**3/11: Drugs**

Recap: exocytosis

Process by which synaptic vessels release transmitters into the cleft

Drugs affect exocytosis

2 classes of transmitters

Large molecule: made in soma, packaged by Golgi complex, transported by microtubules to terminal button

Small molecule: made in terminal button, packaged by Golgi complex, stored next to presynaptic membrane

Microtubules: transport materials

Vesicles: spherical neurotransmitter packages

Small molecule transmitters typically activate ionotropic or metabotropic receptors that act on ion channels

Large molecule transmitters typically activate metabotropic receptors; exert complex effects on workings of cell; transmit slow, diffuse, longer-lasting messages

As long as NT is in a synapse, it is “active” – activity must somehow be turned off

Re-uptake/enzymatic degradation

Re-uptake: NTs “drawn” back into presynaptic buttons & repackaged in vesicles by Golgi complex

Degradation: NTs broken down in cleft by enzymes

Small molecule NTs

Amino acids: glutamate, GABA, glycine

Monoamines

Catecholamines: dopamine, epinephrine, norepinephrine

Indolamines: serotonin

Acetylcholine

Unconventional transmitters

Gases: nitric oxide

Endocannabinoids: anandamide

Large molecule NTs (> 100)

Neuropeptides or peptides: pituitary peptides, hypothalamic peptides, brain-gut peptides, **opioid peptides**, insulin

Neurons synthesize NTs from what we eat

Acetylcholine – from choline in milk, eggs, nuts, etc.

Serotonin – from tryptophan in soy, shellfish, meats, etc.

Transmission is complex

Most neurons release 2 or more NTs

Most *respond* to more NTs than they release

NT effects depend on what their receptors do on postsynaptic cell membrane

Ionotropic effect – NT attaches to receptor, opens ion channels… fast acting

Metabotropic effect – NT attaches to receptor, initiates cascade of slow & long lasting metabolic reactions

Amino acid NTs

Synthesized rom protein in diet

Glutamate – most common excitatory NT  
 Gamma-aminobutyric acid (GABA) – most common inhibitory NT

Glycine – similar actions as GABA, but mainly in spinal cord and brainstem

Monoamine NTs: catecholamines

Share synthesis (production) pathway from tyrosine (in high-protein foods)

Tyrosine 🡪 L-dopa 🡪 Dopamine 🡪 Norepinephrine 🡪 Epinephrine

Dopamine – movement, attention, learning, reinforcing effects of drugs, pleasurable behaviors

Norepinephrine (noradrenaline – key for “fight or flight”, vigilance

Epinephrine (adrenaline) – minor role as NT in CNS, more of a hormone

Important hormone of sympathetic nervous system – released by adrenal glands

Dopamine pathways in brain

\*Mesolimbic – ventral tegmental area VTA to nucleus accumbens, limbic areas

\*Mesocortical – VTA to cortex

Nigrostriatal – substantia nigra to caudate, putamen

Mesolimbic pathway plays major role in drug abuse, reward seeking behavior, and risk taking

NE pathways in brain

Most NE neurons in locus ceruleus – right above pons in midbrain

Project throughout CNS

Monoamine NTs: indolamines

Serotonin or 5-HT – chief indolamine that acts as NT

Synthesized from tryptophan

Involved in mood, impulse control, appetite, sleep, temperature regulation

Key target of drugs for depression

Most 5-HT neurons are in raphe nuclei (in brainstem)

Send 5-HT throughout much of CNS

Acetylcholine (ACH)

Diverse actions – released at neuromuscular junctions, by ANS, & within CNS

Involved in muscular movement, as well as learning, memory, dreaming

Good example of NT deactivated by enzymatic degradation – acetylcholinesterase

ACH neurons dense in pons, midbrain, ventral forebrain

ACH neurons project throughout much of CNS

Endocannabinoids

Endogenous cannabis-like substances

Bind to cannabinoid (metabotropic) receptors, which mediate effects of THC

Anandamide, first discovered “bliss bringer”

Cannabinoid receptors dense in cortex, cerebellum, basal ganglia, hippocampus, substantia nigra

Tetrahydrocannabinol (THC) works by attaching to cannabinoid receptors and mimicking effects of anandamide (other endocannabinoids)

Cannabinoid receptors – located presynaptically, affect transmitter release

Location in specific areas may account for subjective effects – memory impairment

*Not* concentrated in brainstem – impossible to overdose on THC and can’t interfere with vital signs

Neuropeptide transmitters (large molecule)

Chains of 10+ amino acids

Far-reaching, diffuse effects

Act on metabotropic receptors

Endogenous opiates or opioid peptides (opium-like chemicals produced in body – important for pain suppression) – endorphins, enkaphalins, dynorphin

Other major peptide examples include oxytocin and vasopressin, which impact social behaviors

Basic principles – most drugs that affect behavior do so by affecting synaptic transmission and mimicking our own neurochemistry

Drugs largely affect behavior by enhancing or reducing activity of NTs

Agonists – mimic/enhance NT effects

Antagonists – block/reduce NT effects

Agonists and antagonists can affect NT activity at any point in its “life cycle”

Agonists or antagonists

Neurotransmitter production – by altering NT synthesis, affecting amount available for release

Neurotransmitter storage – by altering NT packaging into vesicles, affecting amount available for release

Neurotransmitter release – by modifying NT release in response to an AP

Receptor effects

Can mimic NT action at binding sites

Can block NT action by occupying binding sites

Reuptake effects and enzymatic degradation

Prevent reuptake, block its breakdown

\*Print out slides at end of this lecture\*

**3/16: Drugs (continued)**

THC is not an endocannabinoid

Endogenous to your body; cannabis like substances that your body produces

THC works by attaching to cannabinoid receptors and mimicking effects of other endocannabinoids

Agonistic drug effects

Drug increases synthesis of neurotransmitter molecules

Drug increases number of neurotransmitter molecules by destroying degrading enzymes

Drug increases release of neurotransmitter molecules from terminal buttons

Drug binds to autoreceptors and blocks their inhibitory effect on neurotransmitter release

Drug binds to postsynaptic receptors and either activates them or increases the effect on them of neurotransmitter

Drug blocks deactivation of neurotransmitter molecules by blocking degradation or reuptake

Antagonistic drug effects

Drug blocks the synthesis of neurotransmitter molecules

Drug causes the neurotransmitter molecules to leak from the vesicles and be destroyed by degrading enzymes

Drug blocks the release of neurotransmitter molecules from terminal buttons

Drug activates autoreceptors and inhibits neurotransmitter release

Drug binds to postsynaptic receptors and blocks effect of neurotransmitter

Addiction – persistent drug use despite destructive effects on health & personal/social life

Some combination of tolerance, withdrawal, persistent desire, used in larger amount than intended, give up activities, great deal of time spent to obtain/use/recover, continued use despite problems

Addiction often begins in adolescence/young adulthood (50% of addictions begin at ages 15-18, declines after 20)

Psychoactive drugs – influence experience & behavior by acting on nervous system

Mechanisms of drug action

For psychoactive drugs to exert effects, must get to brain by passing through blood-brain barrier

Action of most drugs inactivated by enzymes in liver

Small amounts excreted in stuff

Once a drug has penetrated CNS, it can influence neurons in many ways

Act diffusely on neural membranes

Interact specifically with particular classes of neurotransmitters & receptors

Drug tolerance develops after repeated use

Decreased sensitivity to drug because of exposure to it

Measured in 2 ways

1. By decrease in response elicited by same dose of drug

2. Increase in amount of drug required to produce same effects

Tolerance shifts dose-response curve to the right

Exposure to 1 drug can produce tolerance to similar drugs – cross tolerance

Alcohol > benzodiazepines

2 Forms of Drug Tolerance

Metabolic – less drug is getting to site of action

Functional (most psychoactive drugs) – decreased responsiveness at site of action (fewer receptors, decreased efficiency of binding, receptors less responsive)

Withdrawal effects

Seen when drug use is terminated

Symptoms opposite to drug’s effects

Withdrawal of anti-convulsants causes convulsions

Withdrawal of sleeping pills causes insomnia

Withdrawal symptoms seen when one is physically dependent – this is the definition of being physically dependent

Withdrawal symptoms do not mean you’re an addict

Withdrawal effects likely result from same mechanisms of tolerance

Body makes changes to offset or oppose drug’s presence – producing tolerance

Without drug present, all you get is offsetting/opposing effects

Effects of heroin – euphoria, constipation, relaxation – lead to withdrawal effects of dysphoria, cramping, diarrhea, agitation

Learning (conditioning) plays a major role in tolerance & withdrawal

Conditioned drug tolerance – maximal tolerance is seen in environment in which a drug is usually taken

If tolerance becomes context specific, addicts would be more likely to overdose in an unfamiliar surrounding

Conditioned withdrawal effects – withdrawal elicited by drug-related cues (stimuli repeatedly paired with drug)

Avoidance of withdrawal is rarely primary motivating force for addictive behaviors

Addicts often renew addictive behaviors after years of abstinence, when simple physical withdrawal symptoms are unlikely to be severe

Tobacco – stimulant

Major psychoactive ingredient is nicotine

70% of those who try smoking become addicted

Only 20% of attempts to stop are successful in long term

Smoker’s syndrome – chest pain, labored breathing, coughing, susceptibility to respiratory infections

Susceptible to various lethal lung disorders – emphysema, lung cancer

Tobacco use is leading cause of preventable death in developed countries

Nicotine acts on nicotinic acetylcholine receptors

Increases activity of dopaminergic neurons of mesolimbic system and causes DA release in nucleus accumbens

**3/18: Drugs (continued)**

E-cigarettes

Not a lot is known – opinions still ahead of science

There are known carcinogens & toxic chemicals (e.g., ethylene glycol)

More powerful e-cigarettes heat nicotine liquid in ways that release carcinogens, formaldehyde, and acetalahyde

Animal models show fetal & newborn exposure to e-cigarette vapor retards lung growth, impairs lung function

Much evidence that e-cigarettes in youth increases risk for smoking (at least trying)

Alcohol – depressant

Depressant (moderate, large doses)

Heritability for alcohol addiction is 55%

Metabolic and functional tolerance both develop

Affects almost every bodily tissue

Alcohol inhibits glutamate (excitatory transmitter) – sedating effect

Increases GABA by acting on GABA-A receptor complex (inhibitory effects)

Effect is sedation, anxiolytic, muscle relaxation, and inhibition of cognitive and motor skills

Actions of alcohol trigger apoptosis (cell death)

Also acts, on opiate, 5-HT, and cannabinoid receptors

Alcohol increases activity of DA neuron mesolimbic system & increases release of DA in NAC  
 Release of DA probably underlies positive reinforcement effects of alcohol, as well as stimulation of other receptors

Effects of chronic alcohol consumption

Severe withdrawal in 3 phases

5-6 hours post-drinking: tremors, nausea, sweating, vomiting

15-30 hours: convulsive activity (because of effects on glutamate receptors)

24-48 hours: delirium tremens – may last 3-4 days

Korsakoff’s syndrome (memory disorder)

Fetal alcohol syndrome - #1 cause of abnormal brain development

Cirrhosis – scarring of liver

Marijuana

THC – active ingredient

Main site of action is CB1 receptor

Endogenous cannabinoids normally bind with CB1 receptor (anandamide)

Administration of drugs that block CB1 receptors abolish “high” produced by marijuana

THC increases DA in nucleus accumbens

Overall, addiction potential is relatively low compared with drugs of abuse

Adverse effects of heavy marijuana use

Hippocampus has a large concentration of cannabinoid receptors

Marijuana probably affects memory over the short and long term for this reason

Long-term use decreases executive functions

Earlier onset disrupts brain development in animal models

Cocaine and other stimulants

Crack – potent, smokable form of cocaine – reaches brain very quickly

Probably most effective reinforcer of all available drugs

Cocaine binges may lead to cocaine psychosis

Looks like paranoid schizophrenia

Tolerance may develop to some effects, but sensitization is seen to others

Although addictive, withdrawal is relatively mild

Blocks dopamine and serotonin reuptake

Dopamine removes inhibition on lower structures by cerebral cortex

Users have deficits in executive functions that involve the pre-frontal cortex

Amphetamines – meth

Cocaine and amphetamines have similar behavioral effects, because both act as potent DA agonists

Cocaine binds with/deactivates dopamine transporter proteins, thus blocking the re-uptake of dopamine after it is released by the terminal buttons

Amphetamine also inhibits reuptake of DA, but its most important effect is to directly stimulate release of dopamine from terminal buttons

Opiates: heroin and morphine

Opium – derived from resin produced by opium poppy, has been eaten/smoked for centuries

Heroin – synthetic opiate made by Bayer in 1898

High risk of addiction

Tolerance & physical dependence develop rapidly, almost immediately

Very high risk of overdose

Many health hazards related to use of needles in heroin abuse

Opiate administration stimulates opiate receptors in different brain areas & produces a variety of effects, including pain relief & sedation

Opiate receptors in midbrain (PAG) are primarily responsible for analgesia, those in reticular formation are responsible for sedation (low arousal)

Opiate receptors in ventral tegmental area and NAC appear to play a role in reinforcing effects

Key aspects of addiction

Compulsion to seek/consume

Inability to control intake

Negative emotional state when not taking drug

Chronic relapse

Biopsychological theories of addiction

Early explanations followed physical-dependence theories

Addicts abuse drugs to prevent or terminate withdrawal symptoms

Treating addiction meant withdrawal from an abused drug in a hospital setting – until systems subsided

Don’t explain why

Addicts relapse long after detoxification

Addictions develop to drugs that don’t produce severe withdrawal

Programs that use gradual detox are largely unsuccessful

Incentive-sensitization theory – addresses key problems

With continued drugs, positive-incentive value (wanting) increases due to memory of pleasure of early drug experience – but hedonic value (liking) decreases due to tolerance

Result: addicts crave/want drugs more but enjoy or actually like them less

Relapse and its causes

Main problem in treating addiction is not to get person to stop taking drugs

It’s preventing them from starting again (relapsing) after they’ve stopped

Stress – drugs used as a coping mechanism

Priming – single – even very small – exposure leads to relapse

Environmental cues – people, places, thoughts, emotions, objects paired with use trigger craving and relapse

**3/23: Emotion**

Introduction and key terms

Emotions – positive or negative responses to situations – no such thing as neutral emotion

Responses consist of expressions, physiological change, & actions

Above responses accompanied by feelings

Most of us usually say “emotion” to mean feelings, not the observable responses

Micro-expressions: small facial expression “fragments”, such as the stretching or tightening of a lip, have been correlated with deception and lying

Mice exposed to nociceptive stimuli show certain facial expressions; some resemble humans in pain, especially with squinting of the eyes

Darwin’s contributions

Overt expressions of emotion evolved from behaviors that signal what we are likely to do next

Conferred adaptive advantage of emotions to our ancestors

Helped to communicate rapidly & effectively

Threat displays, for example, are beneficial – intimidate without costs & risks of actually fighting

Overt behaviors – not private feelings – have consequences for survival & reproduction

Therefore, functions served by overt emotional behaviors are what were important in evolution

3 dominant perspectives

James-Lange: bodily reactions cause feelings

Cannon-Bard: brain causes feelings, reactions at same time

Schachter-Singer: cognitive appraisal of context drives interpretation of feelings as one emotion or another

James-Lange Theory

Physiological, behavioral responses are necessary for emotional experience

Responses for each feeling are distinct & correspond to separate emotions

What we feel is a label for arousal pattern of internal organs & muscles

Cannon-Bard

Cannon – major critic of James-Lange

Internal organs too insensitive, too slow to provide feedback needed for rapid feelings and activity was too diffuse for differentiation

Cutting afferent nerves that provide feedback from internal organs did not alter emotional behavior

Stimulus triggers autonomic and skeletal responses and feelings at once

Autonomic and skeletal responses are independent of feelings

Physical responses and internal feelings occur simultaneously and separately

Schachter-Singer

2 factor theory based on classic study

Administered SNS agonist

Some told what to expect, others weren’t

Some exposed to angry, happy confederate

Unwitting people attributed “arousal” to context of what confederate they encountered

They all had the same physiology because of the SNS agonist, but they labeled it as anger or something else depending on their interpretation of context

Brain systems for emotion

Originally referred to as Papez’s circuit, centered on cingulate cortex

Later referred to as limbic system, which included temporal lobe areas – especially amygdala

MacLean added amygdala because of Kluver-Bucy syndrome

Fearless, reduced aggression

**3/25: Emotion (continued)**

Limbic areas implicated in emotion: anterior cingulate, hypothalamus, septal nuclei, amygdala, insular cortex, basal ganglia

Insula – disgust

Fear and aggression

Scientists study fear & aggression more than happy, peaceful behavior

Types of aggression: reactive-impulsive, controlled-instrumental

Reactive-impulsive aggression

Highly “emotional”, out of control

Limbic structures

Controlled-instrumental aggression

Purposeful

Higher cortical systems

Neuroanatomy of aggression

Lesions to anterior hypothalamus, medial amygdala, bed nucleus of stria terminalis, lateral septum reduce aggressive displays

Lesions to orbitofrontal cortex increase aggressive displays

Conditioned fear

Pair neutral stimulus (sound) with threatening stimulus (shock)

Animals show freezing, escape behaviors with physiology changes

Mapped high vs low road for processing fear stimuli

High road: slow, low road: fast

Thalamus can route sensory info to:

Cortical areas (high road) for slow processing

Or directly to amygdala (low-road) for rapid emotional processing

Controlling fear

fMRI to study fear as subjects move feared object closer/farther using conveyor belt

“Courageous” responses: increased anterior cingulate cortex, but decreased amygdala/insula activity

Value of fear

Fear is adaptive

Amygdala damage, dysfunction leads to dangerous indifference

Work suggests dysfunction in prefrontal-limbic pathways

Phineas Gage

Before injury: serious, industrious, and energetic

Afterward: irresponsible, thoughtless of others

Extreme outbursts of temper

Orbital prefrontal cortex (orbito-frontal cortex)

Region of prefrontal cortex at base of anterior frontal lobes, adjacent to midline

Key for planning and emotion regulation

Those with damage to OFC show decreased guilt (lack of remorse) – psychopathic tendencies (callousness)

OFC integrates physiology with decision making, helps to avoid risk

“Somatic marker hypothesis”

Lack of anxiety (awareness of physiology registered by OFC) may be associated with criminal behavior

Parkinson’s Disease

Movement disorder affecting 0.5% of population

Resting tremor is main symptom

Dementia is not typical

No single cause

Associated with degeneration of substantia nigra – sends dopamine to basal ganglia

Almost no DA in substantia nigra of patients

Autopsies reveal Lewy bodies (protein clumps) in substantia nigra

MPTP model of Parkinson’s disease

Synthetic heroin produced symptoms of Parkinson’s in young addicts

Contained toxin MPTP

Causes cell death in substantia nigra

Used in animal models

Alzheimer’s Disease

Most common cause of dementia – likelihood rises with age

Early stages of confusion/decline in memory/altered smell

Definitive diagnosis difficult without autopsy

Brains of people with AD show amyloid plaques and/or neurofibrillary tangles

May also show decline in acetylcholine

Effective treatments not yet available – AD is terminal

Amyloid plaques – clumps of degenerating neurons and an abnormal protein called amyloid

Neurofibrillary tangles occur within neurons – comprised of mutated microtubule – associated protein called tau

Loss of neurons is common; neuron loss often seen in areas involved in memory – hippocampus, amygdala, entorhinal cortex

**3/30: Stress**

Stress – condition in environment that makes unusual demands on the organism

Stress physiology

Stressors engage 2 systems

Sympathetic nervous system: prepares us for brief “emergency”/”alarm” responses

Hypothalamic adrenal pituitary axis: reinforces SNS effects, supports longer-term responses

SNS prepares us for rapid, “alarm” reactions through rapid effects on cardiovascular system and other internal organs

SNS neurons synapse with cells in adrenal medulla, inducing them to release adrenaline and noradrenaline into circulation, having diffuse effects on all target organs

HPA axis – cortisol releases energy stores to cope with stressors, but impairs immune function when levels are high for long period of time (chronic)

Immune system – complex collection of organs, cells, processes that protect against disease by identifying and killing pathogens and tumor cells

Many studies show that chronic stress alters immune function

Divorce, loss of a loved one, job stress, exam stress

Exam period

Redistribution of lymphocytes (white blood cells)

Decreased ability to respond to antigen

Increased infectious disease

Slow wound healing

Reactivation of dormant viruses

Chronic stress and the immune system

Autonomic nervous system, particularly SNS

HPA axis (cortisol)

Health behaviors (smoking, drinking, sleeping, eating, exercising)

All immune organs receive messages from ANS and HPA axis

Activation of these systems directly affects immune function

Social relationships and the immune system

People who are under stress are more likely to develop infectious or immune related diseases/illnesses

Social support is associated with lower death rates, lower stress, and lower levels of stress hormones

Isolation can lead to loneliness, a potent stressor known to evoke a physiological stress response

Experimentally isolating monkeys is associated with decrease in circulating immune cells

**4/1: Review**

Quiz

Large molecule transmitters are made in soma, small molecule transmitters are made in terminal button

NTs repackaged in Golgi complex during reuptake

Acetylcholine is a small molecule transmitter, not a catecholamine

Nigrostriatal pathway is important for release of dopamine, not acetylcholine

Norepinephrine is mainly produced in locus ceruleus, which straddles the midbrain and the metencephalon

Epinephrine is produced and released in adrenal glands

THC is NOT an endocannabinoid

Drug that blocks uptake is an agonist; antagonist encourages reuptake like a vacuum

Drug tolerance shifts dose-response curve to right

Functional tolerance 🡪 drug is getting to site of action but has less of an effect

Metabolic tolerance 🡪 less of a drug is getting to site of action

Having withdrawal symptoms does not mean that you’re addicted to a drug

Dopamine is a catecholamine 🡪 most drugs of abuse do act on dopamine in the nucleus accumbens

GABA\_A receptor is site of action for alcohol, benzodiazepines, barbiturates, but not THC

Cross-tolerance

Cocaine blocks reuptake and is a dopamine agonist

Amphetamine directly stimulates release of dopamine from terminal buttons

Insula buried in lateral fissure, very important for emotional experiences especially disgust

Cortisol is released from adrenal cortex

Adrenal medulla releases epinephrine and norepinephrine