- Pharmacology: scientific study of actions of drugs and their effects on a living organism
- Neuropharmacology: drug –induced changes in functioning of neurons
- Psychopharmacology: drug-induced changes in mood, thinking, and behaviour
- Neuropsychopharmacology: goal is to identify chemical substances that act upon NS to alter behaviour that is disturbed due to injury, disease, environment
- Drug action vs. effect
    - Drug action: specific molecular changes produced by a drug when it binds to target site or receptor (neuropharmacology)
    - Drug effect: widespread alterations in physio and psych function (psychopharm)
- Therapeutic effects vs. side effects:
    - Therapeutic: drug receptor interaction produces desired physical or behavioral changes
    - Side effects: all other effects
- Cell bodies – makes NT; terminal – releases NT
- Specific vs. nonspecific effects
    - Specific: those based on physical and biochemical interactions of a drug w/ a target site
    - Nonspecific: based not on chemical activity but on unique characteristics of individual; Effected by mood, experience, genes, bodies; Drug needs to have an effect above placebo effect
- Pharmacokinetics – how drug effects body
    - Factors that contribute to bioavailability
    - Routes of admin (A-absorption, D-distribution, M-metabolism, E-excretion)
        - Absorption and distribution: movement of drug from site of admin to blood -> rest of body
        - Binding: to target sites or plasma proteins (can also be stored in fat)
        - Metabolism/inactivation: breakdown of drug
        - Elimination/excretion of drugs metabolic waste products from body (blood, breast milk, sweat, urine)
- Pharmacokinetic factors determining drug action
    - RoA: how and where drug is admin – determines how quickly drug is absorbed and enters bloodstream – influences bioavailability
- Oral admin
    - Safest, most convenient and economical; lower bioavailability
    - Drug must be soluble and stable in stomach fluid (critical feature)
    - Disadvantages: vomiting & stomach distress; hard to know how much of drug will be absorbed due to genetic differences, food in stomach, etc.; stomach acid destroys some drugs, first pass effect – liver metabolism reduced amount of drug that reaches gen circulation
    - E.g. LSD, alcohol, MDMA, caffeine

- Injections
- Intravenous (IV): drug introduced directly into bloodstream/vein
    - Dosage can be extremely precise – efficient
    - Fastest onset of pharm action (& most dangerous route) except for some drugs that are inhaled (e.g. Crack); increased risk of infection, blood borne disease
    - Drugs usually suspended in vehicle solution
- Intramuscular (IM): drugs injected into skeletal muscle
    - faster than in stomach/oral, slower than IV
    - RoA depends on rate of blood flow to muscle
- Subcutaneous (SC): injected under skin
    - Absorption slow and steady; done with animals, rarely done medically
- Epidural injections: membrane that covers spinal cord & nerve roots in spine is called dura membrane; space surrounding dura is epidural space; nerves travel through epidural space to back and into legs (or out into neck & arms)
    - Lots of potential complications (back pain, headaches, nausea, shakes)
- Intraperitoneal: injected by stomach; injected into peratoneal muscle; for rabies, diabetes
- Inhalation
    - Popular for recreational drugs (e.g. Tobacco, marijuana, cocaine, heroin)
    - Lung tissues: large surface area allows for rapid absorption into blood; blood from capillaries of lungs goes straight to brain w/o returning to heart first
    - For some drugs, even faster onset then IV injection
- Intranasal or sublingual
    - Absorbed through membranes in mouth or nose
    - E.g. snorting cocaine powder, nasal decongestants, nicotine gum
    - Wherever there are mucosol membranes
- Transdermal
    - Patches provide continuous, controlled release over hours/day, min side effects through skin
    - E.g. nicotine, estrogen, nitroglycerine, fentanyl
- Factors influencing drug absorption
    - Transport across membranes: Phospholipid bilayer: whether drug can get in cell, all cells have this; complex lipid molecules; negative charged region at one end and 2 uncharged lipid tails
    - Lipid solubility: how readily a drug will pass through lipid barriers to enter brain (passive diffusion via [c] gradient); fat loving; movement always in a direction from higher to lower [c]
        - Ionized drugs: lipophobic/hydrophilic = ionized molecules (charged) – water liking; molecules dissolve in water;
        - Hydrophobic/lipophilic = non-ionized molecules (non-charged) – fat liking; molecules penetrate membranes

- Distribution: how a drug gets to its site of action, or dispersed throughout body
    - Factors that influence: blood flow (transports drug), solubility of drug in fat, binding to proteins of fats in blood -> slows distribution, diffusibility of membranes and tissues (cell membranes, capillary walls, blood-brain barrier, placental barrier)
- Capillaries: connect arteries (rest of body) and veins (heart)
    - Tiny cyclindrical blood vessels; have pores that are larger than most drugs; allow transport of drugs regardless of lipid-solubility; blood and protein are too big for pores; drugs that bind to plasma proteins can't pass through
- Blood-brain barrier (BBB)
    - Brain must protect neurons from toxins; brain has a great need for nutrients and oxygen (it has a high blood flow), which increases risk of toxic danger; solution = (BBB) – differences in endophilial cells; Capillaries in brain don't allows drugs to pass as easily as capillaries in rest of body; caused by tight junctions b/t cells in blood vessels of brain
    - Area postrema (vomiting reflex), median eminence of hypothalamus (move hormones) are barrier free
- Placental barrier
    - Drugs cross primarily by passive diffusion; not a good barrier to drugs – fetus is at least partly exposed to essentially all drugs taken by mother
- Metabolism (biotransformation) – breakdown into constitute parts
    - Chemical changes that usually lower effect of drugs and increase their excretion
    - Typically, change substances from hydrophobic to hydrophilic to aid elimination; lipophilic drugs – into body; lipophobic – eliminated from body
    - Metabolism is done by enzymes in liver, GI tract, kidneys (lowers bioavailability)
- Phase I vs. Phase II metabolism
    - Phase I: less reactive compound is converted to a more reactive molecule (oxidation, reduction, or hydrolysis); oxidation makes compound more water soluble and facilitates further reactions; cytochrome P450 enzymes
    - Phase II: active or toxic molecule is converted to a less active metabolite; oxidized compound is conjugated w/ (couple to) an endogenous (w/I body) molecule (e.g. Sulfate, methyl, glucuronide groups); increase water solubility for excretion
- Elimination
    - Primarily accomplished by kidneys – keep right balance of water and salt in body, filter waste from blood, collect in bladder, and then selectively reabsorb what is required
    - Routes of excretion: kidneys excrete water-soluble drugs and metabolites in urine; liver bile excretes some drug molecules in feces; mothers milk excretes small amounts of drugs; some drugs may be exhaled through lungs (e.g. alcohol)

- Chemical signaling
    - Transmission occurs from presynaptic cell to postsynaptic cell
    - Flow of info: synapse->dendrite->soma->axon->synapse
    - Axodendritic: most common synapse; Axoaxonic: permits presynaptic cell to alter NT release from postsynaptic cell directly @ terminals – presynaptic inhibition/facilitation; axosomatic: closer, less travel, higher graded
- Neurotransmission
    1. NT synthesized; stored in vesicles
    2. Action potential
    3. Depolarization opens Ca2+ channels
    4. Influx of Ca2+ ions
    5. Causes vesicles to fuse w/ presynaptic membrane
    6. NT released via exocytosis
    7. NT binds to receptor in post synaptic membrane
    8. Opening or closing of postsynaptic channels
    9. Postsynaptic current causes inhibitory or excitatory potentials
    10. Retrieval of vesicular membrane
- Neurotransmission in 4 steps
- Step 1: Synthesis and storage
    - NT are derived in 2 gen ways: axon terminal – building blocks from food are pumped (actively transported) into cell via transports: protein molecules embedded w/i cell membrane; cell body – according to instructions contained in DNA; transported on microtubules to axon terminal
- Step 2: NT release
    - At terminal, action potential opens voltage – sensitive calcium (Ca2+) channels -> on membrane of nerve terminal; Ca2+ enters terminal and binds to protein calmodulin forming a complex; complex causes some vesicles to empty their contents into synapse, and others to get ready to empty their contents; vesicles fuse w/i membrane
    - Controlling rate of release: rate of cell firing (strong vs. weak stimulus); probability of transmitter release from terminal – sometimes Ca2+ channels open, but don't release NT (about 10-90%); autoreceptors (2 main forms if activated, prevent release) – terminal: located on axon terminals, inhibit further release; also somatodendritic – on soma or dendrites, slow rate of cell firing, smaller effect
- Step 3: Receptor – site activation
    - After being released, NT diffuses across synapse and activates receptors on postsynaptic membrane (like key and lock)
    - Transmitter – activated receptors: protein embedded in membrane of a cell that has a binding site for a specific NT

    - NT may after binding: depolarize postsynaptic membrane causing excitatory action on postsynaptic neuron – direct effect; hyperpolarize postsynaptic membrane causing inhibitory action on postsynaptic neuron – direct effect; initiate other chemical reactions that modulate either excitatory or inhibitory effect, or influence other functions of receiving neuron – indirect effect
- NT receptors
    - Almost all NTS have more than 1 type of receptor: receptor subtypes; 2 broad categories: ionotropic and metabotropic
- Ionotropic – do not allow for synaptic plasticity
    - Rapid; direct; aka ligand-gated ion channel
    - Made up of several proteins (4-5 subunits) which come together to form complete receptor; center of subunits is pore – ions flow through; possess 1+ binding sites for NT; pore normally closed until NT binds to receptor
- Metabotropic
    - Slower, longer lasting effects; indirect mechanism; aka G protein-coupled receptors (alpha, gabba, beta subunits)
    - Single protein subunit which winds its way back and forth thru membrane 7 times (7 transmembrane domains); no channel/pore, but do have binding site – activated or inhibited receptor; intracellular cascade -> biochemical effect
    - Work either by: stimulating or inhibiting opening of ion channels; stimulating or inhibiting certain enzymes (effector enzymes) -> synthesize or break down 2nd messengers (NT/hormone is 1st messenger), leads to biochemical of physio changes in postsynaptic cell
- 2nd messenger systems – allow for plasticity
    - Work by activating enzymes called protein kinases; phosphorylate (catalyze addition of a phosphate group) molecules, specifically proteins; alter functioning, e.g. Open ion channel enzyme activated, turn on or off genes -> critical in a learning situation
- Tyrosine kinase receptors – has long term consequences, can turn genes on/off in nucleus
    - Mediate action of neurotrophic factors -> specific type of protein, proteins that stimulate survival and growth of neurons during development; also involved in signaling -> e.g. Nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT3) and 4 (NT4); use trkA (NGF), trkB (BDNF; NT4), and trk (NT3) receptors
    - Neurotrophic factors stimulate trk receptors by bringing 2 receptors molecules into close proximity, leading to reciprocal phosphorlylation of tyrosine residues and activation of other protein kinases
- Step 4: Neurotransmitter inactivation
    - Diffusion: NT binds only for certain amount of time; enzymatic breakdown: more common, breakdowns NT into constitute parts, e.g. ACh, lipid and gaseous

transmitters, neuropeptides; transporters: pump back into cell body, e.g. Amino acid transmitters, monoamines; reuptake (same cell), postsynaptic or glial cells, pump NT into glial cells, broken down, take into cell by new mechanism

- Pharmacodynamics: drug receptor interactions
    - Drug agonist is similar to a NT and has a bio effect; facilitates neural transmission binds to receptor
    - Drug antagonist blocks action of NT; occupy receptor -> no biochem effect, lowers likelihood of cell transmission
- Drug response curve describes receptor activity
    - Response for a given drug dose; threshold is dose producing smallest measureable response; plotting on what dose a change is seen
    - ED (100): dose where max response is achieved; ED (50): dose that produces 50% of max response -> critical dose
- Agonists and antagonists
    - Competitive antagonists (naloxone) lower agonists (morphine) potency – need higher doses of drug to produce response; agonist – increase tolerance to pain
    - Noncompetitive antagonists alters dose-response curve of drugs indicates that it acts on a different receptor binding site; or could interfere w/ intracellular process
- Therapeutic index: drug safety and side effects; measure;
    - ED (50): dose where 50% show favorable drug effects; TD (50): 50% show toxic (undesirable) effects
    - Margin of safety good for respiratory depression BUT common side effect at ED (50) would be drowsiness; TI=TD50/ED50

- In vivo – living organism; in vitro – outside living body
- Stereotaxic surgery: in vivo
    - Implant electrodes, needles, etc. Into a specific region of brain; calculated using a brain atlas; distances are measures from skull surface features; accuracy of placement must be determined histologically
- Lesioning and microinjection
    - Lesioning/ablation: position electrode into brain; tissue at tip is destroyed (lesioning – killing off some cells, ablation – killing off whole sections)
    - Electrolytic: radio current – destroys all tissues, neurons/axons, no specificity
    - Chemical: neurotoxins; destroys only cells, spares axons (taken in by reuptake); used to target specific neural pathway utilizing a particular NT; not taken up by axons; e.g. 6-OHDA destroys NA and DA, selective neurotoxin
- Microdialysis; in vivo
    - Measure NT released in specific brain region while subject engaged in behaviour/what NT is released in response to drug

    - Cannula implanted stereotaxically; collects extracellular fluid, pumps in artificial CSF; based on difference in [c], chemicals of interest move across membrane into cannula; analyzed using HPLC; what chemicals are present
    - Permanently implant probe/tube
- In vivo voltammetry
    - Similar to microdialysis; difference is that in vivo voltammetry measures changes in neurochemicals using implanted microelectrodes
    - Small electrical potential applied, changes in current flow reflect changes in [c] of NT and metabolites; measures chemistry of brain; measurements made continuously – real time
- Electrophysiology; can look at from 2 different directions
    - Implanted macroelectrodues; stimulate cells at tip, evaluate change in behaviour; should produce effects opposite to lesion; can also be to record populations of neurons
    - Single cell/unit recording; intracellular or extracellular; anaesthetized vs. freely moving; measures bioelectrical activity of brain
    - Patch clamp electrophysiology: micropipette contains patch of membrane w/ 1+ ion channels; only look at how ion channel is changed
- Radioligand binding; can measure amount at post or pre synaptic
    - Used to study number of receptors in a given brain region
    - Grind up brain region into homogenate; after incubation, wash to remove any unbound radioligand; bound radioligand is quantified using a scintillation counter that detects radioactive particles; as radioligand [c] increase, specific binding to receptors also increase
    - B(max) – all sites are filled; k(d)-50% of receptors are occupied (receptor affinity)
- Receptor autoradiography
    - How many receptors in a specific region of brain? – visualize distribution, use slide mounted tissue instead of homogenate; autoradiographic film placed on top of slides, material bound to receptors acts on film; particles emitted from radioactive tissue expose film, reveal both amount and location
- Immunocytochemistry (ICC); use principles of immune system
    - Antibody: protein produced by WBC to destroy foreign substances (antigen); antibody attaches to antigen wherever cells are present that contain antigen; specific antibodies in response to specific antigens; ICC: detection in cultured cells; immunohistochemistry: detection of antigens in tissue
    - 1. Protein injected into animals; makes antibodies 2. Blood containing antibodies is withdrawn 3. Antibody applied to tissue slices, chemically tagged 4. Only neurons containing antigen to which tagged antibody binds are labeled
- Radioimmunoassay (RIA)
    - Quantify proteins in blood, saliva, or CSF

    - Based on competitive binding of antibody prepares standard curve of binary antigen [c] against which unknown samples can be compared; more unlabeled competitor antigen (experimental samples)=less bound labeled antigen
- In situ hybridization (ISH)
    - Localizing cells in tissue slices that manufacture (vs. contain) particular protein/peptide; mRNA, can measure location and amount (rate of synthesis); make up probes that contain complementary base-pair sequences; label radioactively or w/ dyes; when slices exposed to labeled probe, probes attaches (hybridizes) to complementary base-pair sequences; tissue then exposed to film
- Imagining dynamic cell processes; ex-vivo
    - 2-deoxyglucose autoradiography
    - When cell firing increases, metabolic rate increases; identify which cells take up more glucose; 2DG modified form of glucose, taken up by active cells but not metabolized, don't see breakdown of product; inject animal w/ 2DG, test, then sacrifice and prepare brain; C-fos: transcription factor that increase during protein synthesis
- Imaging
    - CT: X-rays passed through brain; differentially absorbed depending on density of tissue; not just for brain tissue
    - Magnetic resonance imagining: measures waves that different atoms emit when placed in a strong magnetic field; hydrogen (water) – every time its magnetized, it creates a different wave; recreated 3D image, not spots of activity
    - Positron emission tomography (PET): maps distribution of radioactively labeled substance; activity functional, not anatomical
    - Single-photon emission computerized tomography (SPECT): similar to PET but simpler and less expensive; can be combined w/ CT or MRI; looks at more individualized cell structures
    - Functional MRI (fMRI): measure flow of oxygen to cells; anatomical and function info; flow of activity in brain, look at changes over time; rapid (real time), very expensive
- Evaluating behaviour: animal research
- Motor activity
    - Drugs that produce sleep, sedation, loss of coordination
    - Spontaneous locomotor activity; break breaks, automated video tracking, open field test; Look at how much rats are moving, where they are hanging out; if anxious, stay at edges and sniff, go on hind legs
- Analgesia
    - Lower of pain w/o loss of consciousness
    - Tail flick test; measure latency of which rat moves tail to pain; 10 sec max (test) cutoff was applied to prevent tail damage

- Learning and memory
    - Morris water maze: test how long it takes rat to find hidden platform using landmarks; can change location of platform to see if it can reorient itself; test of spatial memory
    - Mainly used to study effects of NMDAr antagonists in relation to mechanisms of memory; utilized for testing of compounds for memory enhancement
- Maze
    - Start box w/ 1+ choice points that lead to final goal box (contains food or other reward); if it has a good memory, wont revisit an arm
    - T-Maze; radial arm maze; learn to forage by visiting each arm only once/day
- Delayed response test: frontal lobe/cortical activity, prefrontal cortex; how long an animal can keep something it its working memory
- Anxiety: rats don't like open spaces, don't like light; animal stays in dark/closed if increased anxiety; light dark box – 2 sides to compartment, look at how much time animal spend on either side; elevated plus maze – 2 arms closed, 2 open, look at how much time it spends in arms, latency to open arms, rearing
- Fear; common in PTSD research; animals learns to freeze in response to tone
    - Conditioned fear
- Reward; Conditioned place preference – tend to return to places they feel good in, see which compartment it goes to after experiencing condition w/ drugs w/ specific compartment; classical conditioning – pair one side w/ drug on odd days, pair other side w/ control on even days, on test day allow animal to explore both chambers in absence of drug – where do they spend their time?
- Operant behaviour: animals learns to bar press to receive food/drug (self admin, IVSA) ; can change schedule of reinforcement to see changes in behaviour – press different amounts to get reward, motivation until break point; higher breakpoint, higher abuse potential; intra-cranial self-stimulation (ICSS)

- Catecholamine
    - Core structure of catchol and nitrogen containing group called an amine; part of monamines; dopamine, norepinephrine, epinephrine (aka adrenaline)
- Synthesis
    - Amino acid tyrosine obtained from dietary protein; transported from blood to brain by astrocytes
    - Biochemical steps: each compound catalyzed by an enzyme; neurons that synthesize dopamine contain TH and AADC; neurons that synthesize NE also contain DBH

    - TH: rate-limiting enzyme; rates of drugs downstream dependent on TH for manufacture; - feedback (high DA/NE, slower TH activity); rate of firing: high rate, high TH; AMPT inhibits TH, negative feedback
- Tyrosine
    - Produced in body from phenylalanine; found in soy products, poultry, fish, nuts, avocadoes, bananas, dairy, lima beans, pumpkin seeds, sesame seeds
- Storage and release
    - Packaged and release from vesicles; needs to be packaged in vesicle and released through exocytosis; vesicular monoamine transporter (VMAT): protein in vesicle membrane that uptakes catecholamines; blocked by reserpine: DA and NE break down, leads to low levels – produces sedation, depression -> if not packaged, dissipates in terminal
    - Catecholamine release is inhibited by autoreceptors; located on cell bodies, terminals, dendrites; lower amount of Ca in response to action potential; D2 receptors; also inhibited by autoreceptors – multiple regulations of NT
- Inactivation
    1. Reuptake via DA/NE transporter; repackaged or broken down – bring back into cell body, frees up transporters; drugs that block transporter protein increase [c] of DA/NE (e.g. Tricyclics, cocaine)
    2. Metabolism/degradation; a)catechol-o-methyltransferase (COMT), b)monamine oxidase (MAO-A; MAO-B) -> give rise to metabolites, DA->homovanillic acid (HVA), NE->MHPG, VMA
        - Drugs that inhibit these enzymes lead to accumulations of DA/NE in synaptic cleft; MAO-inhibitors (anti-depressant), e.g. Phenelzine, tranylcypromine; COMT-inhibitors used to enhance effectiveness of L-DOPA, prevent breakdown of dopamine
- Organization and function of DA system
    - Catecholamine cell ground designated w/ letter A + #1-16; A1-A7 are noradrenergic; A8-A16 are dopaminergic; # = specific pop of neurons
    - 3 major ascending dopaminergic pathways: 1. Nigrostriatal, 2. Mesolimbic, 3. Mesocortical
- Nigrostriatal pathway
    - Cell bodies in substantia nigra (A9); project to areas of basal ganglia (dorsal striatum), notably caudate putamen and globus pallidus (terminal); involved in motor control; damaged in PD (loss of dopamine)
- Mesolimbic pathway
    - Cell bodies in ventral tegmental area (A10); projects to limbic regions, most notably nucleus accumbens, olfactory regions, amygdala, hippocampus (terminal); involved in reward, emotion, motivation; drug abuse – all drugs of abuse effect nucleus accombus, main pathway activated

- Mesocortical pathway: final pathway involving dopamine
    - Cell bodies in A10 project to cerebral cortex (prefrontal), hippocampus (terminal); also involved in motivation and emotion, implicated in drug abuse and schizophrenia
- Dopaminergic receptors
    - 5 main DA receptor subtypes (D1-D5) – all metabotropic; classified as 'D1-like' (D1 & D5) and 'D2-like' (D2,3 & 4); found mainly in cortex, striatum and nucleus accumbens
- D1-like receptors; acts on effective enzyme which activates 2nd messenger
    - Activates G_S; stimulate adenylyl cyclase (AC) activity; increase synthesis of cAMP, alters permeability of postsynaptic membrane and enhances conduction – more responsive to dopamine
- D2-like receptors
    - Activates G_i; inhibit or have no effect on AC; lower rate of cAMP synthesis; also can enhance K^+ channel opening (hyperpolarizing membrane)
- Dopamine receptor agonists and antagonists
    - Apomorphine: stimulates both D1 & D2 (agonist); leads to behavioral activation similar to cocaine and amphetamine, can be used to treat ED by increased blood flow to penis; SKF38393: D_i selective agonists, elicits self-grooming in rats/mice; quinpirole: activates D2 and D3, elicits locomotion and sniffing behaviour; haloperidol: D2 antagonist, leads to catalepsy
- Dopamine and reward; dopamine is a teaching signal
    - When you do something +, dopamine is released and you feel better; when we eat, or have sex, brain processes a + stimuli and dopamine is released in our brain; when brain rewards us in this way for certain behaviour, our impulse is to repeat it, reinforcing that its good for us; eating and drinking water only gives us a tiny dopamine reward, taking drugs gives us a whole heap of stuff
- Neurobiology of pleasure
    - '53: Olds and Milker discovered that animals will actively seek out electrical stimulation of specific brain regions; rats will press a lever as rapidly as 2000 times each hour to obtain electrical brain stimulation; continue responding at this rate for 24 hours or longer; ignore other rewards, such as water or food, to continue working for electrical stimulation; intracranial self-stimulation method investigated "reward system" in brain
- D1 receptor blockage and CPP
    - D1 receptor antagonist infused into shell or core b4 training; morphine injected s.c.; D1 antagonism decreases time spent in drug paired side
- D2 receptor blockade and CPP

    - D2 receptor antagonist infused into shell or core b4 training; morphine injected s.c.; D2 antagonism decreases time spent in drug paired side; spends more time in shell
- Dopamine hypothesis of schizophrenia
    - Classical hypothesis: schizophrenia is caused by hyperactivity of dopaminergic transmission at D2 receptor; dopamine-releasing drugs (amphetamine, mescaline, LSD) can induce state closely resembling paranoid schizophrenia; conventional neuroleptics all have in common ability to inhibit DA (DA antagonists)
- D1 and D2 receptors in schizophrenia brain
    - Sig more D2 receptors in brains of deceased schizophrenics than nonschizophrenic controls; no difference in # of D1 receptors
- D2 receptors and antipsychotics
    - High correlation b/t affinities of many antipsychotic drugs for D2 receptor site (as measured by dose of drug needed to produce antipsychotic effects in schizophrenic patients)
- Is schizophrenia caused by D2 hyperactivity
    - Antipsychotics bind to DA receptors rapidly but clinical improvement develops slowly; clozapine is a very effective atypical antipsychotic; binds D1, D4, and serotonin receptors; in gen, antipsychotics are more effective against + symptoms of schizophrenia (e.g. Hallucinations), then – symptoms (e.g. Catatonia); - symptoms may respond to agonists (suggesting reduced DA activity involved in – symptoms)
- Automatic nervous system
    - Sympathetic system: arouses body action (e.g. Increase heart rate and blood pressure); mediates “fight or flight” response
    - Parasymthetic system: opposite of sympathetic: prepares body to “rest and digest”; reverses “flight or fight: responses
- Organization of noradrenergic system ***
    - NE containing neurons located in brain stem (pons, medulla); locus coeruleus (LC) in pons contains A6 cells – send fibers to most of forebrain, cerebellum, and spinal cord
- Function of noradrenergic system
    - NE plays important role in peripheral NS (sympathetic branch of ANS); NE also secreted by adrenal glands (direct to bloodstream; but not to brain b/c of BBB); cells in LC show slow rate of firing when rats asleep, novel stimuli increase cell firing – play an important role in vigilance
- Synthesis of epinephrine
    - Cells in adrenal medulla synthesize and secrete epinephrine; in humans, cats and chickens, roughly 80,60, and 30% of catecholamine output is epinephrine;

following release into blood, these hormones bind adrenergic receptors on target cells

- NE and E receptors
    - Adrenergic receptors belong to family of metabotropic receptors, mediate both NT and hormonal (EPI) actions
    - Postsynaptic adrenoreceptors: cerebral cortex, thalamus, hypothalamus, cerebellum, limbic system; a_2 autoreceptors also located on nerve terminal and cell bodies in LC
- Peripheral epinephrine
    - Increase rate and force of contraction of heart muscle: this is predominantly an effect of epinephrine acting through beta receptors; constriction of blood vessels: widespread vasoconstriction, resulting in increased resistance and hence arterial blood pressure; dilation of bronchioles: assists in pulmonary ventilation; glycogenolysis: promote breakdown of glycogen in skeletal muscle to provide glucose for energy production; dilation of pupils: particularly important in situations where you are surrounded by velociraptors under conditions of low ambient light
- Medical use of adrengergic agents
    - Frequently used in non-psychiatric medical conditions b/c of peripheral targets; e.g. Gen adrenergic agonists used to treat asthma – stimulates a-receptors to construct blood vessels in bronchial lining -> restricts blood flow; stimulates ß-receptors to relax bronchial muscles – treat with selective ß2 adrenergic agonists (albuterol)
    - Beta blockers: B1 receptors bind NE/epinephrine that is released following sympathetic activation; bind epinephrine that circulates in blood and NE released from sympathetic nerves
    - Beta blockers prevent normal ligand (NE/epinephrine) from binding to ß adrenergic site by competing for binding site; beta-blockers can cause arteries to widen and can slow action of heart and lower its force of contraction
- Beta blockers
    - Some ppl use beta blockers to avoid stage fright and tremor during public performance; physio symptoms of fight/flight response assoc. w/ performance anxiety are sig decreased, thus enabling anxious individuals to [c] on task at hand

- Neuromuscular junction
    - Connection b/t neuron and muscle; muscle cell normally innervated by just one presynaptic axon; release of ACh directly opens single type of ion channel
- Summary

    - Ach mediates parasympathetic functions (inhibit heart); Ach released onto muscles leading to muscle contraction (activates muscle)
- Synthesis
    - Ach formed in a single step from 2 precursors: choline, acetyl coenzyme A (acetyl CoA), catalyzed using choline acetyl transferase (ChAT) – transfers acetyl group from acetyl CoA to choline
- Synthesis: Choline
    - Essential nutrient that is widely distributed in foods, principally in form of phosphatidylcholin and as free choline; also produced in liver
    - Foods richest in phosphatidylcholine (major delivery form of choline) are beef liver, egg yolks, and soya; free choline: beef liver, iceberg lettuce, peanut butter, peanuts and cauliflower
- Synthesis: Acetyl CoA
    - Used in many biochemical reactions; produced during 2nd step of aerobic cellular respiration; occurs in matrix of mitochondria
- Synthesis – ChAT
    - Synthesized w/I cell body (rough ER); transferred to nerve terminal via axoplasmic transport; often used as a marker, immunohistochemically, for motor neurons (motoneurons)
- Release
    - Vesicular Ach transporter transports Ach into vesicles; blocked by vesamicol, leads to lower vesicular Ach, but increase cytoplasmic ACH (normally would be transported into vesicles) - decreased Ach release
- Inactivation
    - Enzymatic breakdown via acetylcholinesterase (AChE) – choline + acetic acid
- Acetylcholinesterase
    - Found in: presynaptic cell (metabolizes excess Ach); membrane of postsynaptic cells (breaks down Ach after release), brings choline back into cell via choline transporter, blocked by hemicholinium-3 (HC-3)
    - At NMJ; rapid breakdown of Ach
- Physostigmine
    - from calabar beans (w Africa)
    - blocks AChE; crosses BBB – therefore exerts its effects on CNS; leads to slurred speech, mental confusion, hallucinations, loss of reflexes, convulsions; coma, death
- myasthenia gravis
    - autoimmune disorder; patients develop antibodies to their own muscle cholinergic receptors; treated w/ synthetic analogs of physostigmine (that don't cross BBB)
    - NOTE: reversible (breakdown restored once drug disassociates from enzyme)
- Nerve Gases

    - Many nerve gases (e.g. Sarin, Soman) and insecticides are potent AChE inhibitors, and thus prolong time course of postsynaptic potentials
        - Ach builds up and continues to act on that any nerve impulses are continually transmitted, and muscle contractions don't stop
        - Death occurs through asphyxiation due to paralysis of muscles of diaphragm; not reversible
- Alzheimer's Disease
    - Assoc w/ a loss of cholinergic neurons which project from basal forebrain to cerebral cortex and hippocampus; loss is progressive and results in profound memory disturbances and irreversible impairment of cog function
    - Tetrahydroaminoacridine (THA, or tacrine) was 1st cholinesterase inhibitor approved for use in Alzheimer's patients; many patients given THA during clinical trials exhibited some alleviation of symptoms and some were able to resume normal activity and personal care
- Ach receptors
    - 2 types of Ach receptors (AChR) that bind Ach and transmit its signal: muscarinic AChRs – G-protein coupled receptors (GPCRs) that mediate a slow metabolic response via 2nd messenger cascades, bind muscaribe (found in mushroom, amanita muscaia); nicotine AChRs – ligand gated ion channels that mediate a fast synaptic transmission of NT, bind nicotine
- Muscarinic Receptors – Location
    - M1 AChRs are common in secretary glands; M2 AChRs are found in cardiac tissue; M3 AChRs are found in smooth muscles and in secretion glands; All types found throughout forebrain, midbrain, and hindbrain
    - M1, M3, and M5 receptors cause activation of phospholipase C, leading to an intracellular increase of Ca; M2 and M4 inhibit adenylate cyclase, thereby lower production of 2nd messenger cAMP
    - Activation of M2 receptor in heart is important for closing Ca channels in order to lower force and rate of contraction
- Nicotine receptors
    - Nictotine AChRs are localized; neuromuscular junctions; ganglionic neurons of both sympathetic and parasympathetic system; neurons in brain
    - Ionotropic; comprises 5 subunits to form pore; 2 α-subunits; different proteins make up neuronal and muscle receptors (smoking)
    - Permit flow of Na+ and Ca+ into cell

- Peripheral serotonin (5-HT)

    - Vast majority of 5-hydroxytryptamine is found in gut; modulates motility and initiates peristaltic and secretory reflexes; alterations in 5-HT synthesis and function in gut can lead to abnormal gastrointestinal motility (irritable bowel syndrome)
- Many normal behaviours appear to depend on intact serotonin function in brain
- Central 5-HT
    - In brain, 5-HT serves as a NT; mediates a large variety of physio processes including sleep, food intake, and sexual behaviour, mood; disruptions in brain 5-HT function are thought to play a role in various psychiatric conditions including anxiety, drug abuse, and mood control
- Tryptophan
    - An essential amino acid: can't be synthesized by organism and must be part of diet
    - Found as a component of dietary protein: oats, bananas, dried dates, milk, yogurt, cottage cheese, red meat, eggs, fish, poultry, sesame, chickpeas, sunflower seeds, pumpkin seeds, and peanuts
- Synthesis
    - Tryptophan entry into brain competes with large neutral amino acids across BBB
    - High protein, low carb diet doesn't increase brain tryptophan; high carb, low protein enhances brain levels and 5-HT synthesis
    - Increase ratio of tryptophan to competing amino acids
- Tryptophan hydroxylase (TrpOH)
    - Rate limiting enzyme in serotonin synthesis
- Depletion of 5-HT
    - In rodents: admin parachlorophenylanine (PCPA) – blocks 5-HT synthesis by inhibiting trpOH
    - In human studies: give tryptophan depleting milkshake; large quantity of amino acids except for tryptophan – depletes 5-HT (temporarily); leads to lower mood in recovered depressives -> doesn't work same on ppl who didn't have depression
- Storage and release
    - 5-HT transported into vesicles using VMAT2; reserpine also depletes neurons of 5-HT
    - Serotonergic autoreceptors control release: either directly (terminal) or indirectly (somatodendritic); inhibit by slowing rate of firing
- Inactivation
    - Reuptake via 5-HT transporter; Prozac (fluoxetine) is selective serotonin reuptake inhibitor
    - Enzymatic degradation via MAO; primary metabolite of 5-hydroxyindoleacetic acid (5-HIAA); used as a marker for serotonergic neurons
- Organization of serotonergic neurons
    - Most 5-HT neurons in CNS found along midline of brainstem
    - Network of cells: raphe nuclei; dorsal raphe nuclei (DRN; B7); median raphe nuclei (MRN; B8) – most of fibers in forebrain
    - Most areas of brain receive at least some inputs from serotonergic neurons

- 5-HT in DND and sleep
    - Awake: slow but regular firing; SWS: slow irregular firing; REM: almost completely shut down
    - Activated during movement: function: to facilitate output of motor systems in brain, suppress sensory processing; loud noise: serotonin system temporarily inhibited (to attend to stimuli)
- Serotonergic receptors
    - '79: 2 distinct pop of 5-HT binding sites were identified in rate brain – 5-HT1 and 5-HT2
- 5-HT1A
    - Hippocampus, septum, parts of amygdala, DRN; can function as somatodendritic autoreceptors (MRN and DRN)
    - 2 different mechanisms: negatively coupled to an adenylate cyclase 2nd messenger system; increase opening of K+ channel; bottom line – decrease firing
    - Agonists: buspirone, ipsopirone, 8-OH-DPAT
    - Antagonists: WAY 100635
    - Leads to: hyperphagia (stimulation of autoreceptors; inhibits 5-HT release in forebrain; gen. 5-HT lowers appetite/food intake; lowers anxiety; hypothermia
- 5-HT2A
    - Widely distributed at varying densities throughout brain; increase density in neocortex
    - Directly coupled to a phosonosital 2nd messenger system; increase Ca+ and activates PKC; in certain brain regions, 5-HT stimulates phosolipase A2 via a 5-HT2 mechanism
    - Agonists: DOI
    - Antagonists: ketoserin, ritanserin
    - Leads to "head twitch" response; hallucination (in humans); used to treat schizophrenia (clozapine, resperidae)