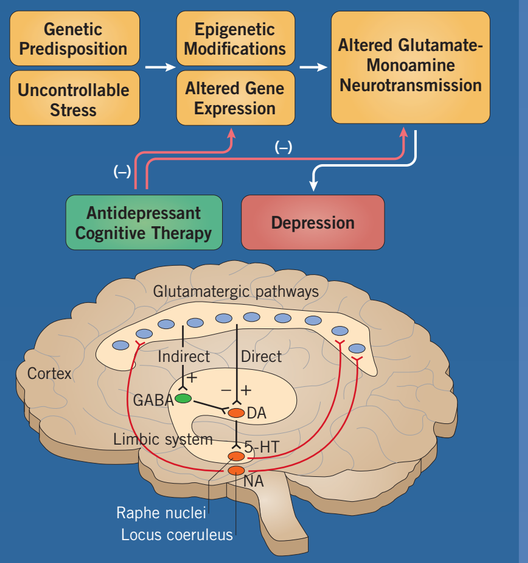
Antidepressants: Current and Future Targets

Phil Skolnick[1], Piotr Popik[2,3] and Ramon Trullas[4,5]

[1]National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892
[2]Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31-343 Kraków, Poland
[3]Faculty of Health Sciences, Medical College, Jagiellonian University, Kraków, Poland
[4]Neurobiology Unit, Institut d'Investigacions Biomèdiques de Barcelona, Consejo Superior de Investigaciones Científicas, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Rosselló 161, 08036 Barcelona, Spain
[5]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain

Major depressive disorder (MDD), often referred to as major depression, is characterized by the core symptoms of depressed mood and a loss of interest and/or pleasure. Other symptoms that may be manifested include significant weight changes (loss or gain), sleep disturbances (insomnia or hypersomnia), fatigue, diminished ability to think or concentrate, feelings of worthlessness or guilt, recurrent thoughts of death or suicide, and psychomotor agitation or retardation. In addition to producing clinically significant distress, a major depressive episode is almost uniformly accompanied by some degree of social and/or occupational impairment, negatively impacting quality of life and contributing to the societal burden associated with loss of work and health care costs. In developed countries approximately 15% of the population has been affected by MDD in their lifetime and around 5% has suffered a major depressive episode during the last year[1]. The risk of developing MDD is almost twice as high in women[2] and the majority of people affected with MDD do not receive standard treatment[3].

Etiology of Depression



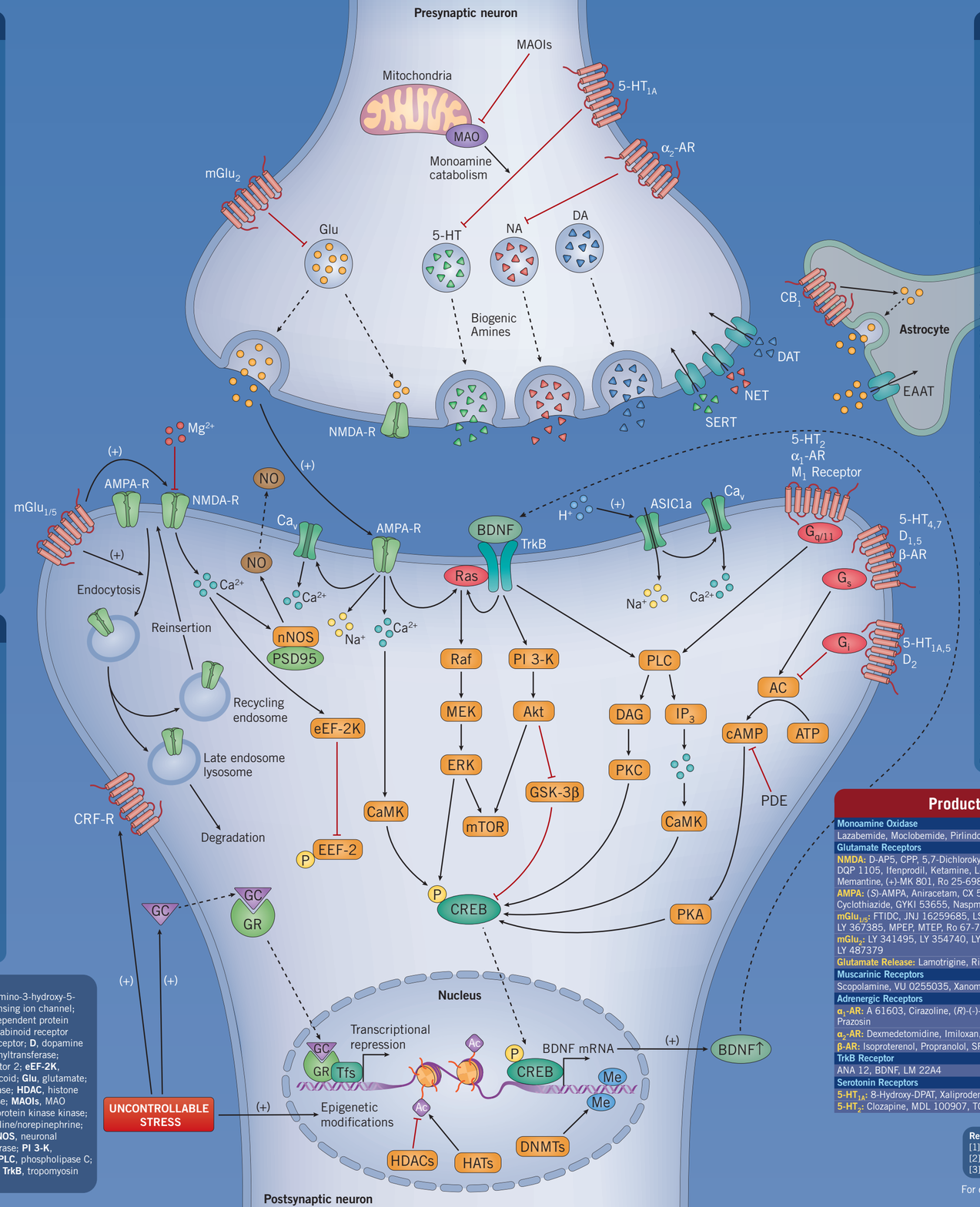
Depression may be triggered by the conjunction of several etiological factors which are capable of altering the function of brain areas associated with mood, such as the limbic system. There appears to be a strong genetic contribution to depression, and although a number of gene candidates have been reported, none have been irrefutably identified. Stressful life experiences may converge to modify gene expression that results in enduring changes in neurotransmission in limbic areas of the brain. Antidepressant drugs and cognitive therapy limit the negative effects of these etiological factors.

Pharmacology of Antidepressant Drugs

All currently approved antidepressants (ADs) increase the synaptic availability of one or more of the biogenic amine transmitters: noradrenaline, dopamine, and serotonin. These ADs act either by inhibition of monoamine oxidase (MAO), an enzyme responsible for the metabolism of biogenic amines, or by inhibiting one or more of the transport proteins that remove these biogenic amines from the synaptic cleft. The latter mechanism is the principal means of terminating the actions of these neurotransmitters. The majority of ADs in current use selectively block the uptake of serotonin and/or noradrenaline. In well controlled, double blind clinical trials, biogenic amine-based ADs require ≥2 weeks of treatment before providing meaningful relief. This "therapeutic lag" has been hypothesized to represent neuroplastic changes that must precede a reduction in depressive symptomatology.

The objective of identifying novel targets that bypass the aminergic synapse is to develop drugs that are both more effective and rapid acting than currently approved agents. Clinical studies performed over the past decade with NMDA antagonists like ketamine and traxoprodil[4], and the muscarinic antagonist scopolamine[5], have demonstrated that it is possible to produce a rapid and robust therapeutic response in depressed individuals, many of whom do not respond to biogenic amine based agents. While many promising targets have been identified, a high safety bar will be demanded of new therapeutics as long as alternative therapies, however imperfect, are available.

Abbreviations
5-HT, serotonin; **Ac**; acetylation; **AC**, adenylyl cyclase; **Akt/PKB**, protein kinase B; **AMPA-R**, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **AR**, adrenoceptor/adrenergic receptor; **ASIC**, acid-sensing ion channel; **ATP**, adenosine triphosphate; **BDNF**, brain-derived neutrophic factor; **CaMK**, Ca^{2+}/calmodulin-dependent protein kinase; **cAMP**, cyclic adenosine monophosphate; **Ca_v**, voltage-gated calcium channel; **CB_1**, cannabinoid receptor type 1; **CREB**, cAMP response element-binding protein; **CRF-R**, corticotropin-releasing factor receptor; **D**, dopamine receptor; **DA**, dopamine; **DAG**, 1,2-diacylglycerol; **DAT**, dopamine transporter; **DNMT**, DNA methyltransferase; **EAAT**, excitatory amino acid transporter/glutamate transporter; **EEF-2**, eukaryotic elongation factor 2; **eEF-2K**, eukaryotic elongation factor-2 kinase; **ERK**, extracellular signal-regulated kinase; **GC**, glucocorticoid; **Glu**, glutamate; **GR**, glucocorticoid receptor; **GSK-3β**, glycogen synthase kinase 3β; **HAT**, histone acetyltransferase; **HDAC**, histone deacetylase; **IP_3**, inositol 1,4,5-trisphosphate; **M**, muscarinic receptor; **MAO**, monoamine oxidase; **MAOIs**, MAO inhibitors; **MAPK**, mitogen-activated protein kinase; **Me**, methylation; **MEK**, mitogen-activated protein kinase kinase; **mGlu**, metabotropic glutamate receptor; **mTOR**, mammalian target of rapamycin; **NA**, noradrenaline/norepinephrine; **NET**, noradrenaline/norepinephrine transporter; **NMDA-R**, N-methyl-D-aspartic acid receptor; **nNOS**, neuronal nitric oxide synthase; **NO**, nitric oxide; **NR2B**, NMDA receptor subtype 2B; **PDE**, phosphodiesterase; **PI 3-K**, phosphatidylinositol-4,5-bisphosphate 3-kinase; **PKA**, protein kinase A; **PKC**, protein kinase C; **PLC**, phospholipase C; **PSD95**, postsynaptic density protein 95; **SERT**, serotonin transporter; **Tfs**, transcription factors; **TrkB**, tropomyosin receptor kinase B



Targets for the Development of Antidepressants

Presynaptic targets:

- Receptors that regulate neurotransmitter release such as the 5-HT$_{1A}$, α_2 adrenoceptor, mGlu$_2$ and NMDA receptor.
- MAO, an enzyme that catabolizes monoamines.
- Neurotransmitter transporters, exemplified by biogenic amine transporters. Inhibiting these transporters increases the availability of neurotransmitter at the synaptic cleft, a key action in the mechanism of most currently prescribed antidepressants.

Postsynaptic targets:

Targets for antidepressant action include both ionotropic and metabotropic receptors, as well as the signal transduction pathways activated by these receptors. These pathways converge in regulating gene expression, release of neurotrophic factors, and synaptic plasticity that may contribute to the mechanism of antidepressant action.

mGlu$_{1/5}$ receptors regulate NMDA receptor function by modulating its trafficking and cell surface expression. The NMDA receptor is blocked by Mg^{2+} at resting membrane potential; when the membrane is depolarized, this block is relieved, allowing Ca^{2+} to enter the cell. Ca^{2+} participates in a number of cellular cascades, including nitric oxide synthesis, which functions as a retrograde neuronal messenger. Ca^{2+} can also enter the cell via voltage-dependent Ca^{2+} channels (Ca_v) where it activates CaMK. Ca_v function can be modulated by other ion channels sensitive to glutamate such as the AMPA receptor. Both AMPA receptors and the TrkB receptor (the receptor for BDNF) influence the activity of signal transduction pathways, such as the Ras-Raf-MEK-MAPK and PI 3-K-Akt-GSK-3β signaling pathways, which may be involved in the mechanism of action of certain antidepressant drugs.

Other metabotropic receptors such as 5-HT$_2$, α_1 adrenoceptors and M$_1$ muscarinic receptors, stimulate PLC and second messengers through $G_{q/11}$ signaling. G_s and G_i proteins are activated by β-adrenoceptors, D$_{1,2,5}$ receptors and 5-HT$_{1A,4,5,7}$ receptors. These G proteins modulate AC activity, which regulates the level of cAMP and thus PKA activity. cAMP concentrations are also affected by drugs that influence PDE enzymatic activity. Scopolamine is a muscarinic receptor antagonist that inhibits M$_1$-M$_5$ with similar affinity; studies with both knock-out mice and selective pharmacological agents[6] indicate that the M$_1$ and to a lesser extent M$_2$ receptor subtypes may be responsible for the rapid and robust antidepressant effects of this drug.

Many of these signal transduction pathways (CaMK, ERK, GSK-3β) appear to converge in phosphorylating transcription factors such as CREB, a transcription factor that binds to DNA sequences (cAMP response elements (CRE)), before inducing transcription and the expression of certain genes in the nucleus of the neuron. Such changes in gene expression induced by antidepressants can modify the genetic and epigenetic alterations caused by inescapable life experiences, as well as other genetic factors that are believed to be involved in the pathophysiology of depression. For example the rapid acting antidepressants (ketamine, scopolamine) have been associated with rapid changes in synaptic morphology, including increases in spine density and spine head diameter[7].

Compounds clinically validated or with preclinical evidence:

- Acetylcholine muscarinic receptor antagonists: **scopolamine**
- NMDA ion channel blockers: **AZD 6765**, **ketamine**, Mg^{2+}, memantine, **Zn^{2+}**
- NMDA receptor (glycine site) partial agonists: ACPC, **D-cycloserine**, **Glyx-13**, HA-966
- NMDA receptor (glycine site) antagonists: 4-chlorokynurenine, 5,7-dichlorokynurenic acid, L-701,324
- Selective NR2B antagonists: **CP 101, 606 (traxoprodil)**, eliprodil, ifenprodil, **MRK-0657**

Compounds highlighted in bold are clinically validated

Products available from Tocris acting on antidepressant pathways

Monoamine Oxidase
Lazabemide, Moclobemide, Pirlindole

Glutamate Receptors
NMDA: D-AP5, CPP, 5,7-Dichlorokynurenic acid, DQP 1105, Ifenprodil, Ketamine, L-689,560, Memantine, (+)-MK 801, Ro 25-6981
AMPA: (*S*)-AMPA, Aniracetam, CX 546, Cyclothiazide, GYKI 53655, Naspm, S 18986
mGlu$_{1/5}$: FTIDC, JNJ 16259685, LSN 2463359, LY 367385, MPEP, MTEP, Ro 67-7476
mGlu$_2$: LY 341495, LY 354740, LY 379268, LY 487379
Glutamate Release: Lamotrigine, Riluzole

Muscarinic Receptors
Scopolamine, VU 0255035, Xanomeline

Adrenergic Receptors
α_1-AR: A 61603, Cirazoline, (*R*)-(-)-Phenylephrin, Prazosin
α_2-AR: Dexmedetomidine, Imiloxan, RS 79948
β-AR: Isoproterenol, Propranolol, SR 58611A

TrkB Receptor
ANA 12, BDNF, LM 22A4

Serotonin Receptors
5-HT$_{1A}$: 8-Hydroxy-DPAT, Xaliproden
5-HT$_2$: Clozapine, MDL 100907, TCB-2
5-HT$_3$: BIMU 8, GR 113808, GR 125487, RS 67333
5-HT$_5$: SB 699551
5-HT$_7$: AS 19, SB 258719, SB 269970

Dopamine Receptors
D$_1$/D$_5$: SCH 23390, SCH 39166, SKF 81297
D$_2$: L-741,626, (-)-Quinpirole, Sumanirole

Neurotransmitter Transporters
SERT: Citalopram, Fluoxetine, Sertraline
DAT: Bupropion, GBR 12909
NET: Reboxetine, Tomoxetine
EAAT: Dihydrokainic, DL-TBOA, TFB-TBOA

Ion Channels
Ca_v: ω-Conotoxin GVIA, Mibefradil, SNX 482
ASIC: Psalmotoxin 1
TASK-3: ML 365
TREK: BL 1249, Spadin

GR
Fluticasone, Mifepristone

CRF-R
Astressin 2B, CP 376395, CRF (human, rat), NBI 35965, Stressin I

FGFR
PD 173074, SU 5402, SU 6668

Vasopressin Receptors
[Arg8]-Vasopressin, SR 49059

Tachykinin Receptors
GR 73632, L-733,060, RP 67580

Signal Transduction
AC: Forskolin, NKH 477, SQ 22536
Akt: API-1, 10-DEBC, GSK 690693
Ca^{2+} Signaling: A23187, Ionomycin
CAMK: A 484954, KN 93, STO-609
DNMTs: Decitabine, SGI 1027, Zebularine
GSK-3: BIO, SB 216763, SB 415286
HDACs: FK 228, SAHA, Trichostatin A
MEK: BIX 02189, PD 0325901, PD 98059, SL 327, U0126
mTOR: KU 0063794, Rapamycin, Temsirolimus, Torin 1
NO: N$^{\omega}$-Propyl-L-arginine, SNAP
PDE: IBMX, Rolipram, Sildenafil
PI 3-K: LY 294002, Wortmannin, 740 Y-P
PKA: H 89, KT 5720, PKI 14-22
PLC: D609, U 73122
Raf: GW 5074, SB 590885

References:
[1] Kessler, R.C., *et al. Annu.Rev.Clin.Psychol.* 2007
[2] Compton, W.M., *et al. Am.J.Psychiatry.* 2006
[3] Kessler, R.C. and Bromet, E.J., *Annu.Rev.Public Health.* 2013
[4] Skolnick, P., *et al. Trends Pharmacol.Sci.* 2009
[5] Drevets, W.C., *et al. Biol.Psychiatry* 2013
[6] Witkin, J.M., *et al. J.Pharmacol.Exper.Ther.* 2014
[7] Voleti, B., *et al. Biol.Psychiatry* 2013