Non-Receptor Sites of Drug Action

Psychotropic drugs action sites:
- axonal transport (colchicine/mescaline)
- neurotransmitter synthesis (AMPT/Antabuse)
- vesicle storage (reserpine)
- neurotransmitter release (Clonidine)
- heteroreceptors or autoreceptors
- neurotransmitter termination = metabolic enzyme or uptake mechanism (Sarin/MAO inhibitors)
- ion channels (nimodipine)
- 2nd messenger systems (lithium)
- regulation of gene transcription

AMPT:
- alpha-methyl-para-tyrosine
- inhibits tyrosine hydroxylase blocking synthesis of catecholamine’s (eg. DA, NA, A)

Antabuse/Disulfiram:
- inhibits dopamine-beta-hydroxylase (NA synthesis)
- inhibits acetyl-aldehyde dehydrogenase (alcohol metabolism)

Clonidine:
- agonist for presynaptic NA α2 receptors
- inhibits NT release by reducing Ca
2+
 entry into terminal

Sinemet:
- changes precursor availability in NT synthesis
- Parkinson’s treatment- increase DA

Tryptophan:
- used to make 5-HT
- however chronic treatment can induce tryptophan pyrroloase and may decrease 5-HT

Reserpine:
- irreversibly inhibits VMAT-2
- vesicles empty out monoamine content and fail to replete

Sarin (and other nerve gases):
- inhibit acetylcholinesterase
- causes paralysis of muscles

Nimodipine:
- L-type Ca2+
 channel blocker

Lithium:
- effects the IP3 (inositol triphosphate) system that regulates intracellular Ca2+

Amphetamine:
- reversal of DAT increases extracellular basal [DA]
- activates receptors over a wider range and for a longer duration
- competitive inhibitor
- increases motor activity
- blocked by catecholamine synthesis inhibition with AMPT
- reserpine increases amphetamine’s effects
- cocaine blocks amphetamine’s effects
- DA uptake blockers reduce DA release produced
- can be transported by VMAT-2 and diffuse across membrane unassisted

Cocaine:
- blocks the DAT increasing extracellular [DA]
- activates receptors over a wider range and for a longer duration
- increases motor activity
- cocaine’s effects are blocked with reserpine
- Ca2+-dependent effects so only effective if there’s electrical activity in DA cells
- nimodipine blocks the conditioning of cocaine’s motor stimulant effects

MAO Inhibitors:
- the enzyme Monoamine Oxidase in either the isoforms of MAO-A or MAO-B is on the mitochondrial membranes in the terminals of monoamine neurons
- some antidepressant/anti-parkinson’s drugs inhibit MAO which increases presynaptic conc. Of DA, NA, 5-HT, etc.
Copy Number Variations and Microcephaly

CNV – sections of the genome are repeated and the number of repeats varies between individuals

How might CNV’s cause microcephaly?
- alterations to gene dosage within CNV region
- alterations to gene dosage beyond CNV
- positional effects resulting from CNV
- alterations to topologically associating domains (TADs)
- haploinsufficiency

1q43-44 CNV
- frequently associated with microcephaly
- in 87 pure cases and 27 complex cases comprising 1q43-44 CNV’s, all showed:
  ~ intellectual disability
  ~ alterations to brain growth
  eg. microcephaly
  ~ seizures
  ~ hypoplasia of corpus callosum

<table>
<thead>
<tr>
<th>Distal 1q Deletion Cases (Total)</th>
<th>Intellectual Disability</th>
<th>Microcephaly</th>
<th>Macrocephaly</th>
<th>Corpus Callosum Abnormality</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89.9%</td>
<td>80%</td>
<td>1.1%</td>
<td>68.4%</td>
<td>71.7%</td>
</tr>
</tbody>
</table>

Cortical Development

Cortical Development
- cells originate in ventricular zone and migrate to more superficial positions
- cortical plate formed lining outside of telencephalic ventricles
- two types of migration:
  ~ somal translocation:
    > slow migration speed
    > multipolar neuron shape
  ~ radial glial guided locomotion:
    > fast migration speed
    > bipolar shape

Malformations of Cortical Development
- <40% intractable childhood epilepsy attributable to malformations of cortical development
- brain development disorders due to defective cortical neuron migration eg. SBH, PVH, FCD, ectopia, mycrogryria, lissencephaly
- all lead to some form of epilepsy
- may underlie other conditions such as ID, Sch, and ASD
- Different forms of cortical malformations resulting from:
  ~ problems with neuronal cell production
  ~ problems with cell migration
  ~ problems with cortical organisation
Anxiolytics

Summary of Anxiolytics
- Benzodiazepines
- Buspirone: 5-HT-1A agonists, new anxiolytic, less sedative
- β-receptor antagonists: reduce some physical aspects eg. tremor
- Others (SSRI, “Z” drugs, etc.)
- Barbiturates: largely obsolete

Benzodiazepines
- Pharmacodynamics:
  ~ bind to regulatory site on GABA receptors and act allosterically to increase affinity of GABA for its receptor
  ~ results in increased frequency of channel opening by a given amount of GABA, but no change in conductance or mean open time of the receptor
- Pharmacokinetics:
  ~ orally active, can be administered through IV or as suppository
  ~ strong plasma protein binding
  ~ many are highly lipid soluble, accumulating in fat and releasing slowly
  ~ several are converted to active metabolites after metabolism (especially long active forms)
  ~ usually conjugated to glucuronide for inactivation and excretion
- Clinical Uses:
  ~ reduction of anxiety and aggression
  ~ sedation and induction of sleep
  ~ reduction of muscle tone
  ~ anticonvulsant (useful in status epilepticus)
  ~ anterograde amnesia
- Acute Side Effects:
  ~ less toxic than other CNS “depressants”
  ~ may be dangerous with alcohol (administer flumazenil)
- Major Side Effects:
  ~ sleepiness
  ~ confusion
  ~ amnesia
  ~ impaired coordination
- Tolerance, dependence and withdrawal effects: flunitrazepam, rhopynol

Animal Models and Drug Development

“Z” Drugs
- eg. zopiclone, zolpidem, & zaleplon
- structurally unrelated to benzos but act similarly
- suggested to be less addictive
- can be used to treat insomnia
- have been reported to induce “fugue state” and severe amnesia

Buspirone
- completely different from benzos
- presynaptic 5-HT-1A partial agonist (can also act on D2)
- reduces serotinergic input whilst enhancing noradrenergic and dopaminergic activity
- major disadvantage is clinical effect takes several weeks
- side effects less severe with no sedation and addiction

Barbiturates
- used till 60s, still used as anticonvulsants
- thousands derivatives synthesised (eg. pentobarbital)
- bind to a distinct site on GABA_A receptors to enhance effect of GABA but less specific
- very dangerous in OD (respiratory / cardiovascular collapse)
- high degree of tolerance and dependence
- strongly induce hepatic cytochrome P450 enzymes and induce their own metabolism as well as the metabolism of many other drugs (drug interactions)

SSRIs
- eg. fluoxetine, escitalopram, etc.
- much less toxic than other antidepressants
- limited to 5-HT syndrome side effects eg. nausea, insomnia, sexual dysfunction
- may be used in anxiety with comorbid depression (also panic attacks and OCD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Ultra Short (&lt;6 hours)</td>
<td>Hypnotic (IV anaesthetic)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Short (8-12 hours)</td>
<td>Anxiolytic/Hypnotic</td>
</tr>
<tr>
<td>Oxazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>Medium (24 hours)</td>
<td>Anxiolytic/Hypnotic</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Long (24-48 hours)</td>
<td>Anticonvulsant, Anxiolytic/Hypnotic</td>
</tr>
</tbody>
</table>
NEUR3310 Practice Exam Questions

Multiple Choice Section

Questions

1. ___, the precursor to dopamine, can penetrate through the blood-brain barrier, whereas dopamine cannot.
   a) L-Tyrosine  b) L-DOPA  c) Norepinephrine  d) GABA

2. Peptide neurotransmitters are stored in what type of vesicles?
   a) Small and dense  b) Small and clear  c) Large and dense  d) Large and clear

3. What is the common genetic basis for Autism and Schizophrenia?
   a) TUBB5  b) 1q43-q44 CNV  c) 16p11.2 CNV  d) ZNF238/RP58

4. What is the name of the enzyme converting glutamate to GABA?
   a) Glutamate transferase  b) Glutamate synthase  c) Glutamate Carboxylase  d) Glutamate decarboxylase

5. Somal translocation in neuronal development and migration has:
   a) slow speed and a bipolar shape  b) slow speed and a multipolar shape  c) fast speed and a bipolar shape  d) fast speed and a multipolar shape

6. ___ can cause a hypertensive crisis due to excess ___ levels that displace NA from sympathetic terminals.
   a) Iproniazid, tyramine  b) Iproniazid, serotonin  c) Imipramine, tyramine  d) Imipramine, serotonin

7. Construct validity is when:
   a) analogy > homology  b) analogy = homology  c) analogy < homology  d) analogy homology

8. What compound inhibits tyrosine hydroxylase, blocking the synthesis of catecholamines?
   a) AMPT  b) Clonidine  c) Tryptophan  d) Nimodipine

9. What are the D1 receptors effects?
   a) Stimulates adenylyl cyclase which increases the rate of cAMP synthesis  b) Stimulates adenylyl cyclase which decreases the rate of cAMP synthesis  c) Inhibits adenylyl cyclase which increases the rate of cAMP synthesis  d) Inhibits adenylyl cyclase which decreases the rate of cAMP synthesis

10. Fluoxetine (Prozac) is a ___ and ___ - receptor stimulated cAMP.
    a) tricyclic antidepressant, reduces  b) tricyclic antidepressant, does not reduce  c) serotonin reuptake inhibitor, reduces  d) serotonin reuptake inhibitor, does not reduce

11. The major risk factor for late onset Alzheimer's disease is
    a) increased ApoE4  b) increased ApoE3  c) presence of presenilin 1 mutation  d) presence of APP mutation

12. What is the specificity of a drug?
    a) selectively activate one receptor system in preference to another  b) binding of a drug to limited receptor types  c) ability of a compound to bind to a receptor  d) ability to activate G-proteins and cause changes to gene synthesis

13. What is reverse tachyphylaxis?
    a) slow and long lasting decrease in response  b) fast and short lasting decrease in response  c) slow and long lasting increase in response  d) fast and short lasting increase in response

14. All the following are examples of schizophrenic endophenotypes except:
    a) smooth pursuit eye movements (SPEM)  b) PET hypofrontality