PHARMACOLOGY OF SLEEP

Changes in sleep and wakefulness are believed to arise from the activity of chemical agents that influence communications between neurons. The firing rate of neurons in most brain areas is lower in NREM sleep than in wakefulness, whereas REM sleep is characterized by intense activity, which contrasts with behavioural quiescence. At least, 30 endogenous compounds have been proposed as chemical mediator of neuronal signalling. The transmitters and putative transmitters that play active role are mononeurones nor-epinephrine, serotonin (SHT) acetylcholine, dopamine and histamine, gamma-aminobutyric acid (GABA) and a purine derivative, adenosine.

The activity of cholinergic system (release of acetylcholine may influence wakefulness and sleep more so REM sleep. Atropine, which blocks the effects of both muscarinic and nicotinic agent suppresses the tonic and phasic component of REM sleep and induces slow cortical activity with apparent behavioural arousal. It is now recognised that there are subtype of muscarinic receptors namely M1 & M2. M2 receptor agonist injected into the medial pontine reticular formations, increases REM sleep, whereas M1 receptor stimulation is without effect. There are wide spread group of cholinergic cells in the brain stem beside gastigial tegmental gigantoecllular field responsible for triggering of REM sleep. There is now much evidence that stimulation or blockade of cholinergic systems in animals and humans modifies wakefulness and REM sleep.

Central norepinephrine activity is mediated by alpha and beta adrenoreceptors. The role of subtype of alpha-receptor, alpha-1 receptor located postsynaptically is not certain in sleep. Alpha- 2 receptors located both post and presynaptically are quite important in regulation of wakefulness and sleep. Clonidine is a potent alpha2 agonist, which at least in small doses is specific. Small doses are inactive, intermediate doses facilitate and larger doses inhibit awake activity. Clonidine inhibits REM sleep in larger doses and also prevents the increase in REM sleep produced by small doses of narcoleptic such as chlorpromazine. Beta adrenoreceptors (B1 & B2) stimulation has sedative effect. Propranalol decreases REM sleep and may cause insomnia and nightmares. 5-hydroxy tryptamine plays a critical role on the production of sleep. In fact some forms on insomnia may due to deficiency of 5HT. Levels of 5-HT in the brain are found increased during sleep. It is now considered likely that 5-HT activity

is important throughout the sleep-wakefulness continuum for the synthesis and use of other sleep factors. Tryptophan is found to shorten the latency to, and increase the duration of REM sleep.

Dopamine receptor (DA) is certainly involved in some aspects of wakefulness. DA receptor antagonists tend to decrease wakefulness and slow wave sleep. Their effect on REM sleep is more complex, small doses tend to increase REM sleep whereas larger doses cause reduction in REM sleep. Histamine may well be involved in the control of arousals. H1 antihistamines have limited effects on wakefulness during sleep in humans but in equal doses in the day, they lead to marked drowsiness. H2 receptor antagonists do not reduce wakefulness during nocturnal sleep in humans although increased slow wave sleep has been observed with cimetidine.

There is increasing evidence that adenosine may be regulator on central activity and involved in the control on sleep and wakefulness. One of the primary actions of adenosine receptor agonist is to enhance or induce sleep. It is now widely accepted that excitatory actions of caffeine and other methylexanthines are related to their antagonism of adenosine receptors rather than to inhibitions of phosphodiesterase activity. Even the anxiolytic action of the Benzodiazepines seams to be related to their ability to inhibit the uptake of adenosine.

GABA-ergic transmission in the brain has been very important subject with research workers as about one third of all synapses in the brain are GABA-ergic. Pharmacological agents that interact with central receptors can be classified as agonist, inverse agonist and antagonist. Most benzodiazepines are agonist and facilitate the effects of GABA. Inverse agonists have the opposite effect and inhibit the activity of GABA. Antagonists do not induce any effect by themselves but prevent the action of the other two categories of compounds.

The knowledge of central receptors, neurotransmitters and pharmacology of various centrally acting drugs, benzodiazepines in particular and understanding of their effects on receptors may deepen our understanding of the mechanism involved in the regulation of sleep and wakefulness.