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DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

SUNALI MEHTA

The brain is responsible for all affective and cognitive process and is capable of coordinating corporeal functions. Sometimes there can be an imbalance in the mental functioning and can result in some of the disorders. The drugs used to treat the disorders are called psychotropic drugs, the mechanism of action is not well understood. These drugs act on chemical transmitter – receptor system within the brain.

Divisions of the brain:

1. Cerebrum consists of the two cerebral hemispheres, the cortex and the associated sub – cortical nuclei.
2. Diencephalon consisting of the thalamus and the hypothalamus.
3. Brain stem and the cerebellum where the brain stem consists of the mid brain, pons and the medulla oblongata and the cerebellum is posterior located between the pons and medulla.

Cerebrum: is responsible for precise perception, interpretation of sensation, initiation of skeletal muscle movement and communication. It is also the seat of intellect and abstract thought

Diencephalon: the thalamus acts as a relay center for the incoming sensory signals sort them and send them to the appropriate regions of the cortex for processing. It also relays motor impulses from the cortex to the lower motor centers. The hypothalamus is involved in visceral functions such as body temp, appetite, hormone pdtn and secretion, fluid levels and biological rythms.

Cerebrum – diencephalons interactions: these cooperate in memory functions as well as in the control of the emotions and behaviour. This system is known as the limbic system and includes area of the cortex, hippocampus, amygdala, fornix, thalamus and hypothalamus.

Brain stem: acts as conduction p/w between the higher and lower centers of the brain of both the sensory and motor info. The medulla oblongata contains control centers for important visceral functions such as heart rate, bp, respiratory center coughing and vomiting.

Brain stem – diencephalons – cerebrum : the brain stem , thalamus and the cortex cooperate and control level of consciousness by a system called the reticular activating system.

Cerebellum is involved in the maintenance of equilibrium and posture.

Motor pathways incorporate two discrete systems: pyramidal and extrapyramidal p/w. The pyramidal p/w is responsible for the activation of skeletal muscle whereas the extrapyramidal p/w dampens and adjusts voluntary muscle movement. It is also involved in the maintenance of muscle tone and balance as well as being concerned with the coordinated movement of the head and eye towards a visual stimulus.

Chemical transmitters:

Noradrenalin

Adrenalin

Serotonin

Dopamine

Ach

Glutamate

Gamma aminobutyric acid.

Glycine and histamine have also been found.

These are involved in the function of neurotransmission and may also act as neuromodulators.

Neuromodulation: they alter the response of a nerve cell or a nerve circuit to its neurotransmitter to either enhance or suppress impulse transmission.

Ach: is thought to play a major role in cognitive functions and memory formation as well as motor control. Cholinergic nerves are associated with the pyramidal p/w. the motor p/w are essentially nicotinic whereas in cognitive function memory and consciousness, M1 muscarinic receptors predominate.

Dopamine: Behaviour, hormone release, motor control and emesis. Areas of the brain where dopaminergic receptors have been found are limbic system, extrapyramidal p/w, the ctz in the medulla and the p/w connecting the hypo and pituitary gland. There are four receptor subtypes that have been found.

Noradrenaline and Serotonin: involved in arousal, sleep, mood, appetite, temperature control and hormone release. Noradrenalin can stimulate the alfa and beta adrenergic receptors. There are two subtype receptors of serotonin found in the brain.

GABA: is distributed throughout the brain and the spinal cord. It is a major inhibitory nt and helps to modulate the excitatory p/w. it is formed from the excitatory nt glutamate. There are two types of receptors. Motor control, arousal, memory formation and consciousness are all inhibited by gaba. GABAa receptors are associated with the Cl ion channels and GABAb is associated with the k and ca channels. Activation of the GABAa receptor induces chloride ion influx into the neuron. This hyperpolarizes the neurons and makes it difficult to fire when stimulated by excitatory nt like glutamate. Drugs that enhance the action of GABA are used as sedatives and muscle relaxant.

Glutamate: distributed throughout the CNS. It can be stimulated by a number of receptors such as NMDA, AMPA and kainate. It also performs a modulatory function on the CNS.

Opioids are also not present in the brain and in the rest of the body.

The drugs involved in the treatment of disorders containing the CNS are antipsychotics, antidepressants, anxiolytics, hypnotics, sedatives, muscle relaxants, anticonvulsants, antiparkinsonian and CNS Stimulant.

How do NT work?

NT are made in the neurons and are stored in the synaptic vesicles, when the neuron is stimulated these NT are released from the vesicle into the synaptic cleft between the two neurons or the effector tissue. Then the NT crosses the synapse and binds to the specific receptor triggering a response or act to pass on the message. Excessive NT are removed from the synapse either by a proton pump or by enzyme degradation.

NT disease can occur either when there is too much neurotransmission or there is not enough of it.

Too much: means that the neurons are excited all the time e.g. seizures disorders e.g. psychosis

Too little: e.g. depression and parkinsonism.

When too little NT is present the drugs can be designed in the following way:

1. agonists
2. can be precursors for NT
3. can inhibit NT from being broken down
4. can inhibit the reuptake of NT.

When too much

1. antagonist
 2. can enhance the action of the inhibitory transmitters such as GABA or inhibit the action or release of the excitatory aa like glutamate.
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Drugs and Parkinson's Disease:

Some of the degeneration of the nervous system is caused genetically and other is due to an autoimmune system being triggered. There is progressive deterioration which is irreversible. Treatment is supportive and not curative.

Parkinson Disease:

It is characterized by a distinctive tremor of the extremities and head as well as difficulty in the coordination of fine muscle movements. The other imp feature is called hypokinesia an inability or slowness in initiating movement.

The defect in the PD is in the basal ganglia portion of the midbrain. On the corticospinal p/w there are muscarinic cholinergic fibers that are excitatory pyramidal p/w and there is another p/w thru the basal ganglia called the nigrostriatal p/w which contains inhibitory dopaminergic fibers of the extrapyramidal p/w. There is always a homeostatic control between the excitatory muscarinic and inhibitory dopaminergic activity. In PD the dopaminergic fibers degenerate and as a result there is less dopaminergic activity and excessive muscarinic activity. There are two methods that can be used to treat this:

Decrease the muscarinic activity

Increase the dopaminergic activity.

Decreasing the Muscarinic Activity: these help to control tremors and rigidity though they are not of much help in hypokinesia. By inhibiting the muscarinic receptors in the basal ganglia the imbalance between the pyramidal and extrapyramidal p/w will be reduced. They have unwanted antimuscarinic side effects like micturition, hallucination and confusion which are undesirable in the elderly.

e.g. benztropine, biperidine, procyclidine and orphenadrine.

These are the drugs useful in the treatment of secondary parkinsonism.

Increasing the dopaminergic activity.

Increasing dopamine levels:

Levodopa: dopamine on its own does not cross the bbb. The immediate precursor of dopamine called levodopa or L – dopa can cross the bbb and then can be converted to dopamine.

It has some serious effects since it is converted into dopamine even by the peripheral mechanism. The enzyme that converts levodopa to dopamine is a decarboxylase. There are several inhibitors of this enzyme and of this two cannot cross the bbb and they are carbidopa and benserazide. By addition of any one of these compounds the peripheral conversion of levodopa is inhibited and thus allowing more levodopa to cross into the CNS. This can reduce the side effects that are caused. Side effects include : nausea, depression, involuntary muscle movements of the extremities, head, lips and tongue, agitation and confusion, increased sexual activity, hypotension, delusions and dysrhythmias. The effect of levodopa decreases with time until no effect is produced. As the years proceed the drug dosing has to become more frequent. This progressive loss of drug activity is due to the continuous degeneration of the dopaminergic neurons.

Other peripheral inhibitors of levodopa conversion.

Entacapone and tolacapone belong to a class of COMT (Catechol – O – methyltransferase) inhibitor. These enzymes are present in the synapse and are

involved in the metabolism of certain nt belonging to the catecholamine group. These do not cross the bbb and therefore produce only a peripheral effect. Clients should be told that the urine may be reddish – brown during treatment. Inc in the liver enzymes and neuroleptic malignant syndrome can occur though very rare. The treatment with decarboxylase inhibitors with levodopa and COMT inhibitors enhances the effect of levodopa to a great extent but liver function should be monitored.

Inhibit the breakdown of Dopamine. This is done so as to achieve prolonged action of dopamine. MAO is an enzyme which is responsible in the degradation of noradrenaline as well as a dopamine and hence drugs used to inhibit the action of MAO are called MAOI's and are also a class of antidepressants. This will result in a rise of the dopamine level. Care should be taken for drug – drug interaction and dietary restrictions. The enzyme present in the brain is different from the rest of the body and is termed as MAOb and Selegiline is an MAOb inhibitor. If given concurrently with levodopa smaller doses can be administered. Dry mouth being the only possible side effect. But dyskinesias can occur.

Stimulate the release of Dopamine:

Amantsdine inhibits the uptake of dopamine and increases and stimulates the release of dopamine. It also has a slight antimuscarinic effect. It by itself is not so potential but it can enhance the potential of levodopa or other antimuscarinic agents. It can cause postural hypotension, ankle oedema, insomnia, hallucinations. It is useful in diminishing tremors in the early stages of the disease.

Mimic Dopamine Action:

Bromocriptine can be termed as a dopamine agonist. Best use in conjunction of levodopa. Lisuride, cabergoline are drugs similar to bromocriptine and are derivatives of ergotamine.

Apomorphine is a non – ergot derivative but it is a derivative of morphine and is used in the treatment since it mimics dopamine.

They mimic dopamine on the pyramidal p/w by stimulating the dopamine receptors.

Side effect is nausea. Lisuride can cause hallucinations, delusions and confusions. Other side effects are vomiting, diplopia and dysrhythmia.

Drugs to know:

Levodopa – addition of dopamine

Sinemet (Levodopa + carbidopa)

Bromocriptine - dopamine agonist

Benzotropine(Cogentin)

Orphenadrine

Antipsychotic Drugs:

There appears to be a disturbance in the catecholamine in the CNS leading to disease like schizophrenia, severe agitation and some forms of dementia. Drugs used to treat psychoses are generally dopamine antagonist which rebalance the system but does not induce a cure. Some of the dopamine antagonist are very specific for the D2 receptor in the brain where the defect appears to be located.

The cause of schizophrenia is a mystery but can be determined genetically or is induced by the inc dopaminergic activity in the brain. Antipsychotic drugs either have a direct effect on the D2 receptors and are termed as typical, or the ones that have less affinity for the D2 receptors and are termed as atypical.

Typical Antipsychotics:

Also called neuroleptics or major tranquillisers. The three common ones are phenothiazines, butyrophenones and thioxanthenes. Their mode of action

remains unelucidated. Their main action is to antagonize dopamine but they also have an antimuscarinic antihistaminic and antiseritonergeric action as well as are alfa blockers. This inc their range of adverse effects.

E.g. of phenothiazine – metoclopramide, chlorpromazine

Adverse reactions: Extrapyramidal effects are often seen. There are four types:

1. drug induced parkinsonian symptoms
2. dystonic reactions which include facial grimacing, wry neck and spasticity of the limbs.
3. There is akathisia with restlessness being the most common.
4. there is tardive dyskinesia which severely affects muscle coordination. Occurs after prolonged treatment.

Rare but a serious result of an antipsychotic is neuroleptic malignant syndrome. This treatment involves the administration of a dopamine agonist like dantrolene and bromocriptine.

Dopamine antagonists can also cause lactation and when it is not post partum it is called galactorrhoea and it can also lead to gynaecomastia in the males. It can cause amenorrhoea in females and loss of libido in males.

When the phenothiazines accumulate in the skin they can result in abnormal pigmentation, skin rashes or urticaria. Also can induce photosensitivity.

Phenothiazines can be used to treat short term severe anxiety.

Antipsychotic also have the antiemetic properties and sometimes can make it difficult to evaluate the effect of other drugs causing nausea.

The thioxanthenes such as flupenthixol and zuclopenthixol are parenteral agents and have mood – elevating properties and can be given to flat patients or depressed. Thiothixene is an thioxanthenes which is used in the treatment of schizo and has been good.

Atypical antipsychotics:

These are less pronounced to producing extrapyramidal effects and this is due to their having differences in their affinities for various central receptors. These also have a tendency to cause weight gain. Chemical groups such as

Benzamides - amisulpiride

Benzisoxazoles (Risperidone)

It is a selective antagonist for 5 – HT₂ and D₂ receptors. No affinity for the muscarinic receptors. Its affinity for the 5 HT₂ receptors may be responsible for its having a lesser incidence of extrapyramidal effects as compared to other D₂ receptor antagonist.

Dibenzodiazepines: Clozapine which is a dopamine antagonist and acts on the D₁ and D₄ receptors and not on the D₂ receptor. It also has sympatholytic, antimuscarinic, antiserotonergic, antihistaminic and arousal inhibiting effect. It causes irreversible neutopenia a type of agranulocytosis.

Drugs to know are:

Chlorpromazine – typical

Fluphenazine – typical depot

Haloperidole – Typical

Clozapine – atypical

Olanzapine – “

Risperidone – “

Antidepressants and Mood stabilizers:

Depression is a state of profound sadness or melancholy. It includes lethargy, apathy, loss of appetite, insomnia, feeling of worthlessness, personal neglect and suicidal tendencies.

There are three types of depression:

1. Which occurs either in response to a life crisis or an adverse reaction.
2. Endogenous form
3. Bipolar affective disorder or manic – depressive state.

There is a link between the levels of the two brain nt NA and 5 HT and the depressed state. There is a depletion of the nt. The action of the antidepressant is aimed at inc the level of either one or both of these nt.

The purpose of the presynaptic receptor is to prevent the overstimulation of the postsynaptic receptor.

The major groups of antidepressants are:

1. Tricyclic Antidepressants TCA
2. Selective serotonin reuptake inhibitors SSRI
3. Monoamine oxidase inhibitor MAOI
4. Reversible inhibitors of Monoamine oxidase RIMA
5. Tetracyclic antidepressants
6. Noradrenalin – serotonin reuptake inhibitors (NSRI)
7. Selective serotonin receptor blockers
8. Selective noradrenalin reuptake inhibitors.

1. TCA: imipramine, amitriptyline, doxepin: they have got their name because of the three ringed structure of the drug molecule itself. The drug primarily acts by inhibiting the amine uptake pump on the presynaptic terminal and as a consequence the level of the nt inc. they are not termed as cns stimulant since they do not have stimulatory effects in a person who is not depressed. They have antimuscarinic, antihistaminic and antiadrenergic activity as a result they can lead to dry mouth, blurred vision, constipation, urinary retention and tachycardia. There can also be confusion and sedation. Also postural hypotension can be present. There is a major chance of individuals suffering from erratic moods and suicidal tendencies are at a greater risk of poisoning themselves. The bp needs to be monitored. The dose should be given at bedtime to assist compliance. They are not the first choice of drug treatment.

2. SSRI's: Fluoxetine, paroxetine, sertraline, fluvoxamine, escitalopram and citalopram. They are considered as the first line of treatment for major depression. These block the amine reuptake pump but selectively affect only the serotonin reuptake and as a result there is an inc in the level of serotonin. They do not have muscarinic, histaminic and adrenergic affinity and hence they have comparatively lower side effects. They are non – sedative and also are not cns stimulants. The common side effects associated are headache, nausea, vomiting, tremor, insomnia, dizziness and diarrhea. There has been a fatal disease that has developed with the use of these and that is serotonin syndrome which can develop and this occurs due to hyperserotonergic state characterized by euphoria, drowsiness, abnormal muscle movements, sweating, intoxication, hyperthermia, diarrhea, loss of consciousness and possible death. These should not be given with TCA but should be accompanied with the MAOI or lithium carbonate.

3. Tetracyclic Antidepressants: Mianserin, maprotiline and mirtazapine are tetracyclic in their molecular structures. These are known as second generation antidepressants are also used in the first line therapy of drug treatment.

These act by blocking the presynaptic alpha 2 receptors and as a result there is an increase in the level of the nt. Common adverse effects include headache, drowsiness, dry mouth and fatigue. There is a risk of hematological toxicity and are contraindicated in cases such as heart or bladder disease.

4. MAOI – Irreversible and non – selective:

These act at the synaptic level by preventing the degradation of the nt by the MAO after its release. These include phenelzine and tranylcypromine. These are irreversible inhibitors. The side effects are less severe as compared to TCA but do include antimuscarinic and antiadrenergic effects. MAO is an enzyme which is used to metabolise tyramine. Tyramine is taken up by the amine pumps and result in a release of noradrenalin which is then broken down by the MAO enzyme when MAOI are used this breakdown is not possible and hence when food rich in tyramine is consumed it can lead to an excess of NA in the periphery and hence can cause life threatening cardiovascular stimulation.

5. RIMA's: there are two isoforms of the enzyme MAO found. MAO type A is found in the brain, peripheral adrenergic nerve and the placenta and is involved in the breakdown of NA and 5ht. whereas MAO type B is found in the liver, brain and platelet and is involved in the breakdown of dopamine. Type A inhibitor is Moclobemide and is a competitive inhibitor of type A MAO and its effects are reversible. Common adverse rxn are nausea, dizziness and insomnia. Since it is a low toxic drug it has been included in the first line therapy of treatment.

6. NSRI: Venlafaxin: it is a phenethylamine and its mechanism of action closely resembles TCA. It basically blocks the uptake of NA and 5ht and to some extent also dopamine. Adverse rxn include nausea, headache, anorexia, sedation and dizziness.

7. SNRI's: Reboxetine: this blocks the reuptake of NA but does not affect the uptake of serotonin and dopamine. Common Adverse reaction include headache,

dry mouth, tachycardia, hypotension, urinary retention, constipation and insomnia.

8. Selective Serotonin Receptor blocker: Nefazodone: its action involves the inhibition of serotonin reuptake presynaptically and this would potentiate the level of serotonin in the brain. It also blocks the 5 HT₂ receptors.

Mood stabilizers: mania is the opposite of depression and is characterized by an elevation of mood, lasting more than a week. The affected person is hyperactive and talkative. Inc experience of insomnia, inc sexual drive, and an inc flow of thoughts and ideas. There is also an inc in the synaptic level of noradrenaline. The person often suffers from cycles between mania and depression. When cycles occur more than four times a year it is known as rapid – cycling bipolar affective disorder. The best agents are lithium carbonate, carbamazepine and sodium valporate.

Lithium Carbonate: is mainly used to prevent mania and cyclic depressive states. Lithium has been known to enhance the action of the amine reuptake pump and hence also inhibit the release of noradrenaline. This results in dec of the nt within the synapse. It has a narrow therapeutic index and hence clients need to be monitored properly. It can cause Gi irritation, tremor, muscle weakness and polyuria. Due to its narrow therapeutic index there can be an exacerbation and can lead to tinnitus, blurred vision, ataxia, muscle twitches and altered consciousness.

Carbamazepine and sodium valporate are useful in the treatment of bipolar affective disorder. Their exact mechanism of action is unknown however it is thought to enhance the activity of the GABA

The common side effects of the TCA and MAOI include anti – cholinergic effects such as dry mouth, blurred vision, constipation , problem in voiding urine and

tachycardia. Antihistaminic effect - sedation and confusion. Antiadrenergic effect – postural hypertension.

Anticonvulsants or antiseizure drugs:

These are used in the treatment of seizures and in a particular the condition characterized by recurrent seizure – epilepsy.

A seizure is the manifestation of an intense transient electrical discharge across the surface of the cerebral cortex. Can involve only one area and is called focal or can arise at different parts of the cortex and is called diffuse. Cause can be either a biochemical imbalance or a structural abnormality.

Antiseizure drugs are based on their chemical structure and their mechanism of action and include:

Hydantoins

Succinimides

Benzodiazepines

Barbiturates

General mechanism of action:

They achieve control by the following ways:

1. Directly stabilizing the nerve membranes
2. Altering the movement of sodium through the membrane channels.
3. Enhancing the activity of nt like GABA
4. Inhibiting the action of glutamate.

Common adverse effects include: GI disturbance, ataxia, headache, nystagmus, mental confusion, skin rash, myelosuppression (inhibition of blood cell pdtn) and sedation.

Most of the antiseizure drugs with the exception of benzodiazepines are suspected teratogens.

Drugs that affect the movement of Sodium across the membrane Channels:

Hydantoin: Sodium phenytoin: it act to promote the intracellular sodium removal during the refractory period of the action potential, as a result it stabilized the cortex nerve against hyperexcitability, especially those located in the motor cortex and prevents discharging neurons from repeated firing. It is useful in the treatment of tonic – seizures and also other seizure. It is also an antidysrhythmic agent and a co – analgesic in the treatment of neuralgia but it is not the first choice of drug. Additional adverse rxn include gum overgrowth and liver damage. Phenytoin decreases the effectiveness of hormonal contraceptives.

Carbamazepine: it is a tricyclic compound and is related to imipramine. It has an antiseizure effect different from phenytoin. It is the choice of drug in symptomatic partial seizures. It promotes sodium efflux across the nerve membrane. It reduces neuronal excitability, especially repeated firing of the same neuron. This does not have much effect on the motor cortex. Severe cardiovascular, altered micturition, liver and kidney dysfunction are the adverse effects.

Oxcarbazepine: used in tonic – clonic seizures: they block the voltage gated sodium channels and as a consequence they inhibit the hyperexcitability of the neurons, nerve impulse transmission is reduced and repetitive firing is inhibited. There is also evidence that it enhances K efflux and Ca influx which may support the drug action.

Drugs that stabilize the nerve membrane directly:

Succinimides: ethosuximide: treatment of childhood absence seizures: stabilizes neuronal excitability thereby raising the threshold to uncontrolled cerebral

discharge, especially within the motor cortex. Adverse reactions include alopecia and muscle weakness.

Drugs affecting the activity of GABA:

Benzodiazepines: Diazepam, clobazam, clonazepam: Diazepam is used to control status epilepticus. The mechanism of these agents is to inhibit the firing of the hyperexcitable neurons thru the enhancement of the action of the inhibitory transmitter GABA. This nt is present everywhere is the cns. These drugs induce fatigue, muscle weakness, hypersalivation and vertigo. Sedative effect and produce tolerance hence cant be used for long term therapy.

Barbiturates: phenobarbitone long acting and short acting amylobarbitone:

Depress the activity of the hyperexcited neuron by the enhancing the action of the inhibitory GABA. Have a narrow therapeutic index and hence are quite toxic.

Vigabatrin: used when seizures are not well controlled by other drugs: this drug is an irreversible inhibitor of the enzyme that degrades GABA and as a result there is an inc amt of GABA in the cns. Weight gain is common adverse reaction and psychotic behaviour has also been reported.

Tiagabine: inhibits the action of reuptake of the GABA and therefore there is prolonged action of the inhibitory nt. It is well absorbed in the gut and should be taken with food and is subjected to significant metabolism in the liver and has a half life of 8 hours. Common adverse reactions include dizziness, tiredness, nervousness and diarrhea.

Other Antiseizure drugs and drugs with combined mechanism of action:

Valporic Acid: Sodium valproate: mechanism is to trigger the release of GABA within the brain and inhibit Na channels that change in voltage during depolarization. Major concern is hepatotoxicity.

Lamotrigine: has a two fold effect: inhibits passage of Na thru the voltage sensitive channels and reduces the release of the excitatory nt glutamate as a result the uncontrolled and repetitive firing of the neurone in the affected area of the cortex is suppressed. Common rxn is skin rash.