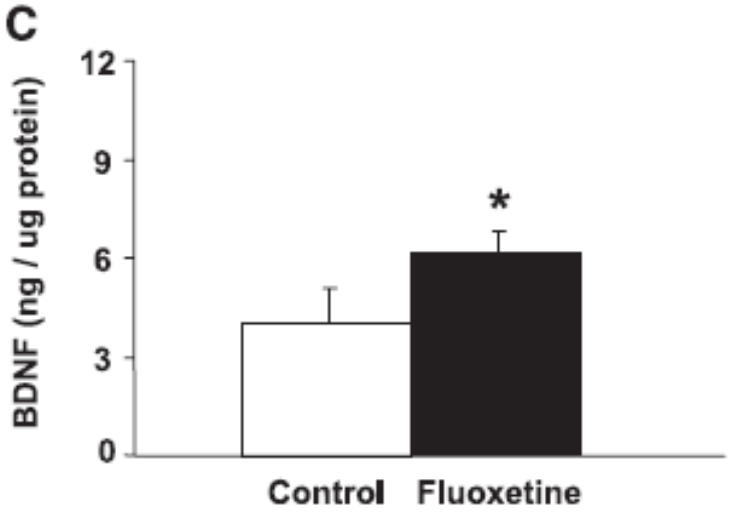


Desenvolvimento normal da visão necessita de estimulação visual em período crítico de desenvolvimento



Oclusão ocular durante período crítico de desenvolvimento pós-natal (termina no dia P55) prejudica arborização de neurônios de projeção do corpo geniculado ao córtex visual e leva à ambliopia





Tratamento por 2 semanas com fluoxetina em rato adulto (P100) restaura acuidade visual no olho ocluído durante o período crítico e aumenta BDNF no córtex visual

Consequências dessa hipótese:

Antidepressivos aumentariam BDNF e com isso favoreceriam plasticidade sináptica.

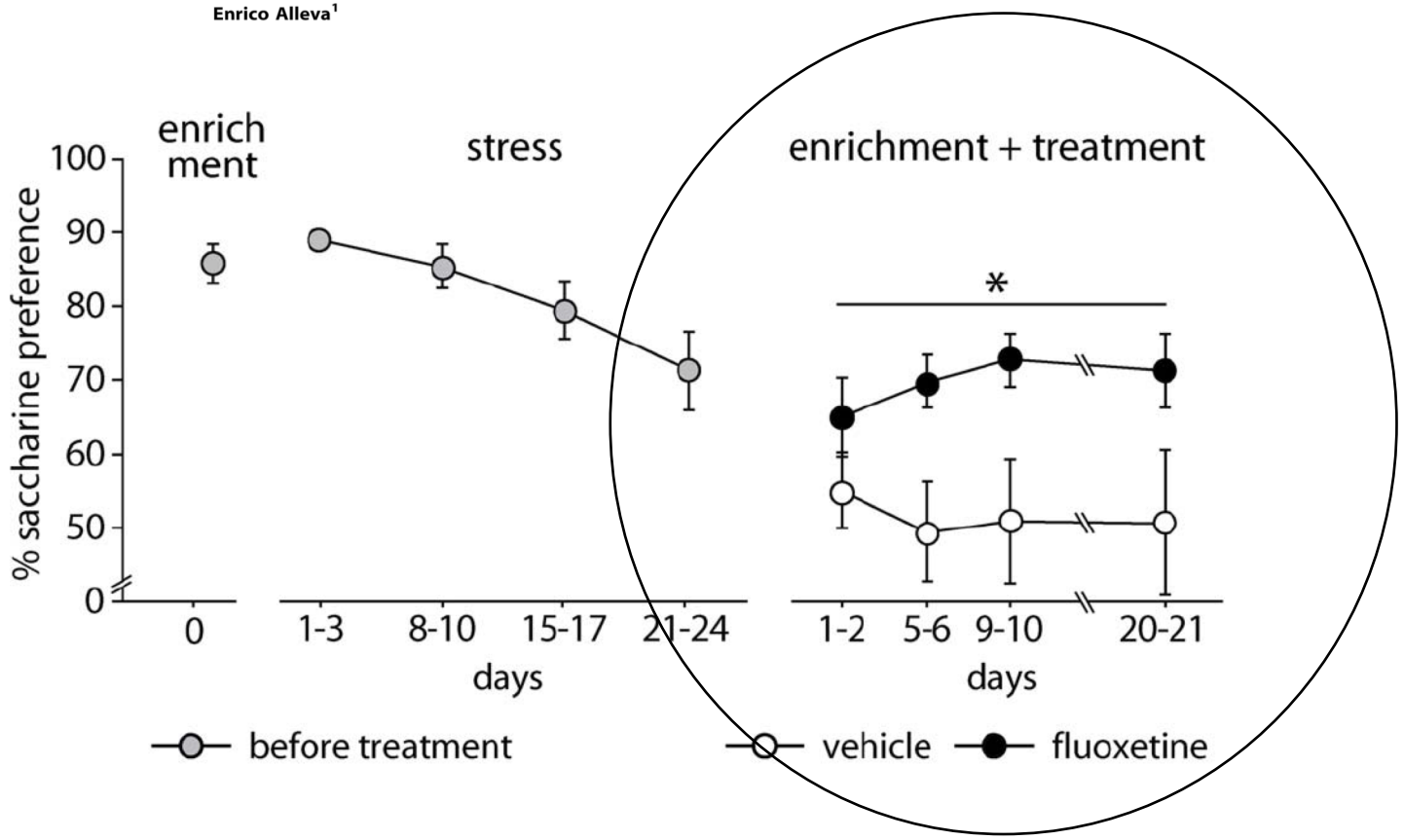
BDNF, no entanto, depende de atividade sináptica para favorecer plasticidade

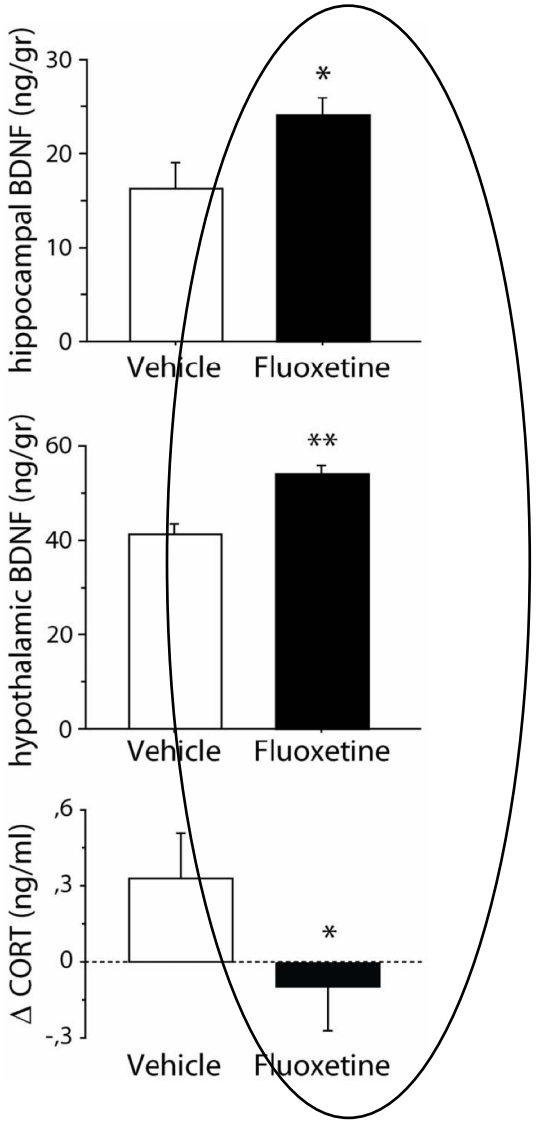
Antidepressivos teriam efeito permissivo, favorecendo a neuroplasticidade e permitindo ao meio ambiente reorganizar a rede neural alterada (importância da psicoterapia)

OPEN ACCESS Freely available online PLOS ONE

Antidepressant Treatment Outcome Depends on the Quality of the Living Environment: A Pre-Clinical Investigation in Mice 2013

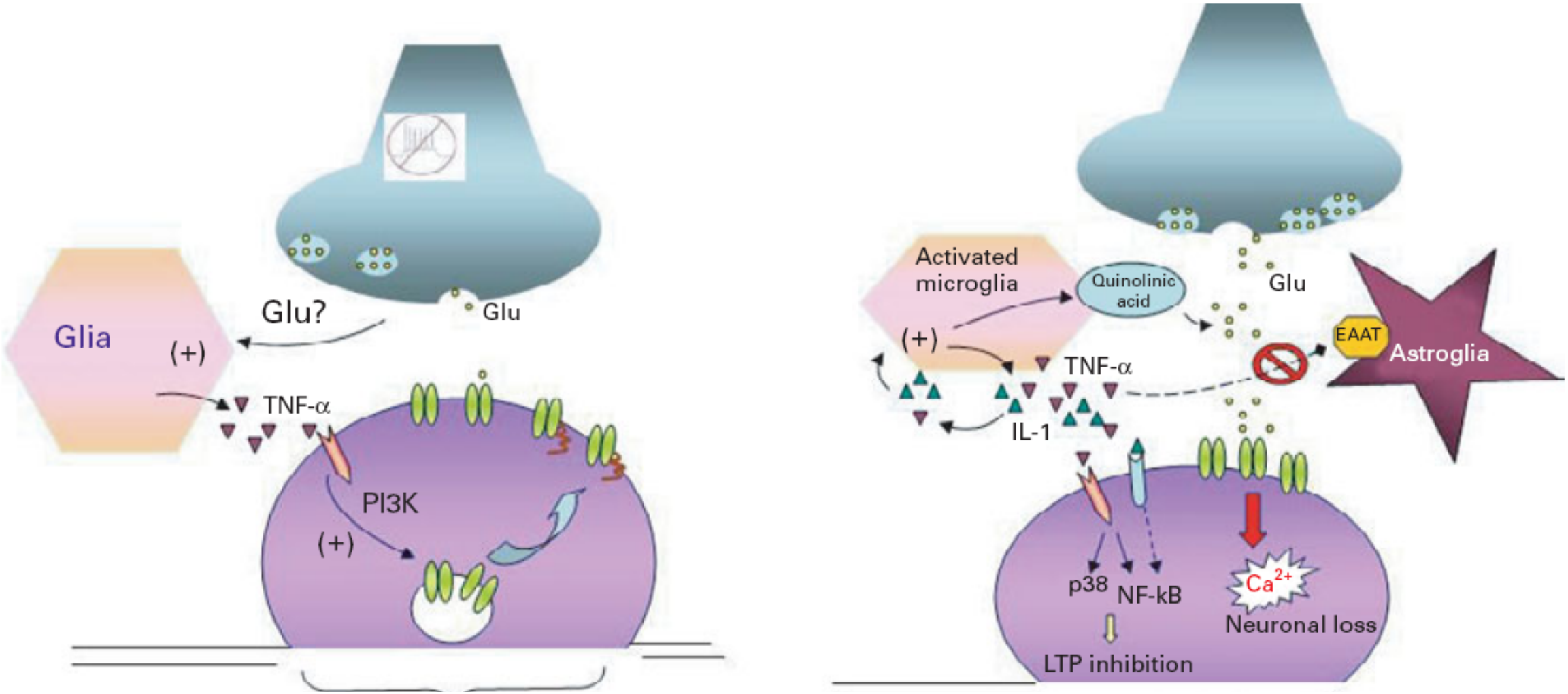
Igor Branchi[1,2*], Sara Santarelli[1], Sara Capoccia[1], Silvia Poggini[1], Ivana D'Andrea[3], Francesca Cirulli[1], Enrico Alleva[1]





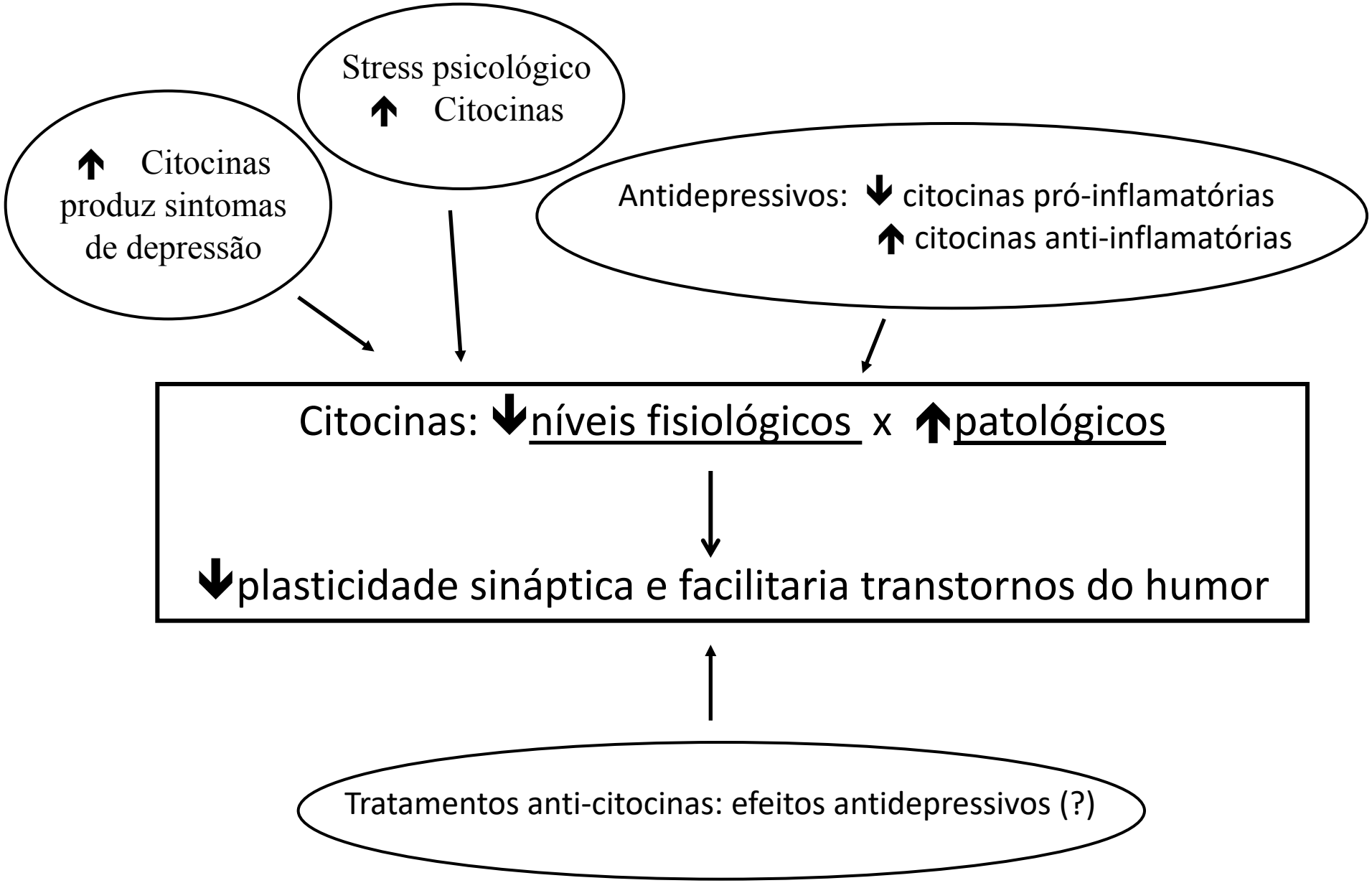
Fluoxetina (10mg/kg, 21 dias) após período de estresse repetido variável (24 dias) só funcionou quando administrada em ambiente enriquecido

Como o estresse afetaria a plasticidade neural: a Hipótese inflamatória da depressão



Como o estresse influencia a plasticidade sináptica?

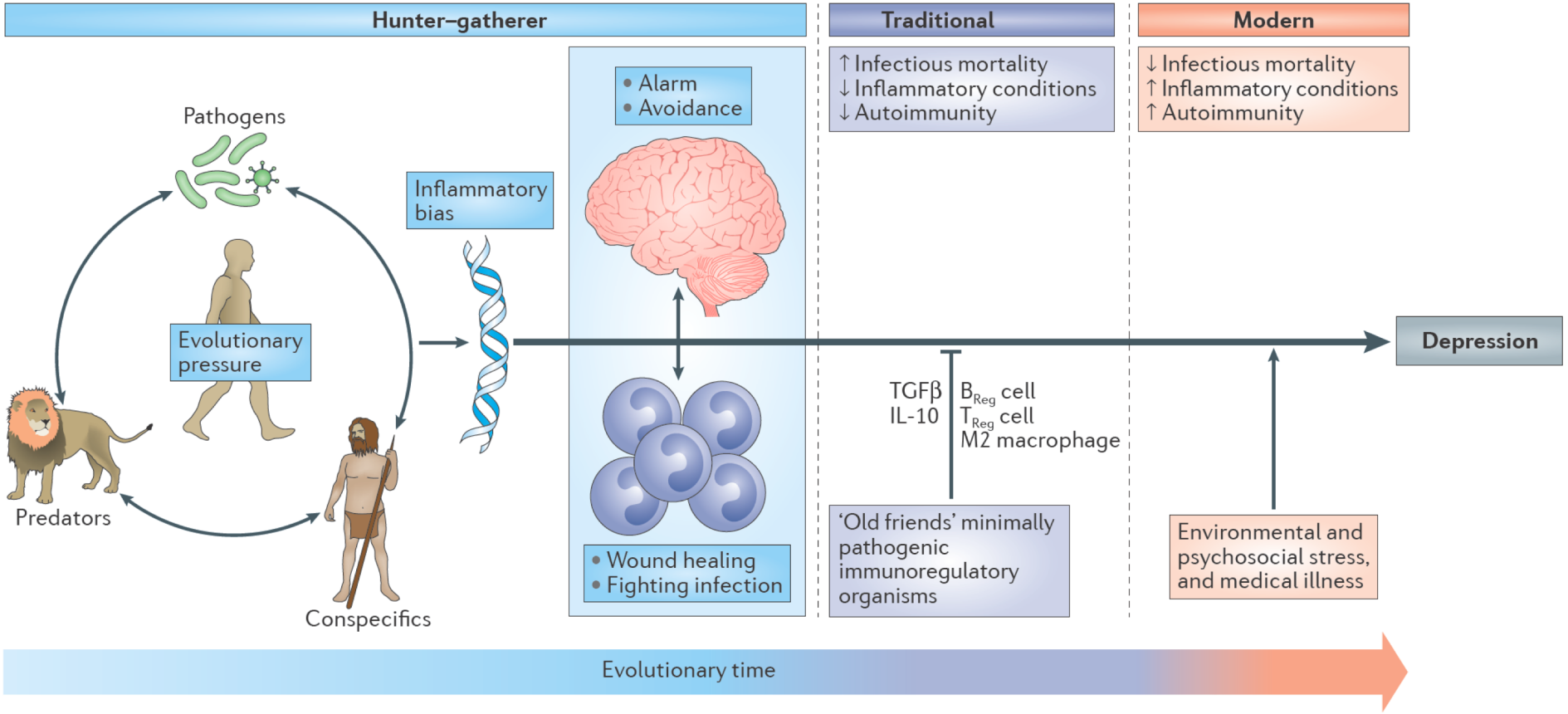
Hipótese inflamatória da depressão



Porquê o stress psicológico ativaria o sistema imune inato?

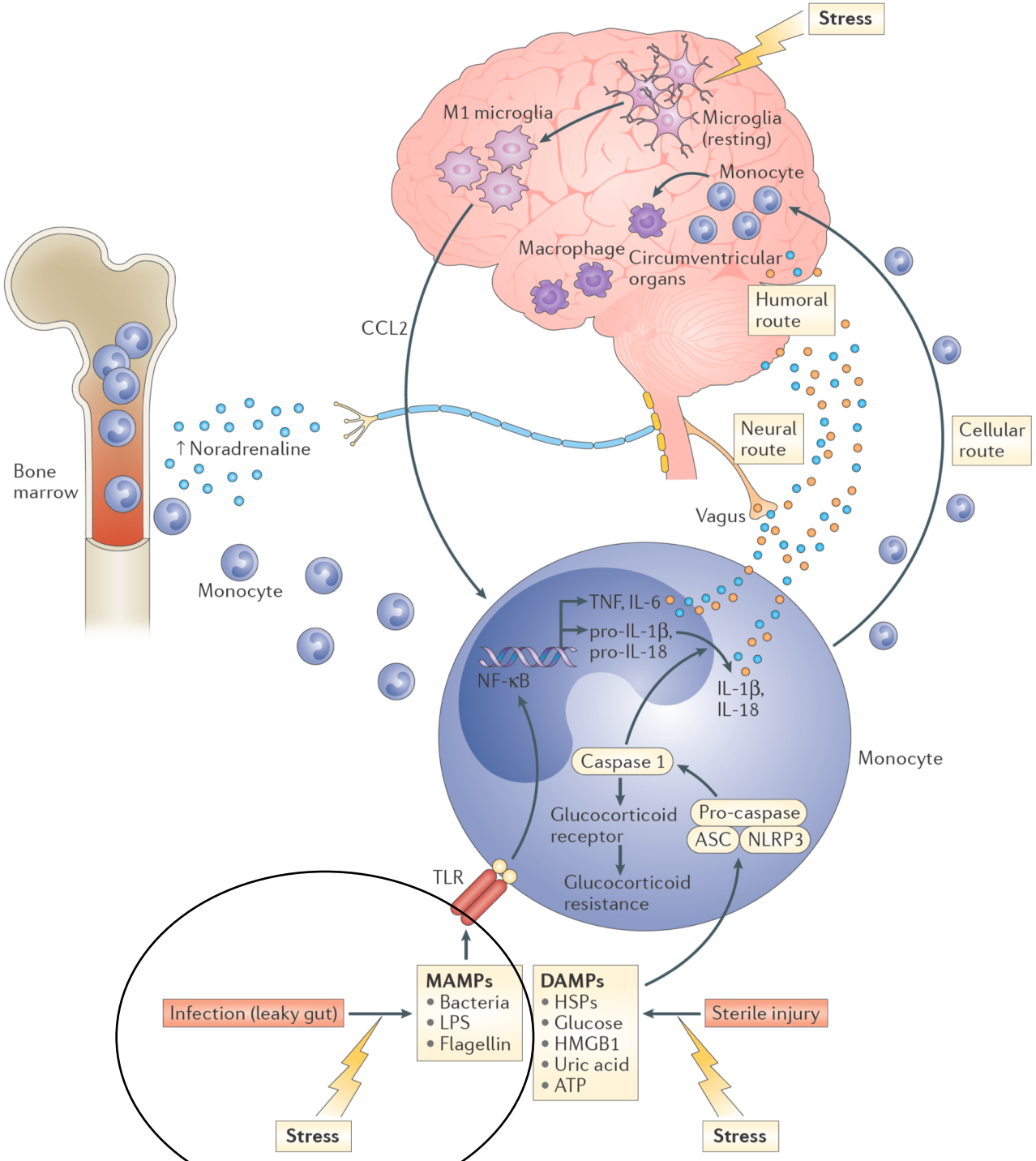
The role of inflammation in depression: from evolutionary imperative to modern treatment target Nature Rev 2016

Andrew H. Miller[1] and Charles L. Raison[2]



Evolutionary pressure to deal with pathogens, predators and conspecific threats result in an inflammatory bias (with immunological and behavioural responses) for fighting infection and healing wounds while preserving vigilance against attack

Como o stress psicológico ativaria o sistema imune?



The role of inflammation in depression: from evolutionary imperative to modern treatment target

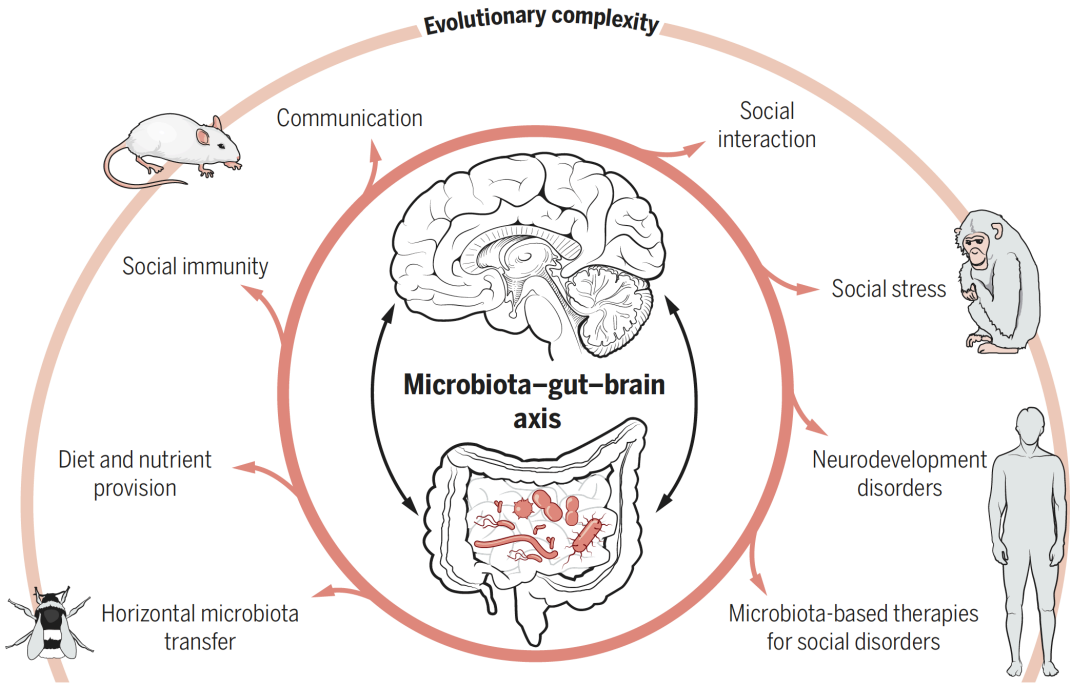
Andrew H. Miller[1] and Charles L. Raison[2]

Nature Rev 2016

Microbiota and the social brain

Science 2019

Eoin Sherwin. Seth R. Bordenstein. John L. Quinn. Timothy G. Dinan. John F. Cryan*



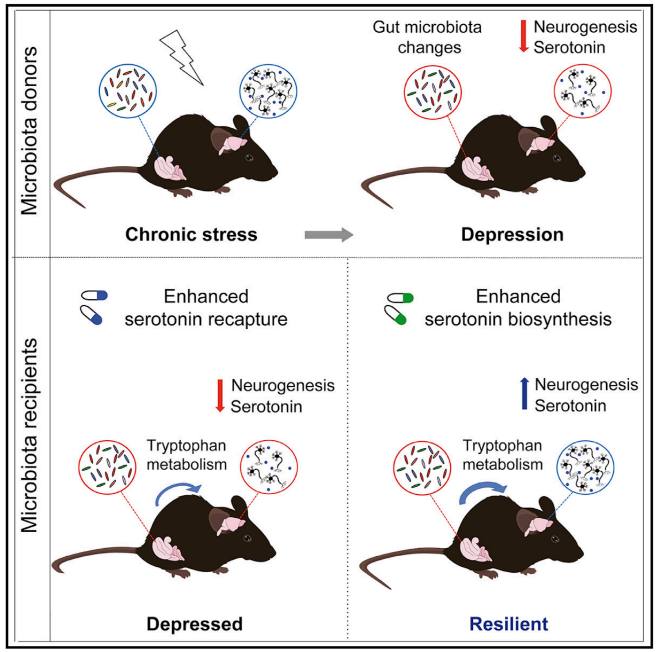
Cell Reports

Report

2020

Changes in Gut Microbiota by Chronic Stress Impair the Efficacy of Fluoxetine

Graphical Abstract



Authors

Eleni Siopi, Grégoire Chevalier, Lida Katsimpardi, ..., Carine Moigneu, Gérard Eberl, Pierre-Marie Lledo

Correspondence

eleni.siopi@inserm.fr (E.S.), pmlledo@pasteur.fr (P.-M.L.)

In Brief

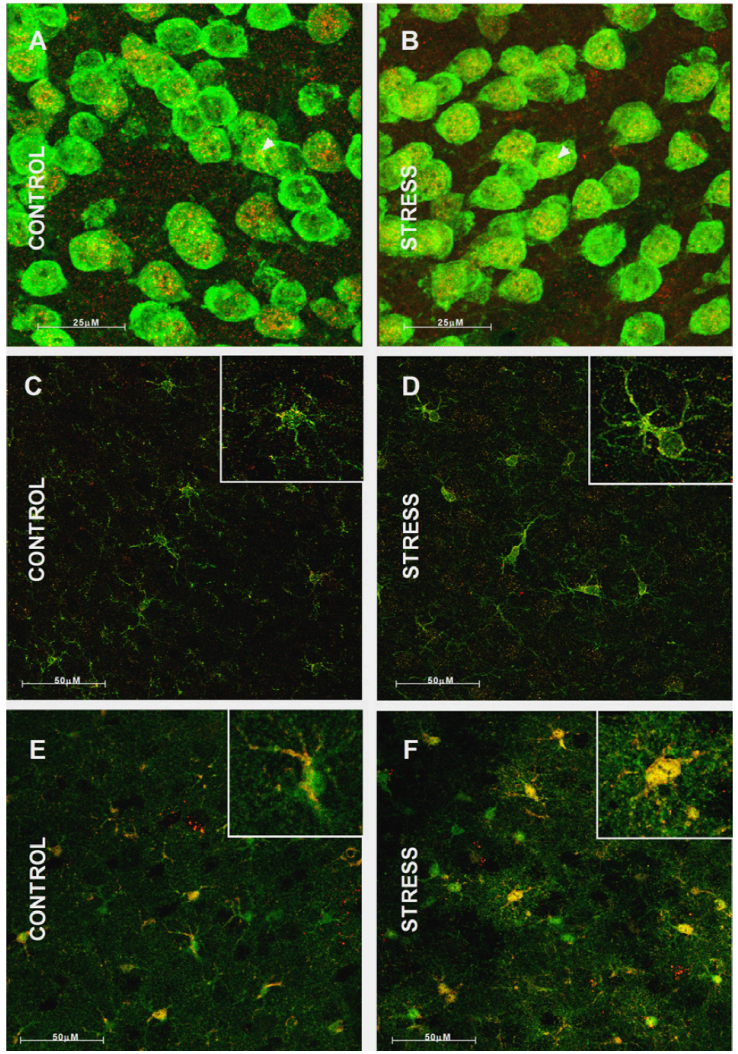
Siopi et al. demonstrate that perturbations in the gut microbiota by chronic stress induce resistance to serotonergic antidepressants via impairments in serotonin biosynthesis and bioavailability. Supplementation with the immediate serotonin precursor 5-hydroxytrytophan restores serotonin levels and neurogenesis in the hippocampus and confers resilience.

Transferência de fezes de animais submetidos a estresse crônico imprevisível (CUS) altera o comportamento (causa efeito tipo pró-depressivo), diminuiu a neurogênese hipocampal e a disponibilidade de serotonina

Stress-Induced Neuroinflammation: Role of the Toll-like Receptor-4 Pathway

Iciar Gárate, Borja Garcia-Bueno, Jose Luis Muñoz Madrigal, Javier Rubén Caso, Luis Alou, Marisa L. Gomez-Lus, Juan Antonio Micó, and Juan Carlos Leza

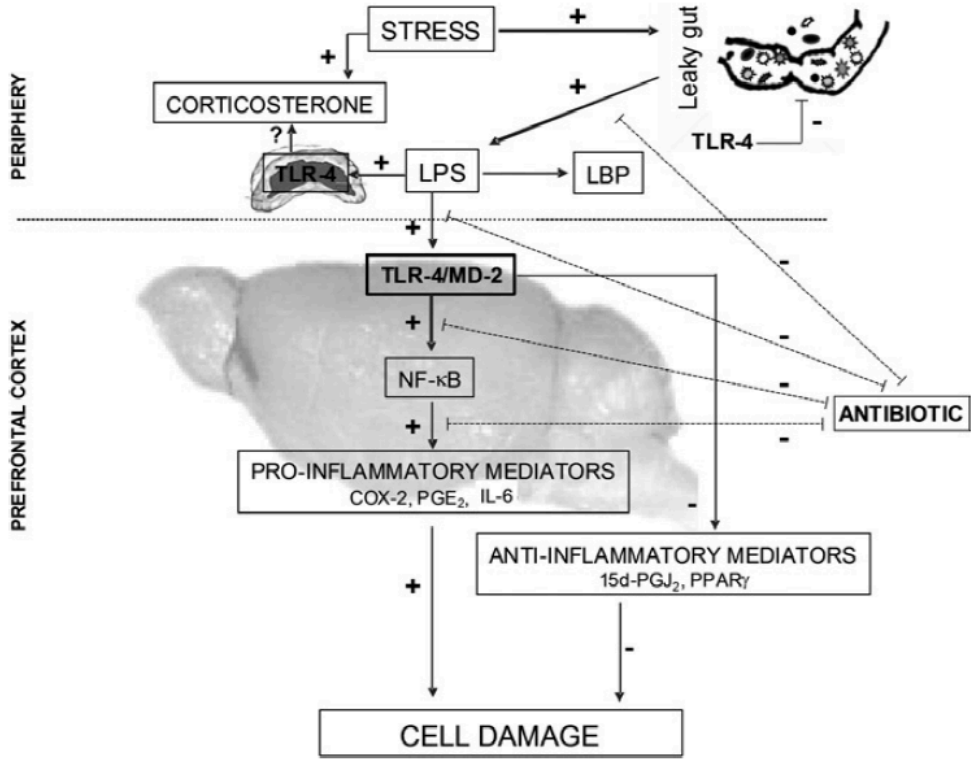
Biological Psych 2012

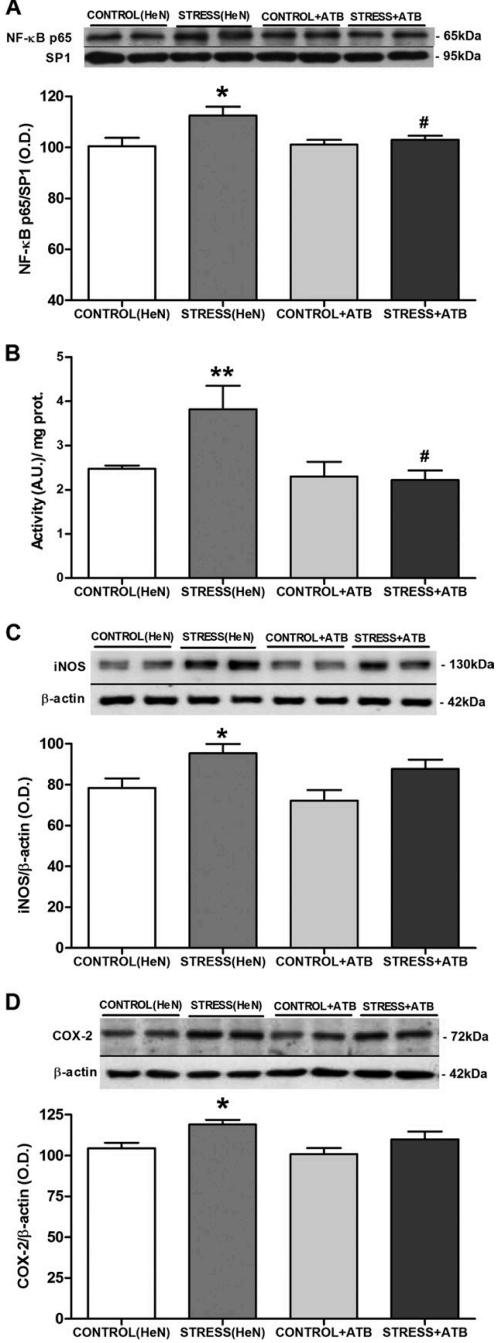


TLR-4 receptors in the prefrontal cortex

Imobilização + estresse acústico (2-h/diapor 2-4 dias) aumenta fatores inflamatórios no córtex pré-frontal

Estes efeitos foram prevenidos pelo tratamento com antibiótico oral (ciprofloxacin)



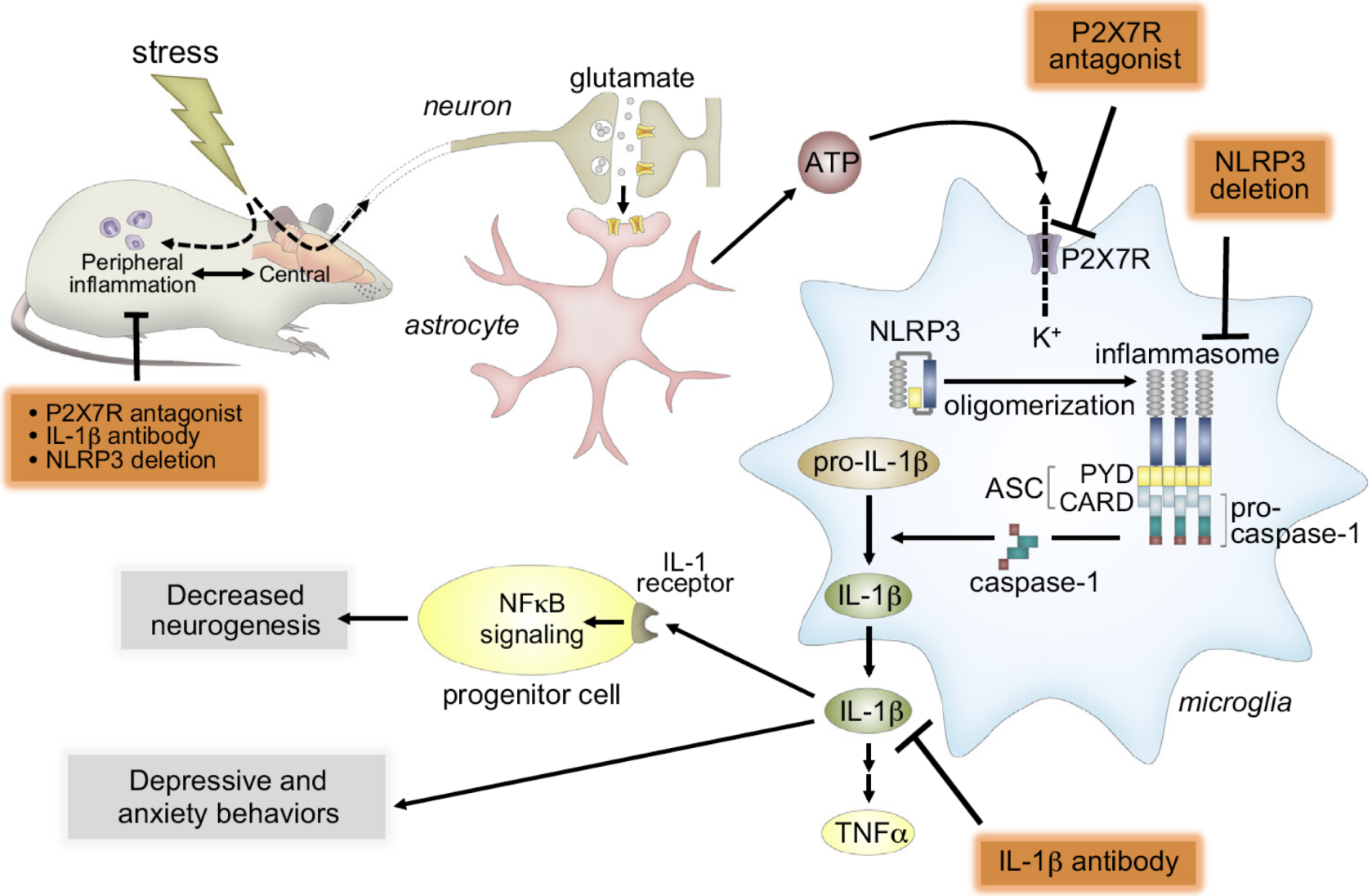


Psychological Stress Activates the Inflammasome via Release of Adenosine Triphosphate and Stimulation of the Purinergic Type 2X7 Receptor

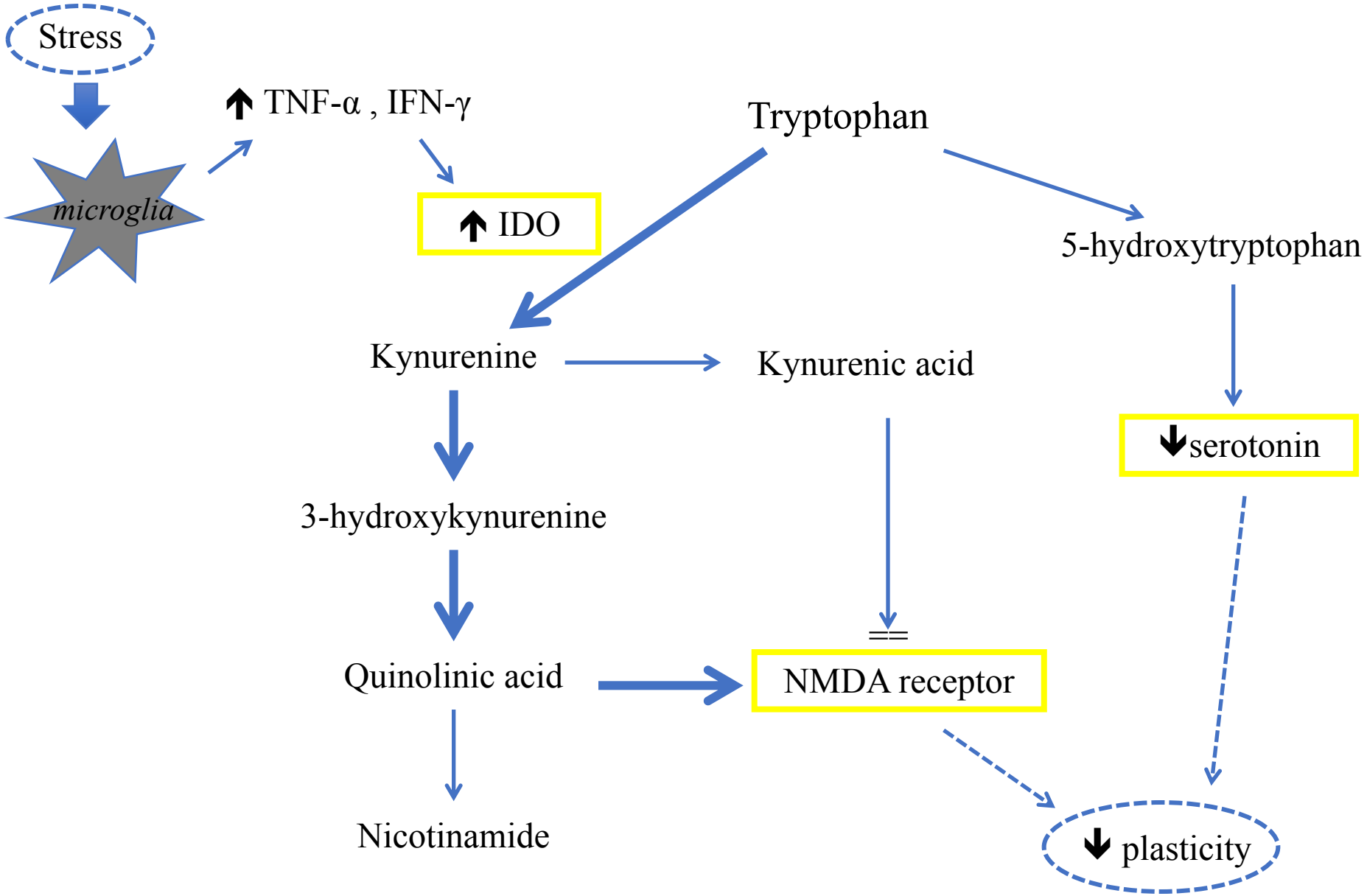
Biol Psych 2016

Masaaki Iwata, Kristie T. Ota, Xiao-Yuan Li, Fumika Sakaue, Nanxin Li, Sophie Dutheil, Mounira Banasr, Vanja Duric, Takehiko Yamanashi, Koichi Kaneko, Kurt Rasmussen, Andrew Glasebrook, Anja Koester, Dekun Song, Kenneth A. Jones, Stevin Zorn, Gennady Smagin, and Ronald S. Di

Estresse pode ativar o inflamossoma em micróglias no SNC



Hipótese inflamatória da depressão: papel da indolamina 2,3 dioxigenase (IDO)



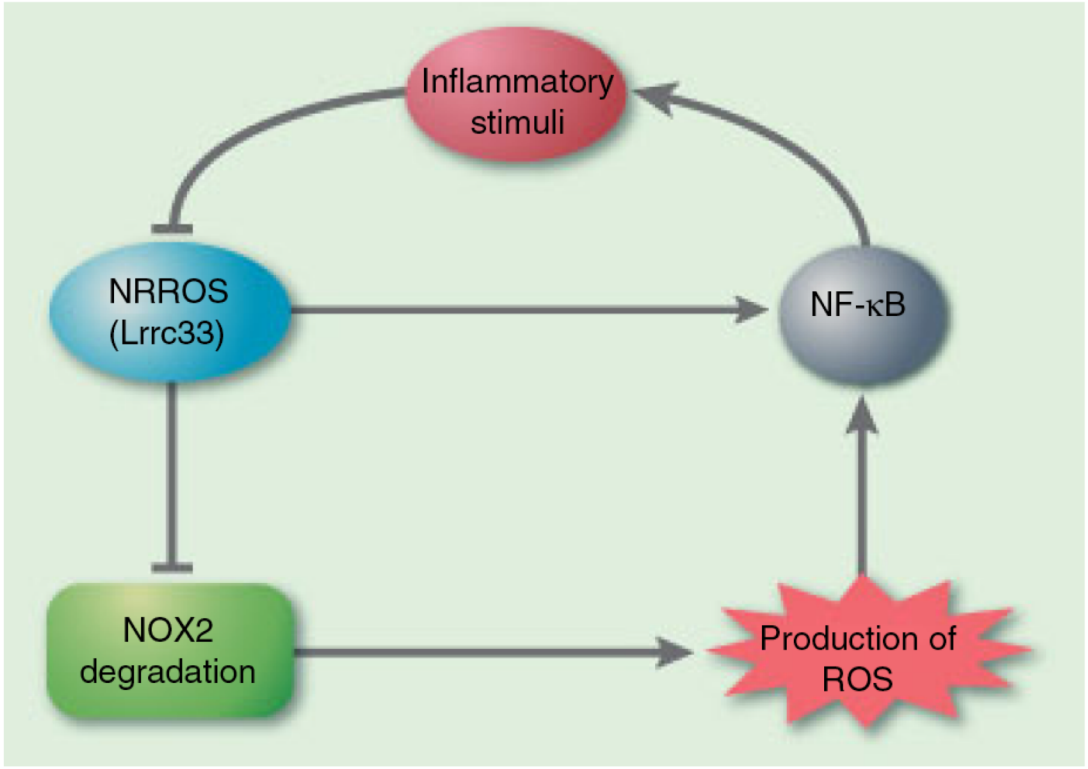
Vias inflamatórias ativadas aumentam a produção de ROS (espécies reativas de oxigêngio)

IMMUNOLOGY REVIEW ARTICLE

2015

Immune mechanisms linked to depression via oxidative stress and neuroprogression

Nataliia Bakunina, Carmine M. Pariante and Patricia A. Zunszain



Interplay between neuroinflammation and oxidative stress

Minociclina poderia ter efeito antidepressivo atuando em vários pontos desta via

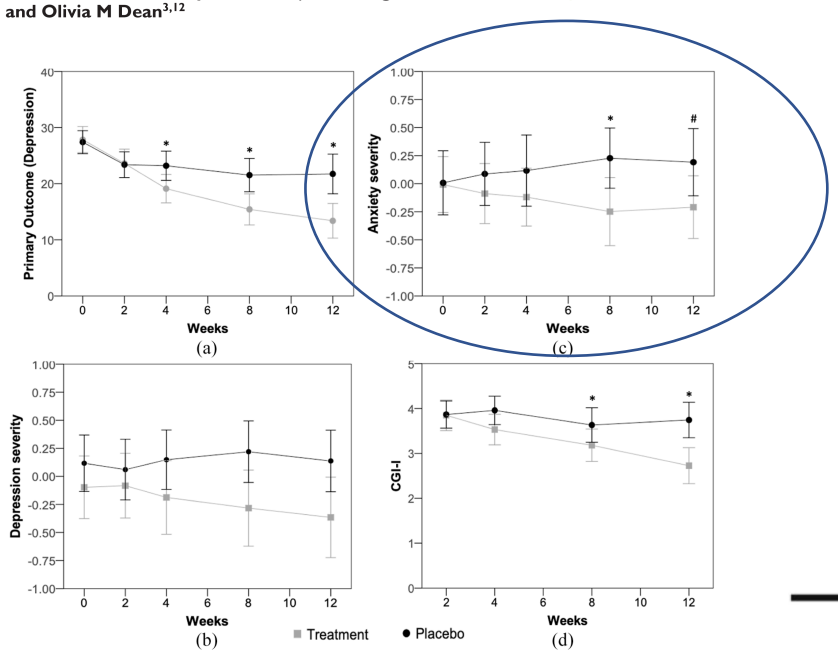
Research

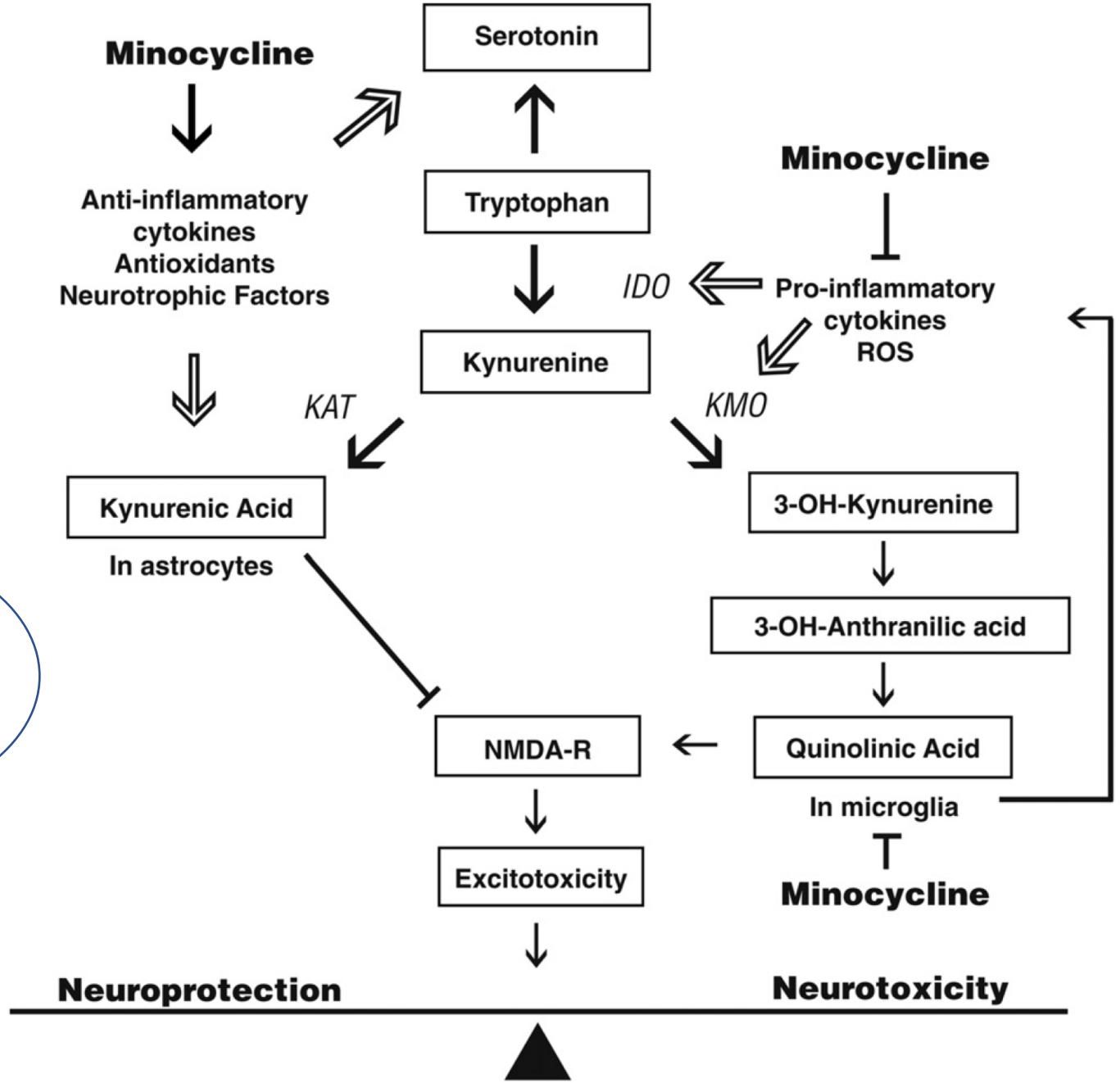
ANZJP

Australian & New Zealand Journal of Psychiatry
1–15
DOI: 10.1177/0004867420965697

Minocycline as adjunctive treatment for major depressive disorder: Pooled data from two randomized controlled trials

Robson Zazula[1,2,3], Muhammad Ishrat Husain[4,5], Mohammadreza Mohebbi[3,6], Adam J Walker[3], Imran B Chaudhry[7,8,9], Ameer B Khoso[8], Melanie M Ashton[3], Bruno Agustini[3], Nusrat Husain[9], JFW Deakin[9], Allan H Young[10,11], Michael Berk[3,12,13,14], Buranee Kanchanatawan[15], Chee H Ng[13], Michael Maes[3,15], Lesley Berk[3,16], Ajeet B Singh[3], Gin S Malhi[17,18,19] and Olivia M Dean[3,12]





Antidepressivos inibidores de recaptação de serotonina possuem efeitos anti-inflamatórios!

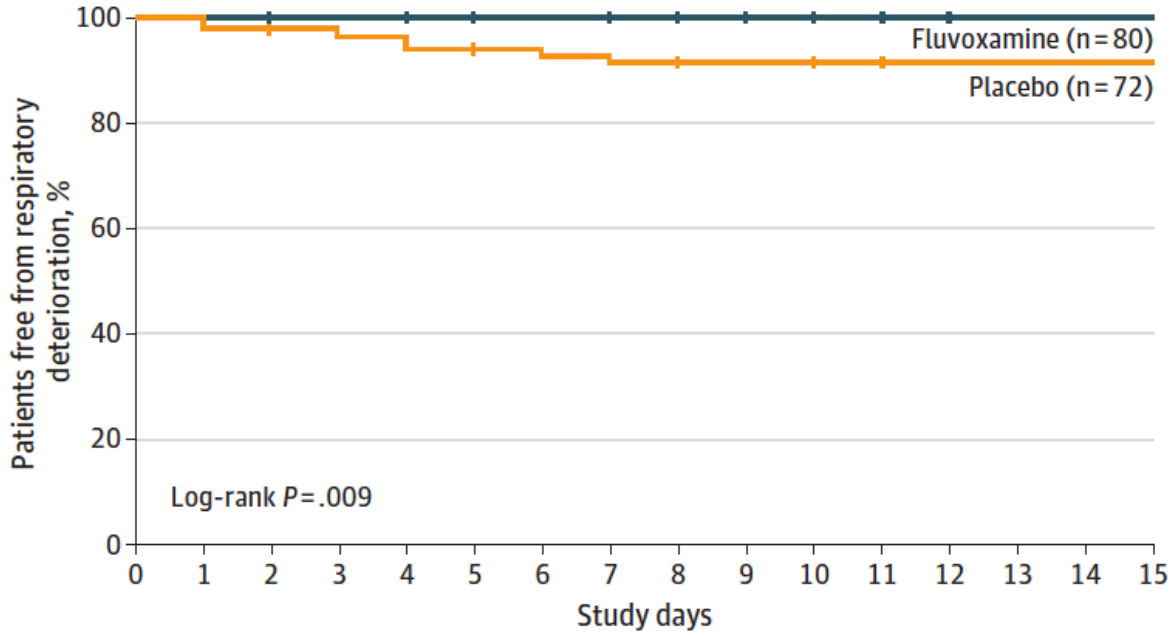
JAMA | Preliminary Communication

Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19

A Randomized Clinical Trial

Eric J. Lenze, MD; Caline Mattar, MD; Charles F. Zorumski, MD; Angela Stevens, BA; Julie Schweiger; Ginger E. Nicol, MD; J. Philip Miller, AB; Lei Yang, MPH, MSIS; Michael Yingling, MS; Michael S. Avidan, MBBCh; Angela M. Reiersen, MD, MPE

Figure 2. Time to Clinical Deterioration in the Fluvoxamine and Placebo Groups



No. at risk																
Fluvoxamine	80	80	80	77	76	75	71	71	70	67	66	64	63	62	62	62
Placebo	72	72	70	68	67	65	64	63	61	59	59	56	53	53	53	53

There is more things in heaven and earth...than are dreamt of by your philosophy.

-William Shakespeare, Hamlet

www.quoteslyfe.com

Conclusão: “it is complicate”