Psychopharmacology

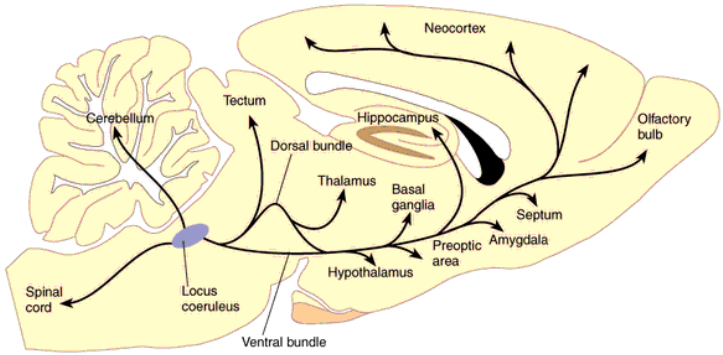
Neurotransmitters and Neuron Communication

- Release of NT across synapse from presynaptic terminal (axon terminal) to postsynaptic membrane (dendritic spine)
    - Ca2+ influx into presynaptic due to AP
    - Exocytosis of NT
    - NT bind to receptors → change in membrane potential or second-messenger signalling → change in excitability/cell response
    - Types of Receptors:
        - Ionotropic: Opens ion channel → change in membrane potential
            - e.g. GABA-A receptor → influx of Cl- → hyperpolarisation
            - Fast changes in membrane potential
        - Metabotropic: Causes signalling cascade inside cell e.g. second-messenger signalling
            - E.g. GABA-B receptor: g-protein coupled receptor → second messenger production
            - Slower changes to cell w/ longer-lasting effect
                - Changing gene expression and phenotype
                - Increasing/decreasing no. of receptors → more/less sensitive
                - Modify activity of other receptors e.g. opening channel → change in membrane potential
- Loewi's experiment: Stimulation of vagus nerve of heart A → decrease in HR of A as well as decrease of HR of B
    - Diffusion of NT through water
- Types of neurotransmitters:

Class	Sub-class	Endogenous ligand	Receptors
Cholines		Acetylcholine ACh	Nicotinic, Muscarinic
Monoamines	Catecholamines	Dopamine DA	D1-5
		Norepinephrine/ Noradrenalin NA	Alpha and beta adrenergic
	Indolamines	Serotonin 5HT	14 types of 5HT receptors
Amino acids	Excitatory	Glutamate	NMDA, AMPA, mGlu, kainate
	Inhibitory	GABA	GABA-A, GABA-B
Peptides	Opioids	Endorphins	Opioid
Lipids	Endocannabinoids	Anandamide	Cannabinoid
Nucleosides	Purine	Adenosine	Adenosine, Purinergic

    - Mainly glutamate and GABA – amino acids

► **Schematic Midsagittal Section of a Rat Brain, Showing the Locations of the Most Important Groups of Noradrenergic Neurons and the Distribution of Their Axons and Terminal Buttons**



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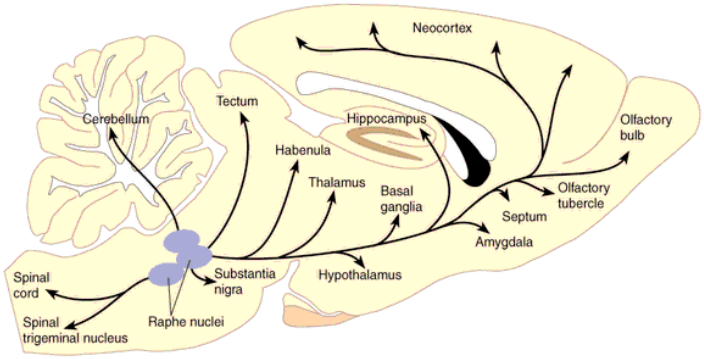
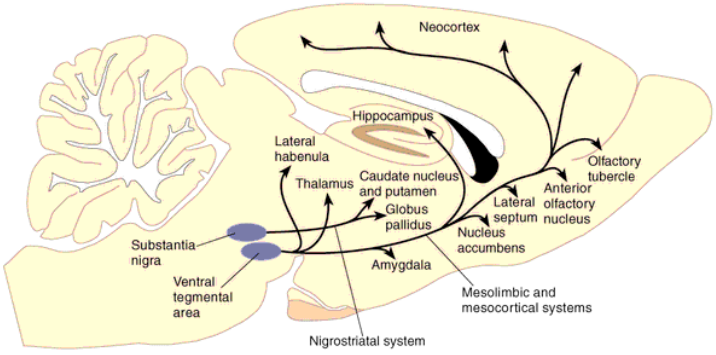
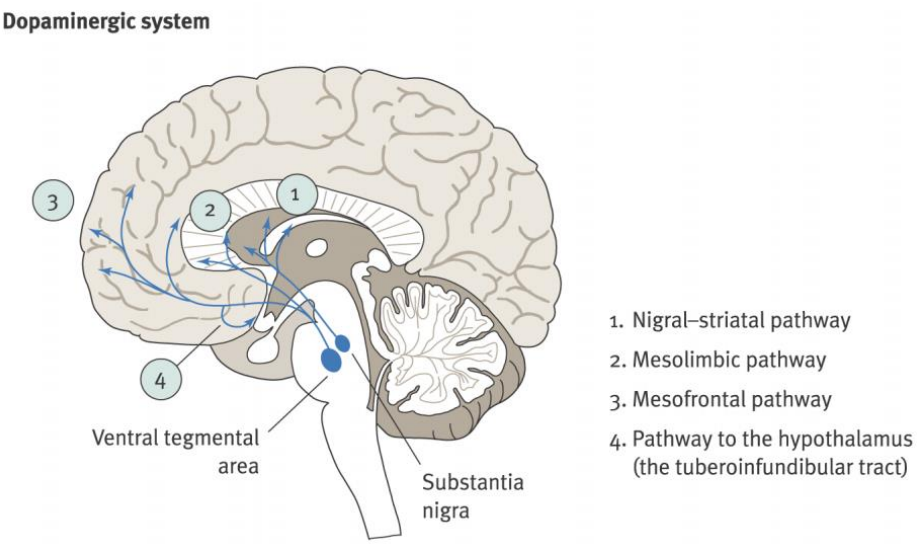
► **Schematic Midsagittal Section of a Rat Brain, Showing the Locations of the Most Important Groups of Serotonergic Neurons and the Distribution of Their Axons and Terminal Buttons**



► **Schematic Midsagittal Section of a Rat Brain, Showing the Locations of the Most Important Groups of Dopaminergic Neurons and the Distribution of Their Axons and Terminal Buttons**





- Dopamine pathways:
  - Mesolimbic: VTA → nucleus accumbens (part of ventral striatum)
    - Involved in reward learning
  - Mesocortical: VTA → cortex
    - Involved in emotion
  - Nigrostriatal: Substantia nigra → striatum i.e. caudate nucleus + putamen
    - Involved in movement planning
- Drug-Receptor Binding
  - Drug-ligand complex <-> Drug + Receptor

Neurotransmitter Recycling

- Reuptake transporter proteins: Take NT back into presynaptic terminal → recycling e.g. SERT, DAT
- NT degrading enzymes: Hydrolysis of NT e.g. MAO-A (serotonin + noradrenaline), MAO-B (dopamine)

Agonists and Antagonistic Drugs

- Agonist: Enhances effect of NT
  - Mimics NT and binds to receptor
    - E.g. THC mimics anandamide → cannabinoid receptor, Valium (benzodiazepine)+ ethanol → GABA, heroin mimics endorphins → opioid receptor, nicotine mimics Ach → nAchR
    - Alcohol: GABA receptors are inhibitory → inhibits regulatory role of pre-frontal cortex → loss of inhibition, inhibiting cerebellum → decreased coordination
  - Enhances release of NT e.g. by being precursor
    - L-dopa → dopamine → noradrenaline (only in noradrenergic neurons)
    - Parkinson's disease: Loss of substantia nigra → loss of dopamine for basal ganglia → impaired voluntary movement and coordination
      - L-dopa → exaggerated movements
    - Encephelitus-induced catatonia: Damaged basal ganglia → no voluntary movement
    - Ecstasy: Serotonin + noradrenaline (+ dopamine to a lesser extent)

        - Amphetamine: Dopamine + noradrenaline
        - Cocaine: Dopamine
    - Blocking reuptake of NT/reversing reuptake transporters
        - Ecstasy and SSRI's prevent reuptake of serotonin
            - Ecstasy reverses transporters
        - Amphetamine and cocaine prevent reuptake of dopamine
        - Tricyclic antidepressants prevent reuptake of serotonin + noradrenaline
    - Blocking enzymes that degrade NT
        - MAO A degrades serotonin + noradrenaline; MAOA drugs for anxiety and depression prevent MAO A activity
            - Ecstasy inhibits MAO A
        - MAO B degrades dopamine; MAO B drugs for Parkinson's and Alzheimer's
            - Amphetamine inhibits MAO B
            - *Cocaine doesn't inhibit MAO B
- Antagonist: Prevents effect of NT
    - Blocking receptors to stop NT from binding
        - E.g. Typical antipsychotics block D2 dopamine receptor
            - E.g. chlorpromazine/thorazine (found through observation) for schizophrenia
            - Reduce +ve symptoms e.g. delusions, hallucinations
            - Does not affect –ve symptoms e.g. catatonia, formal thought disorder, affective flattening (may be due to neurodegeneration)
                - Enlargement of ventricles
                - Loss of PFC
                - Smaller left hippocampal volume
            - Can lead to Parkinson's symptoms as blocks dopamine in basal ganglia
        - Atypical antipsychotics block serotonin 5HT receptors
            - Less movement symptoms, more metabolic symptoms
        - Ethanol blocks glutamate receptors → less excitatory effect
        - Heroin → morphine blocks receptors for substance P pain signal
    - Bind to receptor → changing conformation → cannot bind to NT/downregulation as taken in

Relative Affinities of Drug

- Drugs bind to many receptors w/ diff relative affinities → Diff side effects e.g. typical antipsychotics block D2 receptors in mesolimbic dopamine system, but also nigrostriatal dopamine system → movement reduction
- Efficacy depends on affinity to specific receptor type

Anti-depressant Drugs

- Enhance monoamine NT e.g. dopamine, serotonin, noradrenaline release
- Selective serotonin reuptake inhibitors (SSRIs): Prevent transporter proteins from reuptake of serotonin
- Tricyclic antidepressants: Block reuptake of serotonin and noradrenaline
- Monoamine oxidase inhibitors (MAO): Prevent MAO from degrading NT
    - E.g. iproniazid inhibiting MAO A and MAO B → elevation of serotonin
        - First antidepressant discovered serendipitously (used to treat tuberculosis)

- Need to avoid foods w/ tyramine (which can't be broken down if MAO inhibited)

Theories for Depression

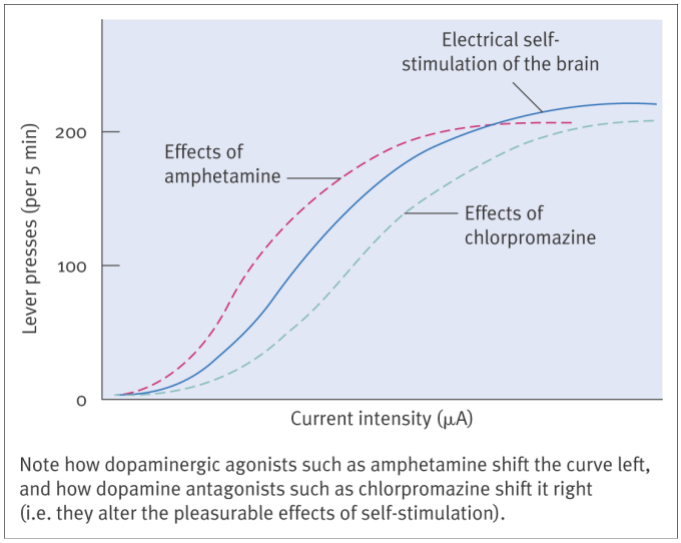
- Monoamine hypothesis of depression: Insufficient cortical/limbic monoamines
  - But increase in monoamines e.g. with SSRI's and MAO A's did not → acute depression relief
  - Some depressed patients had high levels of monoamines
- Receptor sensitivity hypothesis: Used to explain why therapeutic effects of drugs took weeks (not acute like L-dopa)
  - Too many autoreceptors (5HT1) and post-synaptic receptors (5HT2) for serotonin
    - Autoreceptors maintained level of serotonin in receptor → -ve feedback
  - Chronic elevation of serotonin in synapse → decline in no. autoreceptors and post-synaptic receptors → decreased sensitivity
  - Other changes: Upregulation of other receptors e.g. glucocorticoid receptors in hippocampus → regulation of HPA axis → decreased stress, hormones → new synapses

Reinforcement and Dopamine

Evidence of Dopamine in Reinforcement

1. With natural reinforcer/drug:
   a. Dopamine antagonists → decline in effect of reinforcers (natural/drug)
      i. E.g. decline in rat lever-pressing for food/cocaine
      ii. Similar to effect of extinction
      iii. Dose-dependent
   b. Dopamine agonist e.g. amphetamine → greater persistence for better reward even with higher FR schedule
   c. Dopamine antagonist/depletion of dopamine → decreased persistence and effort in working for better reward (giving up)
2. With intracranial self-stimulation: Rats learn to lever-press to self-stimulate
   - Vigorous
   - Little satiety unlike natural rewards e.g. food
   - Modulated by motivational state e.g. hunger
   - Modulated by intensity of stimulus

   a. Stimulating dopaminergic neurons i.e. mfb (axons of neurons from VTA to NAcc) /lateral hypothalamus which stimulates mfb → reinforcing
      i. Modulated by intensity of electrical stimulation: Greater lever pressing for more intense stimulus
   b. Dopamine drugs → affect reinforcing effect of brain stimulation



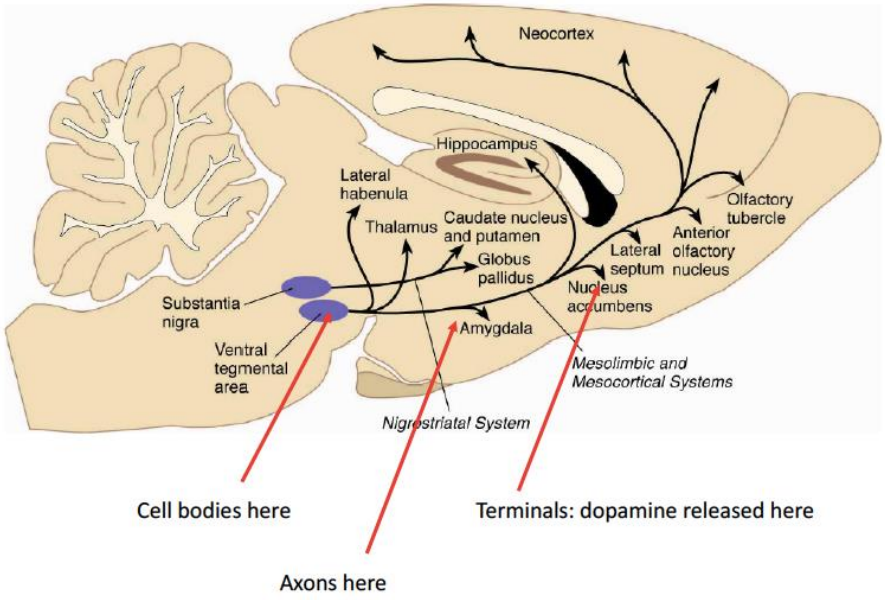
Note how dopaminergic agonists such as amphetamine shift the curve left, and how dopamine antagonists such as chlorpromazine shift it right (i.e. they alter the pleasurable effects of self-stimulation).

i. Dopamine agonists e.g. cocaine, heroin, amphetamine → greater pressing for less intense stimulus
ii. Dopamine receptor blocker e.g. chlorpromazine (antipsychotic) at nucleus accumbens → less pressing even for greater stimulus

c. Microdialysis revealed increase in dopamine levels w/ ICSS

Reward Pathway

Brain dopamine pathways (saggital section)



- Mesolimbic dopamine pathway
- Involves dopaminergic neurons from VTA → axons forming medial forebrain bundle → release of dopamine into nucleus accumbens
- Lateral hypothalamus connected to mfb → highest rates of responding when lateral hypothalamus/mfb was stimulated

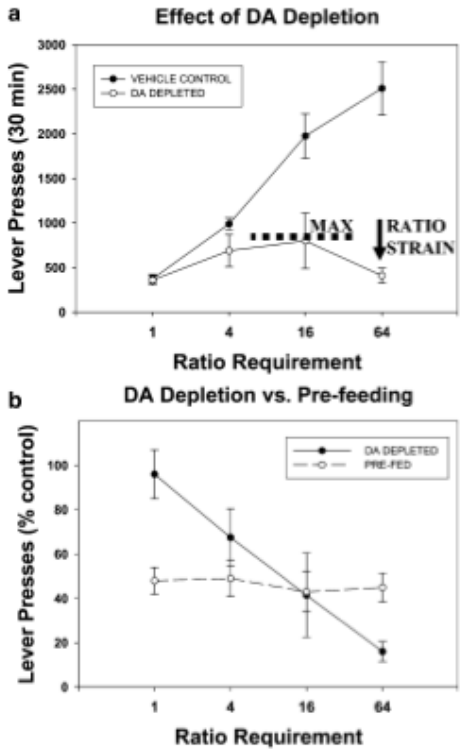
Optogenetics

- Can stimulate particular neuron of interest
- Virus packaged with genes to make photosensitive channel proteins (opsin channel) on targeted neurons e.g. neurons with tyrosine hydroxylase (dopamine neurons)
- Stimulation with light → opening of channels → stimulation of dopamine neurons

Effect of Dopamine

- Anhedonia hypothesis: Dopamine → pleasure from reward
    - BUT: Dopamine drugs do not change consumption level of food w/ free feeding
    - i.e. pleasure from reward is not affected

1. Signals when reward is available
    1. Effect of pairing CS with reward:
        i. Reward → dopamine released
        ii. Pairing CS (light) with reward (food) → dopamine released after CS
        iii. Omission of reward after CS → increase in dopamine after CS, decrease in dopamine after expected time of reward
2. Activates behavior for reward
    1. Levels of dopamine in striatum in discrimination task:
        i. Rewarded movement: Increase in levels of dopamine before movement
        ii. Rewarded non-movement: No increase
        iii. Unrewarded movement: No increase
3. Motivates reward seeking/maximization: Natural reward e.g. food
    1. Dopamine agonist e.g. amphetamine → greater persistence for better reward even with higher FR schedule
    2. Dopamine antagonist/depletion of dopamine → decreased persistence and effort in working for better reward (giving up)
    3. Stimulation of nucleus accumbens in humans → higher reward seeking behavior by choosing activities which are rewarding
        i. Rather than a feeling of euphoria



Stimulation of Nucleus Accumbens

- No experience of euphoria at normal intensities
    - High intensity → euphoria
- Increase in reward-seeking behavior i.e. increased motivation for behavior that increases pleasure
- → lower depression ratings