Chap 11. Addiction

Drug of abuse affects neurons to exert their influence: alter the ways neurotransmitters carry their messages

Some mimic neurotrasmitters Some block them Some alter the way neurotransmitters are released or inactivated

Ultimately, in all cases, the brain reward system is activated inappropriately Drugs themselves change the brain of susceptible individuals in complex ways, leading to symptoms of addiction Brain regions changed by drugs include those involved in executive functions and judgment

The process of becoming addicted is influenced by many factors Motivation Genetic susceptibility Environmental factors Characteristics of the drugs Response of the brain and body to drugs development of tolerance: the progressive need drug dependence: the adaptive physiological state that results in withdrawal symptoms when drug use stops

Principles of general pharmacology





Pharmacodynamics

The underlying mechanisms of drug action (drug interaction with protein targets)

Drug binding (potency: affinity) Drug efficacy Dose-dependent drug response Drug interaction with nonreceptor proteins



Drug binding

Ligands: endogenous or exogenous (drug)

- 4 types
 - Agonist Partial agonist Antagonist Inverse agonist (require intrinsic basal activity)



Nicotine

Acts through the well-known acetylcholine nicotine receptor (nAChRs) nAChRs: Ligand-gated ion channels opened not only by Ach but also by nicotine

Acts as both a stimulant and a sedative

Stimulate adrenal glands to release epinephrine

Stimulates release of many neurotransmitters: acetylcholine, norepinephrine,

epinephrine, vasopressin, histamine, arginine, serotonin, dopamine, autocrine agents, and beta-endorphins



The four major brain (reward) circuits that use dopamine



• Mesolimbic circuit: dopamine-containing neurons that originate in the ventral tegmental area (VTA in midbrain) and innervate the nucleus accumbens (NAc) (ventral striatum), amygdale, hippocampus and the prefrontal cortex. This circuit is known for its role in memory and for motivation. An excess of activity may lead to schizophrenia and hallucinations.

• Mesocortical circuit: also originates in the ventral tegmental area (TVA) but innervate only the prefrontal and orbitofrontal cortex. This circuit is also involved in schizophrenia and hallucinations.

Nigrostriatal circuit; here dopamine-containing neurons originate from the substantia nigra (SN) (located just ventrolateral of the ventral tegmental area) and innervate the caudate nucleus and the putamen (which together form the "dorsal striatum"). They have a motor control function, leading to the right movements for the acquisition and uptake of food. This circuit is affected in Parkinson's disease. Dopamine-containing nerve cells in the substantia nigra develop α-synuclein pathology and consequently degenerate, resulting in many of the motor abnormalities that characterize the disease. However, degeneration of nerve cells and α-synuclein pathology are not limited to the substantia nigra, they are also present in several other regions of the central and peripheral nervous systems.
Tuberoinfundibular circuit: this circuit originates in the hypothalamus and innervates the pituitary. It is known for its control of secretion into the blood of, amongst others, prolactin and ACTH (corticotrophin). Both play a role in determining our behaviour: seeking pleasure and/or avoiding pain (fight or flight).

Bupropione (Zyban)

A mild dopamine reuptake inhibitor A drug primarily used as an atypical antidepressant A drug for smoking cessation: substantially reduces the severity of nicotine cravings and withdrawal symptoms



Varenicline (Chantix)

A nicotine receptor partial agonist: stimulate the nicotine more weakly than nicotine itself doses





Ventral Tegmental Area (VTA) releases dopamine

Nucleus Accumbens contains dopamine sensitive cells causes feelings of pleasure Amygdala and Hippocampus plays role in memory and whether experience is desirable Prefrontal Cortex coordinates all the information and determines behavior of individual

Alcohol affects several neurotransmitter systems

GABA receptor: calm anxiety, impair muscle control, delay reaction time NMDA receptors: cloud thinking and coma

Alcohol works by activating the endogenous opioid system Naltrexone, an opioid receptors blocker, approved for the treatment of alcoholism

Marijuana

The active ingredient in marijuana: tetrahydrocannabinol (THC) Specific receptors: cannabinoid receptors (GPCRs): coordinate movement endocannabinoid, plant cannabinoids, synthetic cannabinoids

There are currently two known subtypes, termed CB1 and CB2. The CB1 receptor is expressed mainly in the brain, but also in the lungs, liver and kidneys. The CB2 receptor is expressed mainly in the immune system and in hematopoietic cells.



Opiates

Any of the narcotic opioid alkaloids found as natural products in the opium poppy plant The major psychoactive opiates are morphine, codeine, and thebaine

The term opiate refers only to the alkaloids found naturally in opium, but is often incorrectly used to describe all drugs with opium- or morphine-like pharmacological action, which are more properly classified under the broader term opioid

Heroin (diacetylmorphine or morphine diacetate (INN)), an opioid analgesic synthesized, is not pharmacologically active. It must first be metabolized to morphine

Opiates mimics the effects of endogenous opioids (endorphins, enkephalins, dynorphins, and endomorphins)

Increase dopamine release in the brain reward system





A standard treatment for opiate addiction

Methadone: a long-acting oral synthetic opioid, prevent withdrawal symptoms

Naloxone, naltrexone: opioid receptor antagonists

Buprenorphine: a weaker agonist of opioid receptor than methadone



Psychostimulants

Cocaine: obtained from the coca plant leaves A nonspecific voltage gated soidum channel blocker A triple (serotonin, norepinephrine, dopamine) reuptake inhibitor Effect on the mesolimbic reward pathway A powerful stimulant: cross BBB far better than other psychoactive chemicals





Amphetamine: a CNS stimulant approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Historically, it has been used to treat nasal congestion, depression, and obesity. Amphetamine is also used as a performance and cognitive enhancer, and recreationally as an aphrodisiac and euphoriant. Most pronounced effects targeting the catecholamine neurotransmitters.



Substituted amphetamines: methamphetamine, ephedrine, cathinone, MDMA ("Ecstasy"), and DOM ("STP")

Anti-cocaine vaccine to be tested on humans (2013)



Mechanism of action of vaccine against cocaine addiction. The vaccine is composed of succinylnorcocaine molecules covalently linked to a carrier protein derived from the cholera B toxin (rCTB), which is suspended in an aluminum adjuvant. This vaccine can stimulate B cells to produce antibodies to cocaine as well as to rCTB. When cocaine is taken at a later time and enters the bloodstream, the antibodies can bind the drug and form antibody–drug compound molecules in the circulation; these molecules are too large to cross the blood–brain barrier. Clinical Pharmacology & Therapeutics **91**, 60-70 (January 2012)