Chapter: 6

The Sleep Neuro-pharmacology
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The basic mechanisms that control sleep regulation have led to considerable improvement in our knowledge of sleep disorders. It is now well accepted that transitions between sleep and wakefulness are regulated by complex neurobiologic mechanisms, which can be delineated as oscillations between two opponent processes, one promoting sleep and the other promoting wakefulness.

The role of several neurotransmitter systems, including noradrenergic, serotonergic, cholinergic, adenosinergic, and histaminergic systems and more recently, the hypocretin/orexin and dopamine systems has been clearly established. Amphetamine-like stimulants are known to increase wakefulness by blocking dopamine reuptake, by stimulating dopamine release, or by both mechanisms. Modafinil may increase wakefulness through activation of noradrenergic and dopaminergic systems, possibly through interaction with the hypocretin/orexin system. Caffeine inhibits adenosinergic receptors, which in turn can produce activation via interaction with GABAergic and dopaminergic neurotransmission. Nicotine enhances acetylcholine neurotransmission in the basal forebrain and dopamine release. Understanding the exact role of the hypocretin/orexin and dopamine systems in the sleep-wake regulation may reveal new insights into future wakefulness-promoting drugs.

Brainstem has specific areas that serve as a locus of certain types of neurotransmitter and neuromodulator systems. Substantia nigra (Dopamine), Gigantocellular nucleus of reticular formation (Acetylcholine), Locus ceruleus (Norepinephrine), Nuclei of the raphe (Serotonin) are some examples of such systems.

Wakefulness is mediated in the Basal Forebrain (Acetylcholine), Tubommaillary Nucleus (Histamine), Suprachiasmatic Nucleus (VTA), Reticular Foundation (Dopamine), Raphe (5-HT or Serotonin), PPT, LDT (Acetylcholine). NREM sleep is controlled by VLPO (GABA), Tubommaillary Nucleus (Histamine), Suprachiasmatic Nucleus (VTA), Raphe, Locus Ceruleus, PPT and, LDT nuclei. REM sleep is induced at PPT, LDT (Acetylcholine) Aminergic nuclei in Locus ceruleus and Raphe' facilitate waking and Cholinergic nuclei in PPT and LDT facilitate REM activity during sleep

There has been a search for an endogenous sleep substance that was conceptualized by Kleitman as Hypnotoxin. Many such substances have been considered but none stands out or meets criteria for an ideal hypnotoxin. The DSIP, factor S, Arginine vasotoxin, GHrF, IL-1, Cholecystokinin, Insulin, deacyl-alpha-MSH, Interferon-alpha-2, Prostaglandin D2, and Uridine all increase the slow wave sleep and have been at one time or the other considered to be potential sleep substances. Vasoactive peptide, GH, Somatostatin and Prolactin increase REM sleep; Tryptophan and Melatonin increase total sleep time and Corticotropin releasing factor, Thyrotropin releasing hormone,

Prostaglandin E2 and ACTH increase the wakefulness. Recently Adenosine has been evaluated for mediating the sleep. However there is no evidence so far of the existence a true Hypnotoxin

The $GABA_A$ receptor is perhaps one of the most important receptor complex that subserves GABA, Benzodiazepine and Barbiturate subunits. The combination of GABA and benzodiazepine agonism causes profound sleepiness due to the larger opening of the chloride channel on the GABA receptor complex. Both Benzodiazepines and Barbiturates increase total sleep time and Stage N2 sleep. Both decrease sleep latency, slow wave stage N3 sleep and REM sleep. Barbiturates are a potent suppressor of REM sleep compared to Benzodiazepines. The withdrawal from Barbiturates may cause severe adverse events and overdose liability is high. The withdrawal from Benzodiazepams leads to rebound insomnia and overdose liability is low. Other drugs which manifest their effects through the GABA receptors include Non-benzodiazepines hypnotics, alcohol, chloral hydrate, steroids and picotoxin.

Adenosine is delivered to preoptic area and anterior hypothalamus to induce NREM sleep. Basal forebrain (BF) Adenosine levels rise during prolonged wakefulness, in BF. They decline during the recovery sleep. BZD decreases adenosine uptake but caffeine does not alter BDZ receptor action. Main Adenosine antagonists are caffeine, Theobromine and Theophylline that increase the wakefulness and reduce the sleep efficiency. Agonist increase sedation and slow wave sleep. Adenosine inhibitor, Mioflazine increases the percentage of the slow wave sleep.

In animal models the specificity of the action of newer hypnotics suggests superiority of these drugs compared to benzodiazepines. Further the GABA receptor subtype affinity of the new generation of hypnotics as well as Benzodiazepines is well defined. Gamma-hydroxybutyrate (GHB) is structurally similar to GABA and its agonism is mediated through $GABA_B$ receptors. GHB may induce G-protein mediated decrease in Acetylcholine, decreased Dopamine release under normal circumstances, and is partially reversible by naloxone. GHB does not bind to mu, delta or kappa receptors. The sleep and endocrine response of GHB is well studied. It decreases sleep latency and wake after sleep onset time, increases sleep efficiency and slow wave sleep. GHB increases the levels of Growth hormone, Prolactin and Cortisol.

The traditional neuroleptic like *Chlorpromazine, Thorazine, Haloperidol, Haldol, Thioridazine and Mellaril* are D2 and D3 receptor antagonists and cause increased sedation, sleep efficiency and slow wave stage N3 sleep and aggravate periodic limb movement of sleep and produce restless leg syndrome like effects. They also decrease REM sleep based on anti-Acetylcholinergic properties. The newer non-D2 receptor neuroleptic drugs like *Clozopine, Clazoril, Olanzapine, Zyprexa, Resperidone and Resperidol* cause variable amount of increase in sedation and decrease in slow wave sleep. These newer compounds also tend to worsen Restless leg syndrome and Periodic limb movement disorder.

Dopamine has significant effect on sleep wake physiology. L-dopa, a precursor of Dopamine at high doses can cause Insomnia. Apomorphine, a dopamine agonist increases

wakefulness. The D2 receptor agonist, Bromocryptine decreases both the REM sleep and the REM rebound. Cocaine is a dopamine reuptake blocker and causes increase in wakefulness and an increase in REM sleep. The two dopamine antagonists, Pimozide and Neuroleptic group of drugs are sedatives.

Some of the clinically used and recreational drugs cause stimulation by affecting Dopamine and Nor-epinephrine, increasing the wakefulness, sleep latency, number of awakenings and REM latency. Obviously, the total sleep time, REM sleep percentage and slow wave sleep are reduced. These drugs include Pemoline, Mazindol, Seleginine, Amphetamines, Methylphenidate, Cocaine and Ecstasy.

Adrenergic drugs exert their actions on sleep and wake via alpha and beta adrenergic receptors. Phenylephrine and Clonidine are alpha1 receptor agonist and reduce the amount of REM sleep. Prazosin, an alpha1receptor antagonist possibly increases the REM sleep. Yohimbine and Mirtazepam are both alpha2 receptor antagonists but have opposite effect on sleep with increased wake and increased sleep respectively. Propanolol, a beta adrenergic receptor blocker increases wakefulness, insomnia, nightmares and reduces REM percentage. Reserpine, not in much clinical use any longer depletes Nor-epinephrine stores and increases REM sleep.

Sleep effects of recreational drugs are different acutely, chronically and upon withdrawal of the drug. The effects of alcohol are dose dependent and include decreased sleep latency, increased amount of slow wave sleep early in the night and decreased REM sleep early and later rebound. Nicotine disturbs the sleep by fragmentation and its withdrawal disturbs sleep. On the other hand THC (Marijuana) acutely causes reduced REM and REM density and increased REM on withdrawal. Chronically, THC does not cause any consistent alteration in sleep. LSD-25 increases early REM sleep, increased arousals and movements and REM intrusion in to the slow wave sleep. Opioids are known to cause sedation, increased stage one sleep, stage REM and slow wave sleep during withdrawal.

Atypical antidepressants drugs like Buproprion increase REM sleep and is less sedating whereas Venlafaxine and Trazadone decrease REM and are very sedating. Nefazodone on the other hand increases REM and is non-sedating.

Serotonin Selective Receptor Inhibitors (SSRI) in general decrease slow wave sleep, REM sleep and are less sedating. Fluoxetine, Paroxetine and Sertraline are few popular SSRI antidepressants used in clinical practice.

Another group of antidepressant are Tricyclic antidepressants. These drugs differ from one another depending on what their effect is on sleep. In general, they tend to increase slow wave sleep, reduce REM sleep and have variable degree of sedation. The exceptions are Trimipramine that has no effect on REM and Clomipramine, that is most REM suppressing but is least sedating. Amitryptaline, Trimipramine and Doxepin are most sleep inducing due to their high affinity for Histamine1 receptor blockage.

Monoamine oxidase (MAO) inhibitors like Phenelzine strongly decrease REM sleep, increase REM sleep latency and cause REM rebound when discontinued. MAO inhibitors do not change slow wave sleep.

Antihistamines exert their variable effects on sleep through histamine receptor antagonism. Cimetidine increases slow wave sleep. Diphenhydramine is sedating and Tripolidine and Brompheramine reduce REM sleep. Astemizole and Terfenadine are histamine2 receptor antagonist and are non-sedating as they do not cross blood brain barrier.

Melatonin provides the human brain a signal for darkness. Exogenous Melatonin can entrain sleep wake cycle in the blind humans. If taken 30 to 90 minutes before bedtime, it advances the sleep phase. Melatonin can cause drowsiness. When taken several hours before bedtime the dosage should be small to avoid sleepiness. Exogenous melatonin has acute sleep-inducing and temperature-lowering effects during 'biological daytime', and when suitably timed (it is most effective around dusk and dawn) it will shift the phase of the human circadian clock (sleep, endogenous melatonin, core body temperature, cortisol) to earlier (advance phase shift) or later (delay phase shift) times."

Modafanil, a wake promoting relatively newer drug seems to selectively reduce GABA in sleep promoting regions. Modafanil also increases histaminergic activity in posterior hypothalamus (wakefulness generating neurons) tuberomammillary nuclei. Modafinil inhibits ventro-lateral preoptic area (sleep generating neurons) activity in anterior hypothalamus.

Caffeine, an adenosine antagonist decreases total sleep time, slow wave sleep and REM sleep. It increases sleep latency and wake after sleep onset time. Caffeine also increases dopamine levels in the same way that amphetamines do. The half-life of caffeine is about six hours. After consuming a big cup of coffee with 200 mg of caffeine at 3:00 p.m., about 100 mg of that caffeine can still be measured in the system by 9:00 p.m.

The past decade has witnessed an explosion of knowledge about the neural mechanisms that control sleep and arousal. The level of arousal is controlled by an intricate interplay between wakefulness- and sleep-promoting nuclei located in the hypothalamus and brainstem. Currently available drugs exert their therapeutic effects in the three major classes of sleep disorder (insomnia, hypersomnia, parasomnia) by modifying neurotransmission at distinct sites within the arousal-controlling neuronal network. This enables classification of therapeutic drugs for sleep disorders on the basis of their modes of action: drugs that interact with the GABAergic sleep-promoting system, drugs that interact with different wakefulness-promoting systems and drugs that modulate the level of arousal.