NEUROPHARMACOLOGY

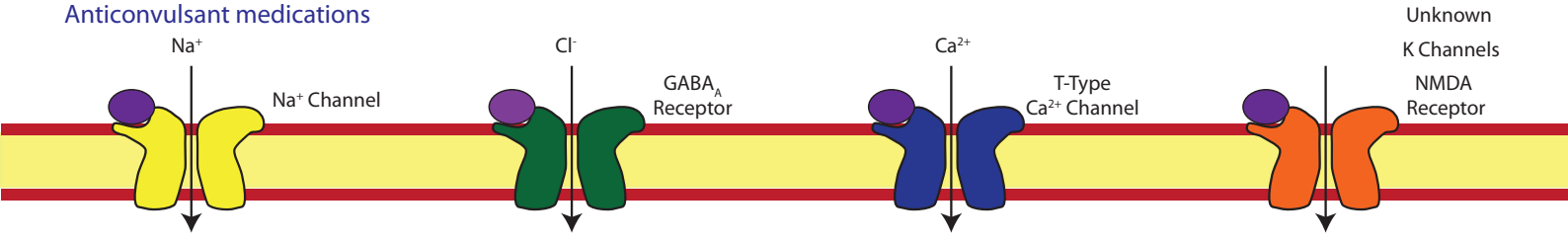
Antipsychotic medications

Classification of antipsychotics is usually based on whether they are older first generation medications with significantly more extra-pyramidal symptoms or newer generation so-called atypical or second generation antipsychotics. Other terms used are neuroleptics which have strong experimental and clinical evidence of antogonism of D_2 dopamine (DA) receptors and are characterised in particular by the supression of spontaneous movements and complex behaviours, although this classification has fallen out of favour in recent times. Pharmaceutical aspects Antipsychotics are avaiable in tablet form although their unpredictable patents of oral absorption make this problematic with some of the agents. Some of the agents are available as wafers for sublingual administration. Other options include IV formulations and IM depots which are preparations of esters of antipsychotics drugs, or incorporated into carbohydrate microspheres, which are absorbed and eliminated much slower than oral and IV formulations. Pharmacodynamic properties The common activity of both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) appears to be post-synaptic blockade of brain dopamine D_2 receptors. The exception, aripiprazole, is a D_2 partial agonist. Several lines of evidence support the role of these receptors in the activity of antipsychotics, including a correlation between receptor binding and clinical potency. SGAs differ from older medications in that serotonin $5HT_2$ receptor binding can exceed their affinity for dopamine D_2 receptors, whereas first-generation generally do not. Largely for that reason, $5HT_2$ activity has been suggested as one basis for the lower risk of extrapyramidal side effects of many of the atypical drugs compared to FGAs, particularly the high-potency agents. The antipsychotic drugs affect all levels of the CNS. Theories on the actions of antipsychotic agents are based on their ability to antagonize the actions of DA as a neurotransmitter in the basal ganglia and limbic portions of the forebrain. The beneficial effects of antipsychotics relate to their demonstrated efficacy in reducing the symptoms of psychoses such as disordered thought processes (including hallucinations and delusions), disorganised or irrational behavours and varying degrees of altered mood. Other beneficial effects of these drugs include anti emetic properties and release of prolactin (which may also a side effect). Pharmacokinetic properties Most antipsychotic drugs are highly lipophilic, highly membrane- or protein-bound, and accumulate in the brain, lung, and other tissues with a rich blood supply. They also enter the fetal circulation and breast milk. It is virtually impossible to remove these agents by dialysis. Elimination half-lives with respect to total concentrations in plasma are typically 20–40 hours. Biological effects of single doses of most antipsychotics usually persist for at least 24 hours, permitting once-daily dosing once the patient has adjusted to initial side effects. The antipsychotic drugs are metabolized largely by hepatic CYPs and by glucuronidation, sulfation, and other conjugation processes. Hydrophilic metabolites of these drugs are excreted in the urine and to some extent in the bile. Most oxidized metabolites of antipsychotic drugs are biologically inactive. Loss of efficacy with prolonged treatment is not known to occur with antipsychotic agents, but some tolerance to sedative effects of antipsychotics usually develops over days or weeks. Side effects are extensive and serious. Neurological side effects can be divided into four acute effects (acute dystonia, akathisia, parkinsonism and neuroleptic malignant syndrome) and two delayed (tarditive dyskinesia and perioral tremor). Cardiovascular effects include postural hypotension (probably due to baroreceptor impairment) and long QT syndrome. Metabolic effects include weight gain and metabolic syndromes, Haem side effects include blood dyscrasias. Endocrine include increased prolactin secretion.

Antidepressant medications

Classification Antidepressant medications may be classified into five major groups. The older generation drugs are the monoamine inhibitors (phenelzine) and the tricyclic antidepressants (amitriptyline). Newer agents include the SSRIs (paroxetine) and SNRIs (venlafaxine). A fifth group including other drugs such as mirtazepine is sometimes added but is not considered here. Pharamaceutical aspects all antidepressants are only available in oral form with the exception of amitriptyline and a related tricyclic imipramine. Pharmacodynamic The amine hypothesis of mood postulates that brain amines, particularly noradrenaline (NA) and serotonin (5-HT), are neurotransmitters in pathways that function in the expression of mood. According to the hypothesis, a functional decrease in the activity of such amines is thought to result in depression; a functional increase of activity results in mood elevation. The amine hypothesis is largely based on studies showing that many drugs capable of alleviating symptoms of major depressive disorders enhance the actions of the central nervous system (CNS) neurotransmitters 5-HT and NA. Difficulties with this hypothesis include the facts that (1) postmortem studies do not reveal any decreases in the brain levels of NA or 5-HT in patients suffering from depression; (2) although antidepressant drugs may cause changes in brain amine activity within hours, weeks may be required for them to achieve clinical effects; (3) most antidepressants ultimately cause a downregulation of amine receptors. The acute effect of tricyclic drugs is to inhibit the reuptake mechanisms (transporters) responsible for the termination of the synaptic actions of both NA and 5-HT in the brain. This presumably results in potentiation of their neurotransmitter actions at postsynaptic receptors, they also demonstate alpha adrenergic effects, muscarininc effects and histamine blocking which leads to many of its side effects. MAOIs decrease NA, dopamine and 5-HT breakdown in the presynapse neuron. SSRIs demonstrate more selective blocking of reuptake at the presynaptic cleft. SRNIs cause blocking of reuptake of both NA and 5 HT. Pharmaocokinetic MAOIs are notable for their prolonged duration of action >1 week, although they are usually dosed daily. The TCAs are well absorbed orally but may undergo first-pass metabolism. They have high volumes of distribution and are not readily dialyzable. Extensive hepatic metabolism is required before their elimination; plasma half-lives of 8-36 h usually permit once-daily dosing. Both amitriptyline and imipramine form active metabolites, nortriptyline and desipramine, respectively. SSRIs are generally very well absorbed orally (up to 100%) lipid soluble, highly protien bound, have large volumes of distribution, half lives which allow daily dosing and metabolised hepatically to inactive metabolites (fluoxetine is the exception with an active metabolite which last several days and allows weekly dosing). SNRIs are variable in their pharmacokinetics, venlafaxine is well absorbed with a high first pass metabolism leading to a bioavailability of 45%, it has a large volume of distribution, a relatively short half life, but an active metabolite which prolongs duration of action. Side effects MAOIs induce sedation and can casue severe orthostatic hypotension. SSRIs and SNRIs have less side effects and but may cause nausea, vomitting and sexual dysfunction. Tricyclic antidepressants routinely produce adverse autonomic responses, in part related to their relatively potent antimuscarinic effects, including dry mouth constipation, dizziness, tachycardia, palpitations, blurred vision,and urinary retention. Cardiovascular effects include orthostatic hypotension, sinus tachycardia, and variable prolongation of cardiac conduction times with the potential for arrhythmias, particularly with overdoses. Weakness, fatigue and weight gain are also common. Overdosage with TCAs or MAOIs can be life threatening with initial excitatory responses seizures, myoclonus and dystonia rapidly progressing towards coma with associated respiratory depression, urinary retention, and cardiac arrythmias. Treatment is gastric lavage and activated charcoal, supportive management (usually ICU/intubation) and phenytoin or lignocaine to treat the arrhythmias.

Anticonvulsant medications



Inactivation of sodium channels

Prototype: Phenytoin (also Carbemazepine)
Indications: partial/tonic clonic not absence seizures
Pharmacodynamics: neuron hyperpolarisation via Na Channels
Pharmaceutical: Oral but Fosphenytoin is a water soluble form for IV preparations
Pharmacokinetics: $t_{1/2}$ 6-24 hrs -non linear metabolism (first order to zero order with increasing concentration). Extensive protien binding >95%, increased levels when competition for binding.
Side effects: cardiac arrythmias, hirsutism in females, gingival hyperplasia, SIADH, skin rash, rarely steven-johnson or SLE

GABA related effects

Prototype: Diazepam - benzodiazepines (also gabapentin, barbituates)
Indications: status epilepticus, anxiolytic, amnesic.
Pharmacodynamics: neuron hyperpolarisation via GABA$_A$ Receptor sensitisation
Pharmaceutical: Oral and IV
Pharmacokinetics: $t_{1/2}$ 1-2 days with prolonged active metabolite (60hrs). v high lipid solubility and protien binding. Effect reduced by rapid redistribution. Tolerance and physiological dependence develops.
Side effects: sedation, synergistic respiratory depression with other agents, lethargy, ataxia, decreased coordination.

Inactivation of Ca^{2+} channels

Prototype: Valproic acid best known, (ethosuximide is actual prototype)
Indications: partial/tonic clonic and absence seizures
Pharmacodynamics: neuron hyperpolarisation via Ca Channels (also Na Channels)
Pharmaceutical: Oral enteric coated
Pharmacokinetics: absorbed rapidly and completely, highly protien bound, diffusion and carrer transport to CSF, hepatic metab, active metabolites, $t_{1/2}$ 15 hours, urine excretion.
Side effects: commonly; anorexia, nausea, vomitting, occasionally; sedation, ataxia, tremor. rarely; fulminant hepatitis.

Other processes of hyperpolarisation

"Prototype": Levetiracetam (others include lamotrigine)
Indications: refractory epilepsy, bipolar disorder.
Pharmacodynamics: unknown, possibly ?K Channels, ?NMDA, ?Na Channels
Pharmaceutical: Oral and IV
Pharmacokinetics: rapid and complete absorption, 100% bioavailability, Vd is near total body water, minimal protien binding, $t_{1/2}$ 6-8 hrs minimal metabolism, inactive metabolites. Urine excretion mostly unchanged (66%)
Side effects: somnolence, asthenia, dizziness, agitation, nausea

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