Psychoactive Drugs.
Diffuse-projecting Neurotransmitter Systems

Lecture 20

Instructor: Anatoli Gorchetchnikov <anatoli@cns.bu.edu>
Teaching Fellow: Rob Law <nosimpler@gmail.com>
Ionotropic receptors

Response is fast
Direct reaction to the transmitter

Excitatory glutamate receptors (AMPA and NMDA)

Inhibitory GABA receptor ($\text{GABA}_A$)

Nicotinic acetylcholine (ACh) receptor

CN 510 Lecture 20
Metabotropic receptors

Responds more slowly
Indirect effect
*G* protein-coupled
Initiates a second signal (messenger) inside the neuron

Muscarinic acetylcholine (ACh) receptor
All dopamine receptors
All norepinephrine receptors
Zoom-in on Channel Structure

A bit less cartoonish picture of an ion channel (GABA_A).

Obviously you can zoom in even closer to see the details of each protein subunit.

This convoluted structure of a channel defines a chemical composition of transmitter.
Agonists and Antagonists

Transmitter and channel are similar to key and lock

Locks can be picked

Channels also can be “picked”

**Agonist** – chemical at least in binding part similar in structure to the transmitter, it opens the same channels when binds to them

**Antagonist** – chemical at least in binding part similar in structure to the transmitter, blocks the channel when binds to it (sometimes called competitive inhibitor)

Often agonists and antagonists are more specific than the transmitter itself

Wide variety of drug effects is based on drug molecule’s similarity to a certain transmitter
Nicotine (ACh Agonist)

Binds to nicotinic cholinergic receptors and opens the respective channels

Higher affinity for receptors in the brain than those in skeletal muscle, though at toxic doses it can induce contractions and respiratory paralysis

40–60 mg (0.5-1.0 mg/kg) can be a lethal dosage for adult humans

Regular smoking decreases the demand on ACh and its production and up-regulates ACh receptors in cerebellum and ventral tegmental area

Quitting withdrawal symptoms are caused by the lack of ACh in the body as well as reduced action of other neurotransmitters

CN 510 Lecture 20
Nicotine (ACh Agonist)

Indirect actions of nicotine include release of
- norepinephrine and dopamine at low doses, acts as a stimulant
- serotonin and beta-endorphine at high doses, acts as a relaxant

Users report relaxation, sharpness, calmness and alertness
- Concentration – due to ACh substitution
- Alertness – due to enhanced NE release
- Relaxation – due to beta-endorphin release
- Sensitivity to reward – due to increase in DA effective time
Morphine and Derivatives (Beta-Endorphine Agonist)

Morphine was the first purified plant alcaloid

Used as a benchmark for pain-killer effectiveness

Binds to $\mu$-opioid receptors and opens the respective channels

Endogenous morphines (endorphins) are responsible for analgesia (reducing pain), causing sleepiness, and feelings of pleasure

Can be released in response to pain, strenuous exercise, spicy food, orgasm, or excitement
Morphine and Derivatives (Beta-Endorphine Agonist)

“Pathological runners” are effectively addicted to endogenous morphines

Psychological dependency develops very fast, physiological dependency takes several weeks/months

Down-regulates the opioid receptors thus reducing the effectiveness of endogenous pain-killing system

Reduces arousal and impairs fine motor control

Effects are hard to study; especially long-term effects
Tetrahydrocannabinol (THC)

Binds to the cannabinoid CB₁ receptors in the central nervous system and the CB₂ receptor in the immune system.

CB₁ receptor is the most abundant G-protein coupled receptor in the brain.

It acts as a partial agonist on both receptors, i.e., it activates them but not to their full extent.

This activation leads to a decrease in concentration of cAMP.

THC has lower specificity and affinity than endogenous cannabinoids, thus acts also as an antagonist.

Endogenous cannabinoids are released from the post-synaptic cell into the synaptic cleft, where binding occurs at receptors present on pre-synaptic neurons, thus modulating neurotransmission.
Tetrahydrocannabinol (THC)

It is also involved in partial activation of the opiate path and dopamine release. DA related action is partially involved in increased appetite especially for tasty food. Altered endorphine release allows it to act as a mild pain suppressor.

Information on dependency is controversial, but it is clearly lower than many other psychoactive drugs.

Low toxicity: ratio of effective dose to lethal dose is about 1:10000
Caffeine (Adenosine Antagonist)

Nonselective antagonist of adenosine receptors

Brain adenosine acts to protect the brain from metabolic stresses by suppressing neural activity and also by increasing blood flow

Adenosine is also used to induce torpor in hibernating animals

Unlike other neurotransmitters, adenosine is generated extracellularly

Caffeine decreases blood flow by 20-30%
Caffeine (Adenosine Antagonist)

Some evidence suggests interactions between adenosine and dopamine systems.

Caffeine also seem to increase norepinephrine levels and lower neuronal activation thresholds.

Generally has a disinhibitory effect on neural activity.

Additional short term effect might free adenosine for more ATP accumulation, long term may result in reduction of ATP synthesis.
LSD (Serotonin et al. Agonist)

LSD affects a large number of the G protein coupled receptors including several serotonin receptors. The primary psychedelic effect is attributed to opening 5-HT$_{2a}$ receptors: most agonists of these receptors have psychedelic properties, antagonists block the effect. Also, affects all dopamine receptors and all norepinephrine receptors.
LSD (Serotonin et al. Agonist)

Exact effect is unknown, but it is thought that it increases glutamate release in the cortex, specifically in layers IV and V.

Panic attacks, anxiety increase and other negative feelings can result (“bad trip”).

People under influence are more suggestible.

Hallucinogen persisting perception disorder (HPPD) might be related to prior LSD use, affects small percent of predisposed users and often requires environmental trigger.

Physical effects like genetic alteration or inducing uterine contractions are not supported by clear evidence.

Very low effective dose makes lethal results rare (none?).

CN 510 Lecture 20
Phencyclidine a.k.a. PCP (NMDA Antagonist)

Inhibits NMDA glutamate receptor (major excitatory receptor in the brain)

Counter-intuitively it does increase cortical activity levels in humans and rodents

Effectively messes up the information processing in the brain

Some versions also inhibit nicotinic ACh and excite D2 dopamine receptors

Alters mood states in an unpredictable fashion, causing some individuals to become detached, and others to become animated

Causes schizophrenia-like brain changes in rats and similar symptoms in humans
Phencyclidine a.k.a. PCP (NMDA Antagonist)

Intoxicated individuals may act in an unpredictable fashion including acts of self-injury, suicide, and attacks on others or destruction of property.

PCP is widely used in animal research because of importance of NMDA channels for learning.

Minor affinity for μ-opioid receptors causes slight anesthetic effects, but long half-life and side effects made it unsuitable for medical applications.
Other Drug Mechanisms

Transmitter action consists of release, binding, and removal (diffusion out of the cleft, reuptake, and enzymatic degradation).

Agonists and antagonists substitute for corresponding neurotransmitters during binding.

Other drugs can alter the release, reuptake, and degradation.

Remember, THC binds to presynaptic receptors and alters the release of transmitters.

Any other drug that binds to axo-axonic synapses will have a similar effect (in biochemical terms).

Altering Ca^{++} levels, spike duration or amplitude at the synaptic terminals will affect the release of transmitter.
Inhibition of Enzymatic Degradation

Monoamine oxidase inhibitors (MAOIs) prevent the breakdown of monoamine neurotransmitters (DA, 5-HT, NE) and thereby increase their availability and effect.

Used as strong antidepressants.

Interact with some foods and wines, which can lead to hypertensive crisis, unless administered not through stomach.

Tobacco also contains MAOI, which is the major cause of addiction to smoking.

Hannibal Lecter mentions that he once ate a liver of a census taker “with some fava beans and a nice Chianti”

– He had named three of the “forbidden foods” for patients taking MAO inhibitors.
Selective Reuptake Inhibitors

Suppress reuptake of a certain neurotransmitter, thus prolonging its action.

Many antidepressants are selective serotonin reuptake inhibitors (SSRIs), some others also inhibit reuptake of norepinephrine or dopamine.

Recently the direct role of serotonin in depression was questioned and more indirect mechanisms of SSRIs are studied.

Norepinephrine reuptake inhibitors (NRIs) are thought to have a positive effect on the concentration and motivation.

Selective nature and more graded indirect effect makes these drugs more suitable for medical use.
Amphetamine (DA, 5-HT, NE Reuptake Inhibitor?)

Increases wakefulness and focus, decreases fatigue and appetite
Elevates cardiac output and blood pressure
Appears to be area specific, neurons releasing dopamine in the hippocampus are not affected, in striatum are affected
Endogenous amphetamine-like chemicals modulate excitement and alertness
Two theories:
- Increasing DA level in the presynaptic cell
- Reversing the action from reuptake to release
Increase of DA in the cytosol is toxic and leads to degradation of the neurons
Amphetamine (DA, 5-HT, NE Reuptake Inhibitor?)

Additional action is similar to MAOI inhibitor.
All these actions combined and long half-life of amphetamine lead to larger DA release than any other drug.

Similar reverse action on serotonin reuptake, also in localized areas.
Increase of serotonin seem to increase the glutamate release in VTA to prefrontal projections – action selection and decision making circuits, as well as working memory.
Use of amphetamine in adolescence can lead to working memory impairments later in life.

CN 510 Lecture 20
Cocaine (DA, 5-HT, NE Reuptake Inhibitor)

Chemical structure allows it to penetrate blood-brain barrier much better than other drugs
Ratio of inhibition is about 3:2:5
Prolonged exposure to cocaine leads to profound up and down regulation of various receptors, especially evident in DA system
The 5-HT$_2$ receptor shows influence in the evocation of hyperactivity displayed in cocaine use

The lack of normal levels of DA and 5-HT are the primary causes of withdrawal symptoms
Cocaine (DA, 5-HT, NE Reuptake Inhibitor)

Cocaine also blocks sodium channels, thereby interfering with the propagation of action potentials

- As a result it acts as a local anesthetic
- Lignocaine and novocaine have similar active site but larger molecules, so they do not penetrate blood brain barrier and are limited to local action
Active/Lethal Dose Ratio and Dependence Potential of Psychoactive Drugs

Legend:
- Narcotics
- Depressants
- Stimulants
- Anesthetics
- Hallucinogens
- Cannabis

Dependence Potential:
- Very high
- High
- Moderate / High
- Moderate
- Moderate / Low
- Low
- Very low

Active Dose / Lethal Dose
Next Time

We will discuss
   - four major diffuse projecting systems in the brain
   - the role of acetylcholine as a diffuse teaching signal and as a modulator of encoding/retrieval switch, including a neurophysiological results and modeling studies

Readings:

Homework due:
   - STDP