Biochemical basis

&

Pharmacology of behavior

Neurotransmission

When the presynaptic neuron is stimulated, a neurotransmitter is released, travel across the synaptic cleft and act on receptors on the postsynaptic neuron. Neurotransmitters are excitatory if they increase the chance that a neuron will fire& inhibitory if they decrease these chances.

The changeability of number or affinity of receptors for specific NT is called neuronal plasticity that can regulate the responsiveness of neurons. When stimulated by NT postsynaptic receptors may alter the metabolism of neurons by the use of second messengers which include cyclic adenosine monophosphate (cAMP).

Availability of specific NTS is associated with common psychiatric conditions.

Monoamines

Monoamines include catecholamines,indolamines, ethylamines &quaternary amines.

Monoamine theory of mood disorder hypothesized that lowered monoamine activity results in depression.

1-Dopamine

Dopamine is synthesized from precursor of dopamine by the tyrosine hydroxylase that act on monoacid tyrosine. At least five dopamine receptors subtypes have been identified(D1-D5)

The major site of action is D2 for traditional antipsychotics while D3,D2&D4 are the sites of action for atypical antipsychotics.

Dopaminergic tracts

A-Nigrostriatal tract

Nigrostriatal tract is involved in the regulation of muscle tone and movement. Treatment with antipsychotics block the postsynaptic dopamine receptors can result in parkinsonism like symptoms that is called the extra pyramidal symptoms.

B-Tubero-infundibular tract

Blockade of dopamine receptors by antipsychotics results in elevated prolactin level & in turn result in symptoms of hyperprolactinaemia that include breast enlargement, galactorrhea &sexual dysfunction.

C-Mesolimbic-mesocortical tract

It may have a role in expression of emotions. Hyperactivity of this tract is associated with the positive symptoms of schizophrenia & its hyperactivity or hypoactivity may be associated with the negative symptoms of schizophrenia.

The increased level of homovanillic acid ,a dopamine metabolite in plasma ,CSF or urine is associated with psychotic disorders while the reduction in its level is associated with Parkinson's disease, depression &with patients who are treated with antipsychotics.

2-Norepinephrine

Most NE neurons are located in the locus ceruleus.The NE metabolite vanillylmandelic acid (VMA) is increased in plasma,CSF or urine in pheochromocytoma (adrenal medulla tumor). The other NE metabolite 3-methoxy-4-hydroxy phenyl glycol (MHPG) decrease in urine ,CSF or plasma is associated with sever depression & attempted suicide.

3-Serotonin(5-HT)

Most serotonergic cell bodies in brain are contained in the dorsal raphe nucleus.

Serotonin play role in mood, sleep &sexuality as well as in impulse control .Heterocyclic block reuptake of serotonin& NE while SSRI block reuptake of serotonin by the presynaptic neurons.

MAOI prevent the degradation of serotonin and NE by monoamine oxidase.

Reduction of serotonin metabolite 5-hydroxy indol acetic acid(5-HIAA) in plasma .CSF or urine is associated with sever depression, attempted suicide ,aggressiveness ,impulsiveness ,fire setting, Tourettes syndrome ,alcohol abuse & bulimia nervosa.

4-Histamine

Is an ethylamine. Histamine blockade with antipsychotics and antidepressants is associated with common side effects of these drugs such as sedation & increased appetite leading to weight gain.

Aminoacid NTS

1-Gama amino butyric acid (GABA)

Is the principle inhibitory NT in the CNS.

Both benzodiazepine and barbiturate increase affinity of GABA for its binding site allowing more chloride to enter the neuron .The chloride-laden neurons become hyperpolarized and inhibited decreasing neuronal firing and ultimately decreasing anxiety.

2-Glycine

Is an inhibitory NT that work on its own &as a regulator of glutamate activity.

3-Glutamate

Is an excitatory NT &may be associated with epilepsy, schizophrenia ,Alzheimer's disease and with mechanism of cell death.

Neuropeptides

1-Endogenous opioids

May mediate the placebo effect that may be block with an opiate receptor blocker such as naloxone.

2-Other neuropeptides

Cholecystokinin & neurotensin have been implicated in schizophrenia.

Somatostatin,substance P,vasopressin,oxytocin & vasoactive intestinal peptide have been implicated in mood disorders.

Pharmacology of behavior

Research workers have examined the action of effective psychotropic drugs in hope that the latter might indicate the biochemical abnormalities in disorder. If an effective drug blocks a particular transmitter system, it can not concluded that the disease is caused by an excess of that NT.e.g.anticholinergic drugs modify the symptoms of parkinsonism but the disease is due to deficiency of dopaminergic transmission rather than to an excess of cholinergic transmission.

There are 2 main problems in association of drugs with the etiology of the disorder

1-Most psychotropic drugs have more than one action &it is often difficult to decide.

2-The therapeutic effect of many psychotropic drugs are slow to develop that usually delay for about 2 weeks suggesting that the adaptive responses of brain to medication are important in the clinical action like that of antidepressant drugs.

Drugs that increase NE&/or 5HT improve mood like in depressive disorders while only drugs that have potent 5-HT reuptake inhibitor properties are effective in the pharmacological treatment of obsessive-compulsive disorder .This suggest that the pathophysiology of OCD is likely to differ from that of major depression.

Most antipsychotic drugs are believed to produce their therapeutic effects through blockade of D2 receptors such as chlorpromazine or haloperidol but clozapine (the most potent antipsychotic) has weak affinity for this binding site& bind potently to certain 5-HT receptor particularly 5-HT2A receptors brought the attention to the role of serotonin in the pathogenesis of schizophrenia.

Alcohol: it has euphoriant effect for some individuals in some settings. Alcohol is associated with disinhibited, criminal& suicidal behaviors.

Opioid intoxication: in which there may be an initial euphoria, dysphoria ,apathy, psychomotor agitation or retardation.

Benzodiazepines intoxication: inappropriate sexual or aggressive behaviors.

Cannabis intoxication: paranoid ideation, maladaptive behavior or even psychosis.

Amphetamine or cocaine intoxication: change in sociability, interpersonal sensitivity, anger &stereotyped behavior.