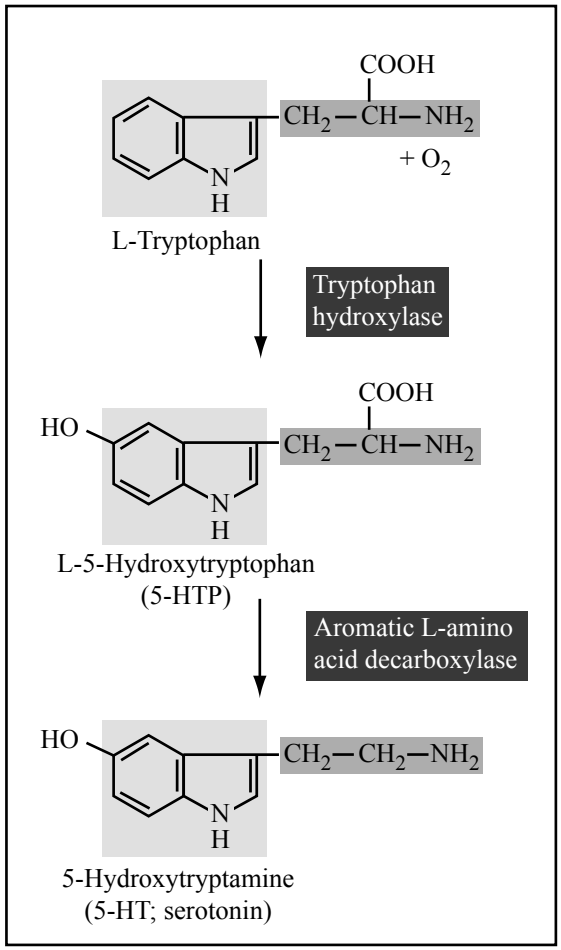
9.98 Neuropharmacology
January (IAP) 2009

5-hydroxytryptamine (5-HT): Serotonin

Involved in depression, anxiety, obesity, aggression and drug addition



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Starting reagent: tryptophan

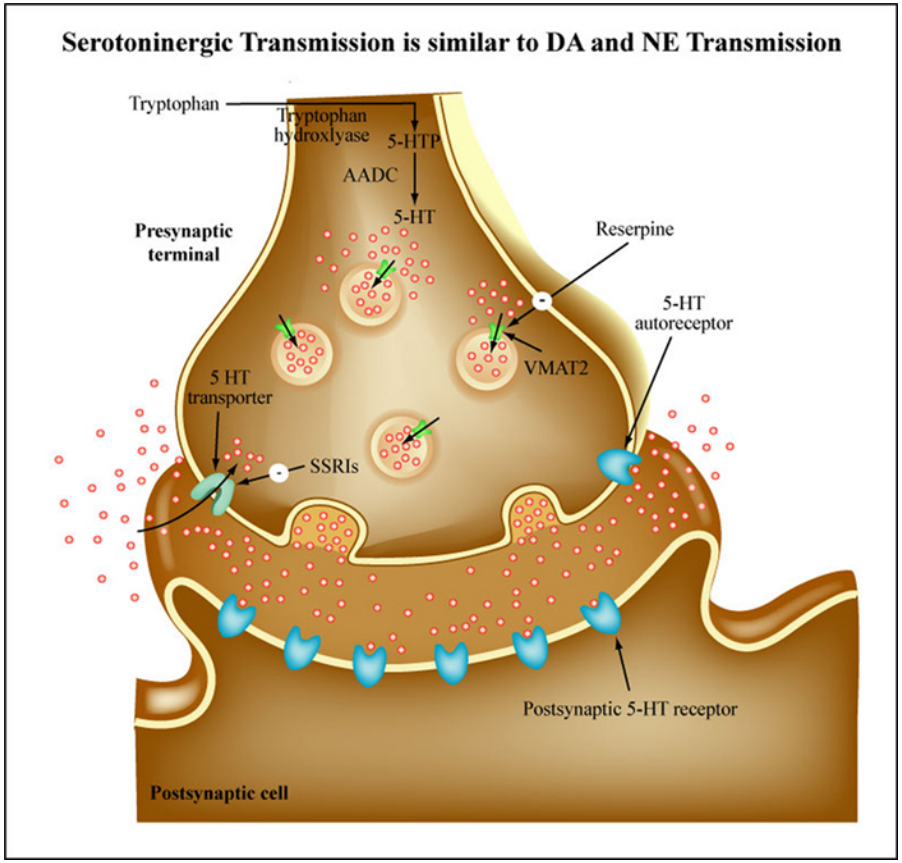
Tryptophan hydroxylase is specific of Serotoninergic neurons

The drug para-chlorophenylalanine (PCPA) selectively inhibits triptophan hydroxylase, Therefore blocking 5-HT synthesis

A diet rich in carbohydrates leads to the increase of insulin which facilitate glucose uptake, and also several other aa, but not tryptophan

Since it is the ratio between tryptophan and other aa that is important for crossing the BBB a carbo-rich diet would increase the uptake of tryptophan and eventually the production of serotonin

Serotoninergic transmission is similar to DA and NE transmission



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VMAT2 transport 5-HT into vescicles (reserpine blocker)

Presence of auto receptors that modulate firing rate- release
5-HT release can be stimulated by drugs with the structure of amphetamines

Once released, 5-HT is removed from the cleft by the e-HT transporter.
A blocker of the transporter is fluoexitine (Prozac) that potentiate 5-HT transmission

Monoamine oxidase (MAO) also catabolites 5-HT producing the metabolite 5-hydroxyindoleacetic acid (5-HIAA)

The majority of serotoninergic nuclei are localized in the brainstem (medulla, pons and midbrain)

These nuclei are called the raphe nuclei and they are localized on the midline of the brain stem

They project to all the forebrain regions

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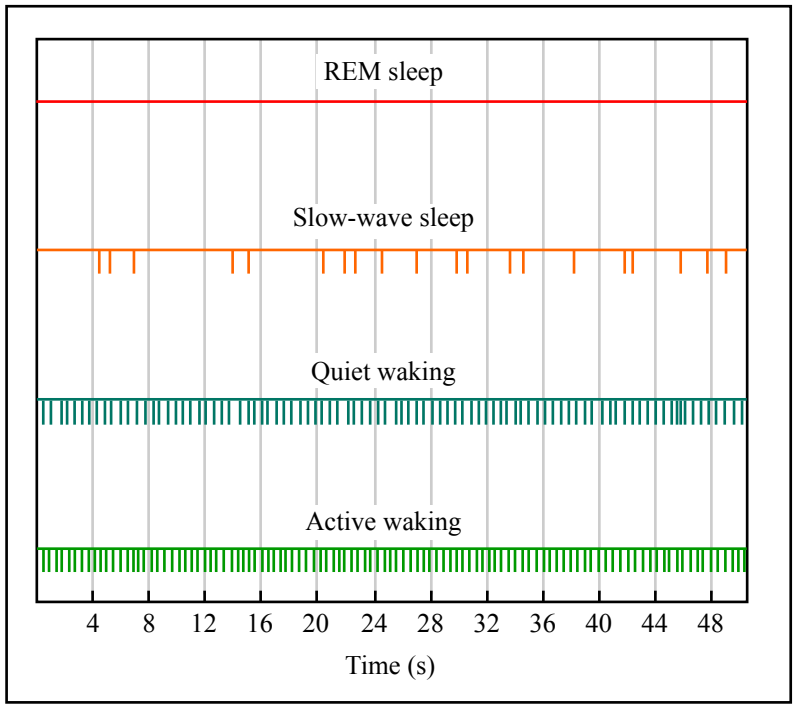
Figure 6.17 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

The firing of the serotoninergic neurons is associated with the behavioral status of the animal: the firing slows down with sleep and shut off during REM sleep



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In general the firing is constant during repetitive movements, like chewing, and it suddenly stops when a new stimulus is presented

Induced lesions of the serotoninergic system in animals show that it modulates food Intake, reproductive behavior, pain sensitivity and learning and memory

5-HT receptors

There are at least 15 receptor subtypes and they are all metabotropic, with the exception of 5-HT3, which is an excitatory ionotropic receptor

5-HT1A is present is many brain areas, including the hippocampus and the amygdala

It acts by inhibiting adenyl cyclase and by opening a K+ channel leading to membrane iperpolarization

Administration of 5-HT1A agonists produce hyperphagia

The most studied antagonist (WAY- from the pharmaceutical company) produced decrease in body weight but it was accompanied by side effects

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Figure 6.19 (Part 1) in Meyer, and Quenzer, *Psychopharmacology*, 2004.

5-HT1A stimulation also produced reduction in anxiety, and this is what is used in the medication Buspar-commercial name for busiprone.

Another effect of 5-HT1A agonist is the inhibition of alcohol consumption

5-HT2A receptors acts by activating protein kinase C, They are present in cerebral cortex.

Agonist of this receptor cause hallucinations, and this
Is supposed to be related to the effects of lysergic acid
Diethylamide (LSD)
The best known agonist is DOI (1-(2,5-dimethoxy-4-iodophenyl)
-2-aminopropane

Known antagonists are ketanserin and ritanserin.

In general, these antagonists can be used for the treatment of schizophrenia.
Recently, drugs that act on both the DA and 5-HT system have shown
the best results for the treatment of schizophrenia with lower side effects

Drugs that affect the Serotonergic system

Drug	*Action*
para-Chlorophenylalanine	Depletes 5-HT by inhibiting tryptophan hydroxylase
Reserpine	Depletes 4-HT by inhibiting vesicular uptake
para-Chloroamphetamine, fenfluramine, and MDMA	Release 5-HT from nerve terminals (MDMA and *para*-chloroamphetamine also have neurotoxic effects)
Fluoxetine	Inhibits 5-HT reuptake
5,7-Dihydroxytryptamine	5-HT neurotoxin
Buspirone, ipsapirone, and 8-OH-DPAT	Stimulate 5-HT_{1A} receptors (agonists)
WAY 100635	Blocks 5-HT_{1A} receptors (antagonist)
DOI	Stimulates 5-HT_{2A} receptors (agonist)
Ketanserin and ritanserin	Block 5-HT_{2A} receptors (antagonists)

Anxiety disorders

Anxiety is a feeling of apprehension, fear, or worry.

Anxiety can be a good thing: It warns for danger and it increases our energy level pushing us to work harder and longer

When anxiety is very intense in can cause discomfort or even terror

Anxiety is commonly associated to depression

There are five principal categories of anxiety disorders:

- Generalized anxiety disorder (GAD)
- Panic disorders
- Phobias
- Post-traumatic stress disorder
- Obsessive-compulsive disorder

Generalized Anxiety Disorders:

Constant worry. Muscle tension and agitation that lead to fatigue, poor concentration, irritability and sleep difficulties.
It tends to run in families

Panic disorders:

Experiencing the effects of a fear reaction without a threatening stimulus. Symptoms: Heart pounding, chest pain, sweating, shortness of breath
This can happen in response to an external cue, or without warning or in situations Where attack occurred previously.
There is a clear genetic predisposition.

Phobias:

Irrational fears related to special objects or situations

Some common (*) and less common phobias

Phobia	*Fear of*
Acrophobia*	Heights
Aichmophobia	Sharp, pointed objects; knives
Ailurophobia	Cats
Algophobia	Pain
Astraphobia*	Storms, thunder, lightning
Claustrophobia*	Tight enclosures
Hematophobia*	Blood
Monophobia*	Being alone
Nyctophobia	Darkness, night
Ochlophobia	Crowds
Pyrophobia	Fire
Thanatophobia*	Death
Xenophobia*	Strangers

Post-traumatic stress disorder (PTSD)

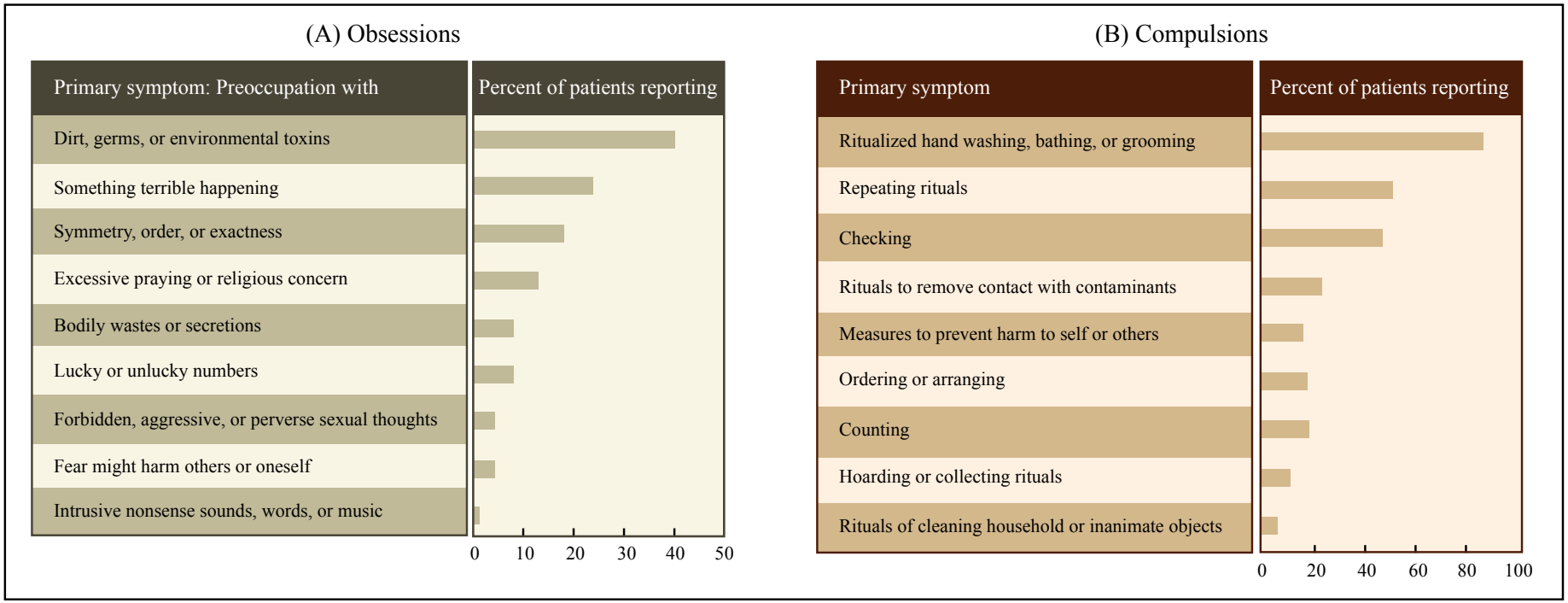
occur after a traumatic event such as war, a terroristic attack, natural disasters
People with PTSD have problems with: substance abuse, marital problems, Depression, sense of guilt
Children whose parents have PTSD have a igher probability of having PTSD
Suggesting that there is a body factor that fecilitate the onset.
Also important are history of chronic stress, trauma, abuse.

Obsessive-compulsive disorders

Characterized by recurrent and persistent thoughts (Obsessions) that cause to the Individual a sense od anxiety, guilt, shame.
In the aim to releive these symptoms the individual performs repetitive rituals (Compulsions) related or not to the obsessions.
The individual thinks that unless the compulsive ritual is completed, disasters will occur.

Some people with OCD also suffer from other movement disorders such as: Tourette's syndrome, Sydenham's chorea and Parkinson's disease

Occurrence of OCD symptoms



Brain areas interested in OCD

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Imaging analysis shows that the following regions are involved in anxiety:
Basal ganglia, frontal cortex, thalamus, and Anterior cingulate cortex. Neurosurgery that destroys the connections in this loop relieves the symptoms of anxiety

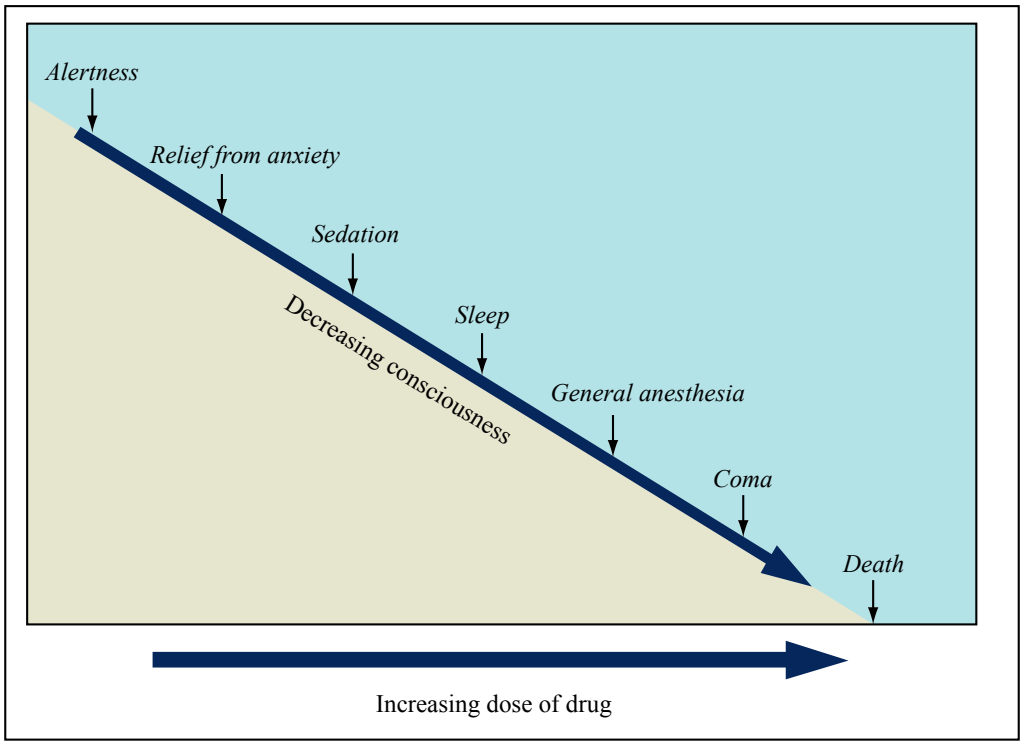
Drugs for treating anxiety

They are called anxiolytics and belong to the CNS depressants

They reduce neuron excitability by enhancing GABA transmission

They are alcohol, barbiturates and benzodiazepines

With increased doses, they cause also sedation, anesthesia and even death



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Barbiturates and benzodiazepines both enhance GABA transmission. Barbiturates increase the duration of the opening of the channel and directly open the Cl- channel without GABA. Benzodiazepines have no effects with no GABA. They increase the frequency of channel opening.

There is a direct correlation between GABA and anxiety

There are less BDZ receptors in patients with anxiety

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There are endogenous diazepam binding inhibitor that induce anxiety

Barbiturates action/applications changes according their solubility

Duration of action and uses of major barbiturates

Duration of action	*Lipid solubility*	*Onset*	*Duration*	*Use*
Ultrashort Thiopental (Pentothal) Methohexital (Brevital)	High	10-20 s	20-30 min	Intravenous anesthesia
Short/intermediate Amobarbital (Amytal) Secobarbital (Seconal) Pentobarbital (Nembutal)	Moderate	20-40 min	5-8 h	Surgical anesthesia and sleep induction
Long Phenobarbital (Luminal) Mephobarbital (Mebaral)	Low	Over 1 h	10-12 h	Prolonged sedation and seizure control

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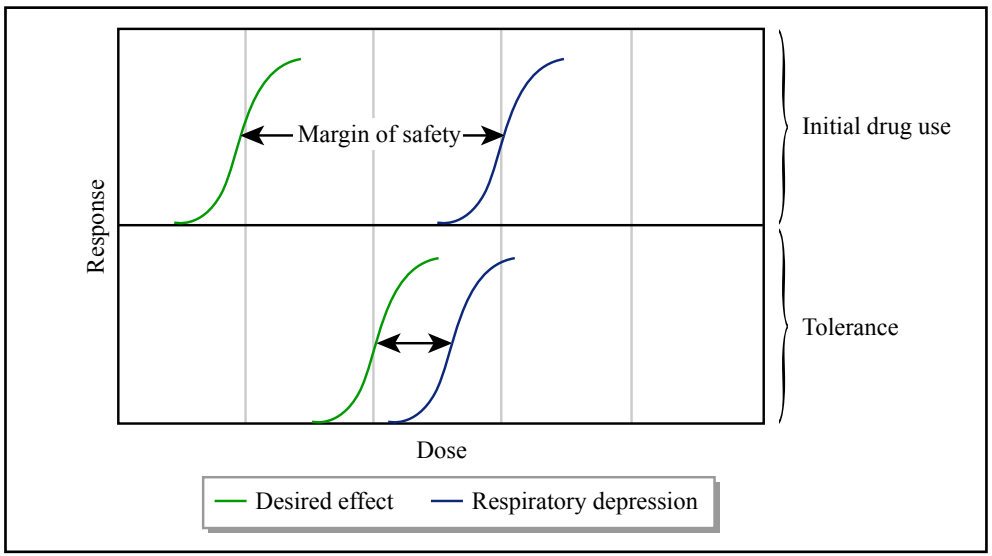
Over time, with tolerance, the balance desired effect-side effect shift toward the last one



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They are used to induce anesthesia

Their interaction with alcohol is dangerous

Different benzodizepines are metabolized in a different way and therefore they have a different interval of action

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Figure 17.11 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

They are used as hypnotics, muscle relaxant
Anticonvulsants.
They have very low effects on respiration, but
They give dependence

A new anxiolytic is Busiprone, that does not interfere with other CNS depressants therefore is safer, but it has a very slow action.

It has no effects on GABA tranmission: it is a partial agonist of 5-HT1A receptor

Often antidepressant drugs are used to treat anxiety

Interactions between anxiety and neurotransmitters

There is a connection between the NE system and anxiety

In general, the NE system is activated by alerting situations

Some of the effects of anxiolytic drugs can be explained with the modulation of LC firing

LC firing is activated by the corticotropin-releasing factor and it is inhibited by GABA and serotonin.

This explain why depression and anxiety are often related and why SSRI are effective in treating anxiety

Also, increased levels of corticotropin-releasing factor (CRF) are related to anxiety

There are indications that increased DA transmission produces anxiety, while Treatments that increase 5HT transmission also reduce anxiety

Affective disorders:

Major depression

Bipolar disorders

Depression

Loss of interest in almost anything
Inability to experience pleasure in anything
Feelings of hopelessness, sadness, worthless, guilt and desperation
Loss of appetite, insomnia, crying, fatigue, thoughts of suicide
Episodes recur throughout life
The mean of onset for depression is 27 years

Bipolar Disorders

Manic individuals feel faultless, full of fun, and energetic. They need less sleep. They make impulsive decisions and have unlimited confidence in themselves. Onset between 20 and 30 years of age and episodes continue throughout life.

Symptoms of manic episodes and major depression (Part 1)

Diagnosis	*Symptom*
Manic episode	Inflated self-esteem or grandiosity
	Decreased need for sleep (e.g., feeling rested after only 3 hours of sleep)
	Greater talkativeness than usual or pressure to keep talking
	Flight of ideas or feeling that thoughts are racing
	Distractibility (i.e., attention too easily drawn to unimportant external stimuli)
	Increase in goal-directed activity (either socially, at work, or sexually); agitation
	Excess involvement in pleasurable activities that have a high potential for painful consequences (e.g., unrestrained buying sprees, sexual indiscretions, or foolish investments)

Source: American Psychiatric Association, 1994.

Symptoms of manic episodes and major depression (Part 2)

Diagnosis	*Symptom*
Major depressive episode	Depressed mood (or irritable mood in children and adolescents) most of the day, nearly every day
	Diminished interest or pleasure in most activities most of the day, every day
	Significant changes in body weight or appetite (gain or loss)
	Insomnia or hypersomnia nearly every day
	Psychomotor agitation (increased activity) or retardation (decreased activity)
	Fatigue or loss of energy
	Feelings of worthlessness or excessive or inappropriate guilt
	Diminished ability to think or concentrate; indecisiveness
	Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

Source: American Psychiatric Association, 1994.

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We all experienced feelings associated with depression and this is not pathologic.
When the symptoms are disproportionate or prolonged it constitute mental illness

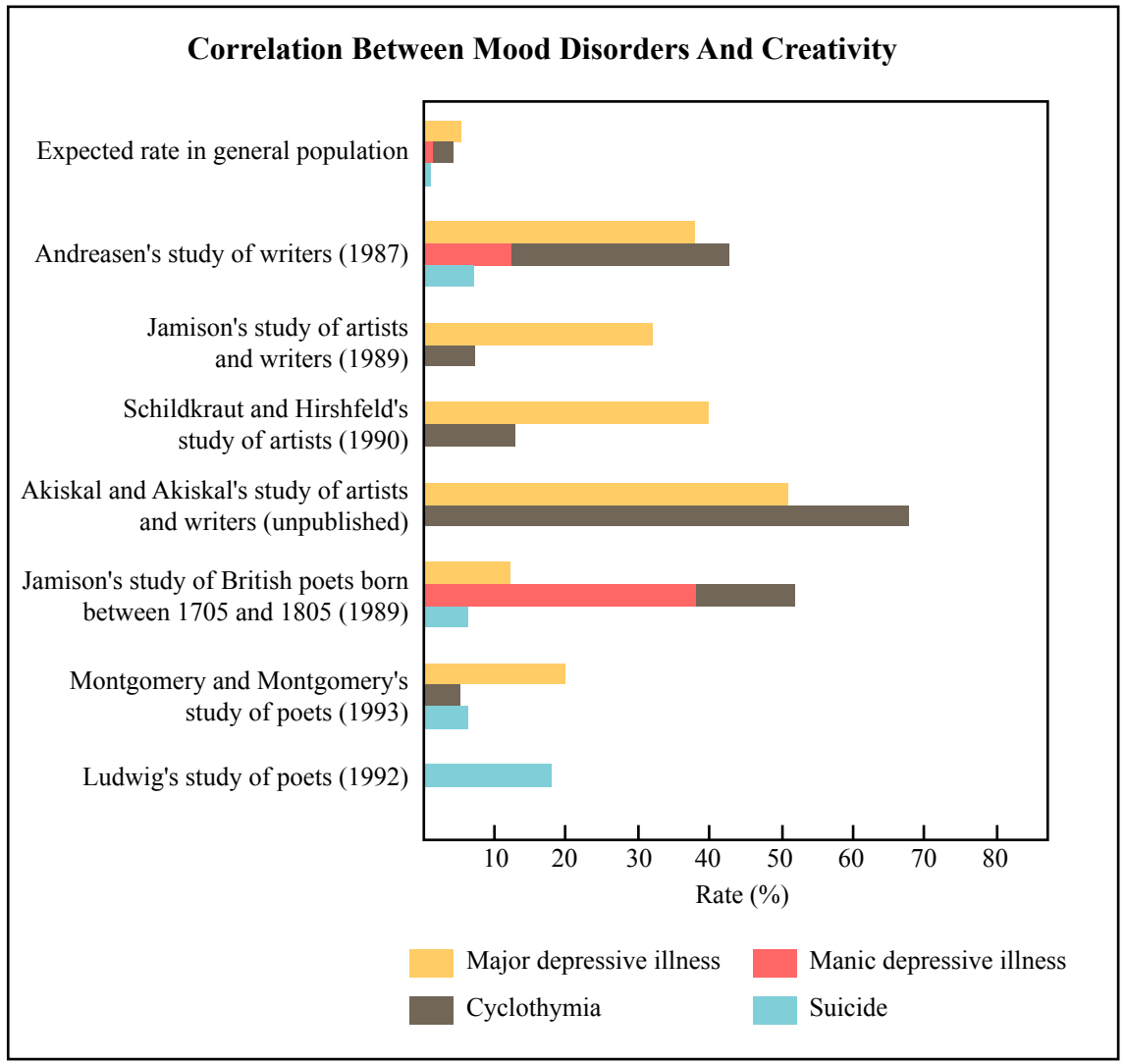
Risk Factors:

Heredity

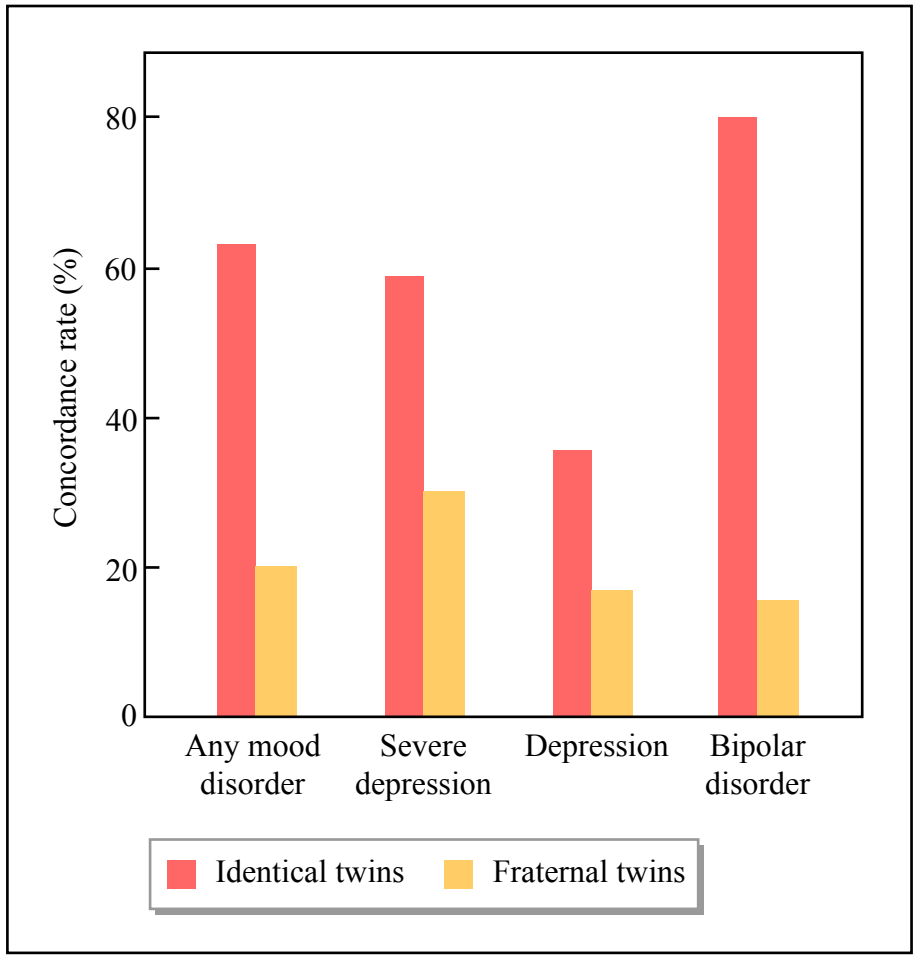
Environmental stress

Altered biological rhythms

Correlation between mood disorders and creativity



Study of concordance in Monozygotic twins and dizygotic Twins indicate a major role for Heredity in bipolar disorders



In response to stress the hypothalamus
Produces the corticotropin-releasing
Factor (CRP) that acts on the pituitary gland
Inducing the release of the adrenocorticotropic
Hormone (ACTH).
ACTH goes in the blood and reaches the
adrenal gland where it increases the secretion
Of glucocorticoids, in particular cortisol.
Cortisol activates the energy to deal with
Stress. Cortisol feedbacks on hypothalamus

This is called the H-P-A axis
(Hypothalamus-Pituitary-Adrenal)

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Figure 16.3 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

In animal models, stress is induced by separating young animals from their mothers for brief periods daily during the first weeks of life.

Stress induces transient surges of cortisol

In depressed individuals there is an abnormal secretion of cortisol

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Figure 16.5 (B) in Meyer, and Quenzer, *Psychopharmacology*, 2004.

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Figure 16.5 (A) in Meyer, and Quenzer, *Psychopharmacology*, 2004.

In this case the hypersecretion is due to an abnormal production of CRP by the hypothalamus.

Antidepressant therapies reduce the CRF level in depressed patients

Dexamethasone (a synthetic glucocorticoid that act as a negative feedback on the hypothalamus) Cause a decrease in the levels of cortisol

The sleep pattern is altered in depressed patients

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Figure 16.5 (Part 2) in Meyer, and Quenzer, *Psychopharmacology*, 2004.

Discovering antidepressants

Animal models

Reduction of psychomotor activity,
Cognitive changes
Eating/sleeping

The interaction between genetic and environmental factors is important for the onset of depression

Genetic factors are considered:
Decrease in the monoamine levels
Increased activity of the HPA axis to stress

Experiments on rodents proved that deprived animals respond more to stress

The discovery of anti-depressive treatments happened by chance

It was observed that reserpine, a drug that reduces high blood pressure
Induces depression as side effect

Therefore the antidepressant are tested as molecules capable of reverse the
Reserpine-induced sedation

Remember that reserpine prevents the packaging of neurotransmitters into vescicles,
Leaving the monoamines in the cytoplasm, where the MAO degrades them

Therefore Reserpine reduces the transmission of monoamines
(dopamine, norepinephrine and serotonin). MAO-inhibitors are therefore used as
Antidepressants.

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Figure 16.7 (Part 1), 16.7 (Part 2), and 16.7 (Part 3)
in Meyer, and Quenzer, *Psychopharmacology*, 2004.

This is known as **MONOAMINE HYPOTHESYS**, and it is based on the following observations:

Manic-like activity produced by amphetamine and cocaine is correlated with an Increase of chatecolamines at the synapses

Reduction of movements in depression

Mechanism of action of the MOAi

It is very likely that NE and 5-HT systems interactions are responsible of depression

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Figure 16.14 (Part 1) and 16.14 (Part 2) in
Meyer, and Quenzer, *Psychopharmacology*, 2004.

The effects of MAO-I according to their time course should be on the post-synaptic Modifications and effects of the second messenger.

Side effects: it enhances the NE transmission in peripheral nerves of the sympathetic Branch and therefore it amplify the effects of all the medications that increase NE: nasal spray, cold medications, antiasthma drugs.

Also the foods that contain tyramine enhance NE transmission in terminals and should be avoided.

Dietary restrictions for patients taking MAO-Is

Food group	*Examples*
Dairy	Unpasteurized milk and yogurt; aged cheese; other cheeses including blue, Boursault, brick, Brie, Camembert, cheddar, Colby, Emmenthaler, Gouda, Gruyere, mozzarella, Parmesan Provolone, Romano, Roquefort, and Stilton
Meat and meat alternatives	Aged game; liver; canned meats; yeast extracts; salami; dry sausage; salted, dried, smoked, or pickled fish such as herring, cod, and caviar; peanuts
Breads, cereals, and grains	Homemade yeast breads with substantial quantities of yeast; bread or crackers containing cheese
Vegetables and fruits	Italian broad beans, sauerkraut, bananas, red plums, avocados, raspberries
Miscellaneous	Alcoholic beverages including red and white table wines, ale, beer, champagne, sherry, and vermouth; yeast concentrates, soup cubes, commercial gravies, or meat extracts; soups containing items that must be avoided; soy sauce; soy bean curd (hoison)

NE transmission increases blood pressure.

MAOi inhibits some liver enzymes that catabolize barbiturates, alcohol, aspirin, therefore amplifying the effects of these drugs.

Possible treatments:

Major Classes of Antidepressants and Their Most Notable Side Effects

Class	Antidepressants	Side effects
Monoamine oxidase inhibitors	Phenelzine (Nardil) Tranylcypromine (Parnate) Isocarboxazid (Marplan)	Insomnia, weight gain, hypertension, drug interactions, tyramine effect
Classic tricyclics	Imipramine (Tofranil) Amitriptyline (Elavil) Desipramine (Norpramine)	Sedation, anticholinergic effects, cardiovascular toxicity
Second-generation:		
Selective serotonin reuptake inhibitors	Fluoxetine (Prozac) Sertraline (Zoloft) Paroxetine (Paxil)	Insomnia, gastrointestinal disturbances, sexual dysfunction, serotonin syndrome
Atypical antidepressants	Maprotiline (Ludiomil) Bupropion (Wellbutrin) Mirtazapine (Remeron)	Varies with individual mechanism of action
Electroconvulsive shock and transcranial magnetic stimulation		Memory impairment, confusion, amnesia

All these methods act enhancing monoamine transmission.
They require chronic administration, suggesting that the clinical effects are due to changes that occur over time

Tricyclic antidepressants act by binding the presynaptic transporter proteins and Inhibiting the reuptake.

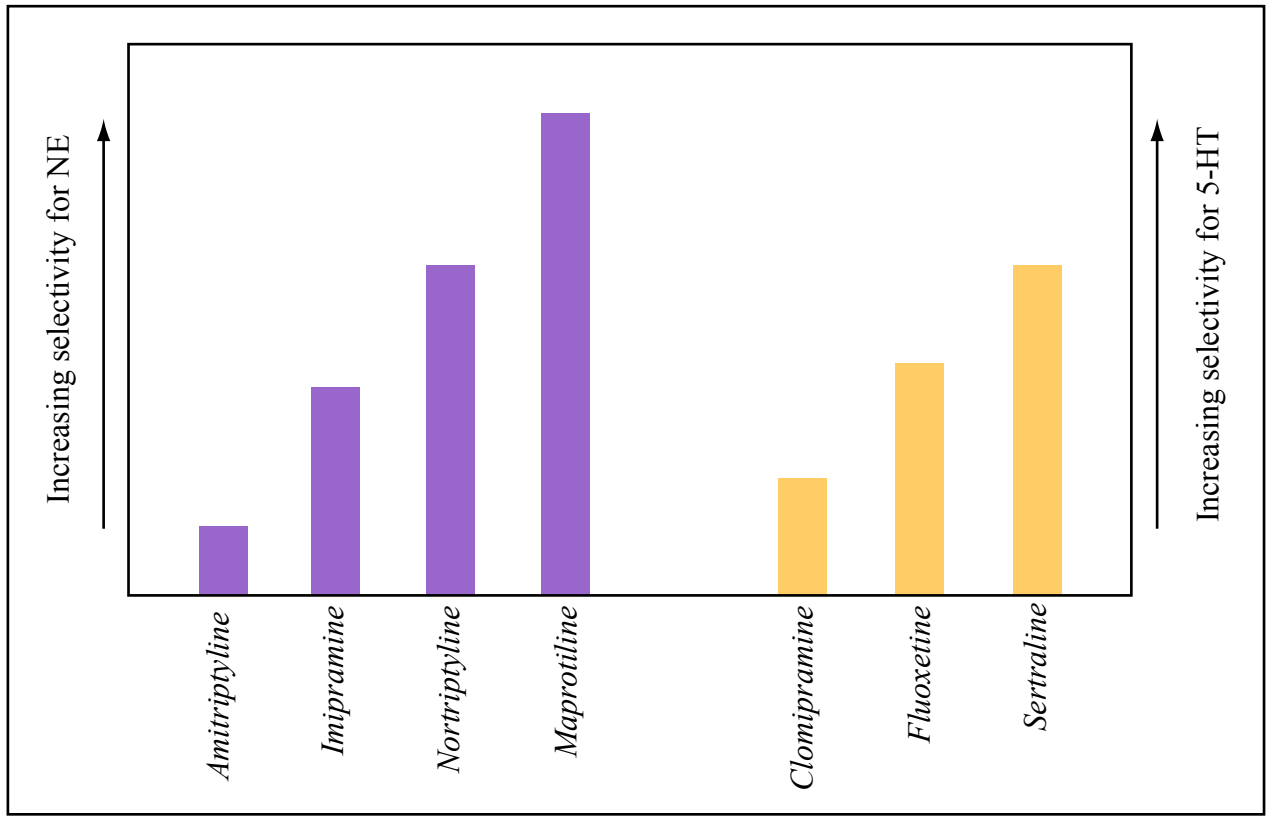


Figure by MIT OpenCourseWare.

They also block acetylcholine, histamine, α-adrenergic receptors, determining: Sedation and fatigue, dry mouth, constipation, cardiovascular problems

Selective Serotonin reuptake inhibitors (fluoexitine, PROZAC)
are used to treat, among others:
Depression, anxiety disorders, obsessive-compulsive disorders, obesity

They act mostly on 5-HT reuptake, and therefore they avoid all the side effects due to increased NE transmission

Side effects: anxiety, restlessness, movement disorders, insomnia, headache and sexual dysfunction

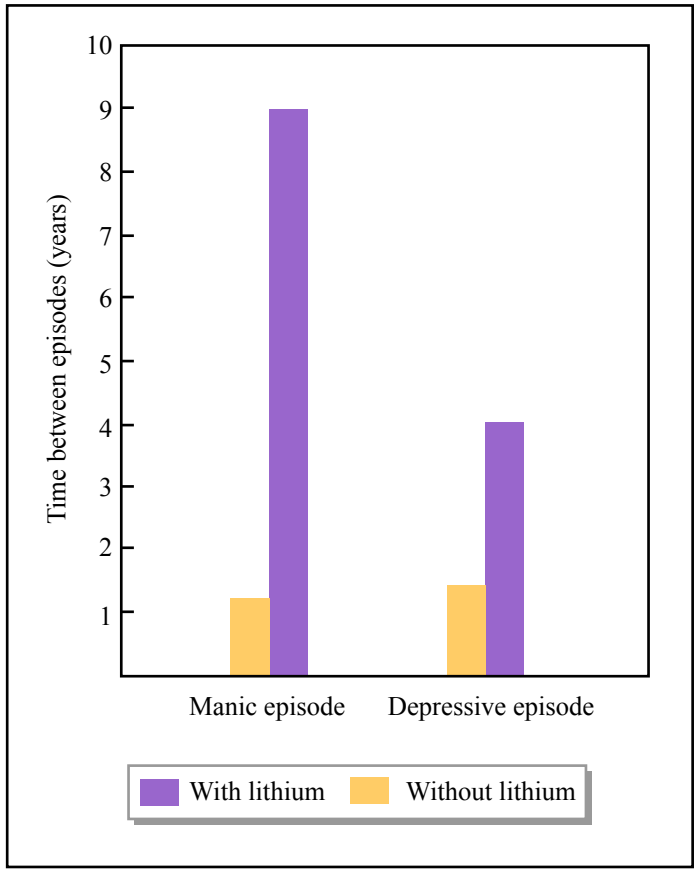
They also cause physical dependence

Electroconvulsive therapy:

It has been observed that there was an improvement of the mood in patients having Spontaneous seizures. Therefore inducing convulsions can be beneficial for Patients that are not sensible to drug treatments.

This treatment is very expensive. It probably works by acting on several Neurotransmitter systems. The main side effect are confusion and memory loss.

Bipolar disorders are treated with Lithium carbonate.
It is usually administered together with another antidepressant drug



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Lithium enhance brain tryptophan therefore enhancing 5-HT actions.
It has effects on second messenger systems and brain neurotrophic factors.

Side effects: Lithium is directly secreted by the kindey at a rate inversely related to Sodium levels. Decrease in sodium levels leads to dehydratation, diarrhea, vomiting, Even seizures, coma and death.
For these reasons it has to be taken in low concentration.

There are several evidences in humans that the serotoninergic transmission is Decreased in depressed patients:

In post mortem brains it has been observed a reduction of the 5-HT metabolite

In post-mortem brains there in an increase in the 5-HT receptors

Depressed patients have a low level of blood tryptophane

PET studies have shown that in depressed patients there is an increase in metabolic Activity in amygdala and orbitofrontal cortex.
The activity is correlated with the severity of depression and with the treatments.

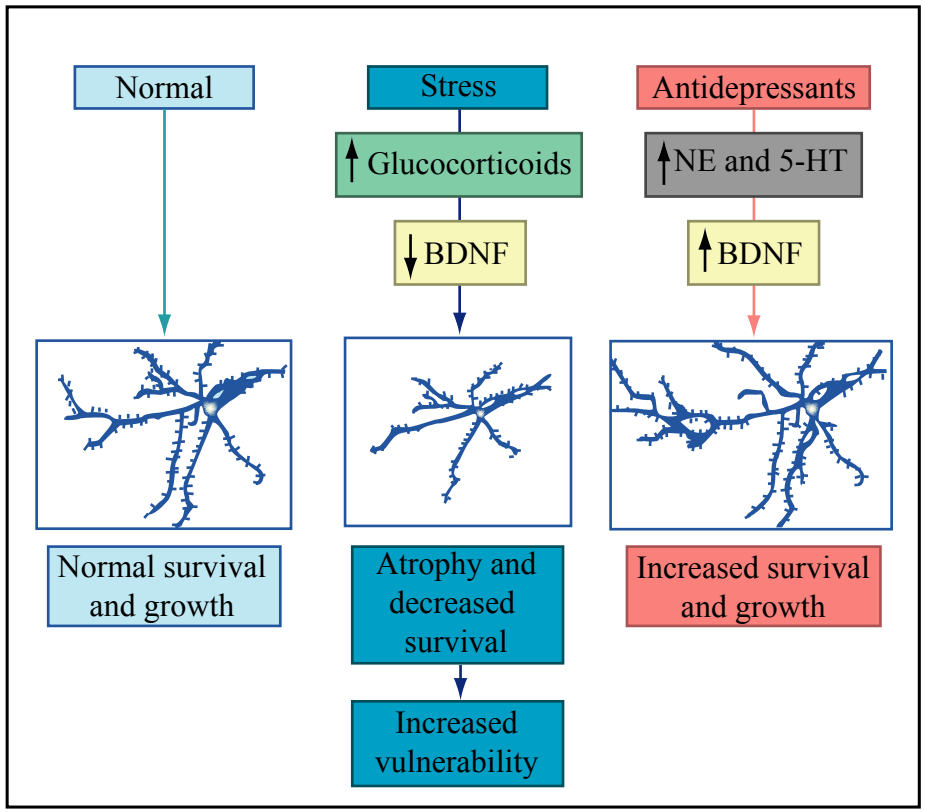
Studies in animals confirmed the involvement of 5-HT in depression

Glucocorticoid hypothesis:

prolonged increase of glucocorticoid levels in blood determines a reduction In the dendritic branching and neurogenesis in the hippocampus, therefore Causing the cognitive deficits associated to depression.

Neurotrophic hypothesis:

Low BDNF is responsible of the impairments



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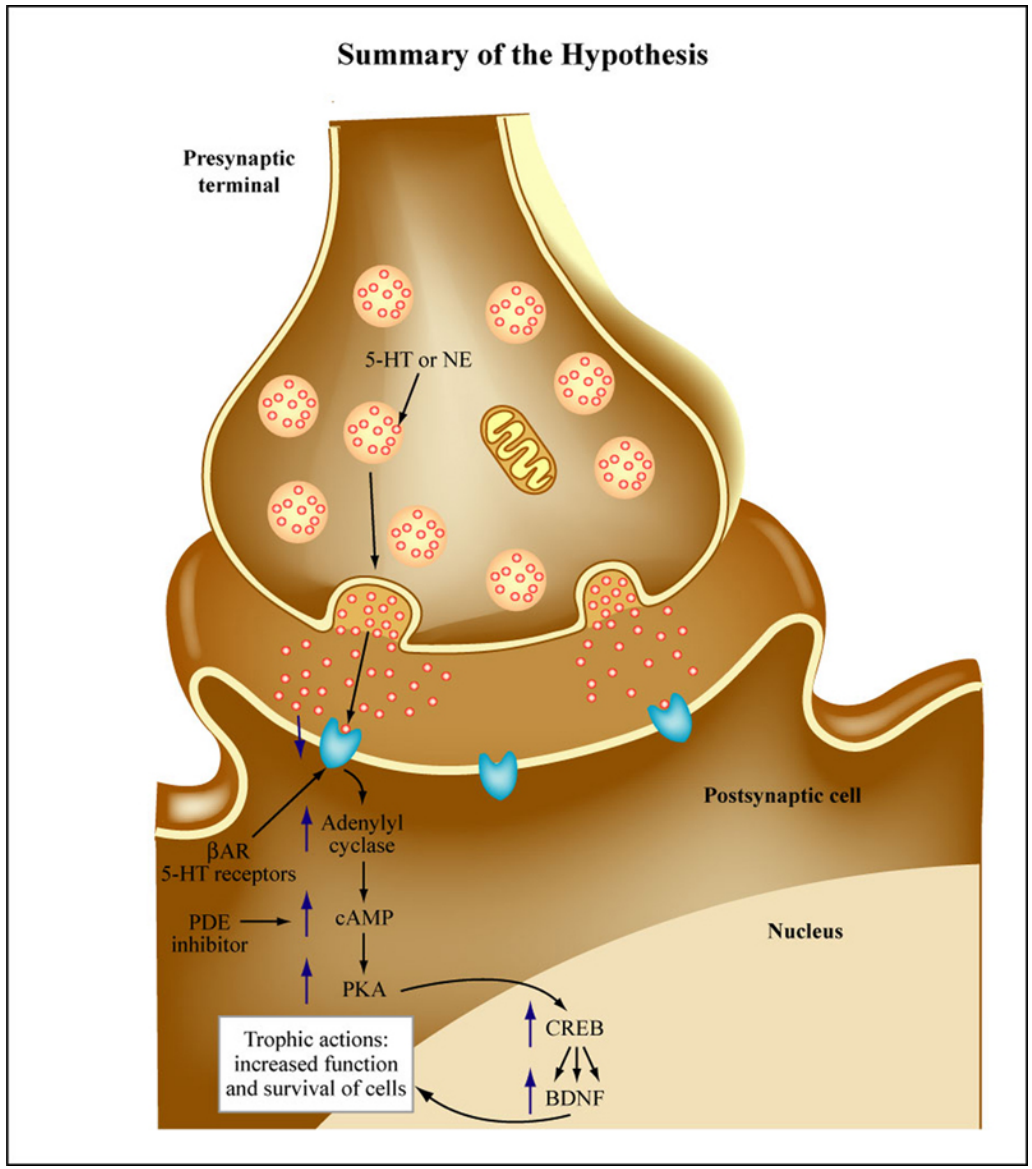
Summary of the hypothesis:



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