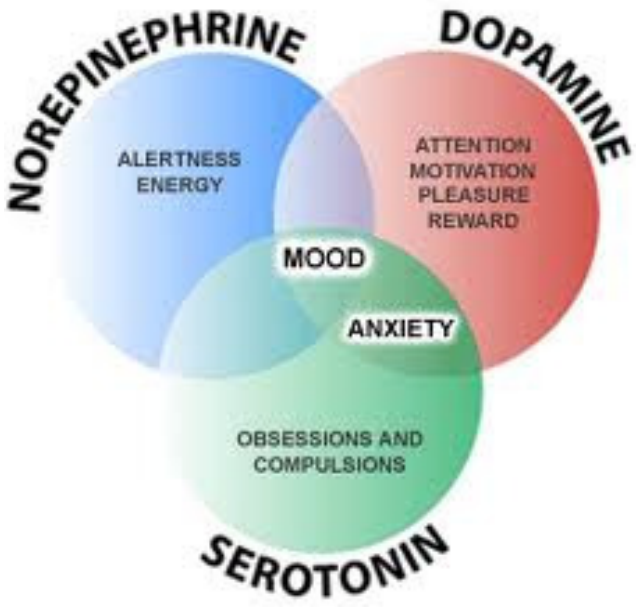
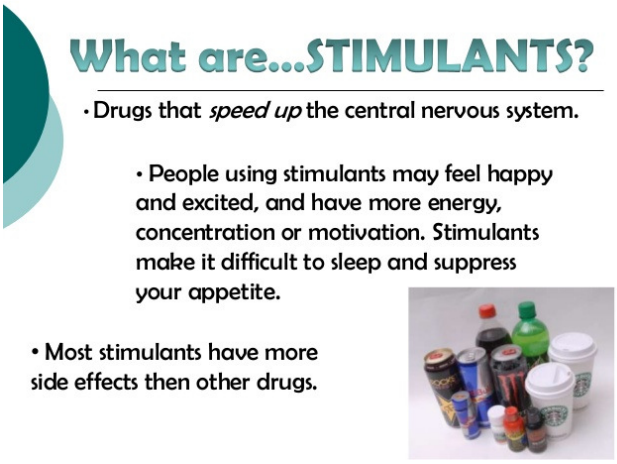
Analeptics

xanthines, amphetamines, nikethamide and ethamivan.



Analeptics

An analeptic is any drug, that stimulates the central nervous system.



Analeptics are *used*

- to treat depression,
- to treat attention deficit hyperactivity disorder (ADHD), and respiratory depression.
- primarily as an anesthetic recovery tool

Side effects: The drugs used (analeptics) as central nervous system (CNS) stimulants are capable of causing convulsions in doses just above those used therapeutically. Hence, their use must be monitored carefully.

ADHD

ADHD is a *disorder* that makes it difficult for a person to pay *attention* and control impulsive behaviors.

He or she may also be restless and almost constantly active. *ADHD* is not just a childhood *disorder*.

Although the symptoms of *ADHD* begin in childhood, *ADHD* can continue through adolescence and adulthood.

Respiratory depression

Respiratory depression means unusually slow or shallow breathing, which can result too much carbon dioxide and not enough oxygen in the blood.

The condition can be life-threatening. ... Another word for respiratory depression is hypoventilation

Recovery from Anesthesia

Anesthesia is one of the most common surgical practices, and also one of the most mysterious.

In the operating room, doctors have no reliable tools to reverse anesthesia once it starts, because no one understands the neurological mechanisms that switch on consciousness.

The only way to pull a patient out of anesthesia is to let the drugs dissipate from the body.

Now, a new study shows that Ritalin — the same drug used to treat attention deficit disorder in children — has the power to wake the brain from general anesthesia.

Analeptics are general CNS stimulants;

• They stimulate vitally important centers: respiratory and vasomotor (constriction or dilatation of blood vessels) of the brain.

•They are also called resuscitating drugs as they restore breathing and blood circulation.

•Awakening action which is manifested by decrease of depth and duration of anesthesia and sleep by restoration of the reflexes, muscular tension and consciousness.

•Toxic doses lead to convulsions.

•The difference between the dose that provides awakening action and the one that causes convulsions is small.

Resuscitation is the process of correcting physiological disorders (such as lack of breathing or heartbeat) in an acutely ill patient.

It is an important part of intensive care **medicine**, trauma surgery and emergency **medicine**.

Well known examples are cardiopulmonary **resuscitation** and mouth-to-mouth **resuscitation**.

•They have been proven to be effective first-line treatments for Attention Deficit Hyperactivity Disorder Jensen et al (1999). Included in this group are methylphenidate and amphetamine.

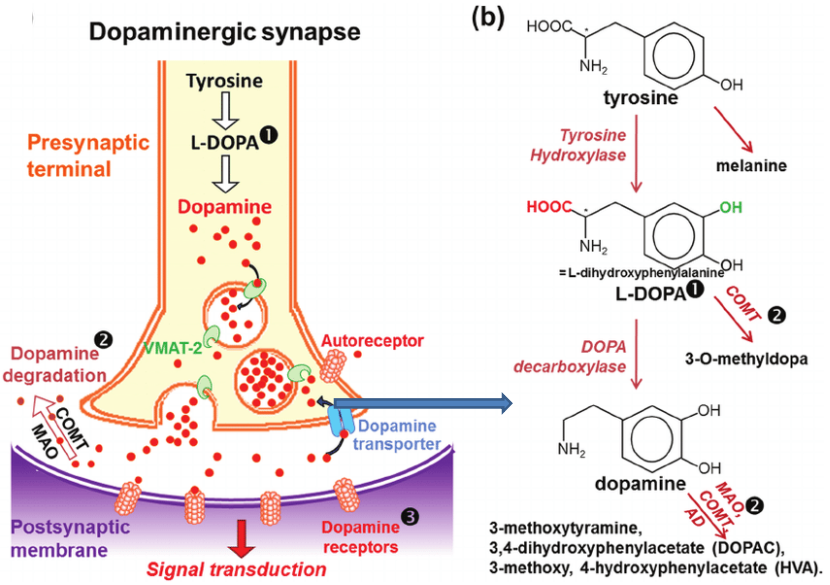
•A respiratory analeptic acts on the central nervous system to stimulate the breathing muscles.

Central nervous system stimulants: MECHANISM OF ACTION

The effect of most of these drugs on wakefulness is primarily mediated through

- An inhibition of dopamine reuptake or transport, leading to increased dopamine levels in the synapse.
- In some cases through increased dopamine release from vesicles in the presynapse.
- Inhibition of norepinephrine and serotonin uptake also probably has some stimulant effects.

Notably, cocaine binds to the DA transporter to inhibit reuptake of dopamine and increases levels of synaptic DA released from nerve terminals ...



ANALEPTICS

I. Xanthines: Methylxanthines: caffeine (coffee), theophyline (tea), theobromide (chocolate).

II. Amphetamines:

III. Khat: Cathinone, methcathinone.

IV. Nikethamide and ethamivan

Amphetamines are classified as analeptics, or central nervous system stimulants.

Clinical Indications for Use of Xanthines

- Use in asthma
- Use in COPD
- Use in apnea of prematurity

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common lung disease. Having COPD makes it hard to breathe.

There are two main forms of COPD:

Chronic bronchitis, which involves a long-term cough with mucus.

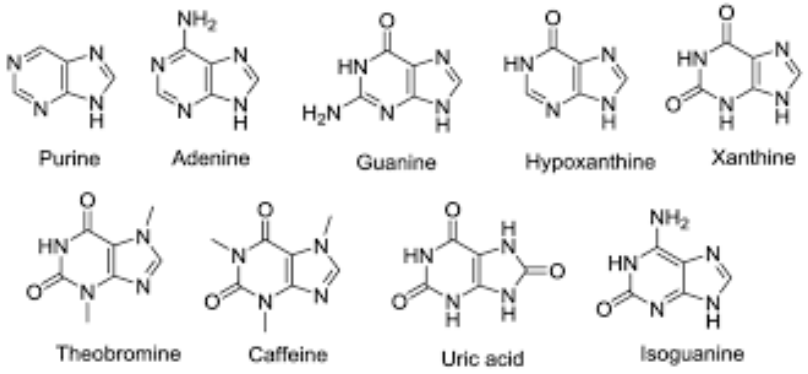
Emphysema, which involves damage to the lungs over time.

Apnea of prematurity is **defined** as cessation of breathing by a **premature** infant that lasts for more than 20 seconds and/or is accompanied by hypoxia or bradycardia.

Apnea is traditionally classified as either obstructive, central, or mixed. ... Central **apnea** occurs when there is a lack of respiratory effort.

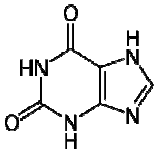
What are methylxanthines?

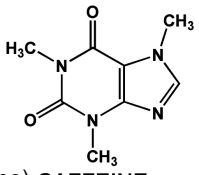
- Methylxanthines are a group of purine alkaloids
  - Purines are crucially important compounds used in nature as the parent compound for formation of the nucleotides that form DNA and RNA
    - The oxidation of purine by adding 2 oxygen atoms forms xanthine.
- **Examples of Methylxanthines:**
  - Caffeine 
  - theophylline,
  - theobromine, and
  - Doxophylline



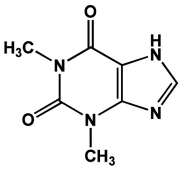
Mehtylxanthine Agents

- Found as alkaloids in plant species
- Theophylline
  - Tea leaves
- Theobromine
  - Cocoa seeds or beans
- Caffeine
  - Coffee beans and kola nuts
  - Cocoa seeds or beans
  - Tea leaves

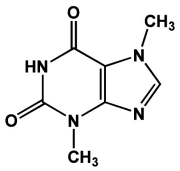




(Trimethylxanthine) CAFFEINE



THEOPHYLLINE



THEOBROMINE

Amphetamines vs Methamphetamines

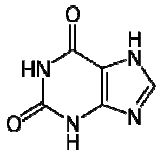
Amphetamine is scientifically known as methylated phenylethylamine. Methamphetamine is double methylated phenylethylamine.

The double process is the primary difference between amphetamine and methamphetamine in a laboratory or scientific instance. Otherwise, the two chemicals or drugs are almost identical in nature causing the same side effects, same dangers and same potential for overdose as well as the same risk of physical dependence and addiction.

Neither methamphetamine nor amphetamine are really safe for use but amphetamines are used in some prescription medications. Amphetamines can be safe for oral use when they are used EXACTLY as prescribed and under the supervision or direct medical care of a doctor. **Methamphetamine is NEVER safe for oral consumption and should not be used by any means!**

A respiratory analeptic acts on the central nervous system to stimulate the breathing muscles.

Xanthine derivatives: Methylxanthines: caffeine (coffee), theophyline (tea), theobromide (chocolate)



Purine dione

Xanthine

Caffeine is the world's most widely consumed legal psychoactive drug.

Caffeine has the most potent effect on all parts of the brain and is preferred for its powerful central stimulant action whereas the other alkaloids have more powerful peripheral actions.

Caffeine also builds up the adrenaline supply, which increases heart rate, gets blood pumping, and opens up airways (results in alterations in perception, mood, or consciousness).

In the lungs caffeine can cause smooth muscle relaxation and bronchial dilatation, possibly accounting for its antiasthmatic effects.

On the circulatory system, theophylline is most powerful and caffeine is least.

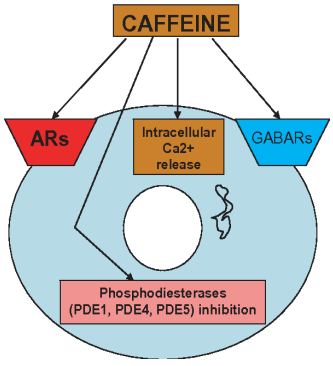
Thus, caffeine is preferred as CNS stimulant while theophylline is used as diuretic (effects of caffeine on the kidney) and for relaxation of bronchial smooth muscles and thus for the treatment of asthma.

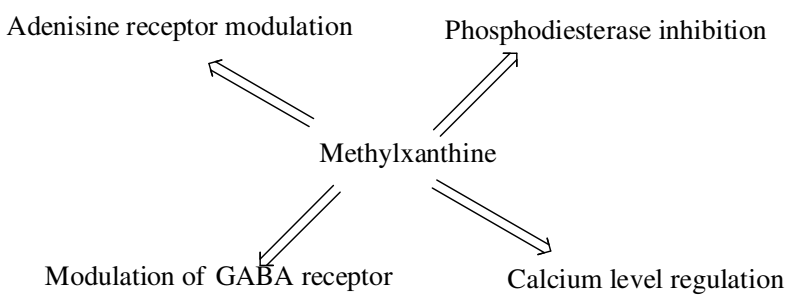
A nonlinear relationship between caffeine intake and depression risk, in which "the risk of depression decreased faster and the association became significant when the caffeine consumption was above 68 mg/day and below 509 mg/day."

Theophylline is used to prevent and treat wheezing, shortness of breath, and chest tightness caused by **asthma**, **chronic bronchitis**, **emphysema**, and other **lung diseases**.

Caffeine is a xanthine which acts in the body's cells by different mechanisms of action and on a wide range of molecular targets.

It intervenes as an antagonist of the adenosine receptors, inhibitor of phosphodiesterase enzymes, sensitizer of calcium liberation channels, and GABA receptor antagonist.





Adenosine

Adenosine (an ATP breakdown product) is an inhibitory neurotransmitter, which promotes sleep and inhibits arousal. It has two components; an adenine nucleotide and a ribose sugar.

Adenosine is a polar molecule and is water soluble. Within the brain, concentration of this neuromodulator increases every hour.

Adenosine binds to G-protein receptors and induces multiple effects.

As adenosine binds G-protein receptors, neural activity begins to decrease and the person feels fatigued and sleepy. A2A receptor is one of many adenosine G protein-coupled receptors.

Adenosine is an ATP breakdown product that in most vessels causes vasodilatation and that contributes to the metabolic control of organ perfusion, i.e., to the match between oxygen demand and oxygen delivery.

In the renal vasculature, in contrast, adenosine can produce vasoconstriction, a response that has been suggested to be an organ-specific version of metabolic control designed to restrict organ perfusion when transport work increases.

However, the vasoconstriction elicited by an intravenous infusion of adenosine is only short lasting, being replaced within 1-2 min by vasodilatation.

Adenosine receptors

The **adenosine receptors** (or **P1 receptors**) are a class of purinergic G protein-coupled receptors with adenosine as endogenous ligand. There are four known types of adenosine receptors in humans: A_1, A_{2A}, A_{2B} and A_3; each is encoded by a different gene.

The adenosine receptors are commonly known for their antagonists caffeine and theophylline, whose action on the receptors produces the stimulating effects of coffee, tea and chocolate.

Therapeutically, **adenosine** is **used** for its antiarrhythmic properties in supraventricular tachycardia (a rapid heart beat). It slows down heart through action on all four adenosine receptors in heart tissue. In brain it produces a sedative effect through action on A_1 and A_{2A}.

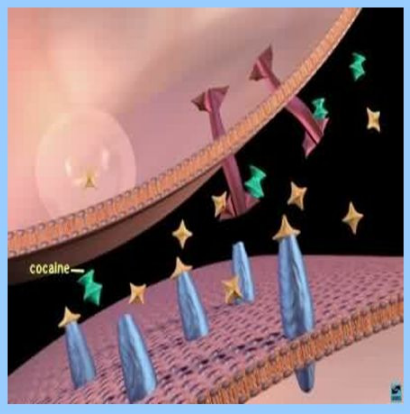
Xanthine derivatives such as caffeine and theophylline act as non-selective antagonists at A_1 and A_{2A} receptors in both heart and brain and so have the opposite effect to adenosine, producing a stimulant effect and rapid heart rate.

Caffeine, as a nonspecific adenosine A1/ A2A receptor antagonist, generates psychostimulant effects through modulating dopaminergic transmission by elevating dopamine levels.

Thus, caffeine keeps you awake by blocking adenosine receptors.

Caffeine and Dopamine

Cocaine Effect Dopamine the Same Way As Caffeine



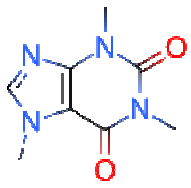
- When caffeine or any stimulant, is present in the synapse of the brain. It binds to the uptake pumps and prevents them from removing dopamine.
- This results in a increased level of dopamine in the synapses.

MECHANISM OF ACTION wakefulness by ANALEPTICS:

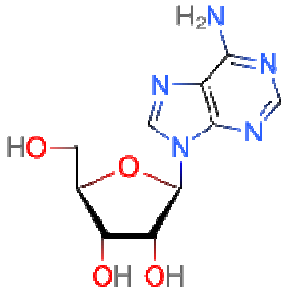
The effect of most of these drugs on is primarily mediated through

- An inhibition of dopamine reuptake or transport
- In some cases through increased dopamine release.

Inhibition of adrenergic uptake also probably has some stimulant effects.



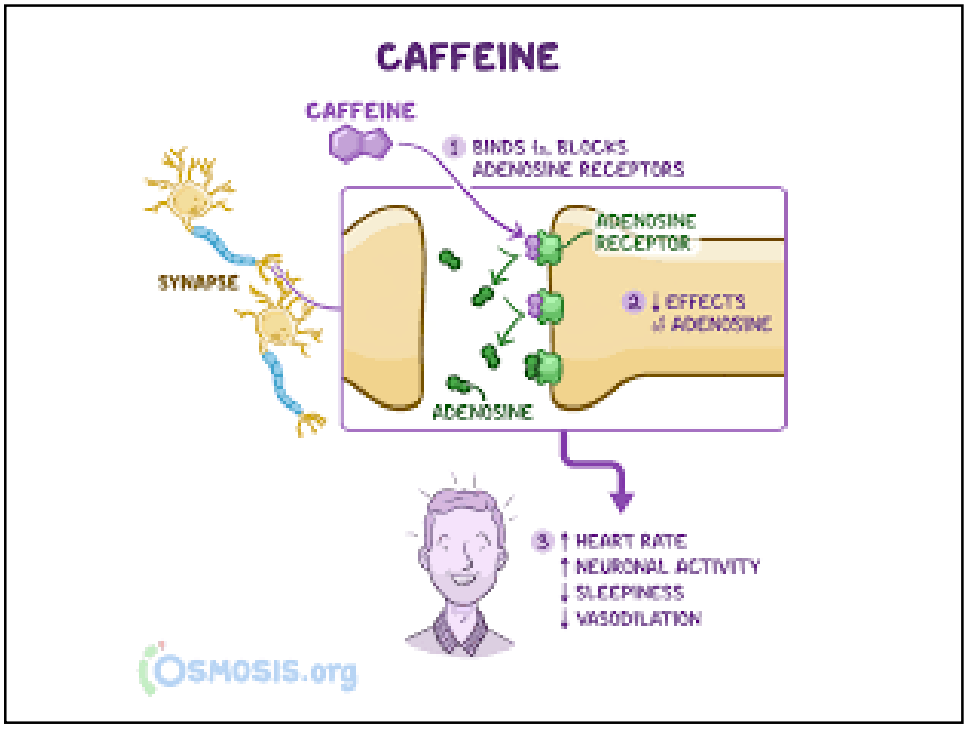
Caffeine



Adenosine

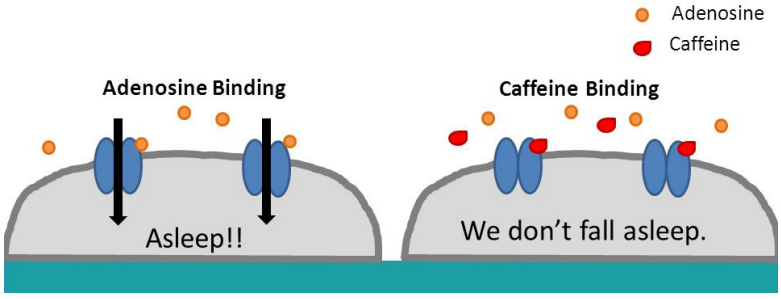
Acts as antagonist at adenosine receptors

Acts as agonist at adenosine receptors

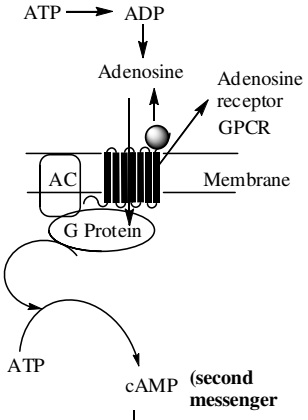


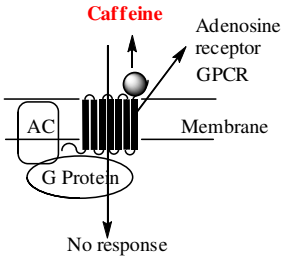
caffeine keeps you awake by blocking adenosine receptors.

- Caffeine binds to the receptors for adenosine, but has no effect on the receptors.
- When caffeine is bound, adenosine can't bind.



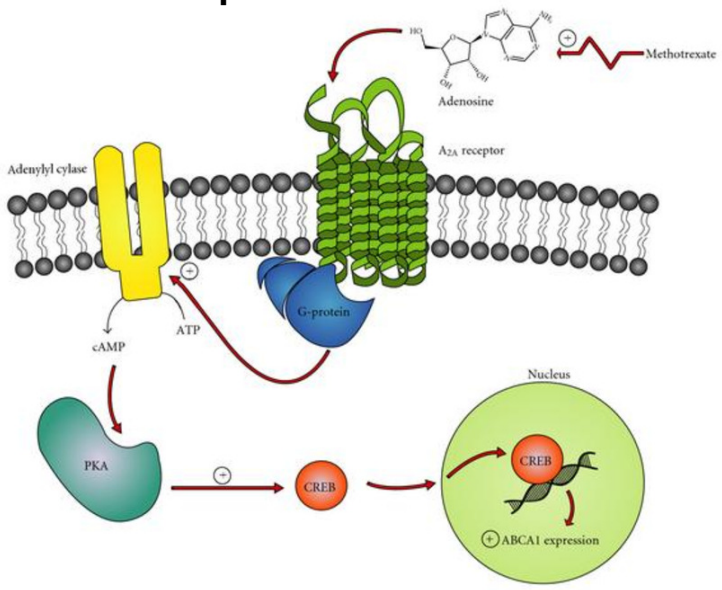
Paraxanthine, the main metabolite of caffeine
Is a more powerful blocker than caffeine.

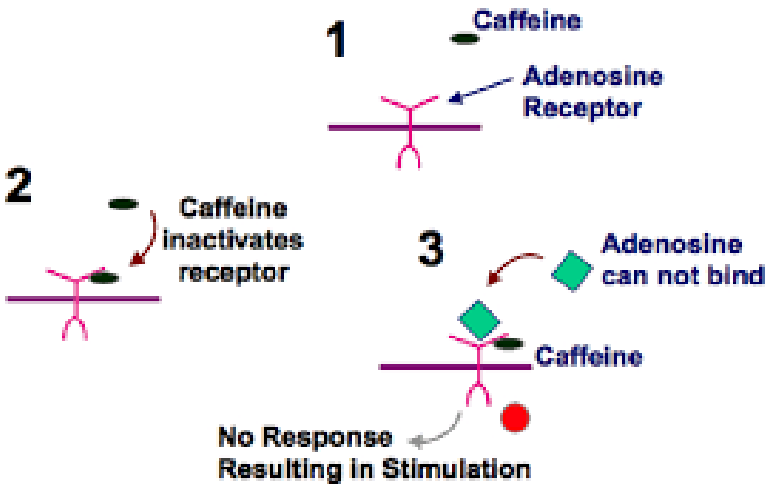




Adenosine is believed to be a
1. neuromodulator in the brain,
2. cardiovascular and other organs
3. contracts smooth muscles, specially bronchial,
4. dilates cerebral blood vessels,
5. depresses cardiac pacemaker
6. inhibits the gastric secretion.

Adenosine receptors



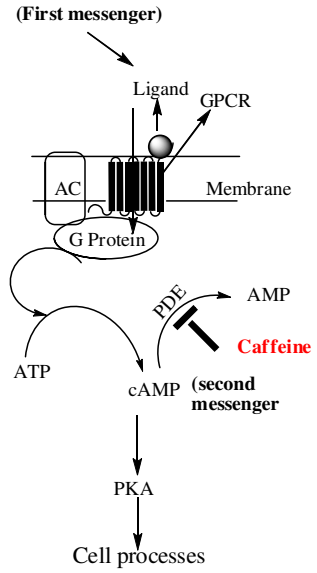


Mechanism of Action:

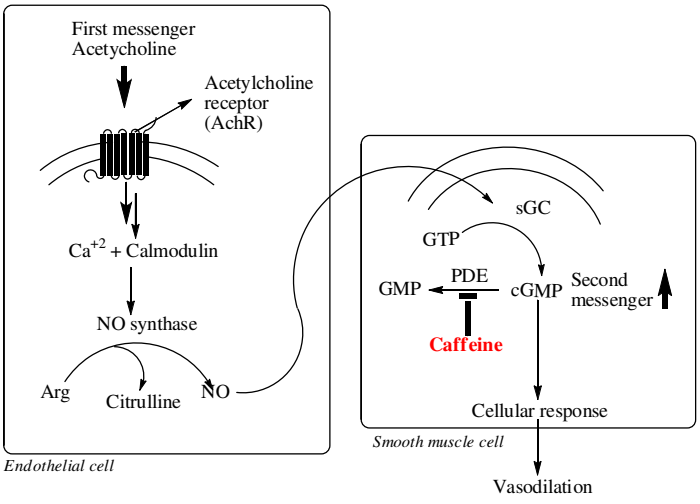
All xanthine alkaloids inhibit the phosphodiesterase enzyme which is responsible for the catabolism of intracellular cyclic neucleotides (cAMP), thus, there is an increase in the cyclic AMP levels which causes various pharmacological actions like increase in force of contraction of heart (cardiac stimulation), relaxation of vascular (vasodilation) and nonvascular smooth muscles (Bronchodilation).

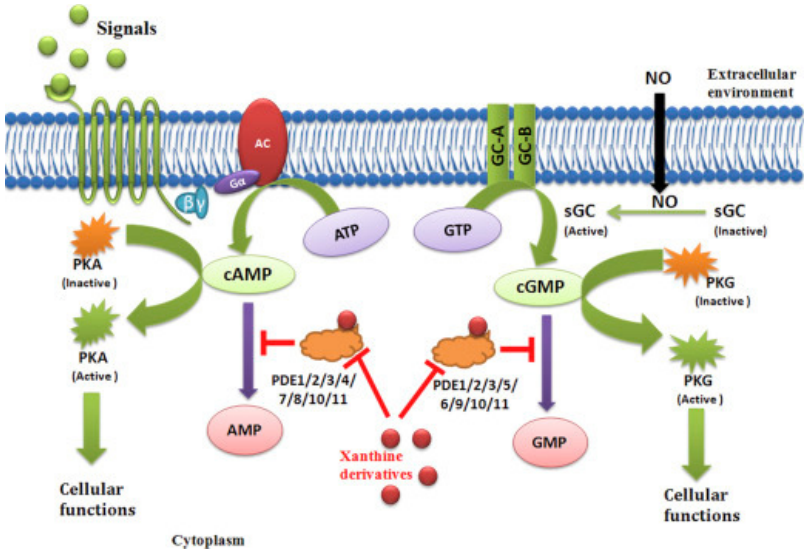
They release Ca^{2+} from the sarcoplasmic reticulum, especially in the skeletal and cardiac muscles.

They also block the adenosine receptors. Adenosine is believed to be a neuromodulator in the brain, cardiovascular and other organs and contracts smooth muscles, specially bronchial, dilates cerebral blood vessels, depresses cardiac pacemaker and inhibits the gastric secretion.



Caffeine competitively inhibits phosphodiesterase (PDE), stimulating even more accumulation of cGMP.





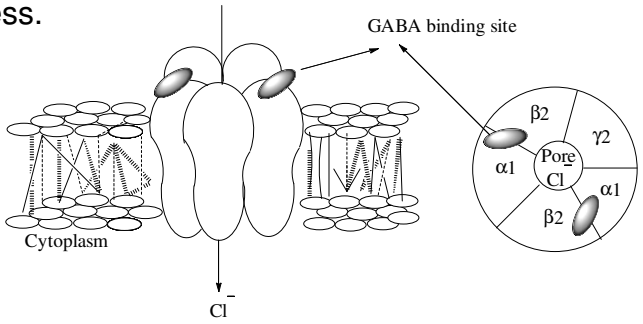
$GABA_A$ modulator

GABA exerts it inhibitory action by binding to receptors present on ligand gated ion channel $GABA_A$ or on GPCR (metabotropic) $GABA_B$. The direct and indirect activation of $GABA_A$ and $GABA_B$ results in the hyperpolarization due to the increased concentration of negative ions (<-55mv) within neurons. This in turn blocks firing of neurons or generation of action potential as part of inhibitory functioning of GABA neurotransmitter.

Thus, the role of GABA is to inhibit or reduce the activity of the neurons or nerve cells. Research suggests that GABA helps to control fear and anxiety when neurons become overexcited.

A lack or lower-than-normal levels of **GABA** leaves your central nervous system with **too many** neuronal signals and causes conditions like ADHD, epilepsy, seizures or mood disorders such as depression and have been linked to schizophrenia, movement disorder Parkinson's disease, anxiety, and sleep disorders.

Meanwhile, **too much GABA** means not enough brain activity and can lead to hypersomnia or daytime sleepiness.



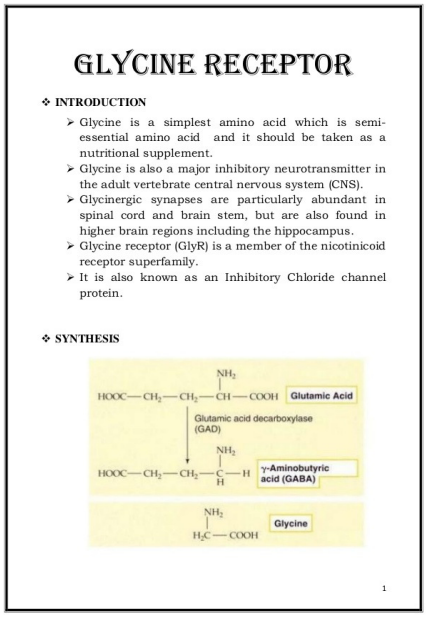
Thus, GABAergic inhibition plays a critical role in the regulation of neuron excitability; and is subject to modulations by many factors.

When GABA attaches to a protein in your brain known as a GABA receptor, it produces a calming effect. This can help with feelings of anxiety, stress, and fear. It may also help to prevent seizures.

Caffeine does have weak antagonistic properties at $GABA_A$ receptors, however, this mechanism requires very high concentrations of caffeine

Caffeine reduces GABAergic inhibition by initiating a release of calcium from stores and activating calcium-dependent phosphatases that dephosphorylate the $GABA_A$ receptor.

It competitively binds and antagonizes the glycine receptor. The blockade of glycine receptor by caffeine could synergistically amplify the stimulatory effect of caffeine on excitatory neurotransmission.



GLYCINE RECEPTOR

❖ INTRODUCTION

- Glycine is a simplest amino acid which is semi-essential amino acid and it should be taken as a nutritional supplement.
- Glycine is also a major inhibitory neurotransmitter in the adult vertebrate central nervous system (CNS).
- Glycinergic synapses are particularly abundant in spinal cord and brain stem, but are also found in higher brain regions including the hippocampus.
- Glycine receptor (GlyR) is a member of the nicotinicoid receptor superfamily.
- It is also known as an Inhibitory Chloride channel protein.

❖ SYNTHESIS

1

ADMET of caffeine

Caffeine is rapidly and completely absorbed in humans, with 99 percent being absorbed within 45 minutes of ingestion
Peak plasma concentrations occur between 15 and 120 minutes after oral ingestion.

Once caffeine is absorbed, there appears to be no hepatic first-pass effect (i.e., the liver does not appear to remove caffeine as it passes from the gut to the general circulation),
Caffeine binds reversibly to plasma proteins, and protein-bound caffeine accounts for about 10 to 30 percent of the total plasma pool.

The distribution volume within the body is 0.7 L/kg, a value suggesting that it is hydrophilic and distributes freely into the intracellular tissue water.

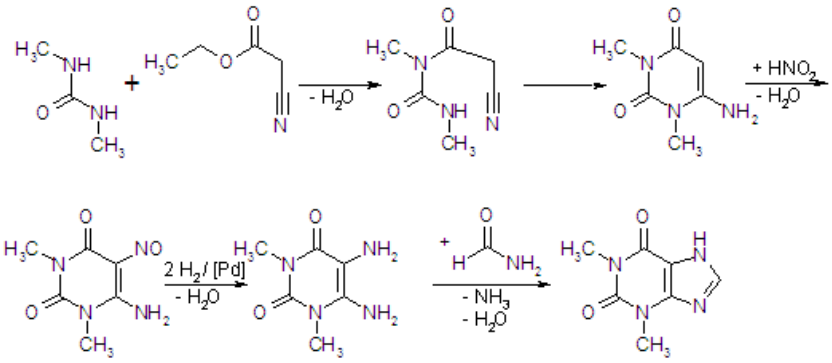
However, caffeine is also sufficiently lipophilic to pass through all biological membranes and readily crosses the blood-brain barrier.

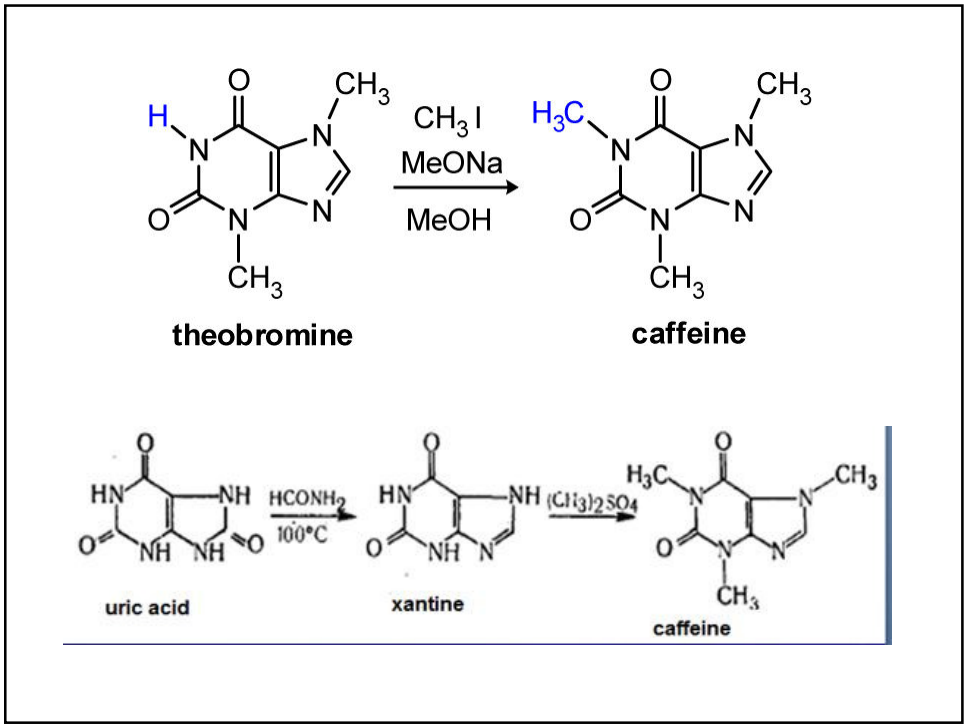
caffeine half-life of 2.5–4.5 hours,

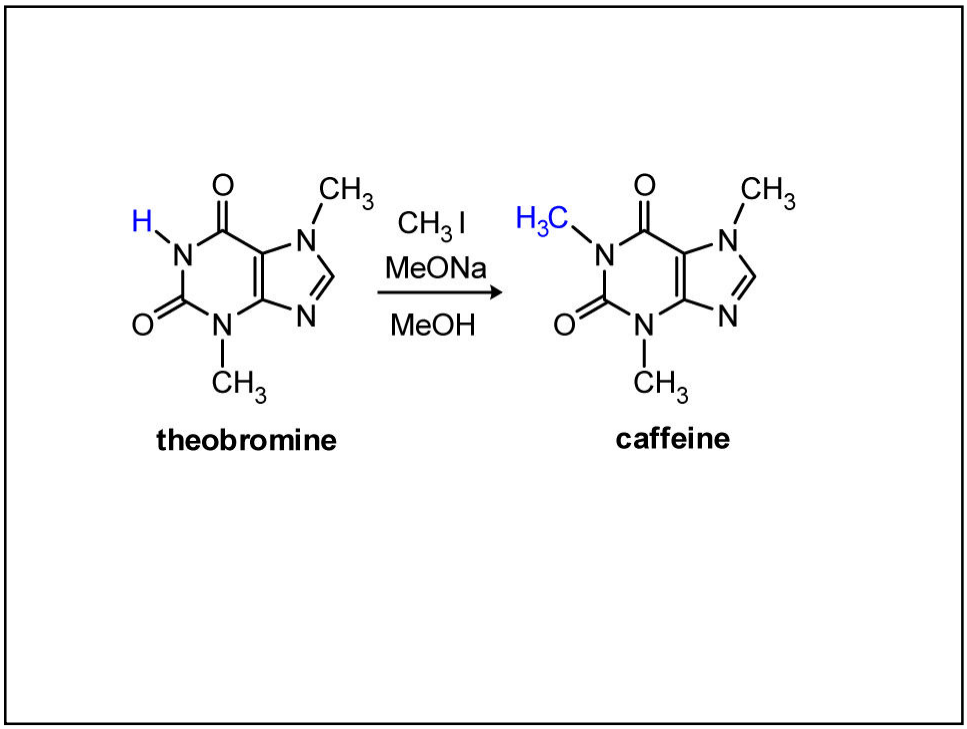
Because caffeine is readily reabsorbed by the renal tubules, once it is filtered by the glomeruli only a small percentage is excreted unchanged in the urine.

Caffeine metabolism occurs primarily in the liver, catalyzed by hepatic microsomal enzyme systems. Paraxanthine is the dominant metabolite in humans, 70–80 percent of caffeine is converted into paraxanthine with no apparent toxic effects following caffeine doses of 300–500 mg/day.

synthesis of theophylline




CH3 I
MeONa
MeOH
theobromine
caffeine
HCONH2
100°C
(CH3)2SO4
uric acid
xantine
caffeine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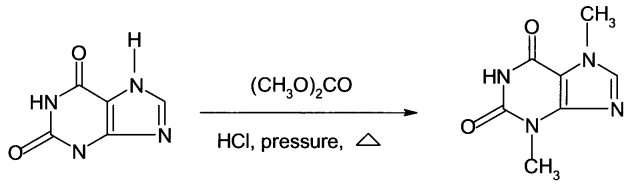


Xanthine

Theobromine

Amphetamines

D-Amphetamine, Methamphetamine, methylphenidate: use to treat attention deficit disorders in children

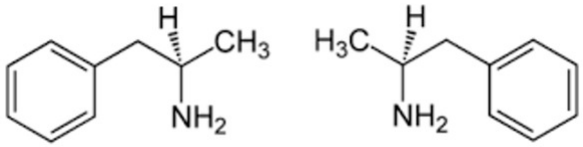
Phenmetrazine (Preludin) - used to treat obesity,

(hallucinogens = MDA, MDMA, DOM; methylenedioxymethamphetamine, "ecstasy," dimethoxyamphetamine).

Amphetamine

Amphetamine is a potent central nervous system (**CNS**) **stimulant** of the phenethylamine class that is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.

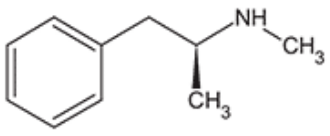
Amphetamine was discovered in 1887 and exists as two enantiomers: levoamphetamine and dextroamphetamine.



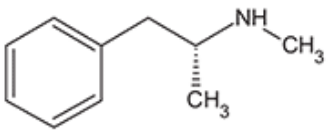
Dextroamphetamine (left) and Levoamphetamine (right)

Methamphetamine

Methamphetamine is a potent central nervous system (CNS) stimulant that is mainly used as a recreational drug and less commonly as a second-line treatment for attention deficit hyperactivity disorder and obesity. *Methamphetamine* was discovered in 1893 and exists as two ...



D-Methamphetamine
(dextro-Methamphetamine,
S(+)-Methamphetamine)



L-Methamphetamine
(levo-Methamphetamine,
R(-)-Methamphetamine)

Clinical use

Appetite suppressant
ADHD
Narcolepsy and chronic fatigue syndrome
Treatment resistant depression

Treatment of ADHD: Amphetamine is combined with methylphenidate to:

- Improve impulse control
- Improve concentration
- Decrease sensory over stimulation
- Decreased irritability and decreased anxiety

Amphetamines vs Methamphetamines

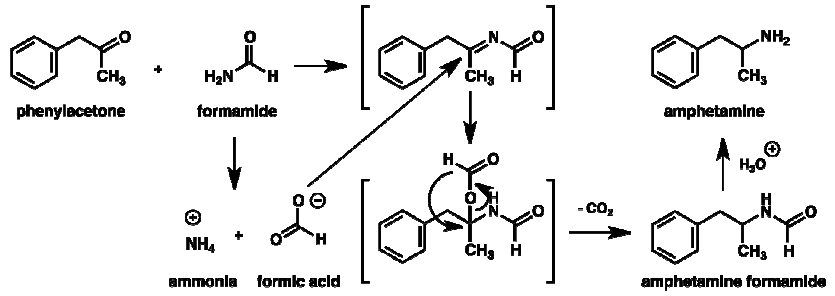
Amphetamine is scientifically known as methylated phenylethylamine. Methamphetamine is double methylated phenylethylamine.

The double process is the primary difference between amphetamine and methamphetamine in a laboratory or scientific instance. Otherwise, the two chemicals or drugs are almost identical in nature causing the same side effects, same dangers and same potential for overdose as well as the same risk of physical dependence and addiction.

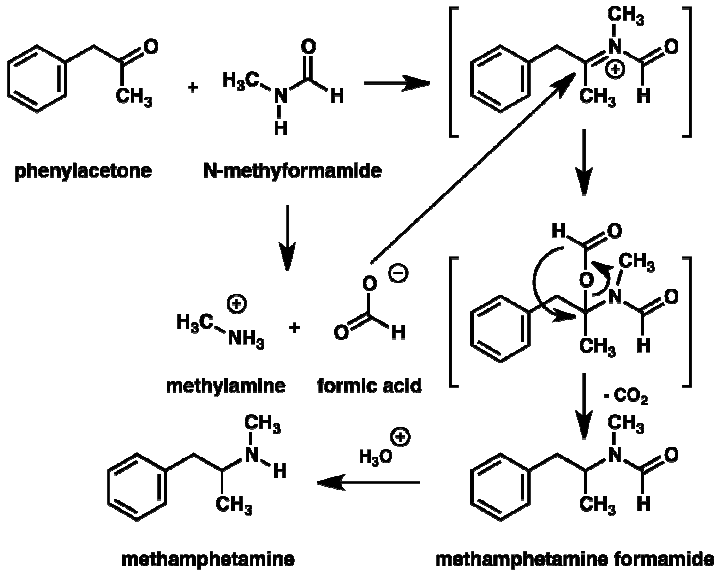
Neither methamphetamine nor amphetamine are really safe for use but amphetamines are used in some prescription medications. Amphetamines can be safe for oral use when they are used EXACTLY as prescribed and under the supervision or direct medical care of a doctor.

Methamphetamine is NEVER safe for oral consumption and should not be used by any means!

Synthesis of Amphetamine

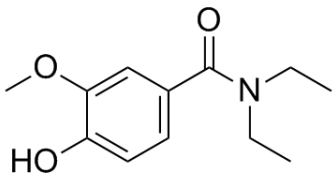


synthesis of Methamphetamines

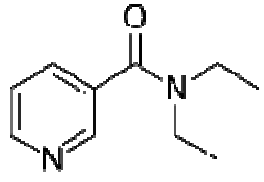


Etamivan (INN) or ethamivan (USAN)

Etamivan (INN) or ethamivan (USAN), trade name Analepticon, is a respiratory stimulant drug related to Nikethamide. It is no longer used in the United States.



Etamivan



Nikethamide

Nikethamide. is a stimulant which mainly affects the respiratory cycle.

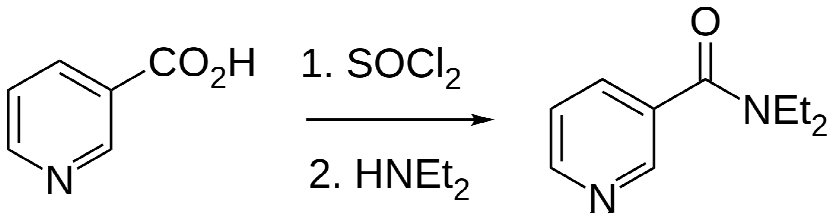
Widely known by its former trade name of Coramine,

it was used in the mid-twentieth century as a **medical** countermeasure against tranquilizer overdoses, before the advent of endotracheal intubation and positive-pressure lung expansion.

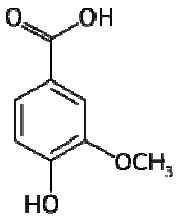
Etamivan is a respiratory stimulant. It was mainly used in the treatment of barbiturate overdose and chronic obstructive pulmonary disease but has now largely fallen into disuse.

Barbiturate (*a class of drugs used to relax and help people sleep.****) overdose*** *is poisoning due to excessive doses of* ***barbiturates****. Symptoms typically include difficulty thinking, poor coordination, decreased level of consciousness, and a decreased effort to breathe (respiratory depression). ... Treatment involves supporting a person's breathing and blood pressure.*

synthesis of nikethamide



Synthesis of Etamivan



Vanillic acid

Central Acting Muscle Relaxants

glyceryl ethers-mephenesin,
alkanediol derivatives-meprobamate, benzodiazepines-librium, diazepam and baclofen.

Spasm in leg muscles/back spasm

A **cramp** is a sudden contraction or tightening of a muscle that usually lasts a few seconds to a few minutes.

A sustained muscle **spasm is** called a muscle **cramp**.

Cramps are caused by muscle **spasms** – involuntary contractions of one or more muscles. Muscle **cramps** and **spasms** are most often experienced in the leg.

Spasms of skeletal **muscles** are most common and are often due to overuse and **muscle** fatigue, dehydration, and electrolyte abnormalities.

The **spasm** occurs abruptly, is painful, and is usually short-lived. It may be relieved by gently stretching the **muscle**.

The same thing is happening when people are experiencing **back spasms**.

Mechanism of Action

Signals normally go from the brain to the muscles, causing a contraction of a muscle.

The **brain** sends electrochemical **signals** through the nervous system to the motor neuron that innervates several **muscle** fibers.

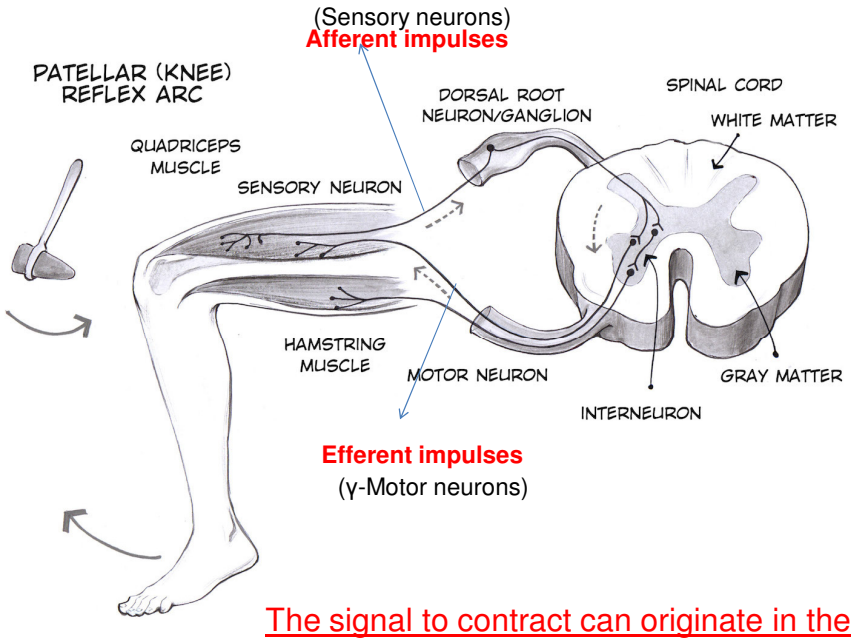
In the case of some reflexes, the signal to contract can originate in the spinal cord through a feedback loop with the grey matter.

Mechanism of Action

Signals are normally going from the brain to the muscles, causing a contraction of a muscle.

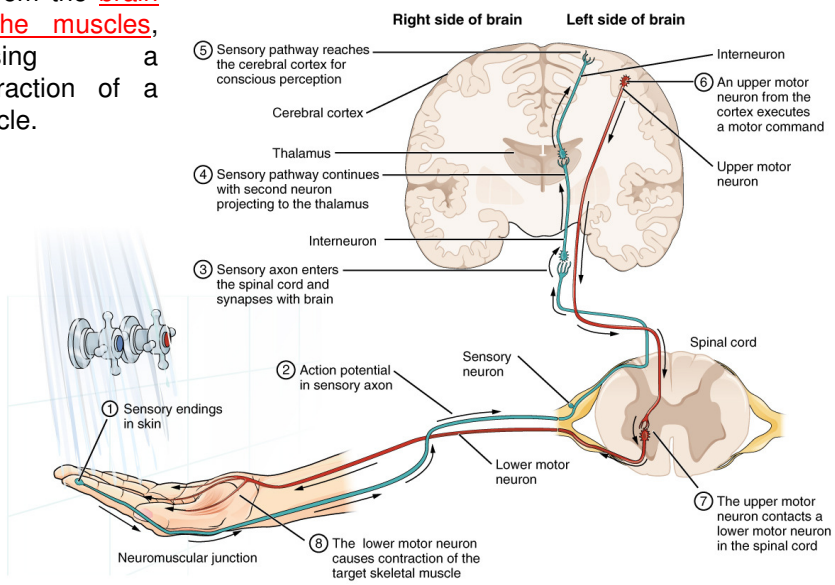
The same thing is happening when people are experiencing **back spasms**.

So if you create a drug that's going to stop this, how would it relax the muscles?



The signal to contract can originate in the spinal cord

Signals normally go from the brain to the muscles, causing a contraction of a muscle.



We don't have a drug that could stop the muscular activity of a certain muscle group.

Instead, muscle relaxants slow down activity in the brain so there's less activity in the brain going out to these muscles.

This would cause a relaxation and you'd feel better.

There is no drug that's going to work specifically on back muscle pain so there's going to be a lot of side effects.

Muscle relaxant:

A **muscle relaxants** is a drug that affects skeletal **muscle** function and decreases the **muscle** tone.

It acts **peripherally** at neuromuscular junction/ **muscle** fibre itself or

It acts centrally in the cerebrospinal axis to reduce **muscle** tone.

It may be used to alleviate symptoms such as muscle spasms, pain, and hyperreflexia.

muscle tone *(residual* ***muscle tension*** *or* ***tonus****) is the continuous and passive partial contraction of the* ***muscles****, or the* ***muscle's*** *resistance to passive stretch during resting state.*

The term "muscle relaxant" is used to refer to two major therapeutic groups:

*N*euromuscular blockers (Acts peripherally)
Spasmolytics (Acts centrally)

Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate *and have no central nervous system (CNS) activity*.

They are often used during surgical procedures and in intensive care and emergency medicine to cause temporary paralysis.

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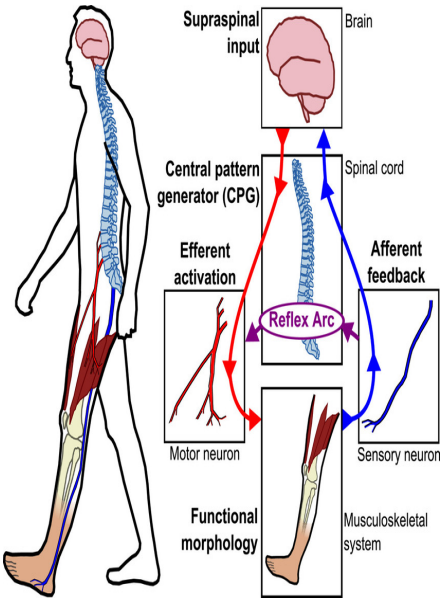
Spasmolytics, also known as "centrally acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions.

Indeed, booth neuromuscular blockers and spasmolytics are often grouped together as muscle relaxants.



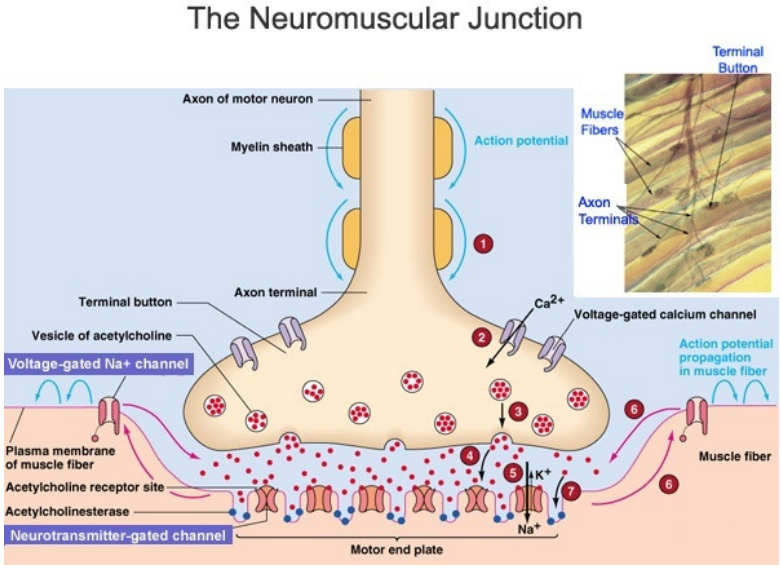
Spasmolytics, also known as "centrally acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions.

While both neuromuscular blockers and spasmolytics are often grouped together as muscle relaxants,

Muscle spasm is an involuntary contraction of a **muscle** that can cause a great deal of pain. When the facet joints of the spine become injured or inflamed, the **muscles** supporting the spine can **spasm** causing low back pain and limitation in motion.

Spasticity is a feature of altered skeletal muscle performance with a combination of paralysis, increased tendon reflex activity and hypertonia. It is also colloquially referred to as an unusual "tightness", stiffness, or "pull" of muscles.

Skeletal **muscle relaxants acts at**



Transmission of nerve impulse

Muscle relaxation and paralysis can theoretically occur by interrupting function at several sites, including the central nervous system, nicotinic acetylcholine receptors, the motor end plate, and the muscle membrane or contractile apparatus.

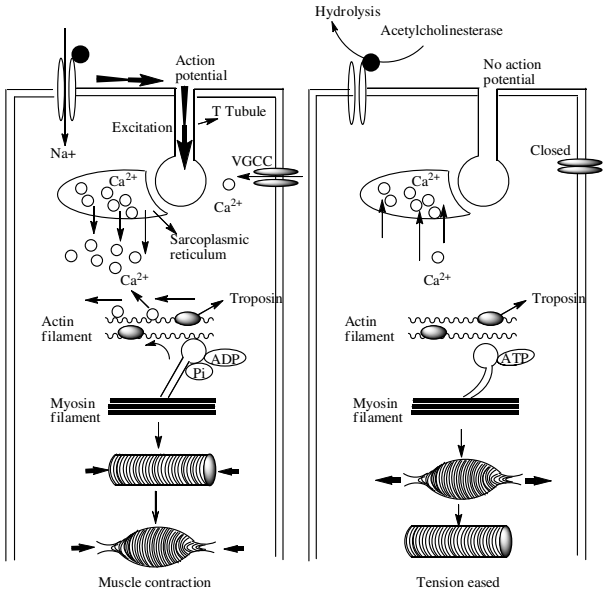
Most neuromuscular blockers function by blocking transmission at the end plate of the neuromuscular junction.

Normally, a nerve impulse arrives at the motor nerve terminal, initiating an influx of calcium ions, which causes the exocytosis of synaptic vesicles containing acetylcholine.

Acetylcholine then diffuses across the synaptic cleft. It may be hydrolysed by acetylcholine esterase (AchE) or bind to the nicotinic receptors located on the motor end plate.

The binding of two acetylcholine molecules results in a conformational change in the receptor that opens the sodium-potassium channel of the nicotinic receptor. This allows Na^+ and Ca^{2+} ions to enter the cell and K^+ ions to leave the cell, causing a depolarization of the end plate, resulting in muscle contraction.

Following depolarization, the acetylcholine molecules are then removed from the end plate region and enzymatically hydrolysed by acetylcholinesterase.



Either depolarize or prevent depolarization

Normal end plate function can be blocked by two mechanisms. Nondepolarizing agents, such as tubocurarine (skeletal muscle relaxant), block the agonist, acetylcholine, from binding to nicotinic receptors and thereby preventing depolarization.

Alternatively, depolarizing agents, such as succinylcholine (GA, to facilitate tubation), are nicotinic receptor agonists which mimic Ach, block muscle contraction by depolarizing to such an extent that it desensitizes the receptor and it can no longer initiate an action potential and cause muscle contraction.

Both of these classes of neuromuscular blocking drugs are structurally similar to acetylcholine, the endogenous ligand.

Action of Central and direct acting muscle relaxants:

They are chemically and pharmacologically different from neuromuscular blockers.

Does not affect neuromuscular transmission but uncouples contraction from depolarization of the muscle membrane.

Reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness.

.

All centrally acting muscle relaxants do have some sedative property.

Reduce rigidity, spasticity and hyperreflexia.

Central Acting Muscle Relaxants

- **Baclofen (Lioresal): A GABA derivative**
- **Diazepam (Valium): A benzodiazepine derivative**
- **Mephenesin group**

Used To Relieve :Muscle Spasm and Spasticity

Muscle spasm is an involuntary contraction of a **muscle** that can cause a great deal of pain. When the facet joints of the spine become injured or inflamed, the **muscles** supporting the spine can **spasm** causing low back pain and limitation in motion.

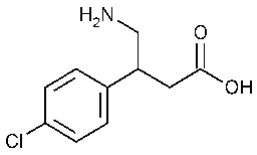
Spasticity is a feature of altered skeletal muscle performance with a combination of paralysis, increased tendon reflex activity and hypertonia. It is also colloquially referred to as an unusual "tightness", stiffness, or "pull" of muscles.

Hypertonia: Increased tightness of muscle tone and reduced capacity of the muscle to stretch caused by damage to the motor nerve pathways in the central nervous system. Untreated **hypertonia** can lead to loss of function and deformity. Treatment can include physical and/or occupational therapy or medications.

Baclofen - Medical Uses

Used To Treat Spasticity In SCI (spinal cord injury) Patients

Used To Treat Spasticity In MS (*Multiple sclerosis* (*MS*) is a cell-mediated autoimmune condition characterised by repeated episodes of inflammation of the nervous tissue in the brain and spinal cord, causing loss of the insulating myelin sheath**) Patients**



In MS, resulting nerve damage disrupts communication between the brain and the body

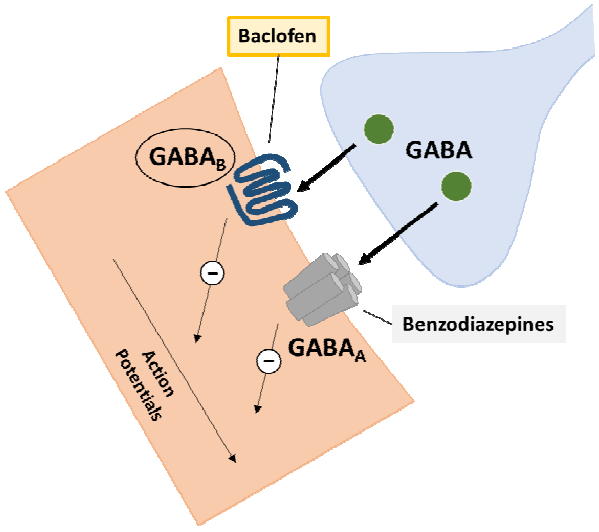
Baclofen - Side Effects

- **Drowsiness**
- **Insomnia**
- **Dizziness**
- **Weakness**
- **Hypotension**
- **Mental Confusion**

The precise **mechanism of action of baclofen** is not fully known.

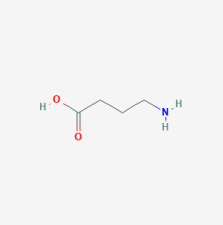
Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although **actions** at supraspinal sites may also occur and contribute to its clinical **effect**. (possibly including the stimulation of GABAβ-receptors).

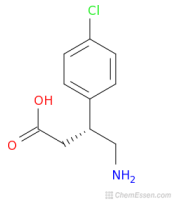
This stimulation results in the inhibition of excitatory neurotransmitter (glutamate and aspartate) release, which may normally contribute to pain and spasticity[15]..



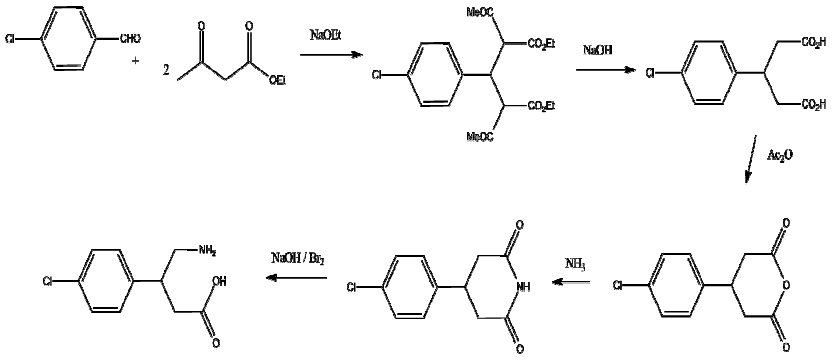
Baclofen is a GABA agonist, and its primary site of action is the spinal cord, where it reduces the release of excitatory neurotransmitters and substance P by binding to the GABAβ-receptor.

Although baclofen is an analog of the inhibitory neurotransmitter gamma-amino-butyric acid (GABA), there are no conclusive data indicating GABA systems are involved in its clinical effects.



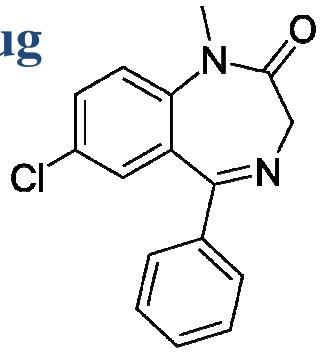


Synthesis of baclofen



Diazepam

- **Diazepam Is A Benzodiazepine**
  - **Has Sedative Qualities**
  - **Has Anxiolytic Capabilities**
  - **Is A Spasmolytic Drug**

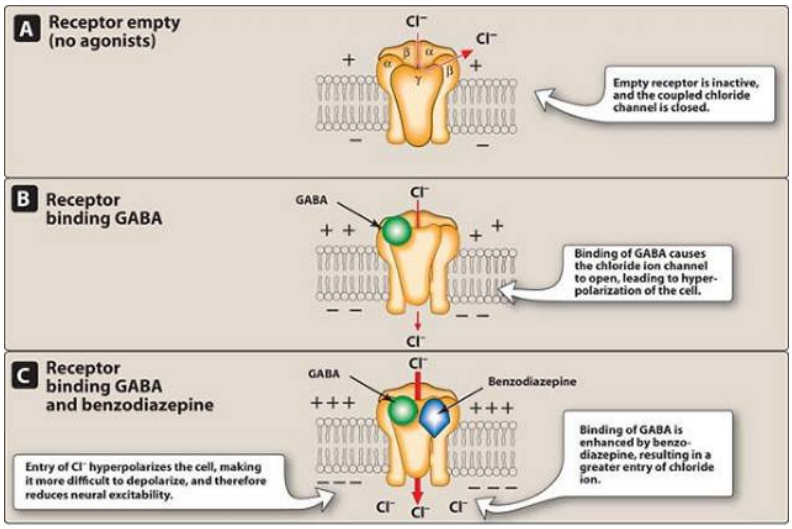


a drug used to relieve anxiety.

power to relieve spasms or convulsions

Mechanism Of Action

- **Potentiates Action of GABA**
- **Increases The Presynaptic And Postsynaptic Inhibition At All Levels In The CNS**



Diazepam - Medical Uses

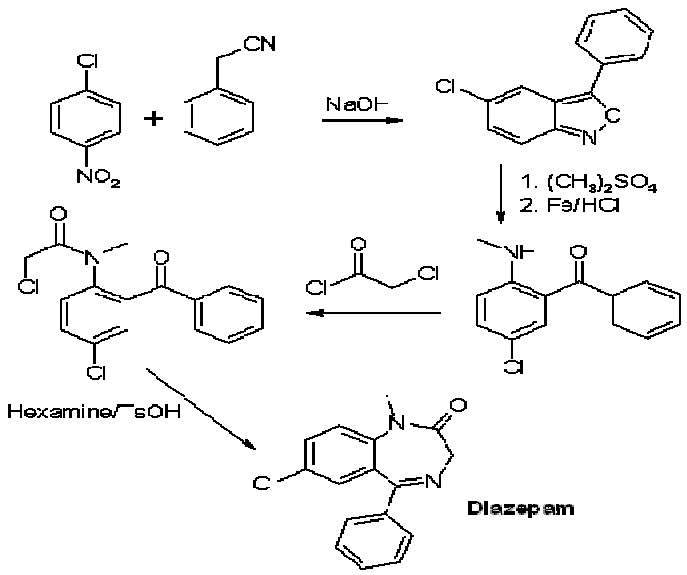
- **A Sedative**
- **As A Hypnotic**
- **As An Anxiolytic**
- **As A Muscle Relaxant**

Diazepam - Medical Uses

- **Relieve The Spasticity of Cerebral Palsy**
- **Induce Mild Amnesia**
- **Control Seizures In Status Epilepticus Patients**

Diazepam - Adverse Side Effects

- **Cardiorespiratory Depression**
- **Drowsiness**
- **Fatigue**
- **Lethargy**
- **Somnolence (Drowsy, Sleepy)**

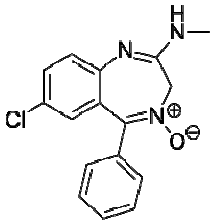


Benzodiazepines-librium

Librium is a prescription *benzodiazepine* that's often abused for its calming effects.

An addiction to *Librium* can develop fast especially when abused for an extended period of time.

Users who are prescribed *Librium* for a medical purpose can still develop a dependence on the drug.



Librium is the brand name for the benzodiazepine medication chlordiazepoxide.

Since Librium, like other medications in its family, is a sedative-hypnotic drug, it is used to calm the firing of some neurons and relax the person taking the medication by changing the chemical balance on GABA receptors in the brain.

This control over the GABA neurotransmitters and their uptake helps manage anxiety, panic disorders, and alcohol withdrawal symptoms like insomnia and seizures. Librium remains in the system for longer than some other benzodiazepines, and it is metabolized into nordiazepam and oxazepam, which can be detected after Librium's effects wear off.

Librium takes 1-4 hours for the full effects to begin working, and the half-life is an astonishingly large 100 hours. Librium's full duration of effect is estimated at 1-3 days.

That being said, like other benzodiazepines, Librium can lead to addiction and physical dependence.

People who take this substance for a long time, either as prescribed or for nonmedical reasons, often experience withdrawal symptoms when getting off the medication.

These symptoms include nausea, depression, anxiety, rebound insomnia, abdominal pain, difficulty with cognition or memory, and muscle weakness.

People who take Librium can also experience side effects like:
Anterograde amnesia
Confusion
Dizziness
Drowsiness, fatigue, or sedation
Depression, irritability, or other changes in mood
Edema
Constipation
Other cognitive impairment

Side effects of any benzodiazepine, including Librium, are rare when the medication is taken as directed. However, people who abuse Librium for nonmedical or recreational reasons, or who become addicted to Librium, are more likely to experience serious side effects. Just like other benzodiazepines, Librium is recommended for short-term use – for 2-4 weeks at most.

Mephenesin

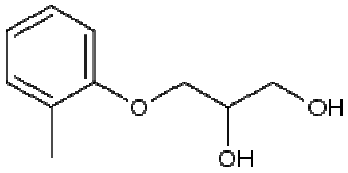
Mephenesin is a centrally acting muscle relaxant. It can be used as an antidote for strychnine poisoning.

Mephenesin however presents with the major drawbacks of having a short duration of action and a much greater effect on the spinal cord than the brain, resulting in pronounced respiratory depression at clinical doses and therefore a very low therapeutic index.

It is especially dangerous and potentially fatal in combination with alcohol and other depressants.

Mephenesin is no longer available in North America but is used in France, Italy and a few other countries.

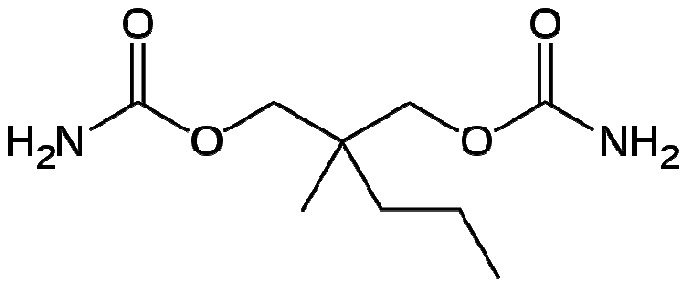
Mephenesin may be an NMDA receptor antagonist



The N-methyl-D-aspartate receptor is a glutamate receptor and ion channel protein found in nerve cells. It is activated when glutamate and glycine (or D-serine) bind to it.

Meprobamate

Meprobamate is chemically a substituted carbamylated derivative of propanediol 1,3 and exert their effects via CNS depressive actions.



Meprobamate is an anxiolytic drug. It was the best selling minor tranquilizer for a time but has largely been replaced by benzodiazepines.

Meprobamate has most of the pharmacological effects and dangers of the barbiturates (though it was marketed as being safer). However, it is less sedating at effective doses.