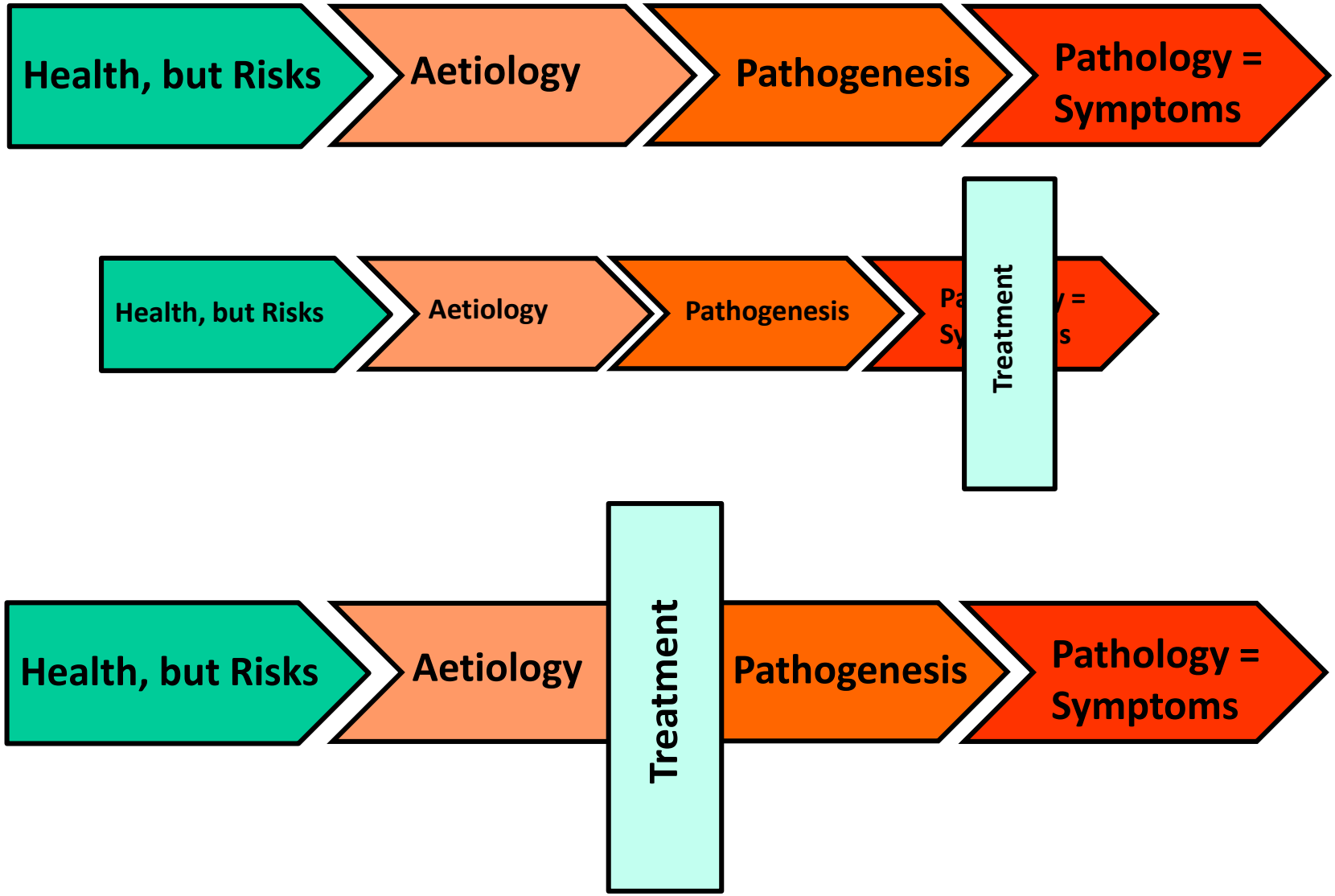
Anti-depressants: the next generation?

- Agomelatine: a novel anti-depressant with a novel mechanism of action
  - Sleep dysfunction and depression
  - Circadian-rhythm and Melatonin
  - Serotonin 2C receptor antagonism
  - Evidence for efficacy in animal models and in depressed patients

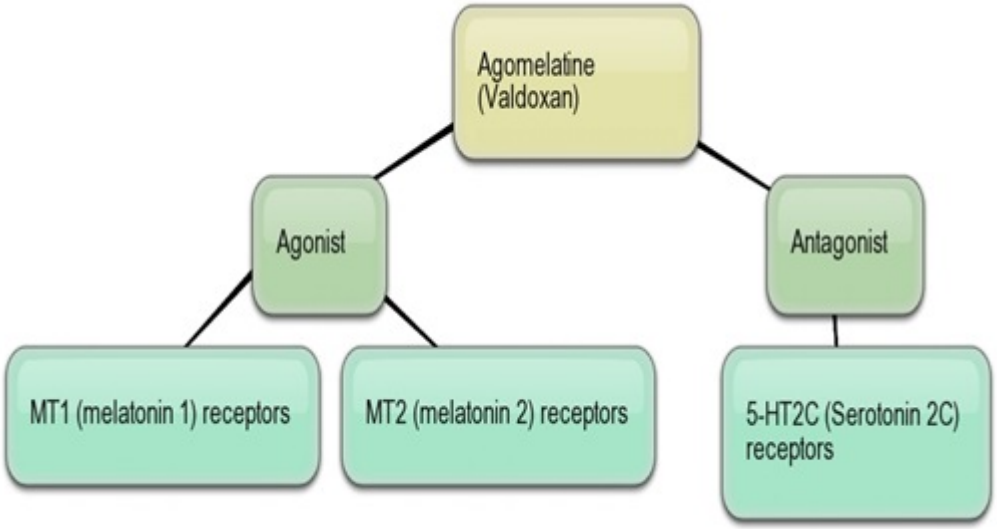
- The psychedelic-drug Ketamine as anti-depressant
  - Rapid onset of anti-depressant effect in chronically depressed patients
  - Evidence for efficacy in animal models
  - A proposed mechanism of action: activation of neurotrophins and synaptogenesis

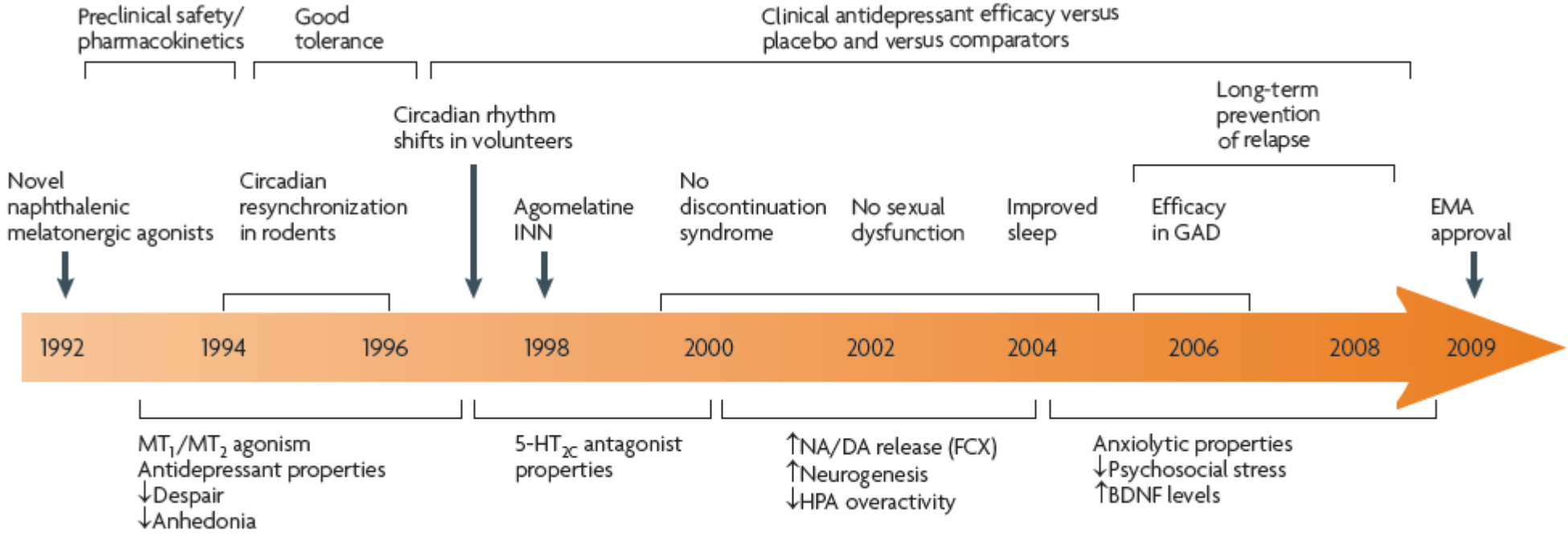
- Anti-depressant treatments focussing on the inflammation hypothesis of depression
  - Ketamine as an antagonist of hyper-activity in the kynurenine pathway
  - Human trial with an antibody for tumor necrosis factor

The Aetiology-Pathogenesis Interface as the key to understanding depression:
Understanding the mechanism underlying a disease is essential to its treatment



Agomelatine/Valdoxan (S20098): registered antidepressant in 2009

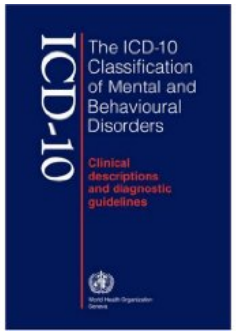




Pharmacological characterization: key observations

de Bodinat et al. (2010) Nature Rev Drug Discovery 9: 628

Diagnostic symptoms for major depressive disorder



Symptom type	ICD-10 classification
	At least two of:
Typical/Core	Depressed mood : pre-occupation with negative events and feelings of sadness, helplessness
Typical/Core	Anhedonia: Loss of interest/motivation and enjoyment/pleasure
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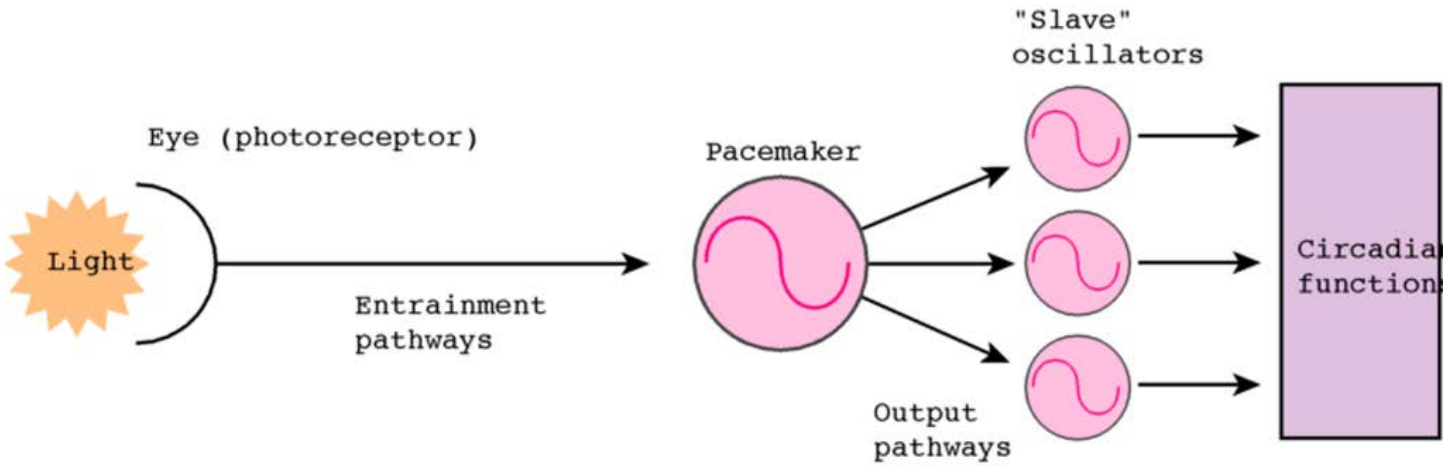
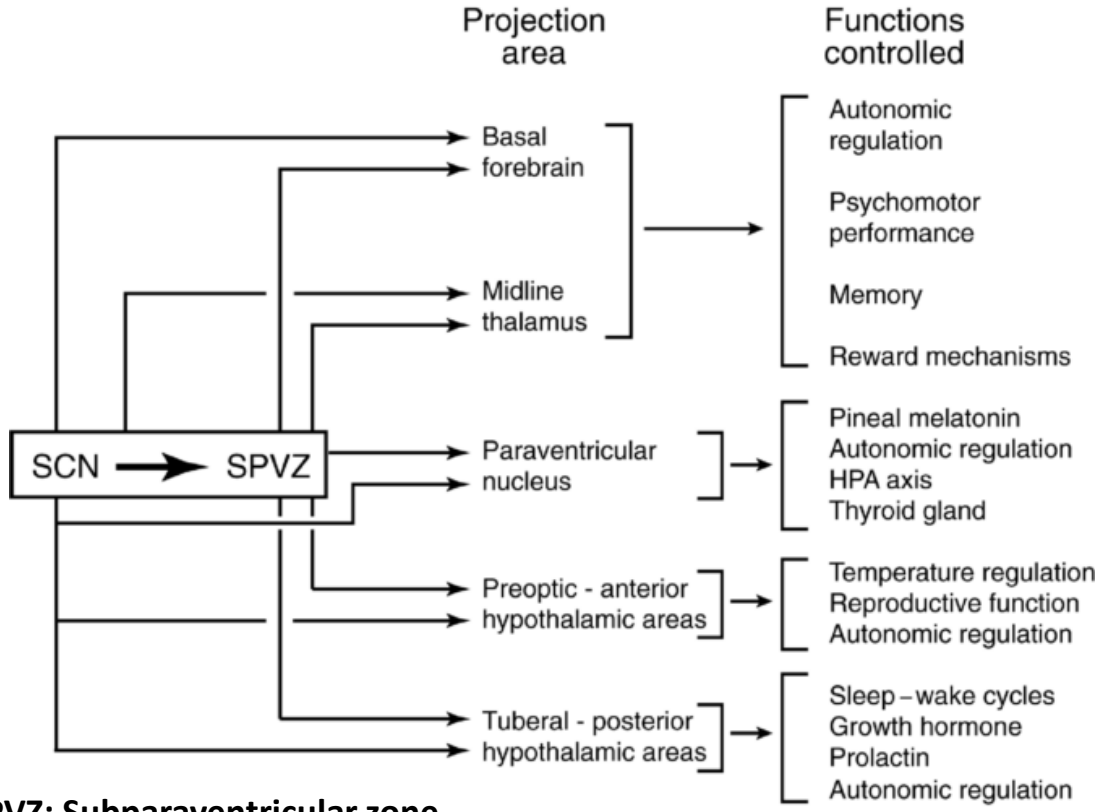
	At least three of:
Common	Reduced concentration and attention
Common	Reduced self-esteem and self-confidence
Common	Ideas of guilt and unworthiness
Common	Bleak and pessimistic views of the future
Common	Ideas or acts of self-harm or suicide
Common	Disturbed sleep
Common	Diminished appetite
Common	Suicide attempt/plan

ICD-10: International Classification of Diseases: Mental and Behavioural Disorders, WHO (1992)

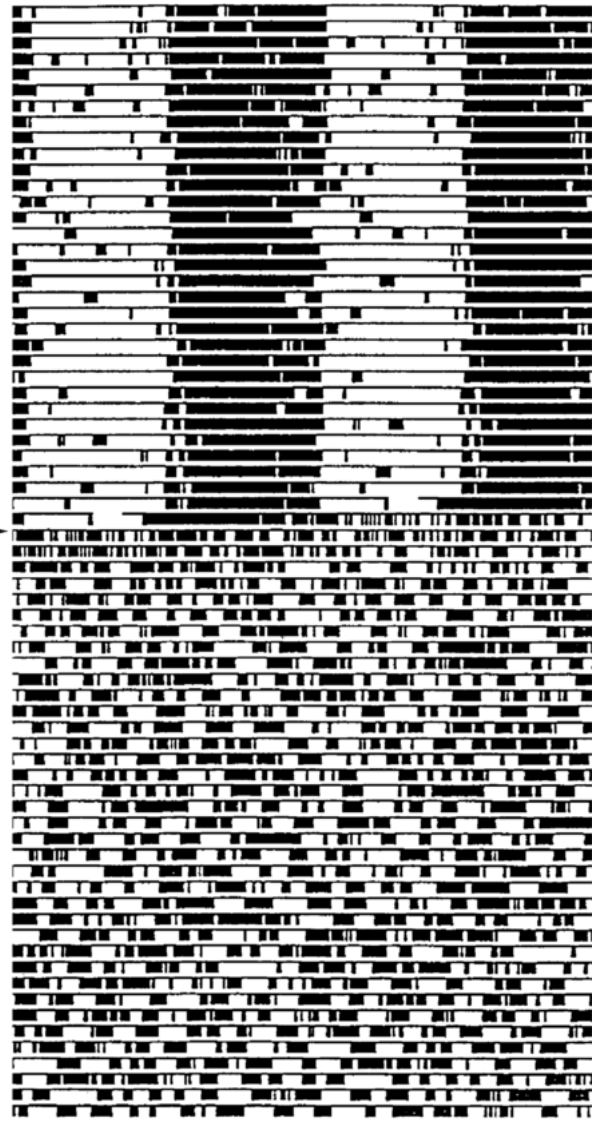
The suprachiasmatic nucleus of the hypothalamus is the Pacemaker of circadian rhythms





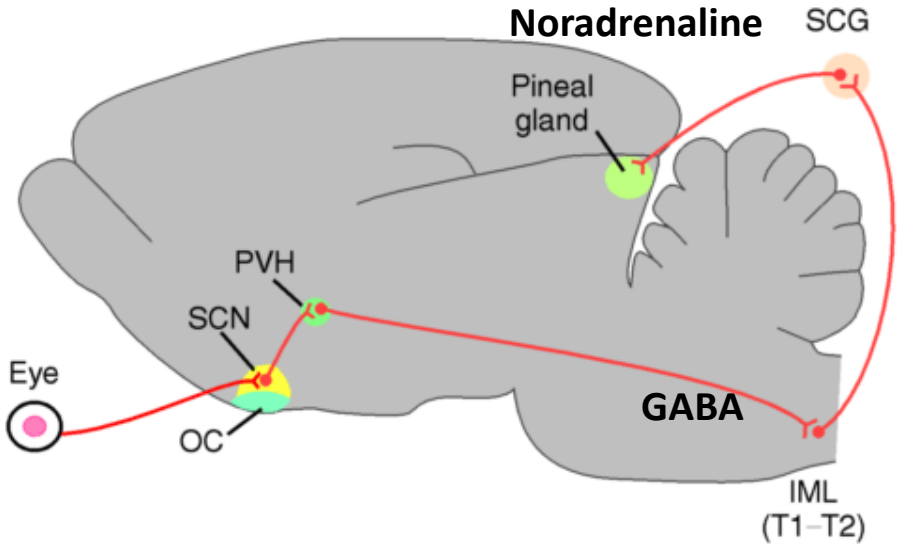
SPVZ: Subparaventricular zone

SCN lesion results in loss of Circadian function

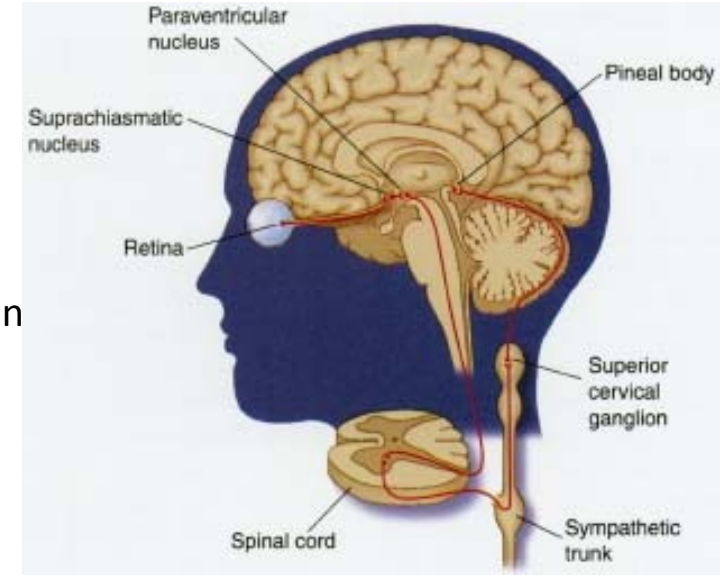


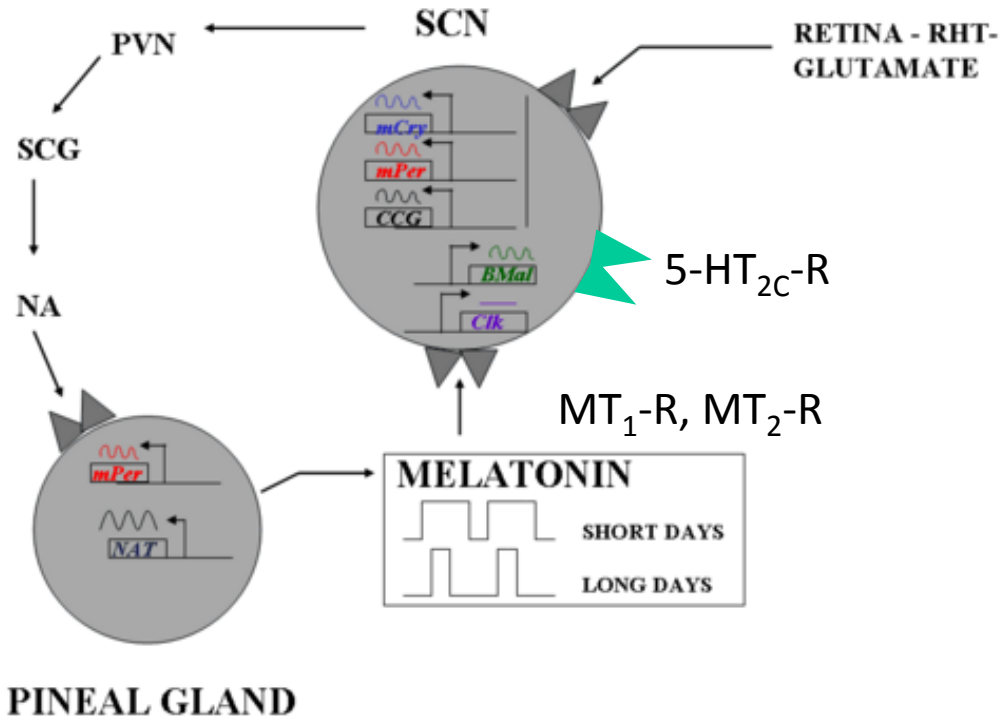
MJ Zigmond et al. (1999) Fundamental Neuroscience Academic Press

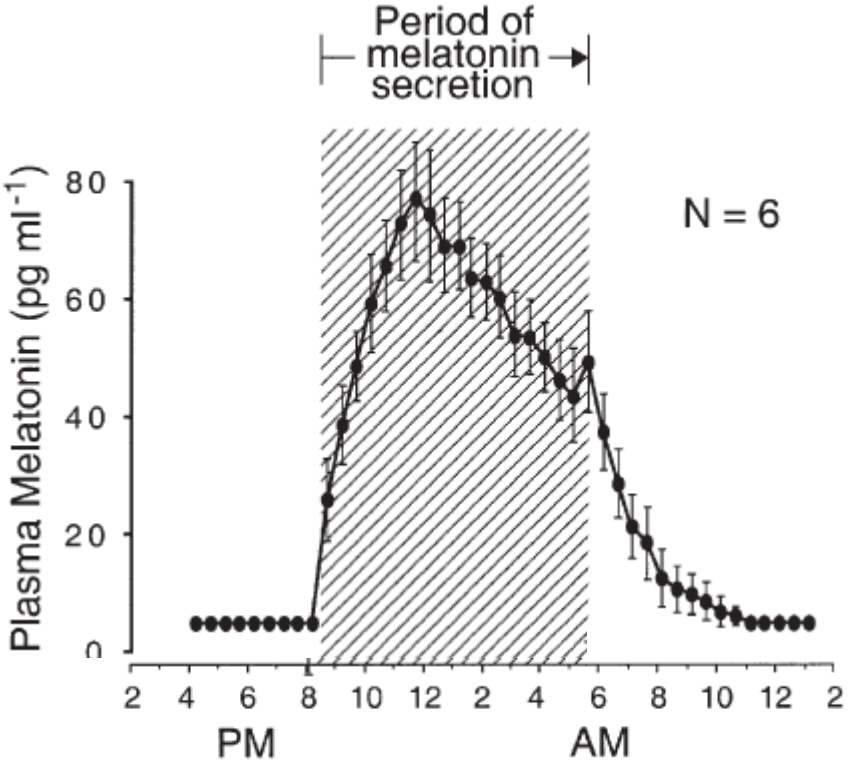
Bi-directional communication between SCN and the Pineal gland-Melatonin



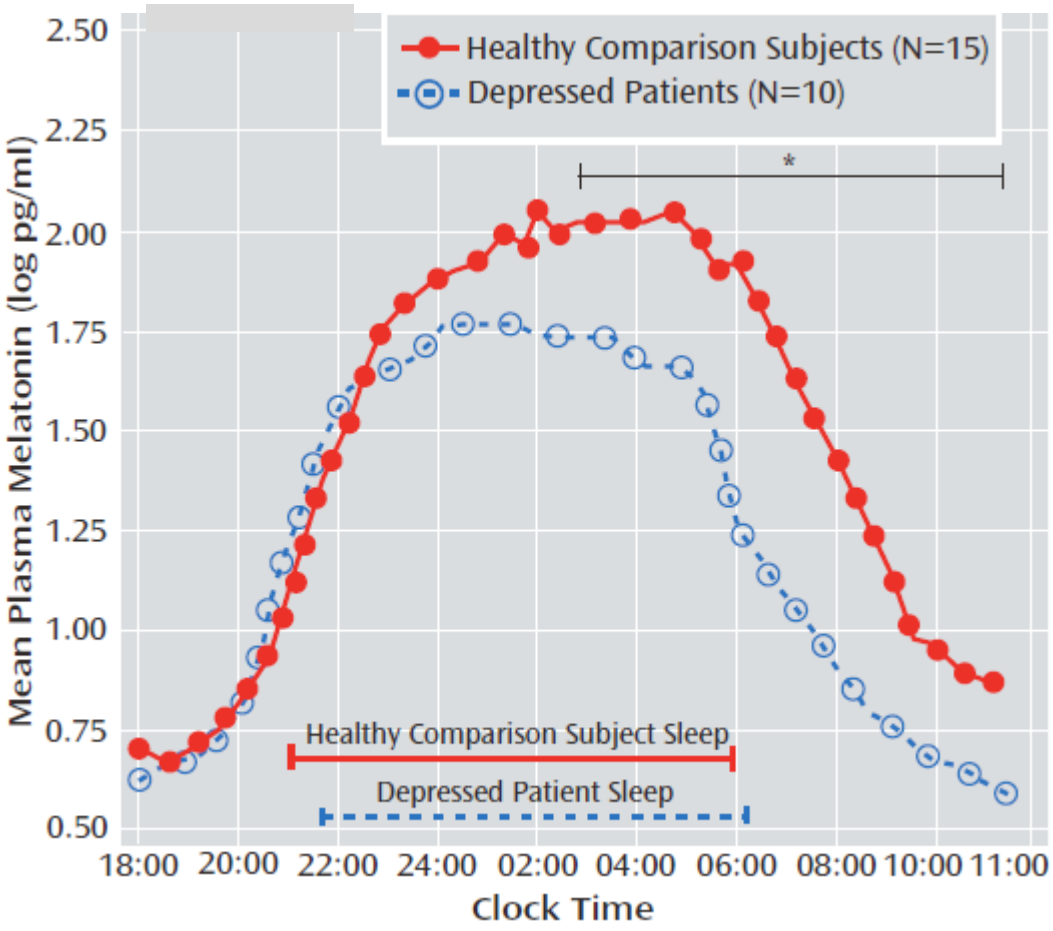
OC, Optic chiasm
SCN, Suprachiasmatic nucleus
PVH, Paraventricular nucleus
IML, Intermediolateral cell column
SCG, Superior cervical ganglion





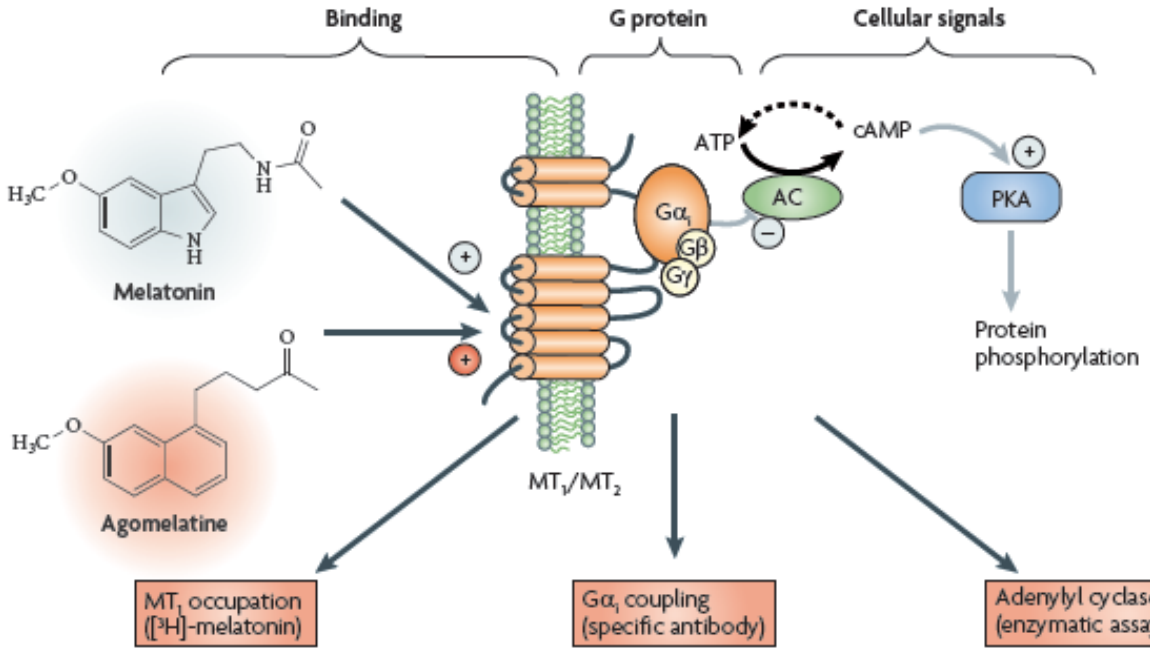


Reduced plasma melatonin levels during the night in people with depression



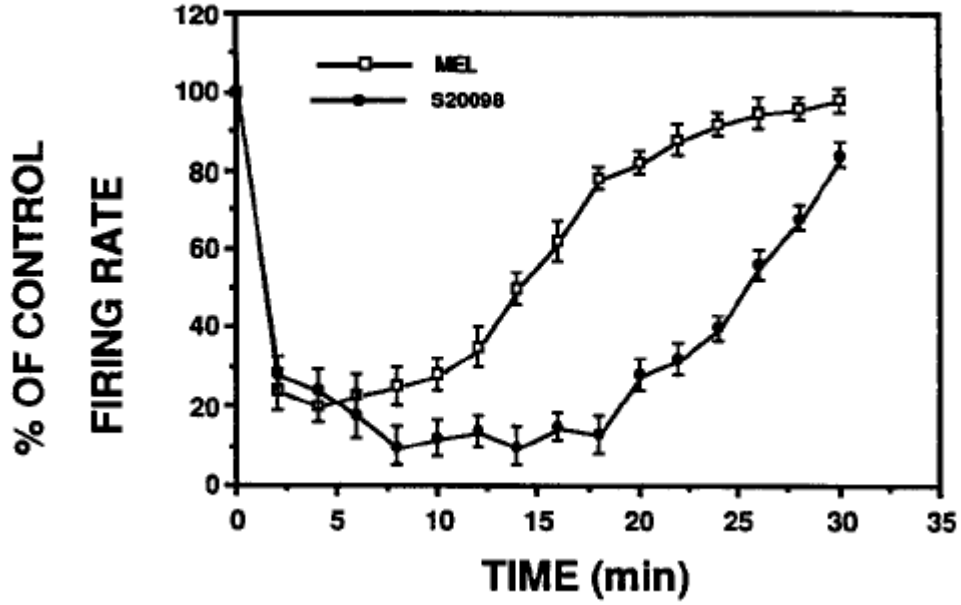
Parry et al. (2008) Amer J Psychiatry 165: 1551

Agomelatine: action as a MT_1-R / MT_2-R Agonist



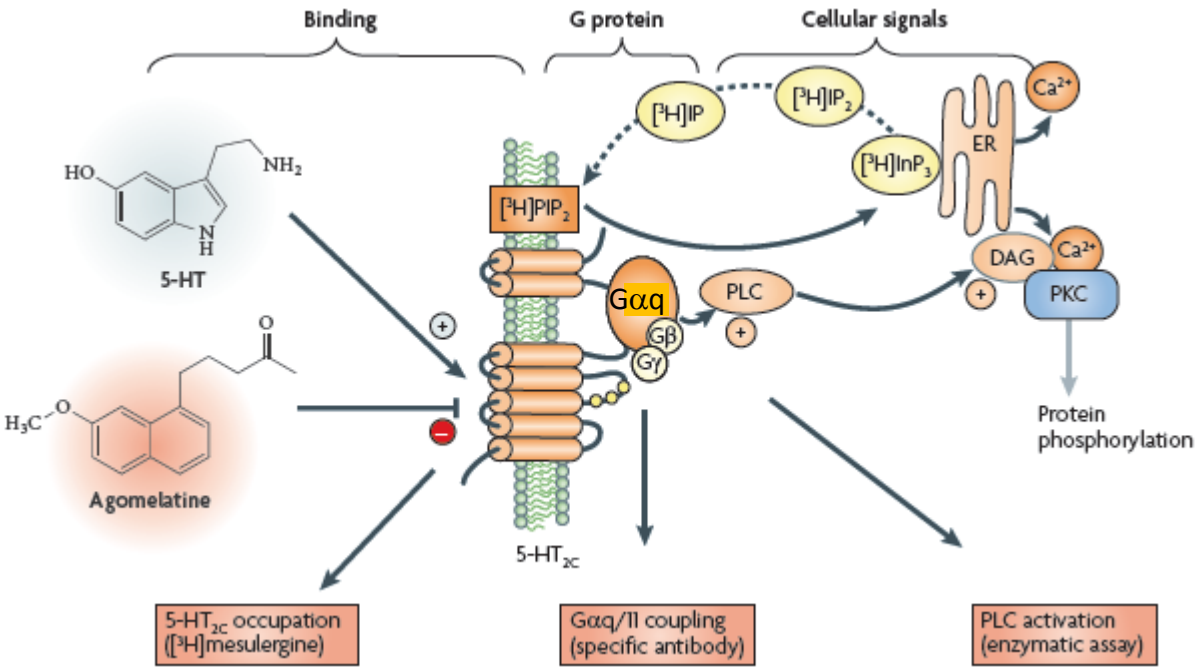
- MT1 and MT2 couple to Gαi
- Gαi inhibits adenylyl cyclase (AC)
- Causes reduced cyclic AMP from ATP
- Causes decreased activity of protein kinase A
- Causes reduced phosphorylation of substrates
- Causes reduced firing rate of SCN neurons

Suppression and recovery of light-sensitive SCN cells



de Bodinat et al. (2010) Nature Rev Drug Discovery 9: 628

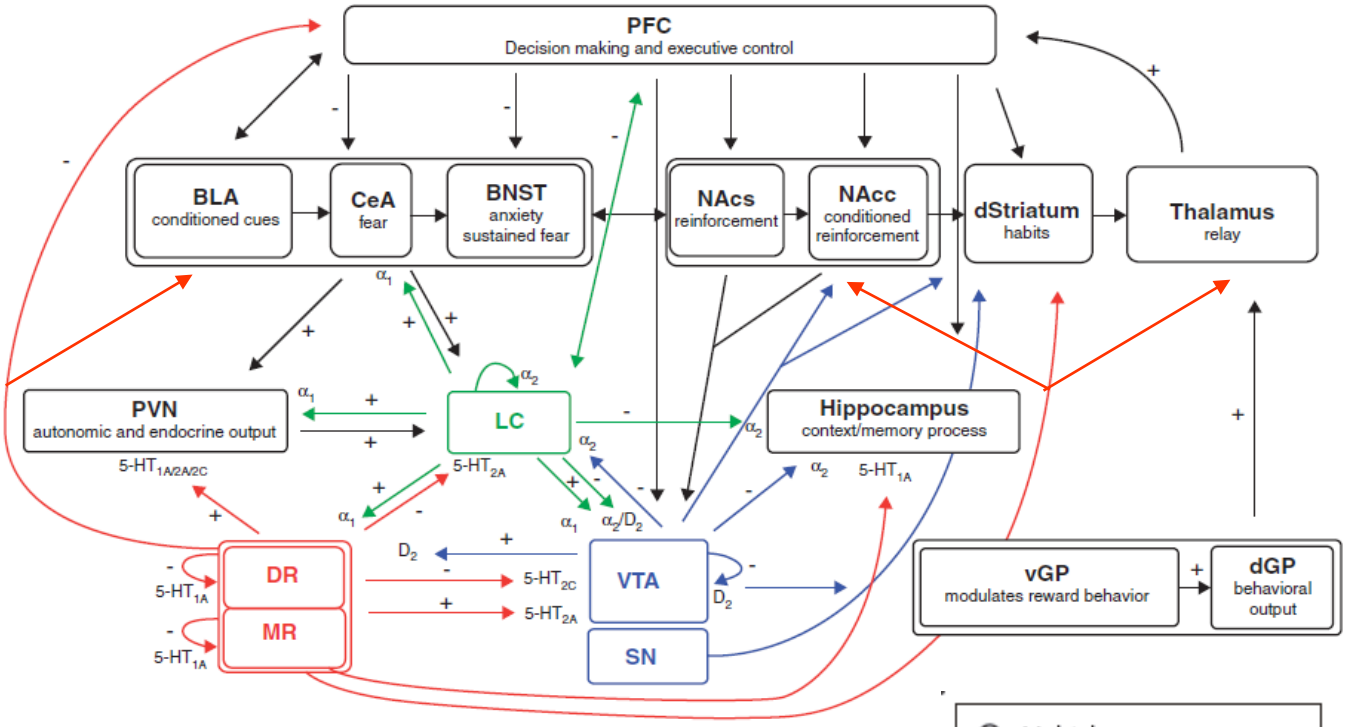
Agomelatine: action as a 5-HT_{2C}-R Antagonist

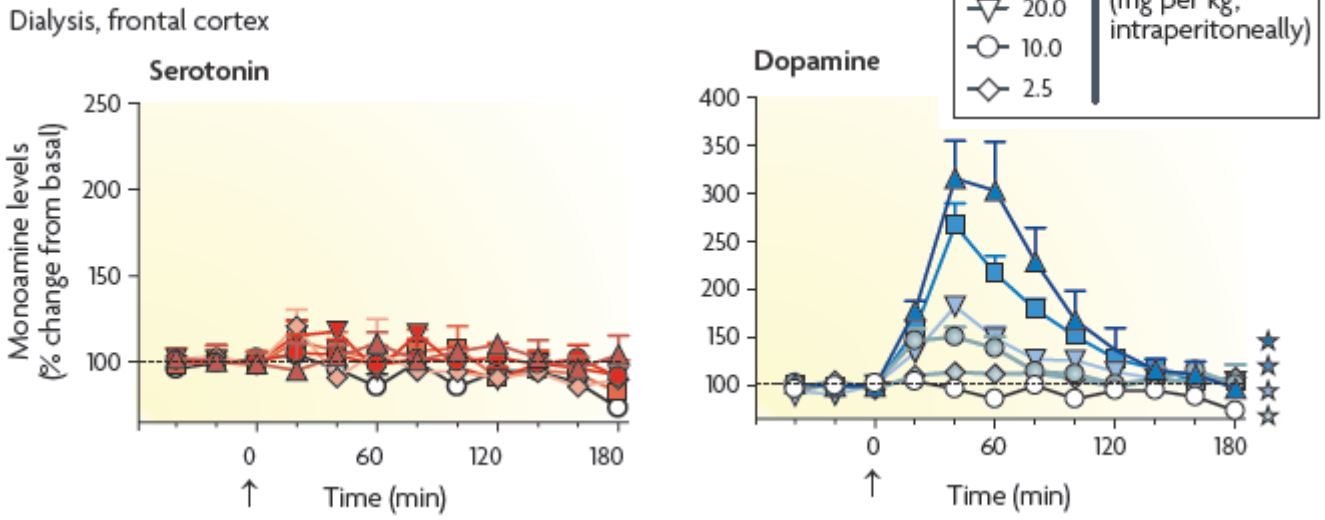


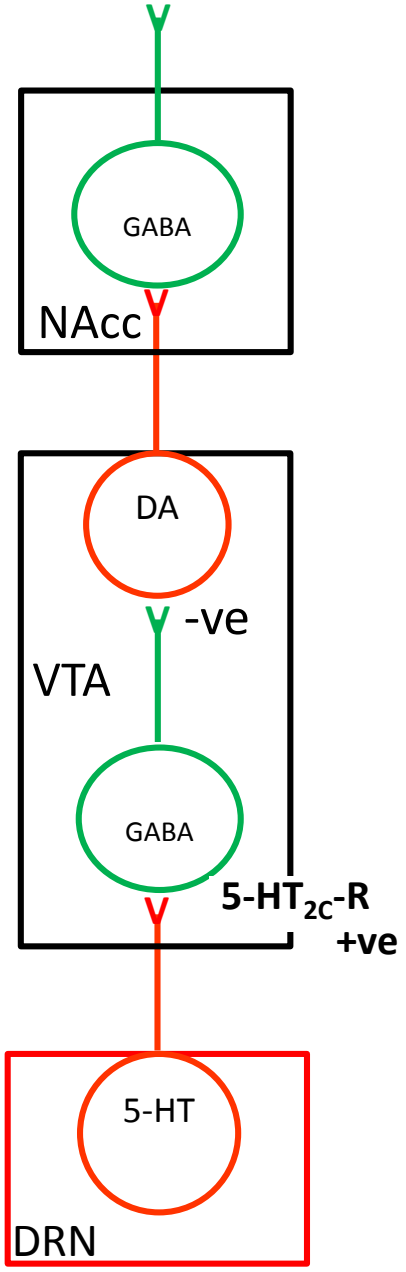
- 5-HT2C couples to Gαq
- Gαq activates phospholipase C (PLC)
- Generates Diaminoglycerol + Inositol triphosphate
- Causes increased activity of protein kinase C
- Causes increased phosphorylation of substrates

de Bodinat et al. (2010) Nature Rev Drug Discovery 9: 628

Agomelatine: action as a 5-HT$_{2C}$-R Antagonist





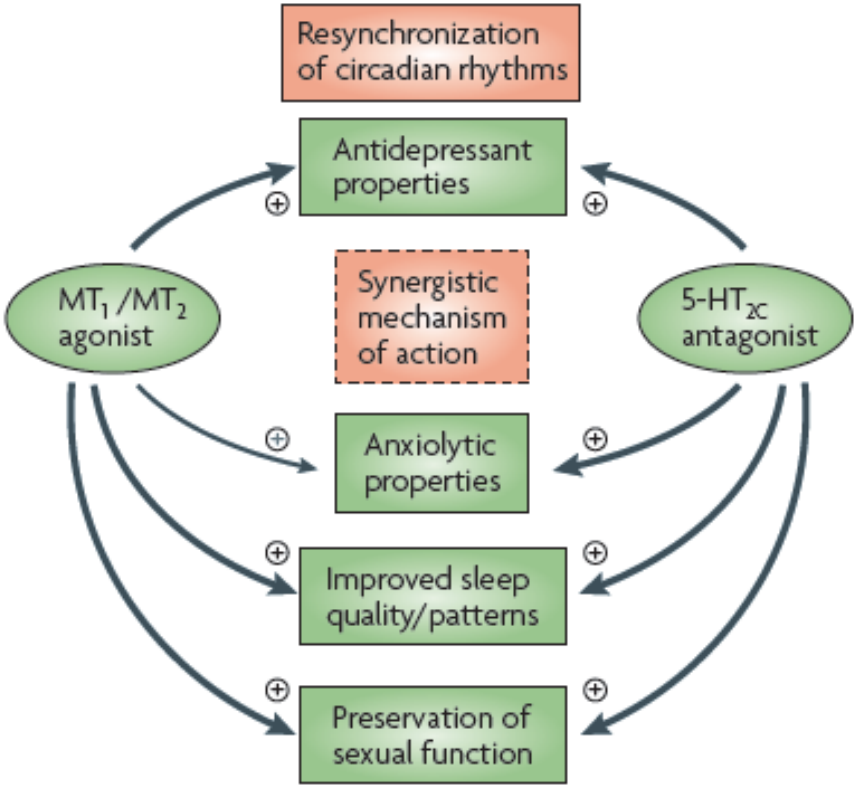


de Bodinat et al. (2010) Nature Rev Drug Discovery 9: 628

Agomelatine: effects in animal tests and models and on neurobiology and a proposal for mechanism of action

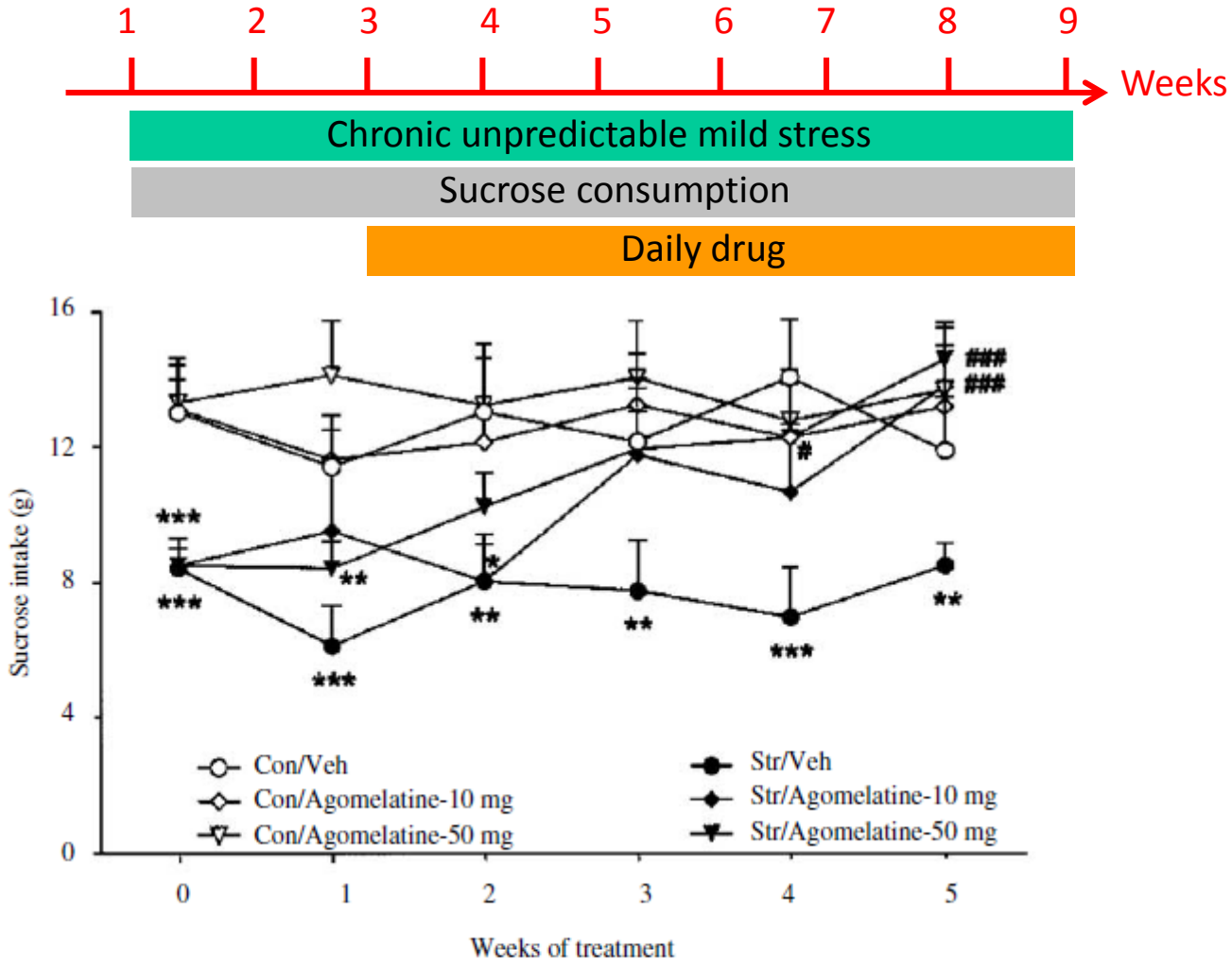
Table 1 | **Overview of the actions of agomelatine in experimental models relevant to depression**

Characteristic	Model	Species	Major observation
Cardinal symptom	Forced swim test (despair)	Rat	Decrease in immobility time
	Learned helplessness (resignation)	Rat	Disinhibition of suppressed responses
	Chronic mild stress (anhedonia)	Rat	Restored sucrose consumption
	Olfactory bulbectomy (motor agitation)	Rat	Decrease in hyperactivity
Circadian disruption	Mutated glucocorticoid receptor	Mouse	Decrease in perturbation of rhythms of corticosterone secretion
	Psychosocial stress	Tree shrew	Decrease in perturbation of rhythms of corticosterone secretion and core temperature
Biological substrate	Noradrenaline/dopamine in frontal cortex	Rat	Increase in extracellular levels
	Hippocampal neurogenesis	Rat	Increase in cellular proliferation and survival
	Levels of brain-derived neurotrophic factor	Rat	Increase in mRNA levels



de Bodinat et al. (2010) Nature Rev Drug Discovery 9: 628

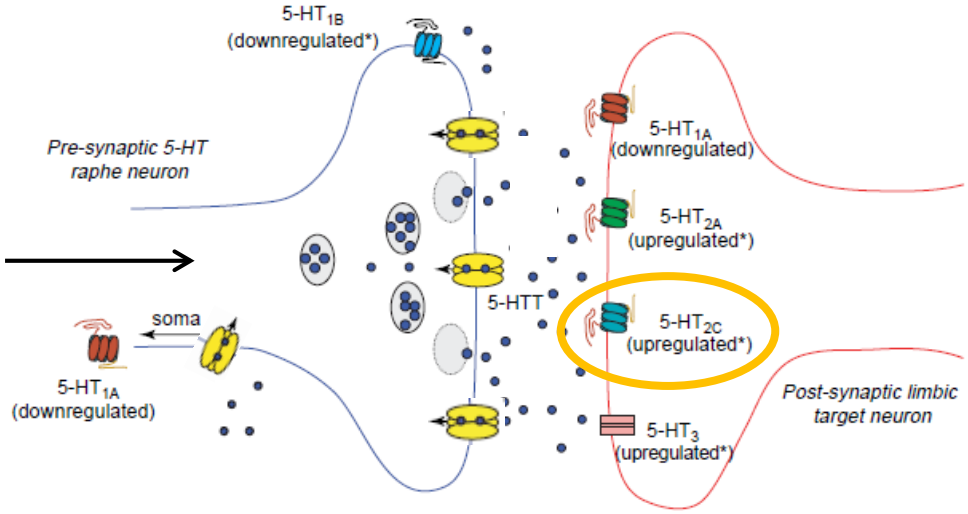
Agomelatine reversal of effect of chronic mild stress on sucrose consumption in rat

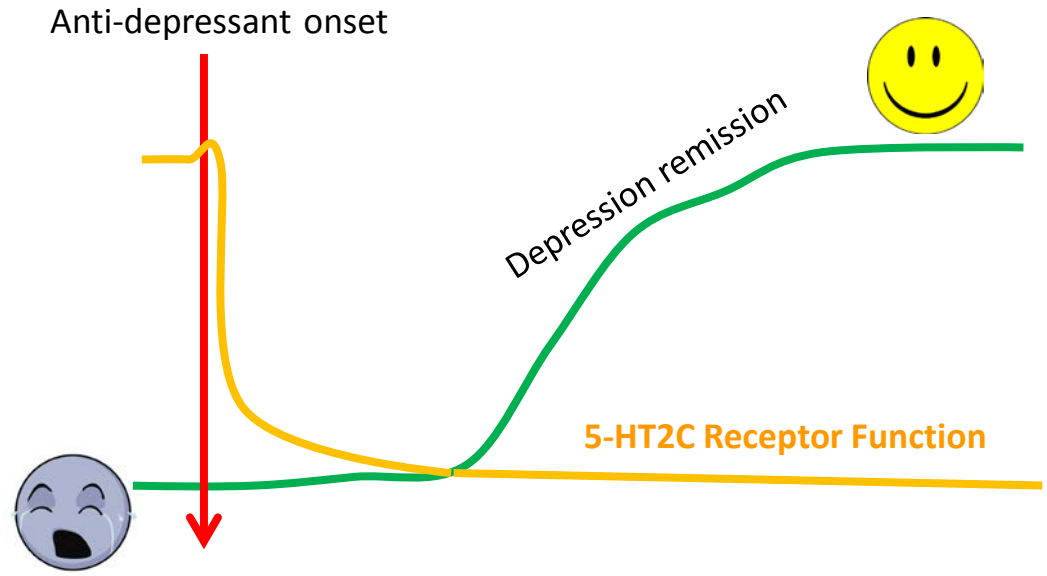


Papp et al. (2003) Neuropsychopharmacology 28: 694

Changes in serotonin signalling in Stress and Depression:
Serotonin levels and pre- and post-synaptic 5-HT receptor function: Focus on 5-HT$_{2C}$

(3) Depression/Chronic Stress

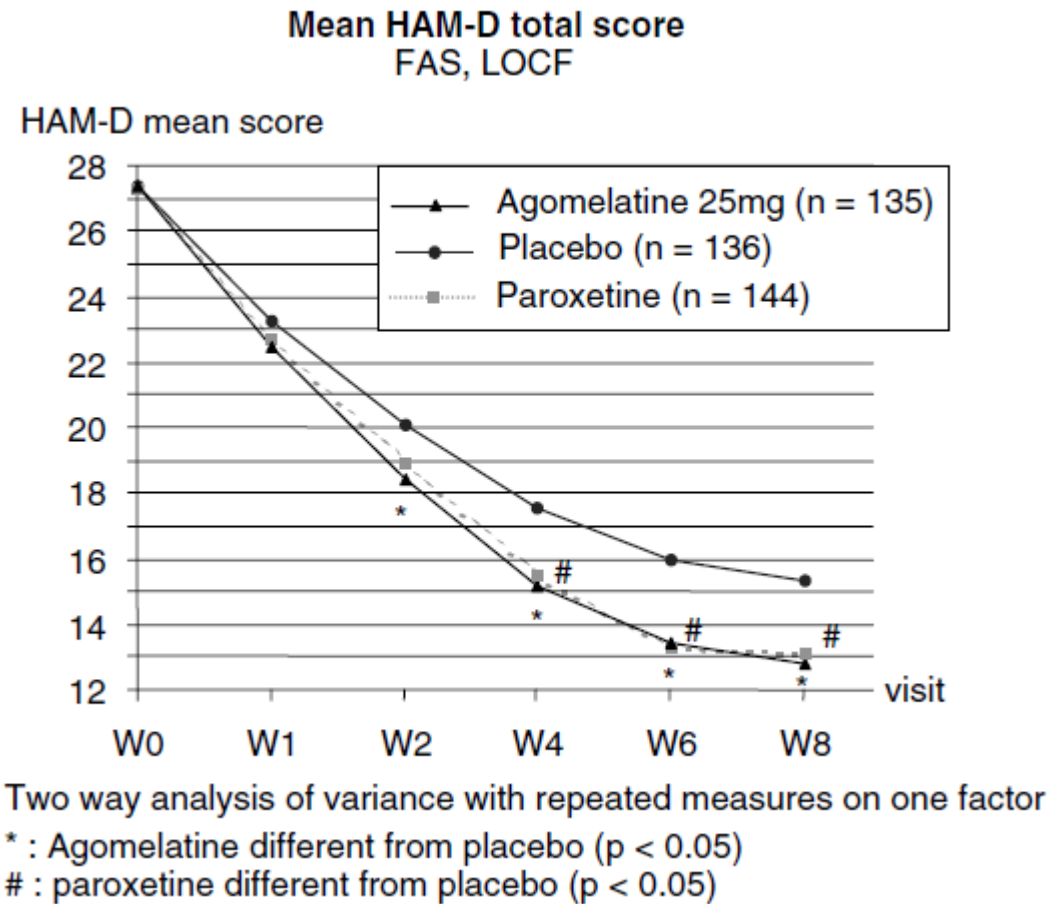




- Low 5-HT synthesis and neuron firing
- Low 5-HT level in synapse
- High pre-synaptic 5-HTT density to compensate for increased 5-HT during acute stress
- Altered 5-HT receptors binding/density to compensate for increased 5-HT during acute stress

Hariri & Holmes (2006) Trends Cogn Sci 10: 182

Agomelatine: double-blind randomized clinical trial in depression



Paroxetine = SSRI

Two way analysis of variance with repeated measures on one factor

* : Agomelatine different from placebo ($p < 0.05$)

: paroxetine different from placebo ($p < 0.05$)

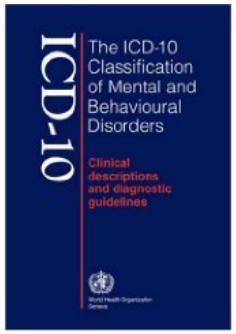
Table 4. HAM-D: mean final value in the subpopulation of severely depressed patients (HAM-D $\geq$ 25 at inclusion)

	Agomelatine (25 mg/day), $n = 120$	Placebo, $n = 114$	Paroxetine (20 mg/day), $n = 110$
Total HAM-D score last assessment mean $\pm$ SD	13.14 ± 8.40*	16.10 ± 9.10	14.10 ± 8.40

*$P \leq 0.05$ (compared to placebo using Dunett's t-test).

Loo et al. (2002) Int Clin Psychopharmacol 17: 239

Diagnostic symptoms for major depressive disorder



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ICD-10: International Classification of Diseases: Mental and Behavioural Disorders, WHO (1992)

Comparison of Agomelatine and Venlafaxine in treatment of Depression / Anhedonia

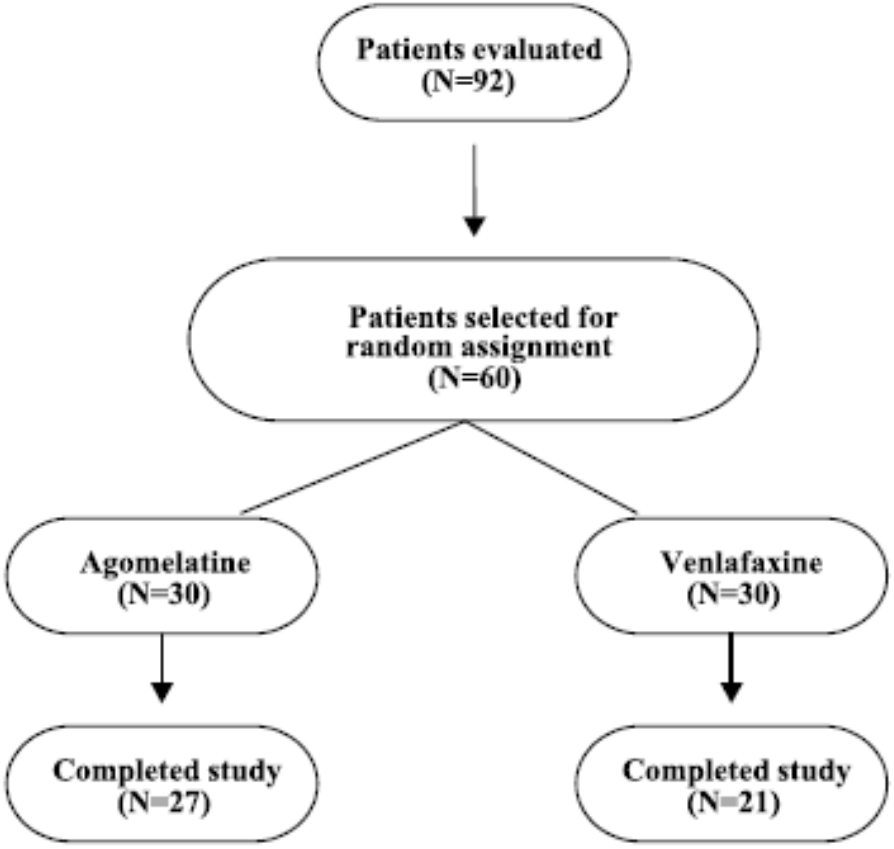


FIGURE 1. Diagram of subject flow by treatment group.

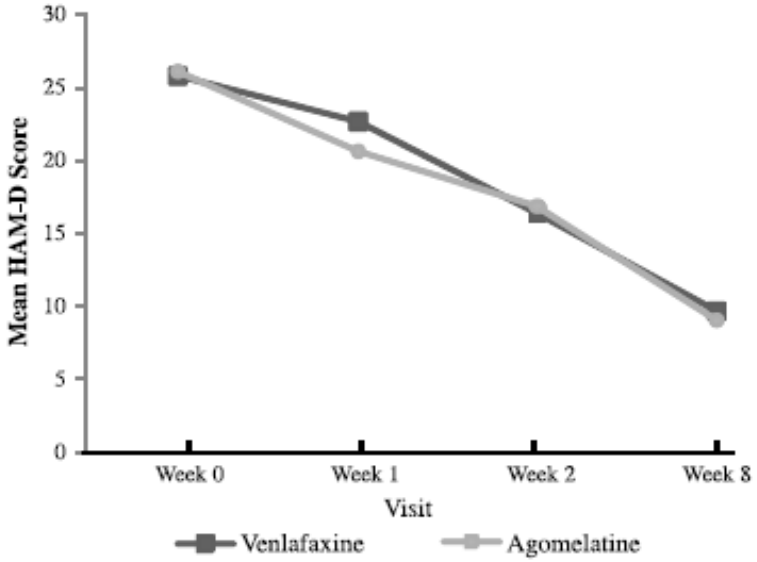


FIGURE 2. Hamilton Rating Scale for Depression (HAM-D): total scores by study visit.

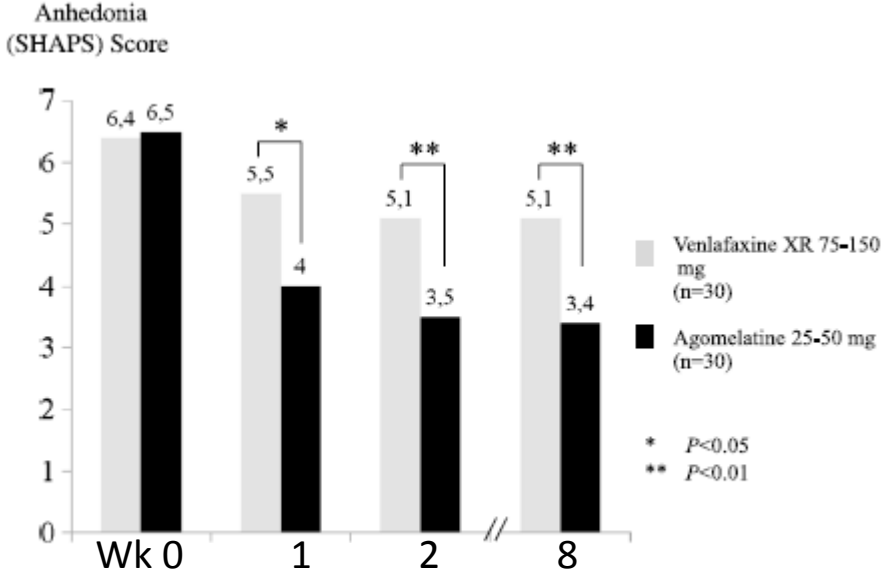
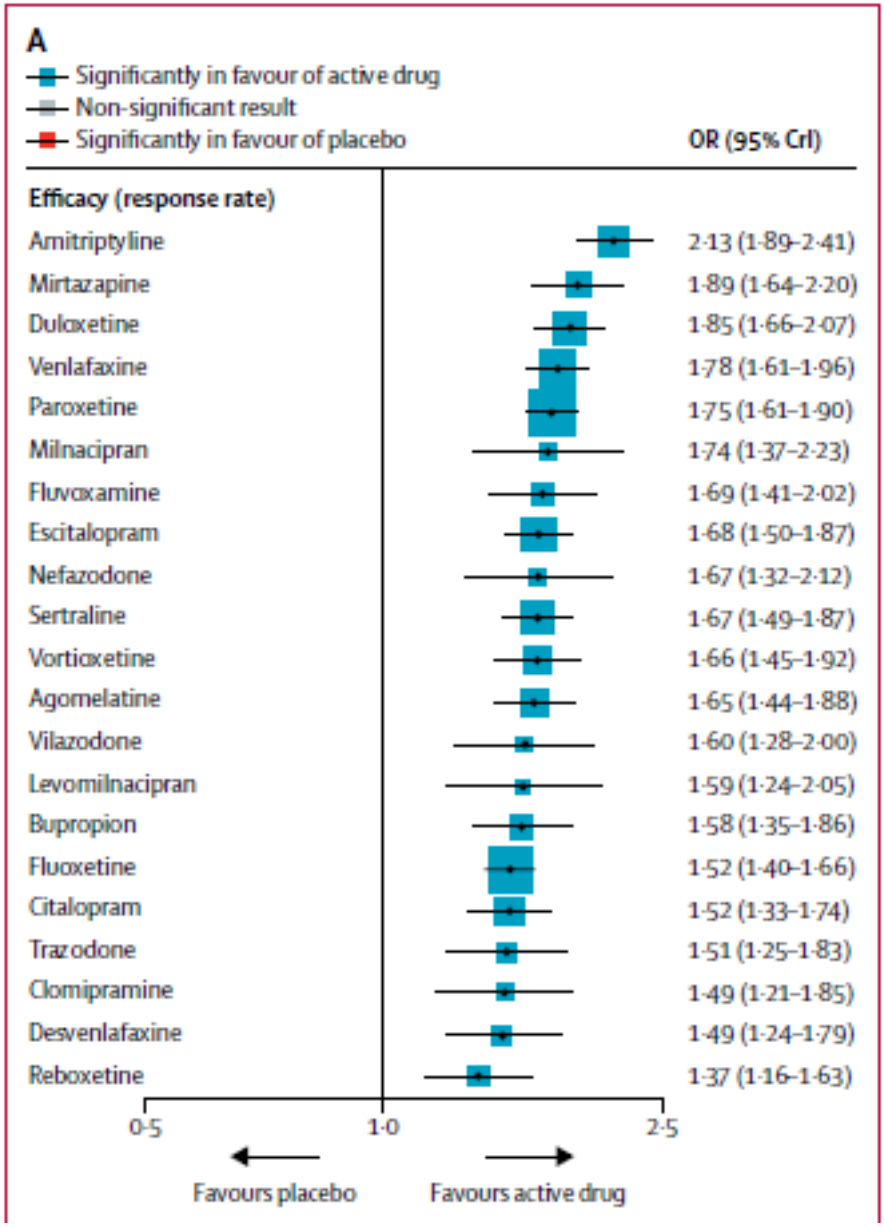


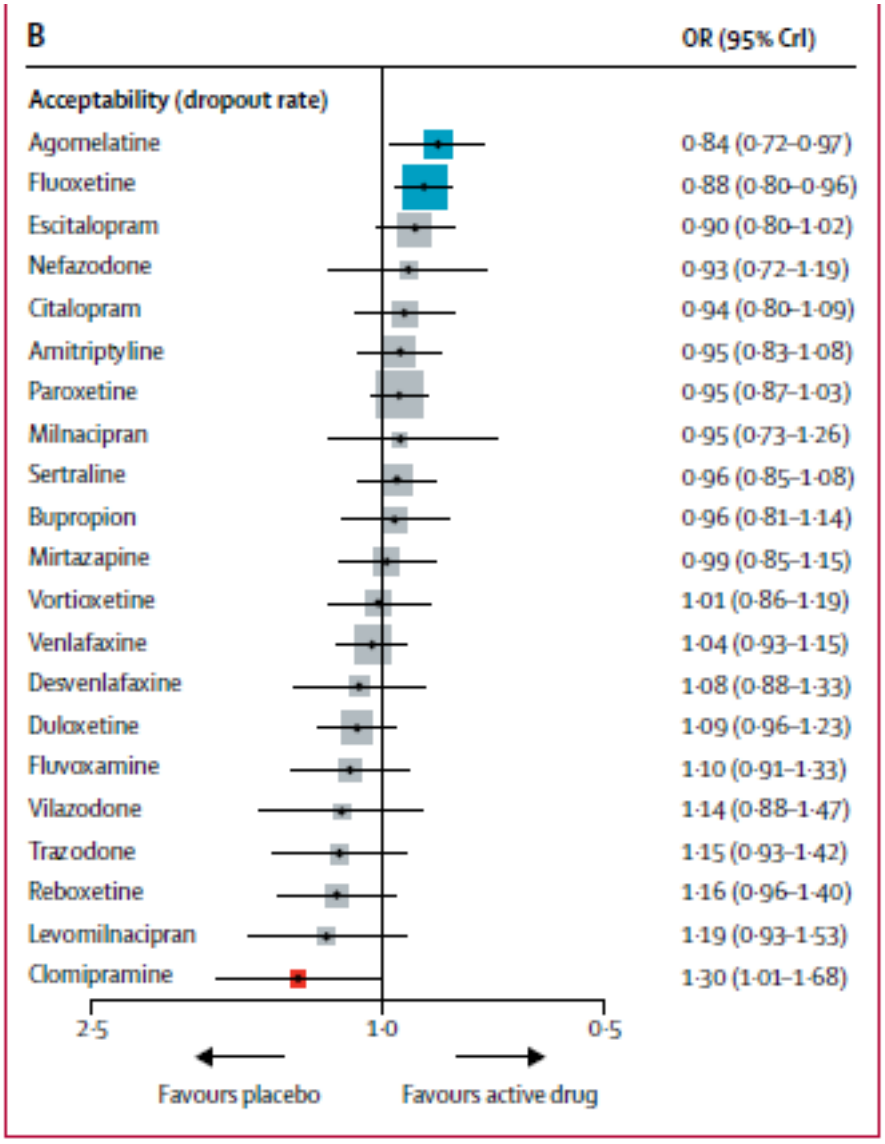
FIGURE 4. Anhedonia scores at different times for patients treated with agomelatine or venlafaxine.

Venlafaxine = SNRI
Serotonin-Noradrenaline
Reuptake Inhibitor

Martinotti et al. (2012) J Clinical Psychopharmacol 32: 487

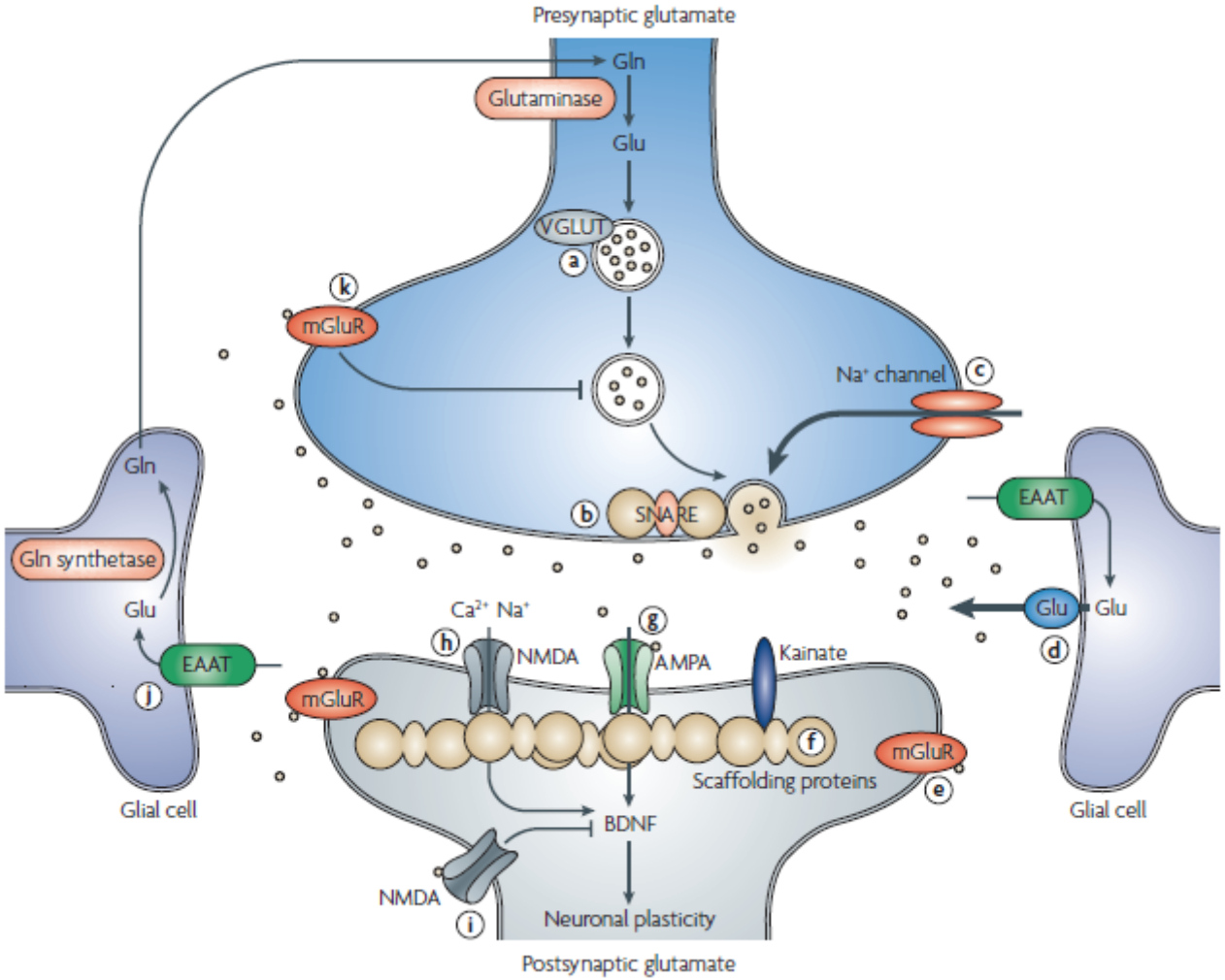
Comparison of Efficacy and Acceptability of different Antidepressants: Meta-analysis





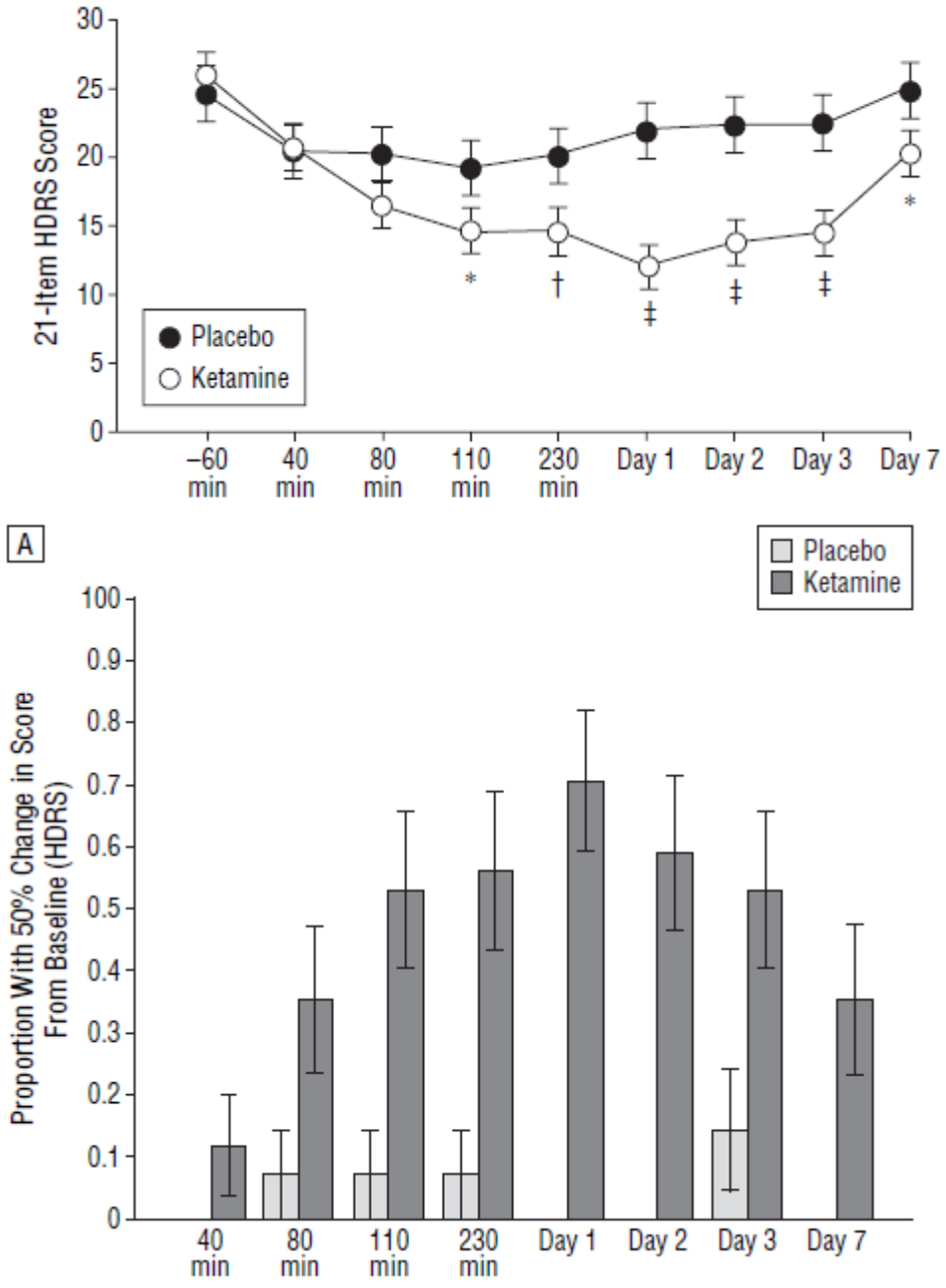
Cipriani et al. (2018) The Lancet 391(10128):1357

Potential novel target for anti-depressant action: modulation of glutamate signalling



Sanacora et al. (2008) Nature Rev Drug Discovery 7: 426

Effect of low-dose ketamine (NMDA-receptor antagonist) on depression: Treatment-resistant chronically-depressed patients

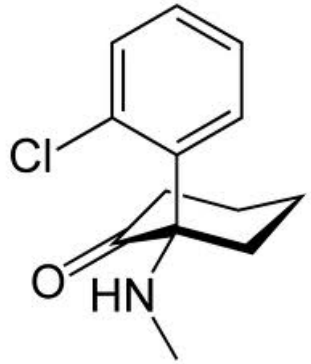


Zarate et al. (2006) Arch Gen Psychiatry 63: 856

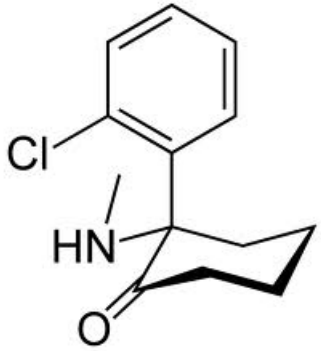
Ketamine: Glutamate NMDA receptor non-competitive antagonist

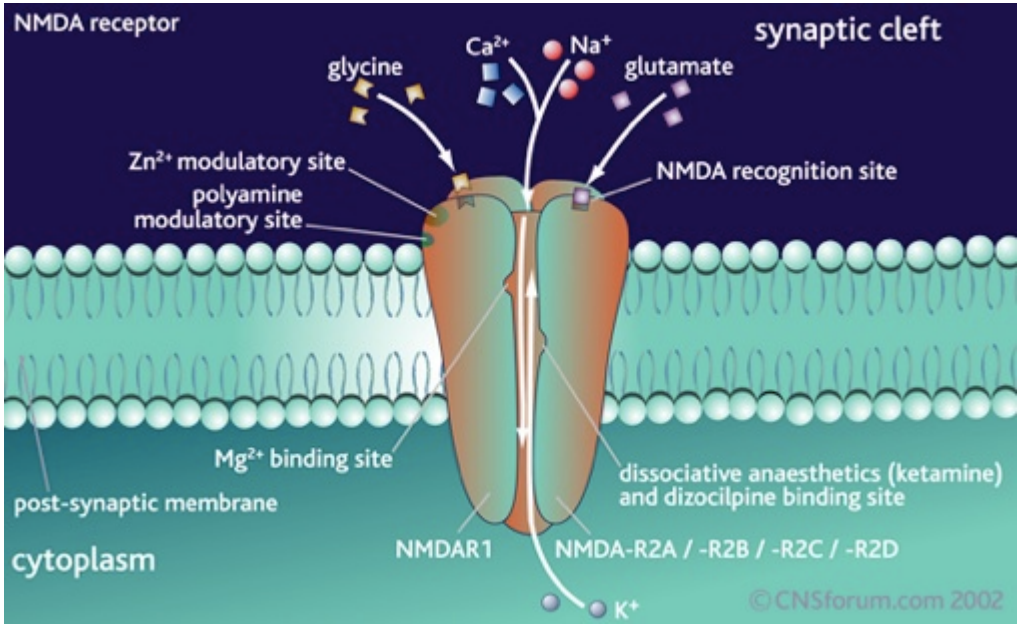
Optical Isomers / Enantiomers

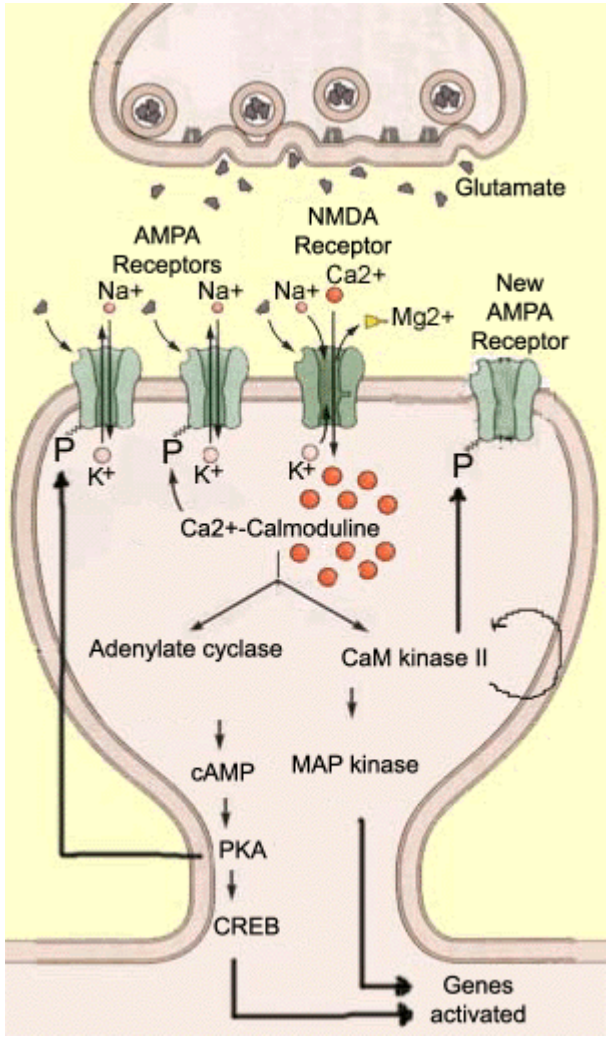
R-ketamine



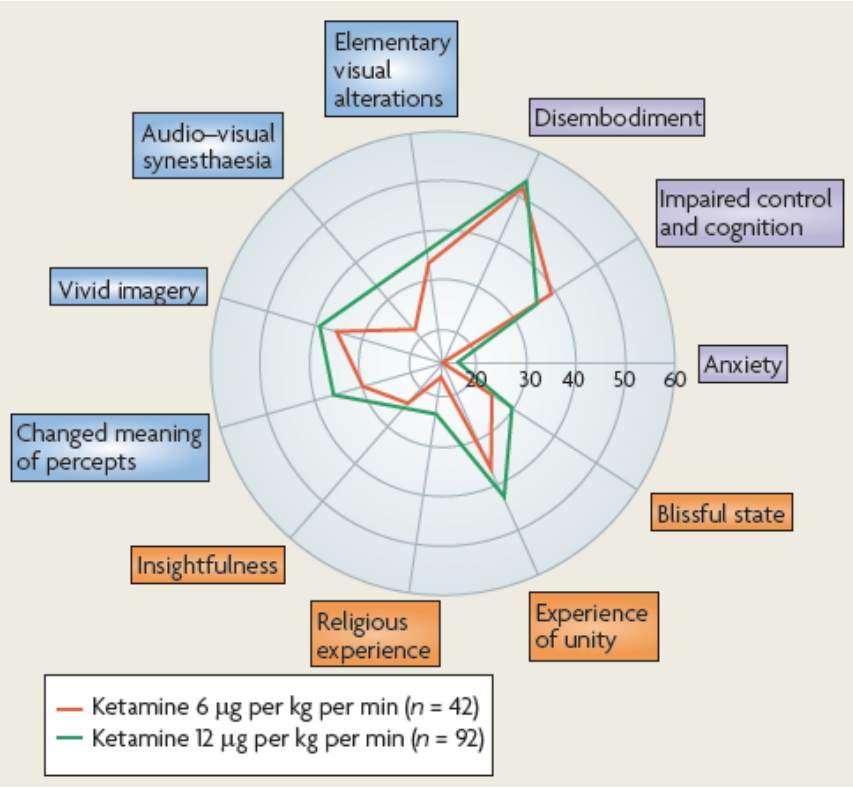
S-ketamine

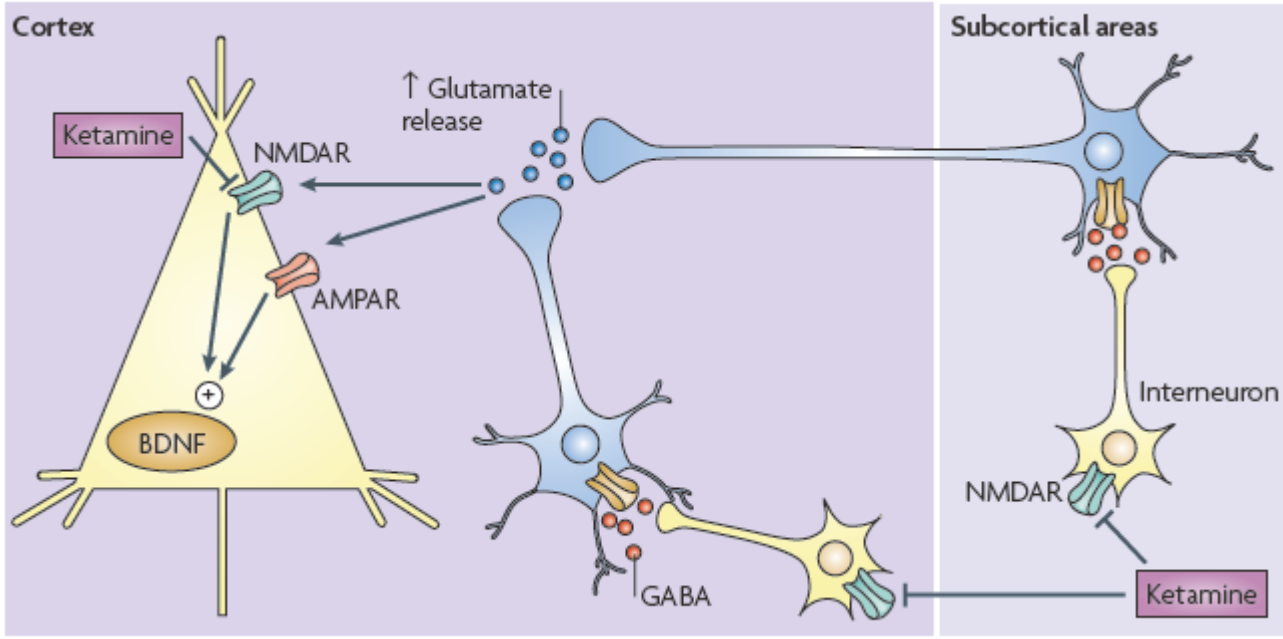






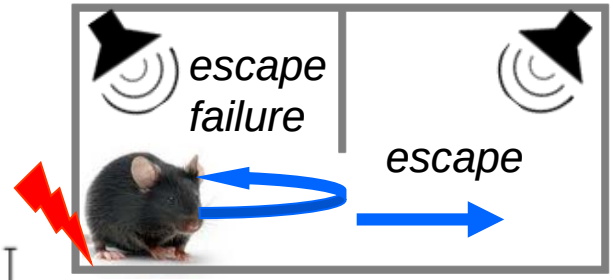
Ketamine: Changes in consciousness and perception, and proposed mechanism of action on glutamate signalling in Prefrontal cortex

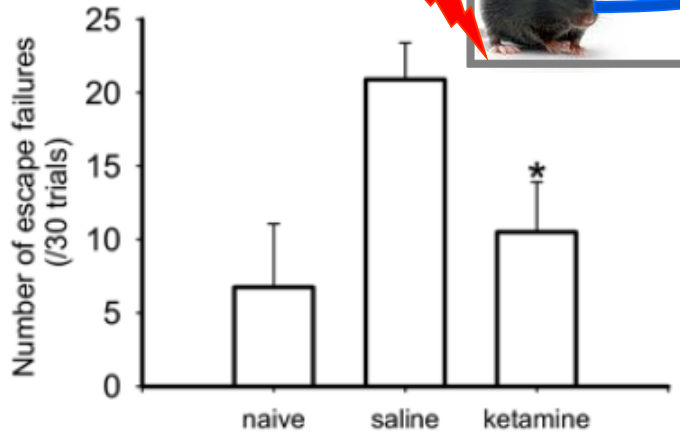


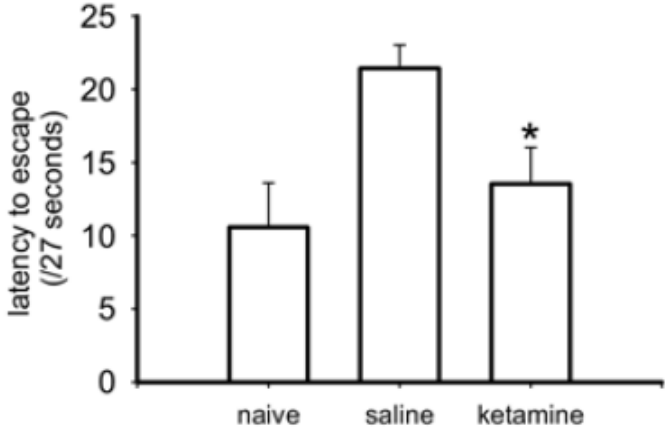


Vollenweider & Kometer (2010) Nature Rev Neurosci 11: 642

Effect of ketamine on 2-way Escape failure in "learned-helplessness" mice

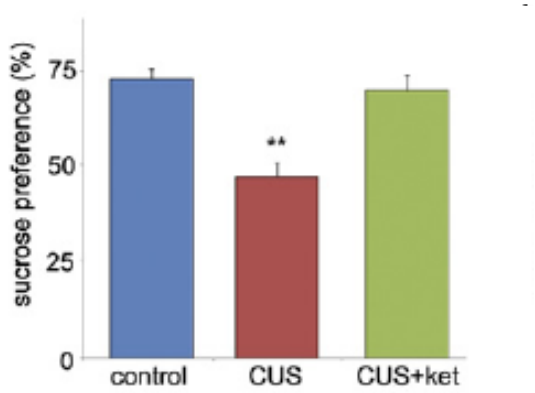


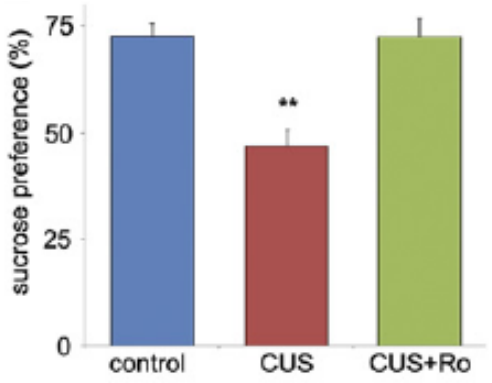


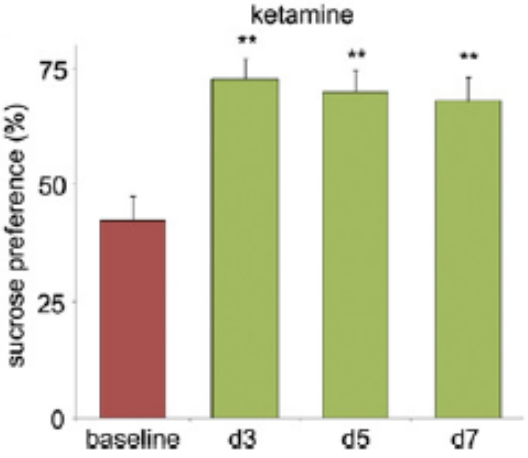


Maeng et al (2008) Biol Psychiatry 63: 349

Effect of ketamine or NMDA2B-R antagonist on Sucrose preference in rats exposed to chronic unpredictable stress



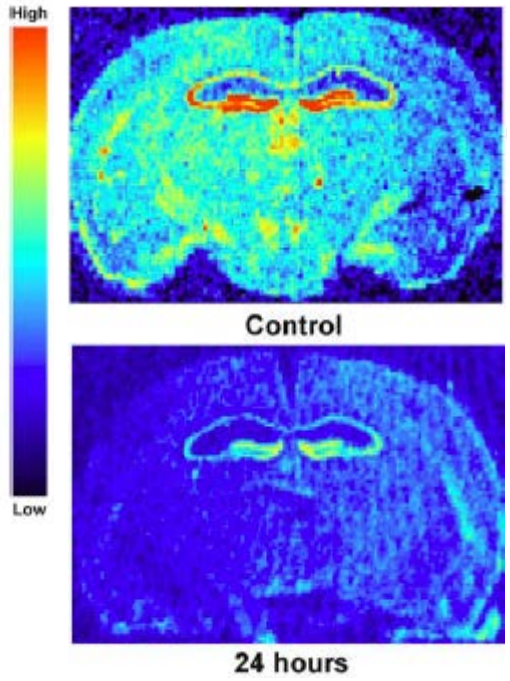


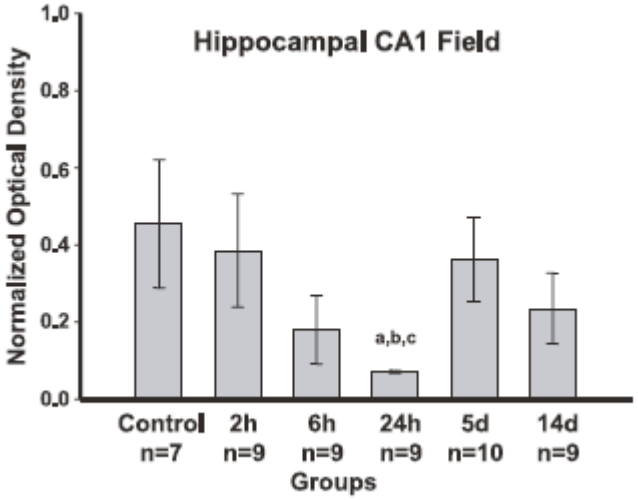


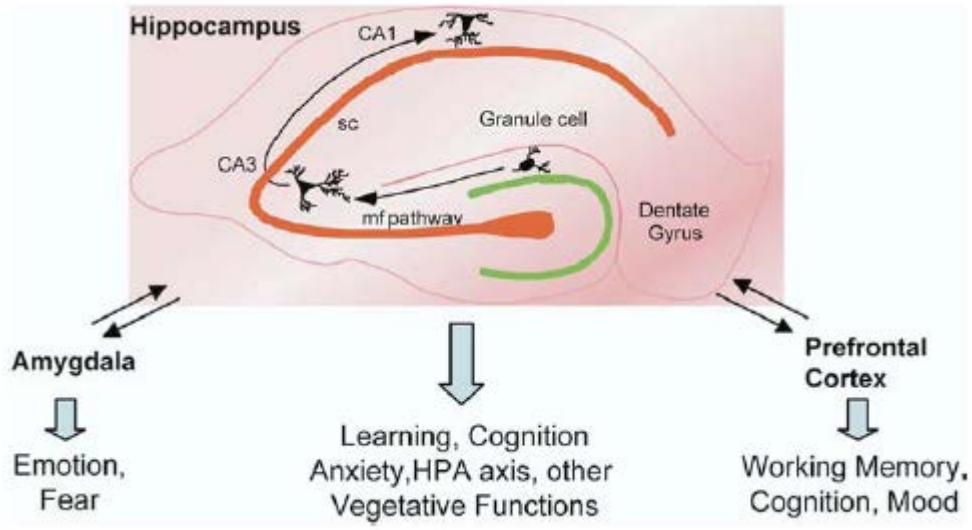
Li et al (2011) Biol Psychiatry 69: 754

Stress decreases Neurotrophins and Synaptic Proteins in Hippocampus and Cortex: Ketamine mechanism-of-action could be to reverse these effects

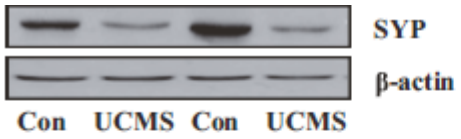
Brain-derived neurotrophic factor (BDNF)



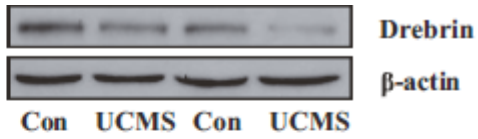


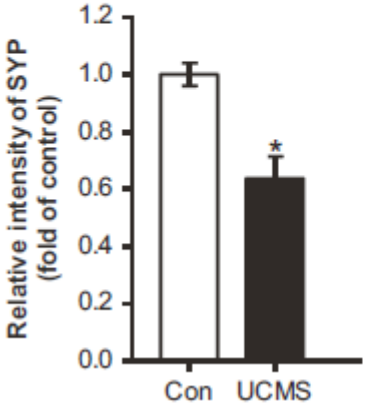


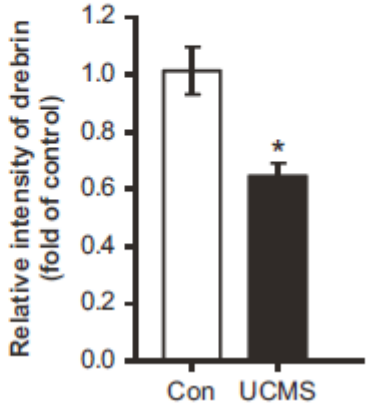
Pre-synaptic Synaptophysin

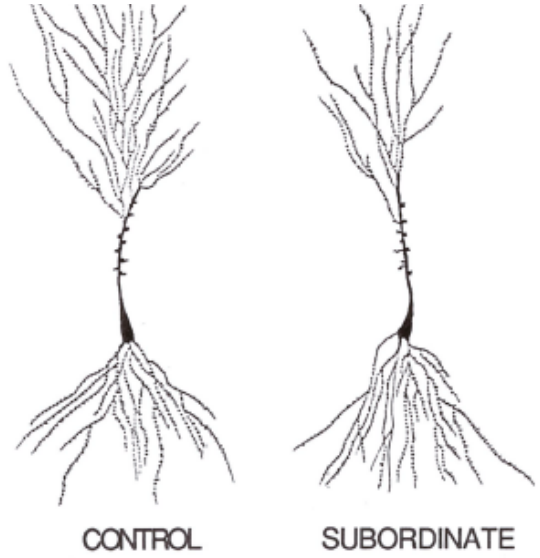


Post-synaptic Drebrin



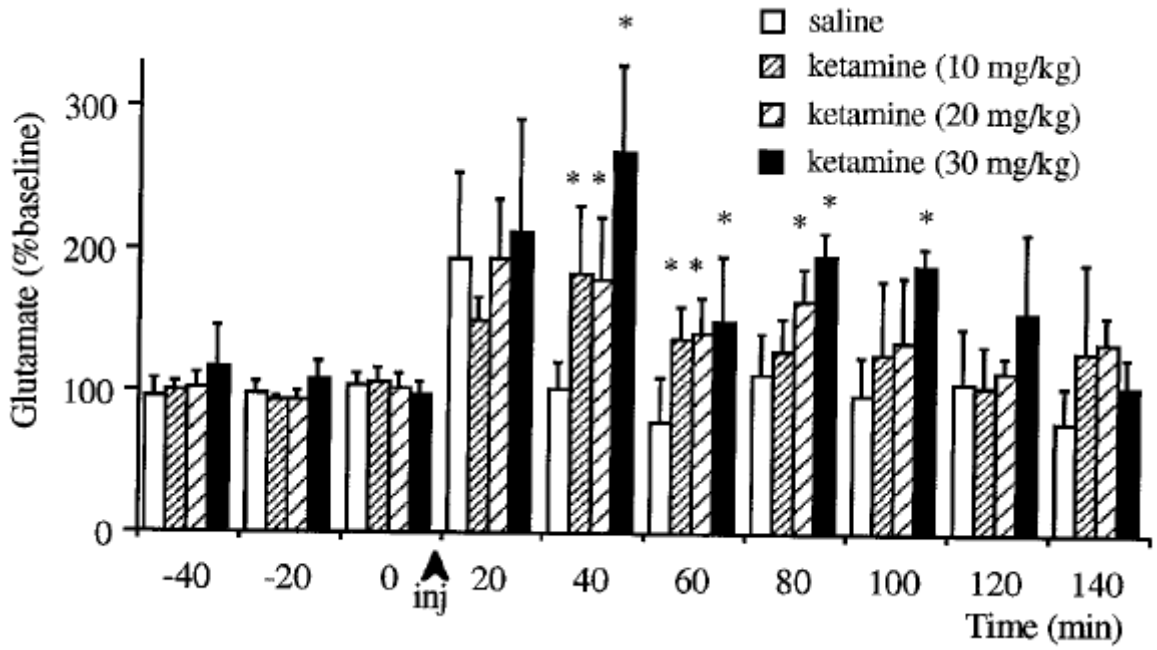




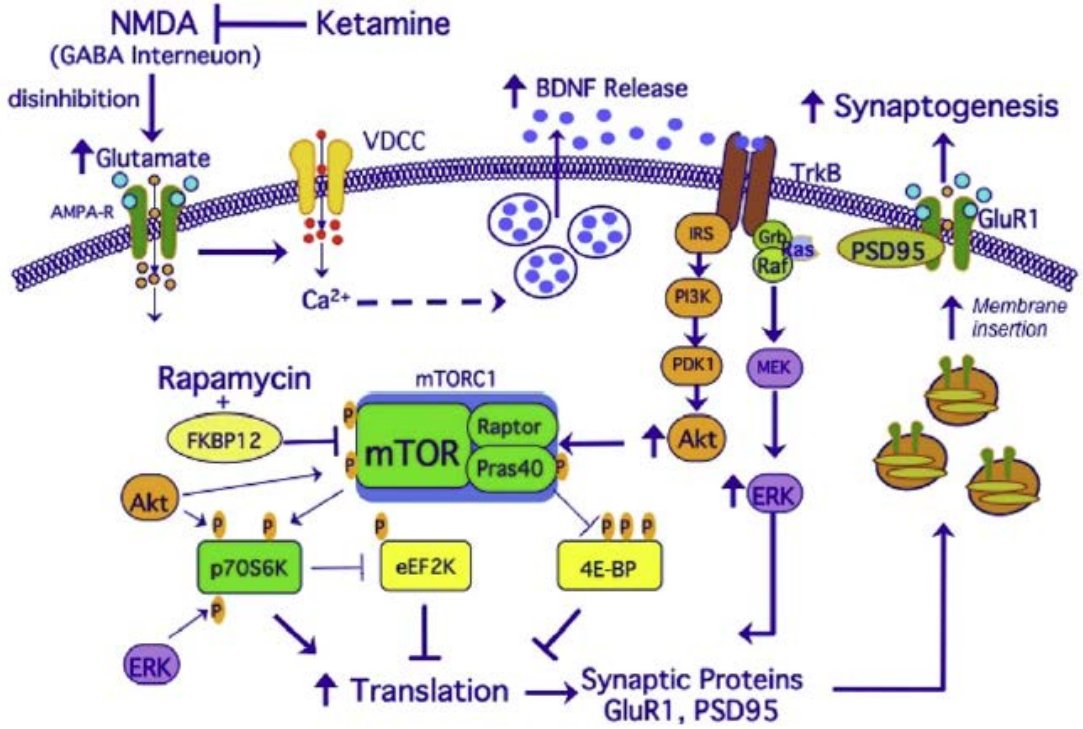


Pizarro et al (2004) Brain Res 1025: 10
Duman & Monteggia (2006) 59: 1116
Zhu et al. (2014) Brain Res 1576: 81

Ketamine: Evidence for stimulation of glutamate release in rat medial prefrontal cortex and Proposed mechanism-of-action on post-synaptic signalling in prefrontal cortex



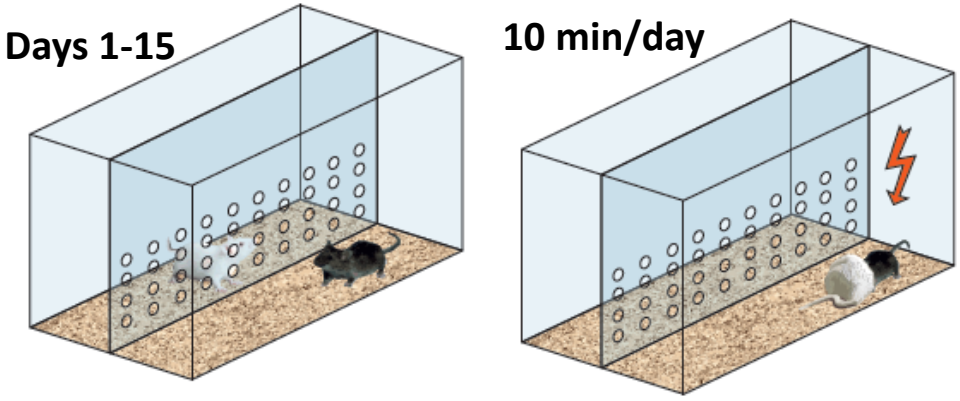
Moghaddam et al (1997)
J Neuroscience 17: 2921

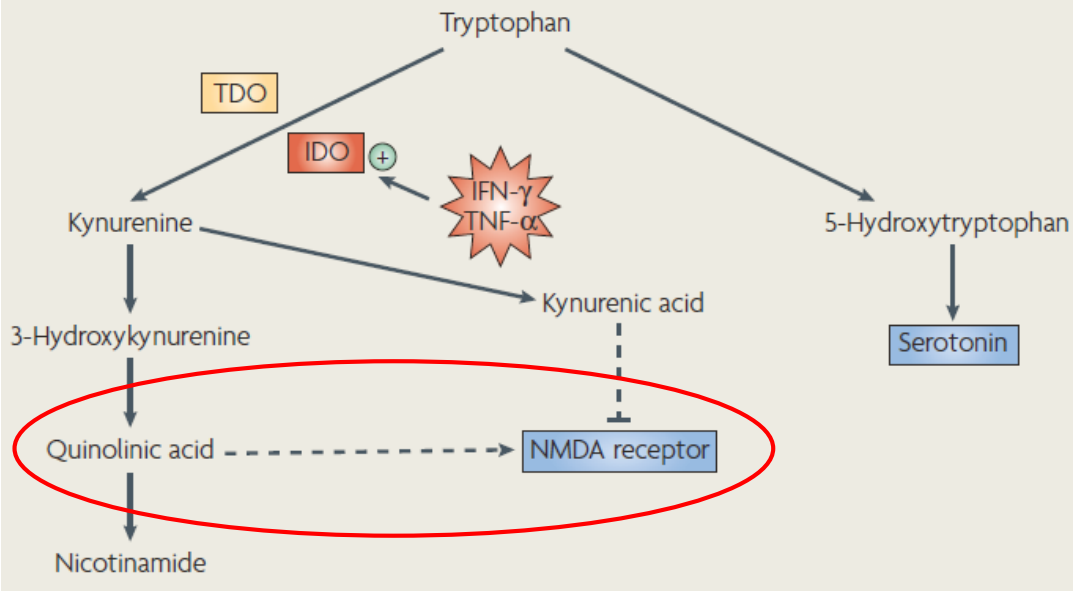


Duman et al (2012)
Neuropharmacol 62: 35

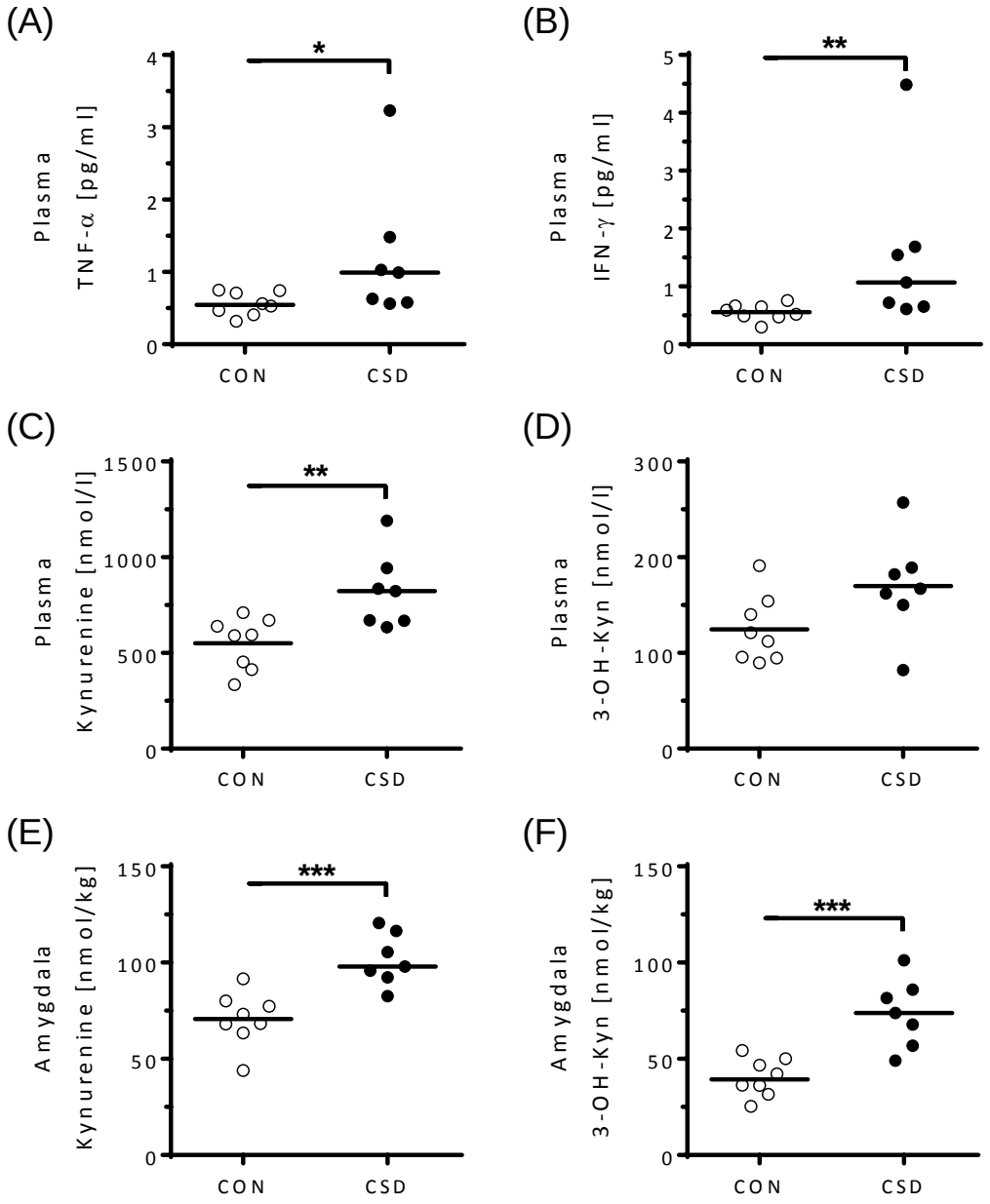
Mouse CSD and Immune-inflammation: Cytokines and Kynurenine Pathway

Chronic social defeat (CSD)



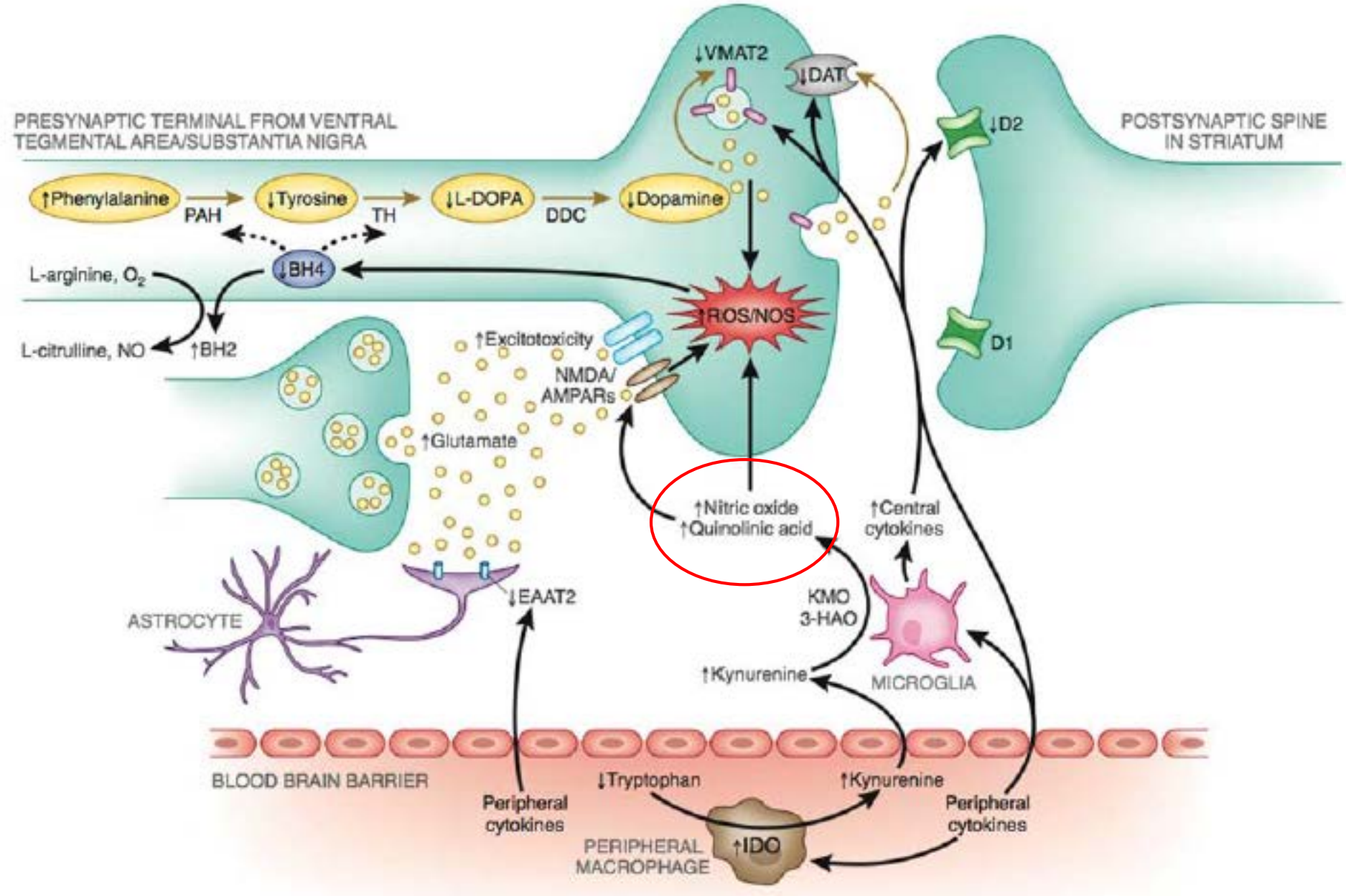


Inflammatory markers



Fuertig et al (2016) Brain, Behavior, Immunity 54: 59

Stress activates Kynurenine Pathway, which can increase glutamate neurotransmission: Ketamine mechanism-ofaction could be to reverse these effects



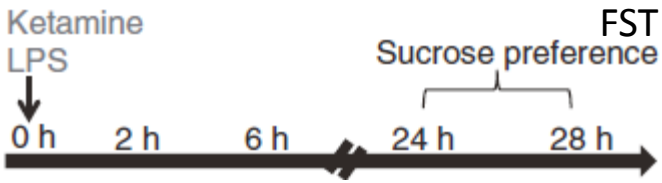
Felger & Treadway (2017) Neuropsychopharmacology 42: 216

Ketamine prevents Inflammation-induced depression-relevant behaviour

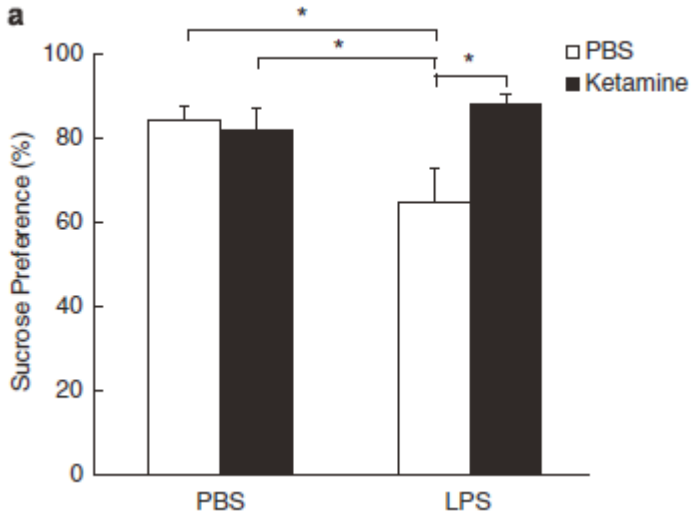
Lipid+Polysaccharide
Outer membrane, Gram-negative bacteria

Lipopolysaccharide → ↑IL-1β, ↑TNF → **Sickness behaviour syndrome (SBS):**
Fever
Anorexia
Increased sleep
Social wihdrawal
Fatigue

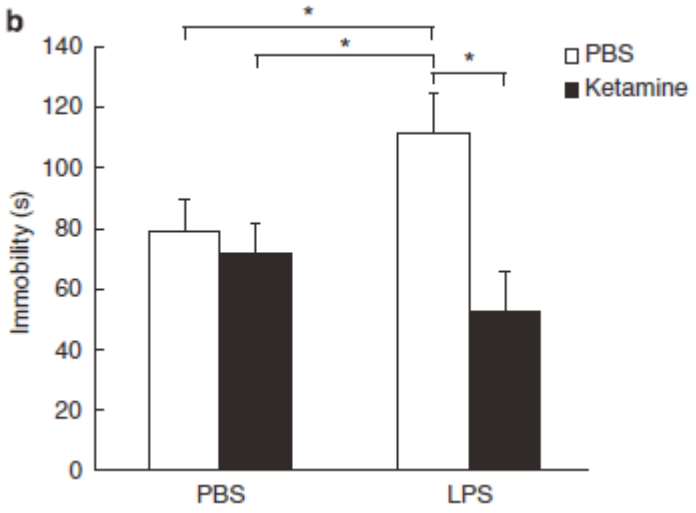
Lipopolysaccharide → ↑IL-1β, ↑TNF → **Depression-relevant behaviour:**
Forced swim test floating
Sucrose preference
Operant behaviour for reward



Sucrose preference test



Forced swim test

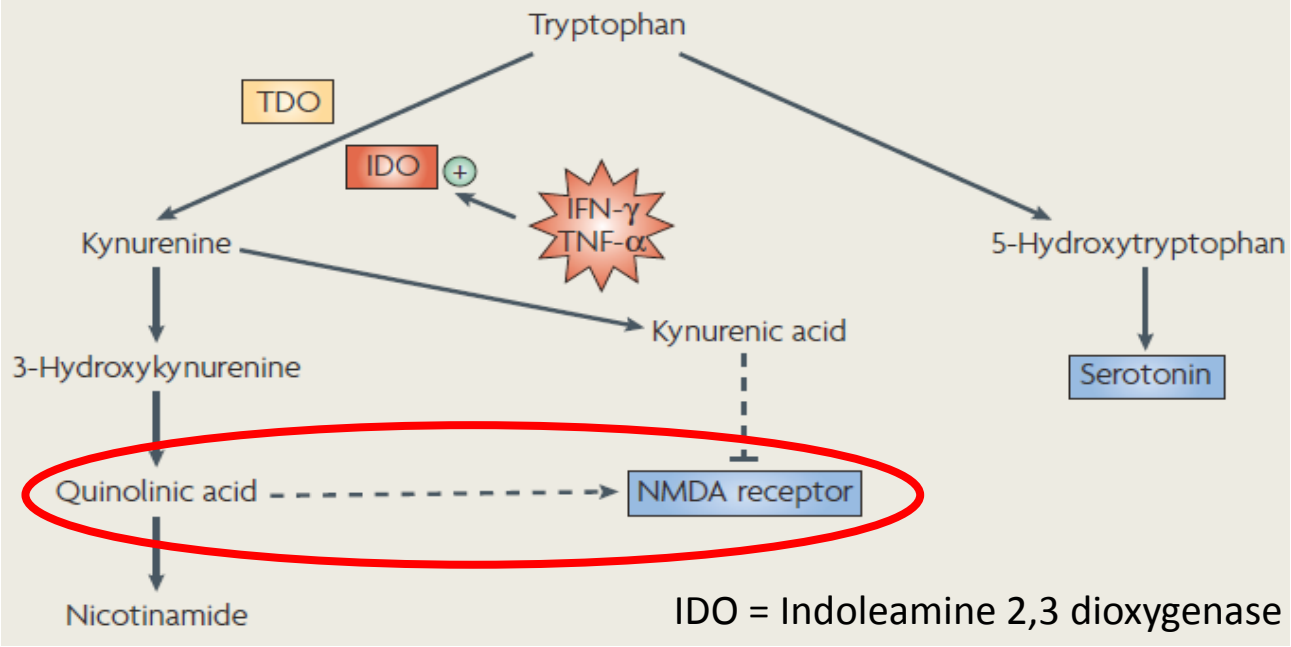


Walker et al (2013) Neuropsychopharmacol 38: 1609

Possible mechanism-of-action of Ketamine in preventing Inflammation-induced depression-relevant behaviour

Table 1 Mean Concentration of Tryptophan and Kynurenine Metabolites (±SEM) in the Brain (pg/mg) for Mice Treated with lipopolysaccharide (LPS) ($n=8$) or Phosphate-buffered Saline (PBS) ($n=10$).

	Brain (pg/mg)	
	Saline	**LPS**
Tryptophan	4316.58 (128.14)	5332 (161.60)**
Kynurenine	75.85 (15.08)	230.05 (20.06)**
3-hydroxykynurenine	77.50 (13.33)	293.60 (33.15)***
3-hydroxyanthranilic acid	0.62 (0.12)	1.94 (0.18)***
Quinolinic acid	3.90 (0.36)	12.18 (1.57)***



Walker et al (2013) Neuropsychopharmacol 38: 1609

Human evidence for an inflammation aetio-pathophysiology of depression

- **Candidate gene (SNP) case-control association studies:**

TNF	Tumor necrosis factor	Pro-inflammatory cytokine
DCNP1	Dendritic cell nuclear protein-1	Dendritic cells activate T cells and B cells
NPY	Neuropeptide Y	T helper cell differentiation

- **Increased post mortem CNS expression levels of pro-inflammatory cytokines:**

  E.g. Prefrontal cortex TNF receptor 1, IFN-γ receptor

- **Increased blood levels of:**

  Pro-inflammatory cytokines (TNF, IL-6)

  Cytokine-dependent monoamine-regulating enzymes and products (E.g. Indoleamine 2,3-dioxygenase)

- **Pro-inflammatory cytokines used to treat disease associated with high rates of depression:**

  E.g. IFN-α and Hepatitis C

- **Depression and autoimmune disorders are highly co-morbid:**

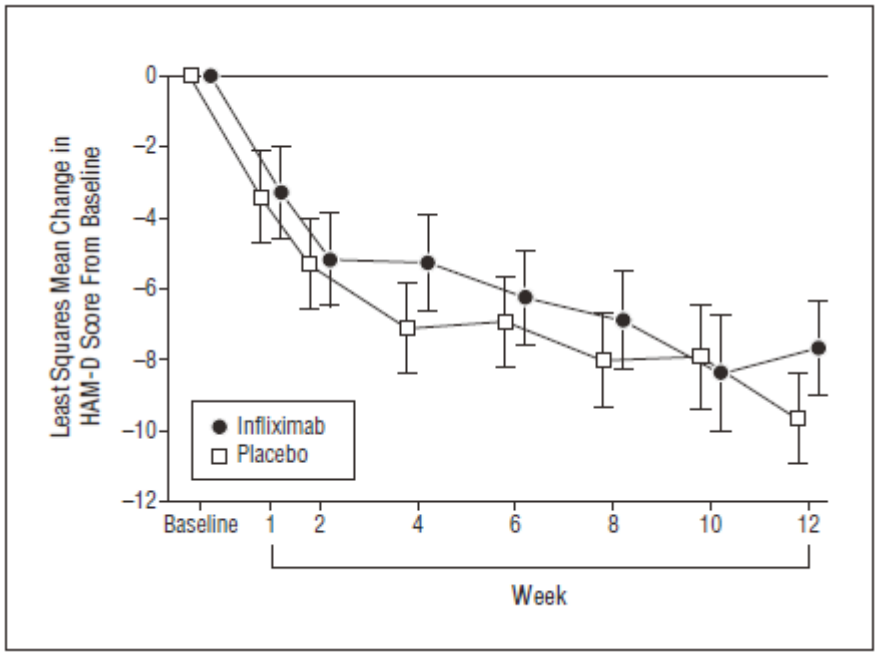
  E.g. Multiple sclerosis, Rheumatoid arthritis

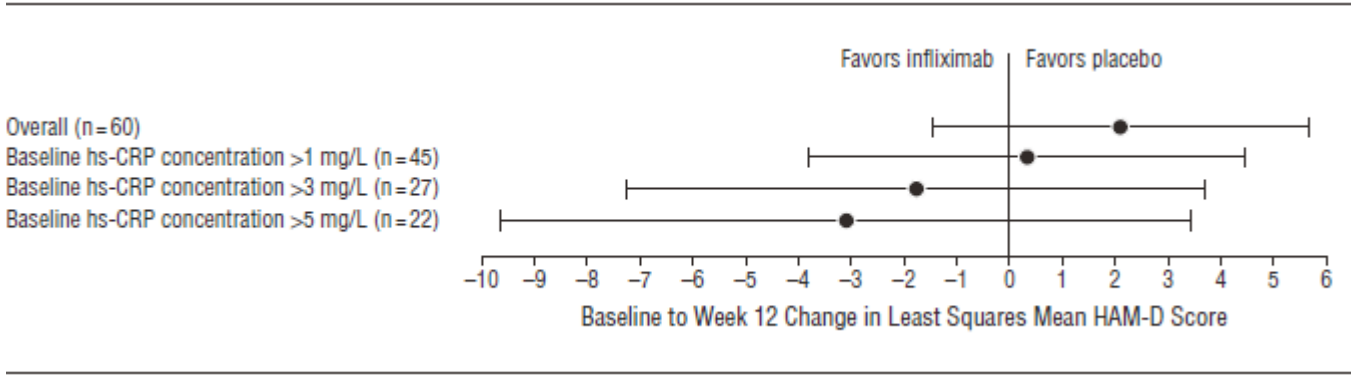
- **Positive proof-of-concept data for anti-inflammatory biologics as anti-depressants:**

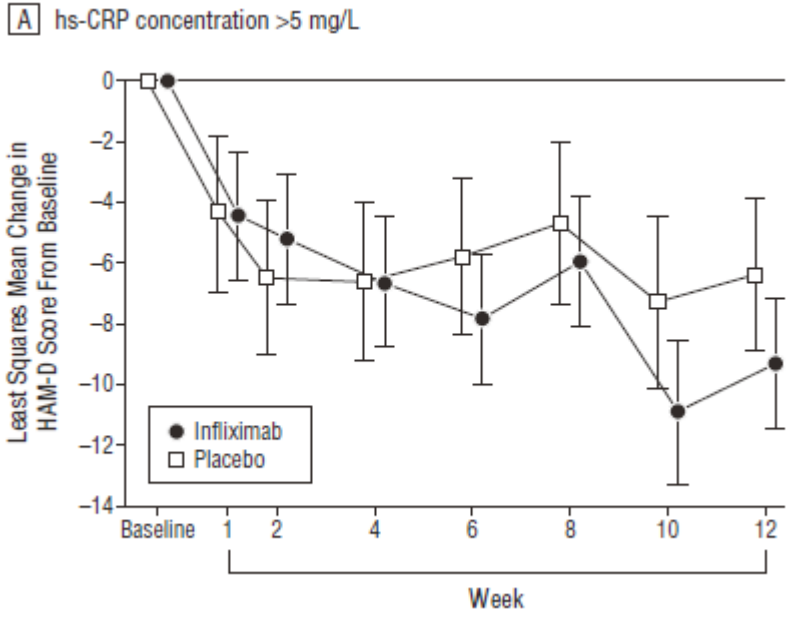
  E.g. TNF antibody Infliximab

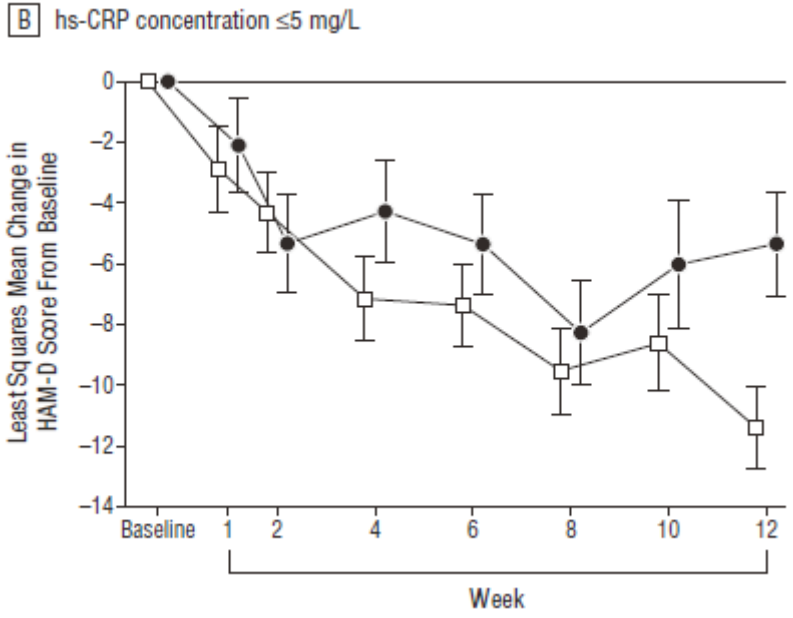
A trial with the tumor necrosis factor antibody Infliximab for treatment-resistant depression

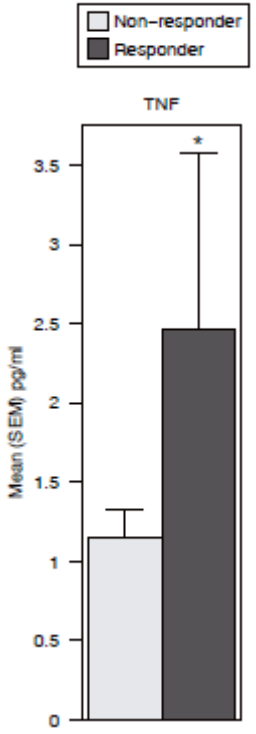
Subjects were grouped according to blood levels of the inflammation marker C-reactive protein





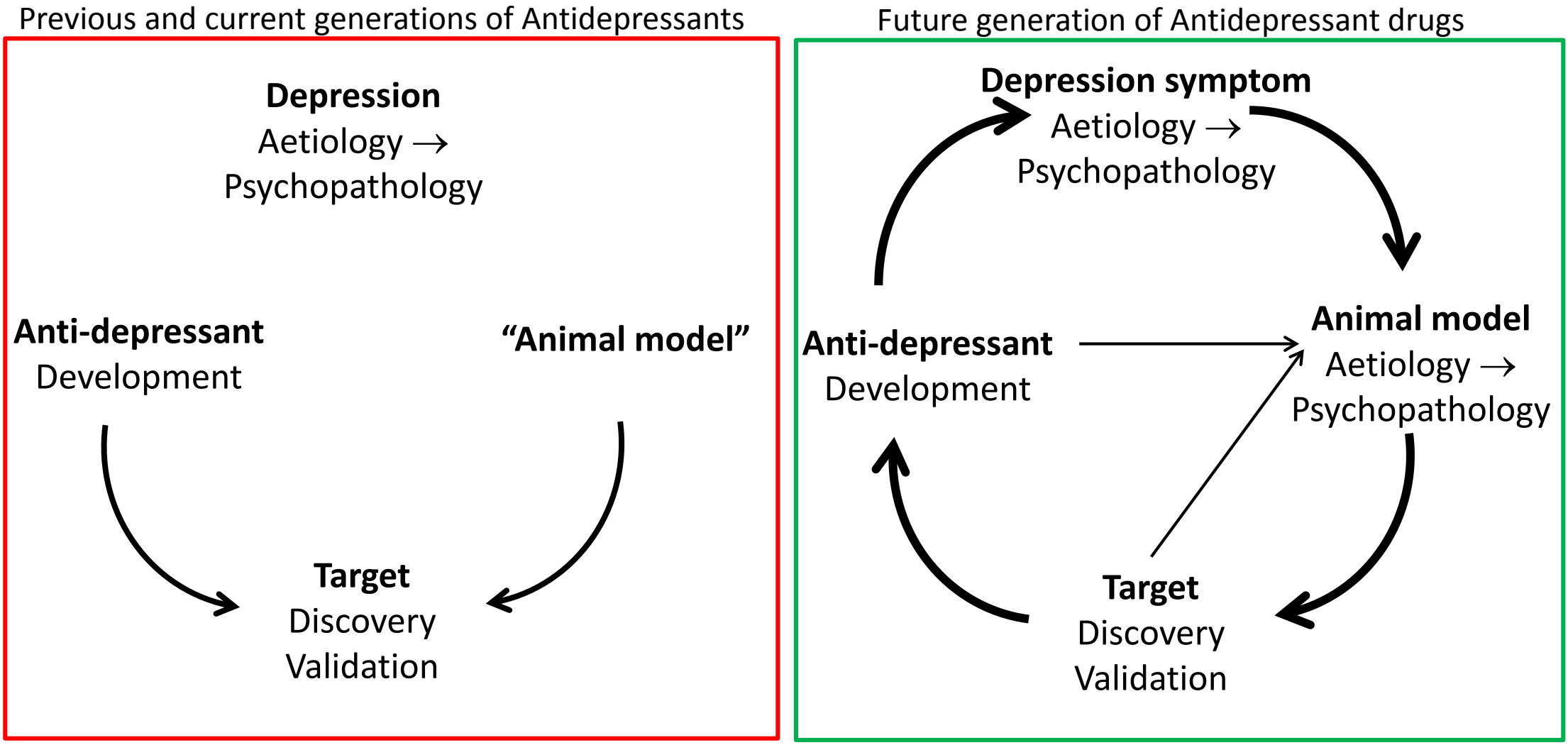




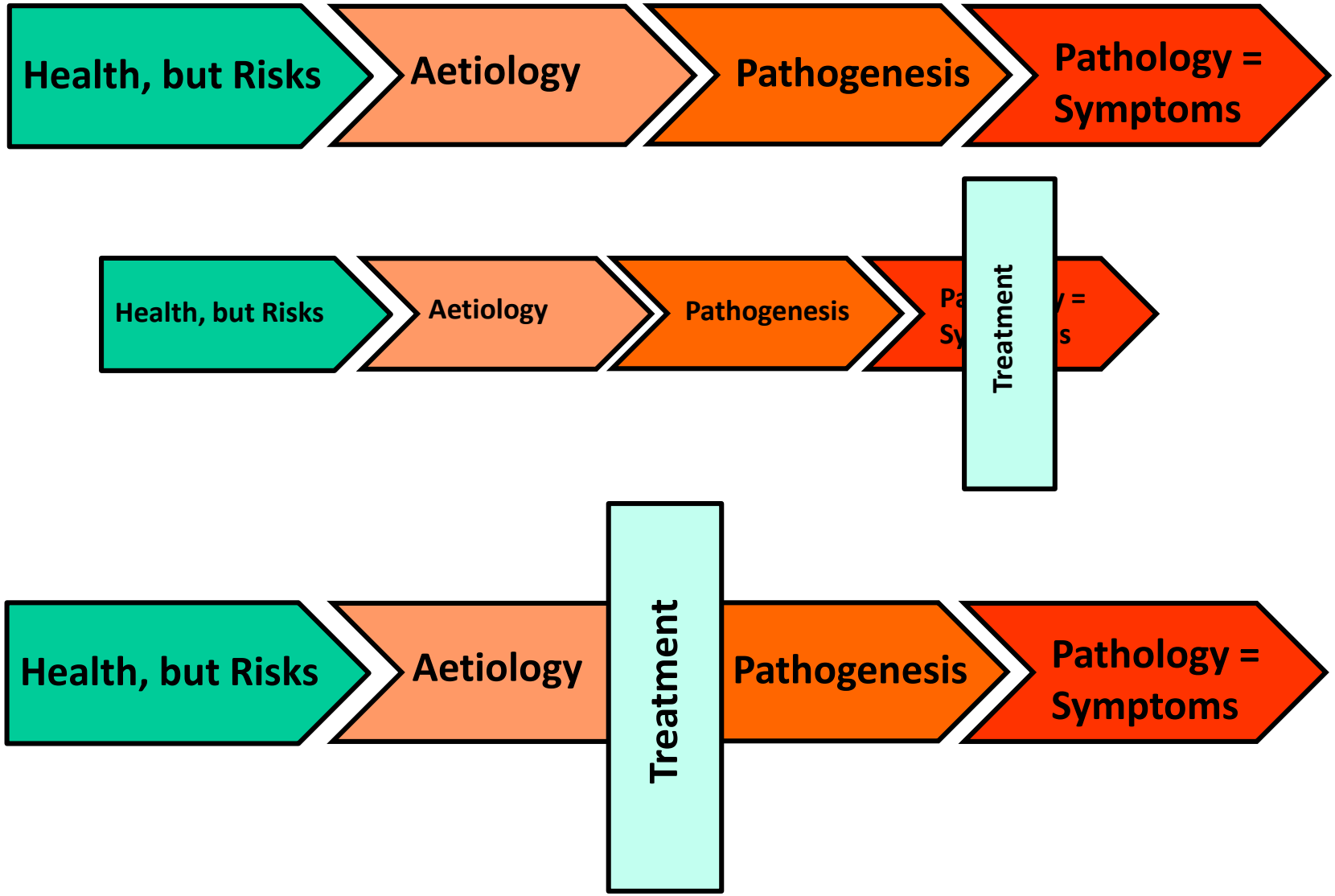


Raison et al (2013) JAMA 70: 31

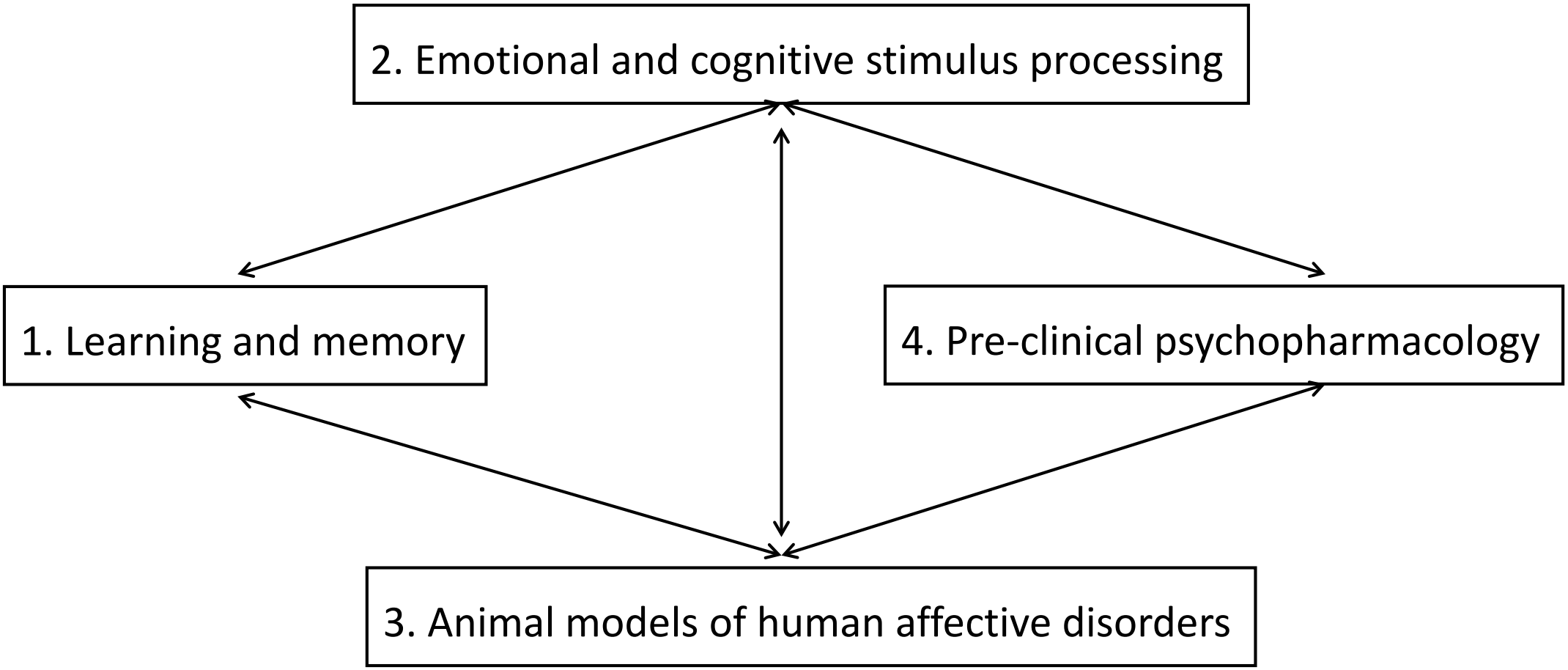
Lack of Animal model relevance/validity has Inhibited Antidepressant Discovery



The Aetiology-Pathogenesis Interface as the key to understanding depression:
Understanding the mechanism underlying a disease is essential to its treatment



Themes for Comparative behavioural neuroscience



Aim: The whole is greater than the sum of its parts

Anti-depressants: the next generation?

- Because of the limited efficacy of selective serotonin reuptake inhibitors, improved anti-depressant drugs are essential
- Agomelatine is a new anti-depressant that has two properties: melatonin receptor agonist and serotonin 2C receptor antagonist
- Disturbed sleep is a common symptom of depression
- The suprachiasmatic nucleus of the hypothalamus (SCN) is the pacemaker of circadian rhythms.
- In addition to endogenous circadian rhythm, there are Zeitgeber, and the most important of these is light-dark.
- With respect to light-dark control of circadian rhythm, there is bi-directional communication between the SCN and the pineal gland.
- Inhibition of the pineal gland by the SCN is driven by light. In the absence of light, melatonin is released from the pineal gland and binds to MT1/2 receptors on the cells of the SCN. This melatonin input is important in re-setting the activity of the SCN
- In depression, plasma melatonin levels are decreased
- Agomelatine binds to MR1/2 receptors which are G protein-coupled. Via Gαi, cell signalling is decreased. In SCN neurons this leads to decreased cell firing
- Agomelatine binds to 5-HT2C receptor which is G protein-coupled. Via Gαq, cell signalling is increased. Therefore, as a 5-HT2C antagonist, agomelatine inhibits firing of neurons expressing 5-HT2C. This leads to disinhibition of dopamine neurons
- Valid animal models demonstrate that agomelatine recovers reward sensitivity
- Clinical trials demonstrate that agomelatine recovers reward sensitivity (anhedonia) better than SSRIs
- The NMDA antagonist ketamine has been demonstrated to have rapid-onset anti-depressant effects in treatment-resistant depression patients
- Subsequently, ketamine has been demonstrated to have relevant effects in animal models of depression

• Ketamine could be anti-depressant because it antagonizes the NMDA receptor agonist effects of quinolinic acid (see Lecture 10). Interestingly, ketamine blocks the depression effects of lipopolysaccharide injection
• Further evidence that anti-inflammatory drugs are anti-depressant includes: (1) Reversal of increased fear in chronic social defeat mice by an indoleamine dioxygenase inhibitor; (2) Reduction of depression in patients with high inflammatory marker by an antibody for tumor necrosis factor (TNF)